ACID-CATALYSED C-RIBOFURANOSYLATION OF BENZENE DERIVATIVES; SOME NOVEL CONVERSIONS OF C-RIBOFURANOSYL DERIVATIVES

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The C-ribofuranosylation of 1,2-dimethoxybenzene, 1,4-dimethoxybenzene, 1,2,3-trimethoxybenzene, 1,4-bis(2-bromoethoxy)benzene, 1,3,5-trimethylbenzene, and 1,4-dihydroxybenzene has been described. Transformation of C-ribofuranosyl derivatives *IVβ*, *XIV* and *XXII* has furnished anomeric 2-D-ribofuranosyl-1,4-benzoquinones, 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2,3,4,5-tetraacetoxybenzene, and 1-(β-D-ribofuranosyl)-3,4-dimethoxy-6-nitrobenzene. The configurations of C-ribofuranosyl derivatives *IXβ*, *XVI*, *XXIII* and *XXIV* have been ascribed on the basis of hydrogen bonding measurements of derivatives, the *cis* diol system of which was protected by the isopropylidene or cyclophenylboronate group.

In some naturally occurring substances, the β-D-ribofuranosyl residue is attached by means of a C—C bond to a heterocyclic aglycone, *e.g.*, in pseudouridine[1,2], the constant component of s-RNA, and in some antibiotics such as formycin, laurusin, pyrazomycin, showdomycin[3], and the recently isolated oxazinomycin[4]. The synthesis of compounds of this type is rather difficult, particularly because of the C—C attachment of the β-D-ribofuranosyl residue to the aglycone. There are only few methods for realisation of this bond type, *e.g.*, C-glycosylation of mercuric cyanide and organometallic reagents[5,6] and the acid-catalysed electrophilic substitution of aromatic compounds[5–7]. Most C-glycosylations have been performed with the pyranose forms of saccharides while the C-ribofuranosylations are rather rare. Thus, *e.g.*, mercuric cyanide[8] and salts of some nitrogen-containing aglycones have been successfully C-ribofuranosylated. In the first synthesis of pseudouridine[9], the lithium salt of 2,4-dimethoxypyrimidine was C-ribofuranosylated by the action of 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride while in the case of benzene[10] and 2,6-dibenzyloxypyridine[11], the organocadmium compounds were used.

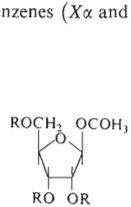
Since in numerous naturally occurring substances the glucopyranosyl or ribofuranosyl group is attached by means of the C—C bond to the aromatic aglycone at such a position which is most inclined to the electrophilic substitution, we have focussed our attention to the acid-catalysed C-ribofuranosylation of polysubstituted benzenes with a special regard to the preparation of intermediates suitable for the synthesis of showdomycin.

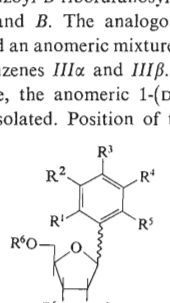
Hurd and Bonner[12] have reported glycopyranosylations of benzene (a great excess has been used) under catalysis of aluminium chloride. Under these conditions, the protecting acetyl groups are split off under the formation of free acidolabile glycosyl derivatives of benzene, the yields

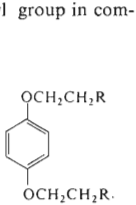
of which are low. In the case of the more reactive toluene[13], the pyranose ring of the corresponding glycosyl derivative is opened while undefined products are obtained in analogous glycosylations of naphthalene. Reactive aromatic systems may be C-glycosylated by the method of Treibs[14,15] consisting in the reaction of acylated halogenoses with a aglycone in an inert solvent and in the presence of zinc oxide. This method has been successfully used in glycosylation of some azulenes[14] and pyridine N-oxides[15].

The method of Treibs has been used by us in two cases. Thus, the reaction of 1,3,5-trimethoxybenzene with 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide afforded a fair yield of 1-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-2,4,6-trimethoxybenzene[16] while the analogous C-ribosylation of the less reactive 1,2-dimethoxybenzene led to a complex mixture of products. We have therefore drawn attention to the acid-catalysed C-ribofuranosylations with a special regard to the use of suitable catalysts and mild reaction conditions. The C-ribosylation of 1,2-dimethoxy-, 1,4-dimethoxy-, and 1,2,3-trimethoxybenzene has been successfully accomplished by the action of 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (*I*) in the presence of aluminium chloride in ether (procedure *A*). In the case of less reactive benzene derivatives, *e.g.*, 1,3,5-trimethylbenzene, stannic chloride in benzene was used as catalyst (procedure *B*). The reaction conditions of the acid-catalysed C-ribofuranosylations of polysubstituted benzenes must correspond to the reactivity of both starting compounds and reaction products to avoid the formation of polymers in the case of reactive aglycones.

The C-ribofuranosylation of 1,4-dimethoxybenzene with the acetate *I* afforded the anomeric 1-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-2,5-dimethoxybenzenes (*IIα* and *IIβ*) by both procedures *A* and *B*. The analogous reaction of 1,2,3-trimethoxybenzene (procedure *A*) afforded an anomeric mixture of 1-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-2,3,4-trimethoxybenzenes *IIIα* and *IIIβ*. After the alkaline methanolysis of the crude reaction mixture, the anomeric 1-(D-ribofuranosyl)-2,3,4-trimethoxybenzenes (*Xα* and *Xβ*) were isolated. Position of the ribofuranosyl group in com-







I, R = C_6H_5CO

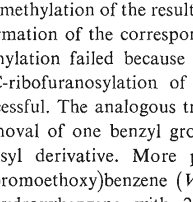
IIα,β, $R^1 = R^3 = R^4 = H$; $R^2 = R^5 = OCH_3$
IIIα,β, $R^1 = R^2 = H$; $R^3 = R^4 = R^5 = OCH_3$
IVα,β, $R^1 = R^4 = R^5 = H$; $R^2 = R^3 = OCH_3$
Vα,β, $R^2 = R^4 = H$; $R^1 = R^3 = R^5 = CH_3$
Xα,β, $R^1 = R^2 = R^6 = H$; $R^3 = R^4 = R^5 = OCH_3$
VIα,β, $R^1 = R^3 = R^4 = H$; $R^2 = R^5 = OCH_2CH_2Br$

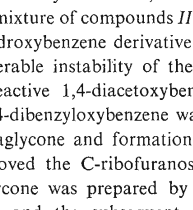
VII, R = OH
VIII, R = Br

In formulae *II* – *VI* $R^6 = C_6H_5CO$

pounds $X\alpha$ and $X\beta$ was determined by analysis of NMR spectra (two characteristic doublets in the aromatic region, δ 6·70 and 7·14 p.p.m., of $J_{5,6}$ 9 Hz; the signals correspond to two vicinal protons at positions 5 and 6). The ribosylation of 1,2-dimethoxybenzene (procedure *A*) afforded an anomeric mixture of compounds $IV\alpha$ and $IV\beta$ from which 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-3,4-dimethoxybenzene ($IV\beta$) was isolated. Position of the ribofuranosyl group was determined by conversion of compound $IV\beta$ to the 6-nitro derivative XV and then by alkaline methanolysis to the free 1-(β-D-ribofuranosyl)-3,4-dimethoxy-6-nitrobenzene (XVI), the NMR spectrum of which was analysed. Two singlets (δ 7·49 and 7·79 p.p.m. $J \to 0$ Hz) are present, indicating the mutual *para* position of protons. Ribosylation (procedure *B*) of 1,3,5-trimethylbenzene afforded a fair yield of anomeric 1-(2,3,5-tri-O-benzoyl--D-ribofuranosyl)-2,4,6-trimethylbenzenes $V\alpha$ and $V\beta$.

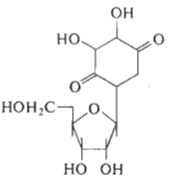
For the intended synthesis of showdomycin, 2-(β-D-ribofuranosyl)-1,4-benzoquinone appeared as the suitable starting material. We have first attempted to prepare this benzoquinone derivative *via* the C-ribofuranosylation of 1,4-dimethoxybenzene and demethylation of the resulting anomeric mixture of compounds $II\alpha$ and $II\beta$ under the formation of the corresponding 1,4-dihydroxybenzene derivative; the attempted demethylation failed because of the considerable instability of the furanose ring. The C-ribofuranosylation of the poorly reactive 1,4-diacetoxybenzene was also unsuccessful. The analogous treatment of 1,4-dibenzyloxybenzene was accompanied by removal of one benzyl group from the aglycone and formation of the O-ribofuranosyl derivative. More promissing proved the C-ribofuranosylation of 1,4-bis(2-bromoethoxy)benzene (*VIII*). The aglycone was prepared by the reaction of 1,4-dihydroxybenzene with 2-chloroethanol and the subsequent replacement of the hydroxylic functions of the resulting 1,4-bis(2-hydroxyethyl)benzene (*VII*) by bromo atoms on treatment with phosphorus tribromide. The 2-bromoethyl



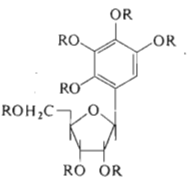


IX, R = C_6H_5CO
XII, R = H

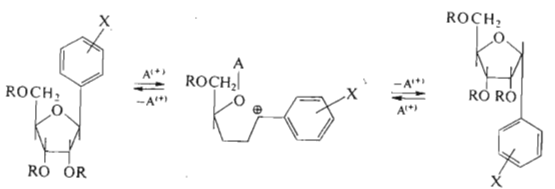
XI, $R^1 = R^2 = R^5 = H$; $R^3 = R^4 = OCH_3$
XIII, $R^1 = R^4 = OH$; $R^2 = C_6H_5CO$; $R^3 = R^5 = H$
XIV, $R^1 = R^4 = OH$; $R^2 = R^3 = R^5 = H$
XV, $R^1 = NO_2$; $R^2 = C_6H_5CO$; $R^3 = R^4 = OCH_3$
XVI, $R^1 = NO_2$; $R^2 = H$; $R^3 = R^4 = OCH_3$
XVII, $R^1 = NH_2$; $R^2 = C_6H_5CO$; $R^3 = R^4 = OCH_3$
XVIII, $R^1 = R^3 = R^5 = OCH_3$; $R^2 = R^4 = H$



XIX

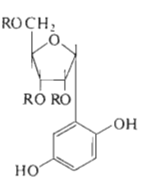


XX, R = CH_3CO

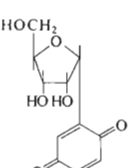


R = C_6H_5CO

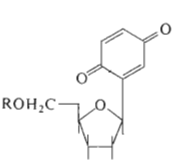
SCHEME 1



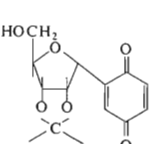
XXI, R = C_6H_5CO
XXII, R = H



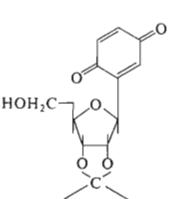
XXIII



XXIV, R = H
XXV, R = CH_3CO



XXVI

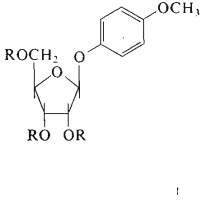


XXVII

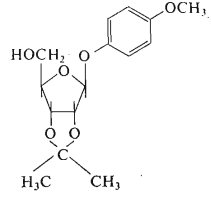
groups of compound *VIII* may be readily removed by the action of zinc in a mildly acidic medium under the formation of the starting 1,4-dihydroxybenzene. Despite the lower reactivity of the bromo ether *VIII* in comparison with 1,4-dimethoxybenzene, 1-(2,3,5-tri-O-benzoyl-α-D-ribofuranosyl)-2,5-bis(2-bromoethyl)benzene (*VIα*) was isolated in a satisfactory yield from the ribosylation mixture. The ribofuranosylation of 1,4-dihydroxybenzene affords 4-hydroxyphenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside (*IX*) which is converted by the action of acidic catalysts to the C-ribofuranosyl derivative *XIII*; alkaline methanolysis of compound *XIII* affords 1-(β-D-ribofuranosyl)-2,5-dihydroxybenzene (*XIV*).

The C-ribofuranosyl derivative *VIα* was converted by the action of zinc in methanol in the presence of ammonium chloride to 1-(α-D-ribofuranosyl)-2,5-dihydroxybenzene (*XXI*) which was deblocked and the resulting 1-(α-D-ribofuranosyl)-2,5-dihydroxybenzene (*XXII*) oxidized with silver oxide in ethyl acetate under the formation of the crystalline 2-(α-D-ribofuranosyl)-1,4-benzoquinone (*XXIII*). Oxidation of the free C-ribofuranosyl derivative *XIV* under otherwise identical conditions afforded the anomeric 2-(β-D-ribofuranosyl)-1,4-benzoquinone (*XXIV*).

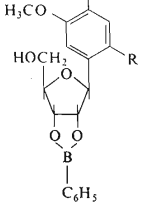
It was assumed that the synthesis of showdomycin could comprise the oxidative cleavage of C-ribofuranosyl derivatives of hydroxy- or amino-benzoquinones under the formation of β-D-ribofuranosylmaleic acid[17]. The reported[18] hydroxylation of 1,4-benzoquinone was therefore applied to 1-(β-D-ribofuranosyl)-2,5-dihydroxybenzene (*XIV*). Oxidation of compound *XIV* with osmium tetroxide afforded compound *XIX* which without isolation was acetylated under the formation of 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2,3,4,5-tetraacetoxybenzene (*XX*). Another type of the intermediate which would contain amino-1,4-benzoquinone as the aglycone could be obtained from the above mentioned nitro derivative *XV*. Reduction of compound *XV* with stannous chloride or iron in acetic acid afforded 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2-amino-4,5-dimethoxybenzene (*XVII*). Compounds *XVII* and *XX* were deblocked and subjected to the oxidative cleavage leading in both cases to complex



XXVIII, R = C_6H_5CO
XXIX, R = H



XXX



XXXI, R = H
XXXII, R = NO_2

mixtures which were not suitable for the synthesis of showdomycin. Later on, this synthesis was successfully effected with the use of a different procedure[16].

The furanose ring of free C-ribofuranosylated benzenes is readily opened especially in that case when the position $C_{(1')}$ is activated by methoxyls at ortho and para positions of the benzene ring. By the action of 0·1M-HCl at room temperature, about 50% of 1-(β-D-ribofuranosyl)-2,4,6-trimethoxybenzene (*XVIII*) are isomerised in the course of 5 min. The course of isomerisation was followed by thin-layer chromatography on silica gel (calcium sulfate as binder) in 9 : 1 ethyl acetate–2-propanol solvent mixture. The less mobile product (R_F 0·3) was found to consume 2 moles of the periodate almost immediately; this finding speaks in favour of the 1-D-ribopyranosyl-2,4,6-trimethoxybenzene structure which is also in accordance with the mass spectrum. As expected, the analogous isomerisation of 1-(β-D-ribofuranosyl)--3,4-dimethoxy-6-nitrobenzene (*XVI*) does not occur under similar conditions.

The configuration of the anomeric center in glycosyl derivatives possessing the furanose ring can be determined by NMR spectra in special cases only[19,20]. The NMR spectrum is of similar limited value also in the case of the C-ribofuranosyl derivatives where, moreover, the proton signals at positions 1, 2, and 3 of the sugar moiety are poorly resolved. To our experience, the configuration can be reliably determined in this case by analysis of hydrogen bonds. We have made use of that circumstance that the formation of hydrogen bonds between the hydroxylic function at position 5 of the ribofuranosyl residue and the aglycone is limited to the C-ribofuranosyl derivatives of the β-configuration and possessing a suitably protected *cis*-diol system. Both anomers also form weak hydrogen bonds between the hydroxylic function and the furanose ring oxygen atom. The *cis*-diol system of 2-D-ribofuranosyl-1,4-benzoquinones (*XXIII* and *XXIV*) was therefore protected by the isopropylidene grouping and hydrogen bonds of the 2',3'-O-isopropylidene derivatives *XXVI* and *XXVII* were measured. On the basis of these measurements, compounds *VIα* and *XXI* to *XXIII* were unequivocally ascribed the α-configuration and compounds *XIV* and *XXIV* the β-configuration. The course of ORD spectra of the anomeric 2-D-ribofuranosyl-1,4-benzoquinones (*XXIII* and *XXIV*) is opposite as expected. In a similar manner, the glycoside *IX* was ascribed the configuration β. Compound *IX* was methylated with dimethyl sulfate in acetone in the presence of potassium carbonate and the resulting 4-methoxyphenyl 2,3,5-tri-O-benzoyl-β-D--ribofuranoside (*XXVIII*) converted by alkaline methanolysis to the free 4-methoxyphenyl β-D-ribofuranoside (*XXIX*). Reaction of compound *XXIX* with acetone in the presence of *p*-toluenesulfonic acid afforded the 2',3'-O-isopropylidene derivative *XXX* the IR spectrum of which exhibits an intensive band corresponding to the hydrogen bonding between the free hydroxylic function and the glycosidic oxygen atom. The *cis*-diol system of the highly acidolabile C-ribofuranosylbenzenes was protected by the cyclophenylboronate group[21] which may be introduced under almost neutral conditions. On the basis of IR analysis of hydrogen bondings, 1-

-(β-D-ribofuranosyl)-3,4-dimethoxybenzene 2',3'-O-cyclophenylboronate (*XXXI*), the 6-nitro derivative *XXXII*, and consequently, the compounds *IVβ*, *IX*, and *XV* to *XVII* were unequivocally ascribed the β-configuration.

The first stage of the acid-catalysed C-ribofuranosylation of benzene derivatives is assumed to afford the ribofuranosyl derivatives of the β-configuration at the anomeric center $C_{(1')}$ due to participation of the protecting benzoyl group at position 2, the influence of which on the steric course of glycosylations is generally accepted in the literature. Compounds of the α-configuration are to our opinion formed by the subsequent anomerisation. The occurrence of anomerisation might be explained by the character of the anomeric center at $C_{(1')}$ carbon atom of the C-ribofuranosyl derivatives of substituted benzenes similar to that of activated benzyl ethers where a ready opening and closure of the furanose ring may be expected by the action of acidic catalysts (Scheme 1). This idea is supported by the considerable dependence of the steric course of C-ribosylations on reaction conditions and particularly on the catalyst used. Thus, *e.g.*, the optical rotation of the product (*IIα* and *IIβ*) obtained by the C-ribofuranosylation of 1,4-dimethoxybenzene was $[\alpha]_D^{25}$ +27·2° ($CHCl_3$) when the reaction was performed in the presence of aluminium chloride in ether (procedure *A*), and $[\alpha]_D^{25}$ +6·8° ($CHCl_3$) when stannic chloride in benzene (procedure *B*) was used as catalyst. The optical rotation of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,5-dimethoxybenzene (*IIβ*) obtained by methylation of compound *XIV* and the subsequent benzoylation was quite different, $[\alpha]_D^{25}$ −22·9° ($CHCl_3$).

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Unless stated otherwise, the analytical samples were dried for 10 h at 20°C/0·05 Torr. The preparative chromatography was performed on a column of silica gel partially deactivated with 8% of water. The purity of substances was checked by thin-layer chromatography on silica gel (calcium sulfate as binder; the spots were detected by spraying with 20% aqueous sulfuric acid and the subsequent heating). Infrared spectra were taken on a double-beam Zeiss UR 10 spectrometer. NMR spectra were recorded on Varian HO 100 aparatus and ORD spectra on a Jasco Model ORD/UV-5 polarimeter (concentration of about 0·01 g per 100 ml). Mass spectra were measured on a MS 902 mass spectrometer.

C-Ribofuranosylation of 1,2-Dimethoxybenzene

The ribofuranose derivative[22] *I* (2·50 g; 5·0 mmol) and 1,2-dimethoxybenzene (1·0 g; 7·2 mmol) were added to a solution of aluminium chloride (4·0 g) in ether (10 ml) and the whole stirred at room temperature for 1·5 h. Benzene (25 ml) was then added and the mixture decomposed under cooling by a portionwise addition of water (25 ml). The organic layer was separated, washed with water, dried, evaporated under diminished pressure, and the residue chromatographed on a column of silica gel (100 g) in 19 : 1 benzene–acetone. The corresponding fractions (R_F, 0·6 on thin layers of silica gel in the same solvent system) were combined and evaporated under diminished pressure. The residue was crystallised from ether–ligth petroleum to afford 1·5 g (51%) of the β-anomer *IVβ*, m.p. 114–115°C, $[\alpha]_D^{25}$ −106·4° (*c* 0·50, chloroform). For $C_{34}H_{30}O_9$ (582·6) calculated: 70·09% C, 5·19% H; found: 70·16% C, 5·27% H.

1-(β-D-Ribofuranosyl)-3,4-dimethoxybenzene (*XI*)

A suspension of the ester *IVβ* (1·17 g; 2·0 mmol) in methanol (25 ml) was treated with 1M methanolic sodium methoxide (0·3 ml), the whole stirred at room temperature for 20 h, neutralised with acetic acid, and evaporated under diminished pressure. The residue was chromatographed on a column of silica gel (30 g) in 9 : 1 ethyl acetate–2-propanol to afford 510 mg (95%) of compound *XI*, m.p. 125—128°C (after drying at 100°C/0·5 Torr), $[\alpha]_D^{25}$ −48·9° (*c* 0·50, water). For $C_{13}H_{18}O_6$ (270·3) calculated: 57·77% C, 6·71% H; found: 57·67% C, 6·71% H.

C-Ribofuranosylation of 1,4-Dimethoxybenzene

Method A. The acetate[22] *I* (2·50 g; 5 mmol) and 1,4-dimethoxybenzene (1·0 g; 7·2 mmol) were added to a solution of anhydrous aluminium chloride (4·0 g) in ether (10 ml), the whole stirred at room temperature for 1·5 h, and processed as above. The corresponding fractions (R_F 0·55) were combined and evaporated to afford 1·4 g (48%) of the mixture of compounds *IIα* and *IIβ*. Optical rotation: $[\alpha]_D^{25}$ +27·2° (*c* 0·50, chloroform). For $C_{34}H_{30}O_9$ (582·6) calculated: 70·09% C, 5·19% H; found: 70·36% C, 5·27% H.

Method B. A mixture of the acetate[22] *I* (2·50 g; 5·0 mmol) and 1,4-dimethoxybenzene (1·00, 7·2 mmol) was treated with 1M-$SnCl_4$ in benzene (5 ml), the whole shaken at room temperature for 15 min, diluted with benzene (25 ml), decomposed with water (15 ml), and processed as above to afford 1·70 g (58%) of the mixture of compounds *IIα* and *IIβ*. Optical rotation: $[\alpha]_D^{25}$ +6·8° (*c* 0·50, chloroform). For $C_{34}H_{30}O_9$ (582·6) calculated: 70·09% C, 5·19% H; found: 70·03% C; 5·22% H.

C-Ribofuranosylation of 1,2,3-Trimethoxybenzene

The acetate[22] *I* (2·5 g; 5·0 mmol) and 1,2,3-trimethoxybenzene (1·2 g; 7·0 mmol) were added to a solution of anhydrous aluminium chloride (4·0 g) in ether (10 ml). The mixture was stirred at room temperature for 1·5 h, diluted with benzene (25 ml), washed with three 25 ml portions of water, dried, and evaporated under diminished pressure. The residual esters were diluted with methanol (25 ml) and 1M-$NaOCH_3$ in methanol (0·3 ml). The resulting mixture was kept at room temperature for 15 h, neutralised with acetic acid, and evaporated under diminished pressure. The residue was dissolved in water (10 ml) and the aqueous solution extracted successively with benzene (10 ml) and four 30 ml portions of ethyl acetate. The ethyl acetate extract was dried over magnesium sulfate, evaporated, and the residue chromatographed on a column of silica gel (40 g) in 9 : 1 ethyl acetate–2-propanol to afford 1·0 g (66%) of the amorphous mixture of compounds *Xα* and *Xβ*. Optical rotation: $[\alpha]_D^{25}$ −38·3° (*c* 0·19, water). For $C_{14}H_{20}O_7$ (300·3) calculated: 55·99% C, 6·76% H; found: 55·90% C, 6·84% H.

C-Ribofuranosylation of 1,3,5-Trimethylbenzene

A mixture of the acetate[22] *I* (2·50 g; 5·0 mmol) and 1,3,5-trimethylbenzene (1·8 g; 15 mmol) was treated with 1M-$SnCl_4$ in benzene (5 ml), the whole stirred magnetically at room temperature for 2·5 h, diluted with benzene (15 ml), and decomposed with water (15 ml). The organic layer was washed with water (25 ml), dried, evaporated under diminished pressure, and the residue chromatographed on a column of silica gel (150 g) in 9 : 1 benzene–ether. The corresponding fractions (R_F, 0·7 on a thin layer of silica gel in the same solvent system) were evaporated to afford 2·5 g (88%) of a sirupous mixture of compounds *Vα* and *Vβ*. Optical rotation: $[\alpha]_D^{25}$ −95·7° (*c* 0·50, chloroform). For $C_{35}H_{32}O_7$ (564·6) calculated: 74·46% C, 5·71% H; found: 74·68%, 5·49% H.

1,4-Bis(2-hydroxyethoxy)benzene(*VII*)

A solution of sodium hydroxide (90·0 g; 2·25 mol) in water (250 ml) was added under nitrogen to 1,4-dihydroxybenzene (110·1 g; 1·0 mol) and the alkaline mixture was treated dropwise under cooling with 2-chloroethanol (140 ml; 2·1 mol); after 2 days at room temperature, the thick suspension was diluted with acetic acid (20 ml) and water (250 ml), heated to 80°C and then cooled down. The solid was collected with suction and washed with water. Yield, 180 g (90%) of compound *VII*, m.p. 119—121°C (water). For $C_{10}H_{14}O_2$ (198·1) calculated: 60·59% C, 7·12% H; found: 60·80% C, 7·06% H.

1,4-Bis(2-bromoethoxy)benzene(*VIII*)

Compound *VII* (10·0 g; 50 mmol) was added under cooling to a mixture of phosphorus tribromide (5·6 ml), pyridine (2 ml), and chloroform (5 ml), the whole heated on a steam bath for 20 min, allowed to cool, and diluted with chloroform (50 ml). The chloroform solution was poured onto ice, washed with water, dried over magnesium sulfate, and evaporated under diminished pressure. The residue was triturated with ethanol, the solid collected with suction and washed with ethanol. Yield, 8·0 g (49%) of the ether *VIII*, m.p. 116—118°C (acetone–methanol). For $C_{10}H_{12}Br_2O_2$ (324·0) calculated: 37·05% C, 3·70% H, 49·38% Br; found: 37·25% C, 3·92% H, 48·97% Br.

C-Ribofuranosylation of 1,4-Bis(2-bromoethoxy)benzene (*VIII*)

The ribofuranose derivative *I* (2·50 g; 5·0 mmol) and 1,4-bis(2-bromoethoxy)benzene (2·25 g; 7·0 mmol) were added to a solution of aluminium chloride (4·0 g; 35 mmol) in ether (10 ml), the whole refluxed for 1·5 h, diluted with benzene (20 ml), and decomposed cautiously with water (15 ml). The organic layer was washed with water (20 ml), dried, and evaporated under diminished pressure. The residue was chromatographed on a column of silica gel (150 g) in 19 : 1 benzene–ether solvent mixture. The corresponding fractions (R_F 0·6 in thin layers) were combined, evaporated under diminished pressure, and the residue crystallised from ether to afford the α-anomer *VIα* (1·0 g; 26%), m.p. 117—118°C, $[\alpha]_D^{25}$ +27·7° (*c* 0·50; chloroform). For $C_{36}H_{32}Br_2O_9$ (768·4) calculated: 56·25% C, 4·19% H, 20·78% Br; found: 56·15% C, 4·05% H, 20·57% Br.

O-Ribofuranosylation of 1,4-Dihydroxybenzene

Boron trifluoride etherate (10 ml) was added to a solution of the ribofuranose derivative *I* (10·1 g; 20·0 mmol) and 1,4-dihydroxybenzene (6·0 g; 54·0 mmol) in ether (10 ml) and the whole mixture was shaken at room temperature for 30 min. The suspension was dissolved in chloroform (150 ml), the solution washed with saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, and evaporated under diminished pressure. The residue was crystallised from acetone–methanol to afford 9·0 g (81%) of the O-ribofuranosyl derivative *IX*, m.p. 185 to 186°C, $[\alpha]_D^{25}$ +8·0° (*c* 0·50; chloroform). For $C_{32}H_{28}O_9$ (554·4) calculated: 69·31% C, 4·73% H, 0·18% H (act.); found: 69·36% C, 4·89% H; 0·20% H (act.).

4-Hydroxyphenyl β-D-Ribofuranoside (*XII*)

Methanolic 1M-$NaOCH_3$ (5 ml) was added to a suspension of the tribenzoate *IX* (2·77 g; 5·0 mmol) in methanol (25 ml), the mixture kept at room temperature for 20 h, neutralised with acetic acid, and evaporated under diminished pressure. The residue was dissolved in water (20 ml), the aqueous solution washed with two 25 ml portions of ether, and passed through a column

(10 ml) of Amberlite IRC 50 (H^+) ion exchange resin. The effluent was concentrated under diminished pressure to the volume of about 4 ml to deposit the furanoside *XII*, m.p. 155—157°C, $[\alpha]_D^{25}$ —89·5° (*c* 0·50, water). For $C_{11}H_{14}O_6$ (242·2) calculated: 54·54% C, 5·83% H; found: 54·35% C, 5·92% H.

C-Ribofuranosylation of 1,4-Dihydroxybenzene

The ribofuranose derivative *I* (5·0 g; 10·0 mmol) and 1,4-dihydroxybenzene (3·0 g; 27·0 mmol) were added to a solution of anhydrous aluminium chloride (8·0 g) in ether (20 ml), the whole heated on a steam bath for 15 min, cooled down, diluted with benzene (50 ml), and poured onto ice. The organic layer was washed with two 50 ml portions of water, dried over anhydrous magnesium sulfate, and evaporated under diminished pressure. The residual sirup was dissolved in methanolic 0·2M-$NaOCH_3$ (30 ml) and the solution kept under nitrogen at room temperature for 20 h. The alkaline mixture was neutralised with acetic acid, evaporated under diminished pressure, the residue dissolved in water (25 ml), the aqueous solution washed with three 20 ml portions of ether and concentrated under diminished pressure to the volume of 10 ml. The concentrate was continuously extracted with ethyl acetate, the extract dried, and evaporated under diminished pressure. Crystallisation of the residue from a small amount of 2-propanol afforded 1·0 g (45%) of 1-(β-D-ribofuranosyl)-2,5-dihydroxybenzene (*XIV*), m.p. 170—171°C, $[\alpha]_D^{25}$ —25·8° (*c* 0·50, water). For $C_{11}H_{14}O_6$ (242·2) calculated: 54·54% C, 5·18% H; found: 54·30% C, 5·90% H.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-3,4-dimethoxy-6-nitrobenzene (*XV*)

A suspension of compound *IIβ* (1·0 g; 1·73 mmol) in acetic acid (10 ml) was treated at room temperature with nitric acid (*d* 1·5; 1·0 ml) containing a small amount of nitrogen oxides; the mixture was stirred for 10 min and poured into water. The precipitate was collected with suction, washed with water, and recrystallised from acetone–methanol to afford 650 mg (55%) of compound *XV*, m.p. 153—154°C, $[\alpha]_D^{25}$ —106·8° (*c* 0·50, chloroform). For $C_{34}H_{29}NO_{11}$ (627·3) calculated: 65·03% C, 4·65% H, 2·23% N; found: 65·08% C, 4·74% H, 2·27% N.

1-β-D-Ribofuranosyl-3,4-dimethoxy-6-nitrobenzene (*XVI*)

A suspension of the ester *XV* (1·0 g; 1·6 mmol) in methanolic 0·015M-$NaOCH_3$ (20 ml) was shaken at room temperature until the solid dissolved. The solution was then neutralised with acetic acid and evaporated under diminished pressure. The residue was extracted with ether and recrystallised from water to afford 350 mg (70%) of compound *XVI*, m.p. 190—193°C, $[\alpha]_D^{25}$ —122·3° (*c* 0·50, water). For $C_{13}H_{17}NO_8$ (315·3) calculated: 49·52% C, 5·44% H, 4·44% N; found: 49·78% C, 5·49% H, 4·68% N.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-2-amino-4,5-dimethoxybenzene (*XVII*)

A mixture of the ester *XV* (650 mg; 1·04 mmol), stannous chloride dihydrate (2·0 g; 9·0 mmol), ether (10 ml), ethyl acetate (5 ml) and concentrated hydrochloric acid (2 ml) was shaken at room temperature for 30 min, the resulting solution diluted with ether (20 ml) and neutralised with solid potassium carbonate. The ethereal layer was washed with water, dried, and concentrated under diminished pressure to the volume of 2 ml to deposit a solid. Recrystallisation from ethanol afforded 510 mg (80%) of compound *XVII*, m.p. 129—130°C, $[\alpha]_D^{25}$ —100·8° (*c* 0·50, chloroform). For $C_{34}H_{31}NO_9$ (597·6) calculated: 68·33% C, 5·23% H, 2·33% N; found: 68·41% C, 5·32% H, 2·35% N.

1-α-D-Ribofuranosyl-2,5-dihydroxybenzene (*XXII*)

A mixture of the tribenzoate *VIα* (768 mg; 1·00 mmol), powdered zinc (650 mg; 10 mmol), ammonium chloride (1·0 g), and methanol (25 ml was refluxed for 1 h under vigorous magnetical stirring, filtered, and the filtrate evaporated under diminished pressure. The residue was dissolved in chloroform, the solution washed with water, dried, and evaporated under diminished pressure. The residual chromatographically (R_F 0·18 in 9 : 1 benzene–acetone) homogeneous (1-(2,3,5-tri-O-benzoyl-α-D-ribofuranosyl)-2,5-dihydroxybenzene (*XXI*; 550 mg; 99%) was dissolved under nitrogen in methanolic 0·3M-$NaOCH_3$ (7 ml), the solution kept at room temperature for 20 h, neutralised with acetic acid, and evaporated under diminished pressure. The residue was chromatographed on a column of silica gel (15 g) in 9 : 1 ethyl acetate–2-propanol solvent mixture to afford 220 mg (91%) of the free C-ribofuranosyl derivative *XXII*, $[\alpha]_D^{25}$ −37·9° (*c* 0·50, water). Compound *XXII* is extremely hygroscopic and does not afford a satisfactory elemental analysis. For $C_{11}H_{14}O_6$ (242·2) calculated: 54·54% C, 5·83% H; found: 54·14% C, 6·69% H.

2-(α-D-Ribofuranosyl)-1,4-benzoquinone (*XXIII*)

A mixture of compound *XXII* (425 mg; 1·77 mmol), silver oxide (2·8 g; 12 mmol), and ethyl acetate (50 ml) was vigorously stirred at room temperature for 1·5 h, filtered and the filtrate evaporated under diminished pressure to 1/20 of the original volume to deposit 380 mg (94%) of the benzoquinone derivative *XXIII*, m.p. 150–153°C, $[\alpha]_D^{25}$ +31·6° (*c* 0·50, water). ORD spectrum: 315 nm, $[\Phi]$ +1270°; 345 nm, $[\Phi]$ 0°; and 376 nm, $[\Phi]$ −1810°. IR spectrum: 1642 cm^{-1} (C=O), 1601 cm^{-1} (C=C). For $C_{11}H_{12}O_6$ (240·2) calculated: 55·00% C, 5·04% H; found: 54·80% C, 5·01% H.

2-(β-D-Ribofuranosyl)-1,4-benzoquinone (*XXIV*)

Compound *XIV* was oxidized analogously to the anomer *XXII*. Yield, 58% of the benzoquinone derivative *XXIV*, m.p. 106–107° (ethyl acetate), $[\alpha]_D^{25}$ −102·8° (*c* 0·50, water). ORD spectrum: 289 nm, $[\Phi]$ −5950°; 347 nm, $[\Phi]$ 0°; and 362 nm, $[\Phi]$ +645°. IR spectrum: 1656 cm^{-1} (C=O) and 1597 cm^{-1} (C=C). For $C_{11}H_{12}O_6$ calculated: 55·00% C, 5·04% H; found: 54·80% C, 5·01% H.

2-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-1,4-benzoquinone (*XXV*)

A solution of the benzoquinone derivative *XXIV* (160 mg; 0·67 mmol) in acetic anhydride (2·5 ml) containing 2% of trifluoroacetic acid was heated at 50°C for one hour, evaporated under diminished pressure, and the residue chromatographed on a column of silica gel (10 g) in 9 : 1 benzene–acetone solvent mixture to afford 220 mg (90%) of the sirupous triacetate *XXV*, $[\alpha]_D^{25}$ −50·4° (*c* 0·50, chloroform). For $C_{17}H_{18}O_9$ (366·3) calculated: 55·74% C, 4·95% H; found: 56·02% C, 4·87% H.

1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-2,3,4,5-tetraacetoxybenzene (*XX*)

A mixture of compound *XIV* (0·96 g; 4·0 mmol), 1% ethanolic solution of osmium tetraoxide (0·2 ml), 2M-$NaClO_3$ (5·0 ml), and 0·1M-HCl (5·0 ml) was kept at room temperature for 60 h, neutralised with 0·1M-NaOH, and evaporated under diminished pressure. The residue was diluted with pyridine (10 ml) and then acetic anhydride (10 ml) was added under cooling. The reaction mixture was kept at room temperature for 15 h, decomposed by pouring onto ice, and extracted

with chloroform. The extract was washed with 5% hydrochloric acid, water, and saturated aqueous sodium hydrogen carbonate, dried, and evaporated under diminished pressure. The residue was chromatographed on a column of silica gel (80 g) in 1 : 1 benzene–ethyl acetate solvent mixture to afford 840 mg (37%) of the heptaacetate *XX*, m.p. 115—117°C, $[\alpha]_D^{25}$ −20·9° (*c* 0·50, chloroform). NMR spectrum (deuteriochloroform: δ 2·00, 2·02, and 2·05 (s, 3 × CH_3 of acetyl groups of the ribose moiety), 2·18—2·20 and 2·25 (s, 4 × CH_3 of acetyl groups of the aromatic moiety), 4·13—4·35 (m, 2 × 5′-H and 4′-H), 5·02—5·33 (m, 1′-H, 2′-H, and 3′-H) and 7·34 p.p.m. (s, 6-H). For $C_{25}H_{28}O_{15}$ (568·4) calculated: 52·70% C, 4·95% H; found: 53·00% C, 4·99% H.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-2,5-dimethoxybenzene (*IIβ*)

Anhydrous potassium carbonate (2·1 g) and dimethyl sulfate (0·96 ml) were added to a suspension of compound *XIV* (240 mg; 1·0 mmol) in acetone (10 ml), the mixture refluxed under stirring for 30 min, cooled down, the excess dimethyl sulfate decomposed with concentrated aqueous ammonia (1 ml), and the filtrate evaporated under diminished pressure. The residue was chromatographed on a loose layer of silica gel (one plate, 18 × 42 cm) in 2 : 1 benzene–acetone solvent mixture. The band of the R_F value 0·25 afforded sirupous 1-(β-D-ribofuranosyl)-2,5-dimethylbenzene (90 mg; 33%), the mass spectrum of which exhibied characteristic fragmentation and molecular maximum (270). The sirup was dissolved in pyridine (2 ml) and the solution was treated under cooling with ice-cold water with benzoyl chloride (0·5 ml). After one hour at room temperature, the mixture was decomposed with water (5 ml) and the product extracted with benzene (20 ml). The extract was washed with 2% aqueous ammonia, dried, and evaporated under diminished pressure. The residue was coevaporated with three 10 ml portions of toluene and chromatographed on a loose layer of silica gel (one plate, 18 × 42 cm) in 19 : 1 benzene–acetone solvent system. Yield, 130 mg (26%) of the sirupous ester *IIβ*, $[\alpha]_D^{25}$ −22·9° (*c* 0·50, chloroform). For $C_{34}H_{30}O_9$ (582·6) calculated: 70·09% C, 5·19% H; found: 69·64% C, 5·38% H.

4-Methoxyphenyl 2,3,5-Tri-O-benzoyl-β-D-ribofuranoside (*XXVIII*)

A mixture of the ester *IX* (1·1 g; 2·0 mmol), potassium carbonate (4·2 g; 30 mmol), dimethyl sulfate (1·26 g; 10·0 mmol), and acetone (5 ml) was refluxed under stirring for 30 min and diluted with benzene (25 ml) and water (25 ml). The benzenic layer was washed with water (25 ml), dried over anhydrous magnesium sulfate, and evaporated under diminished pressure. Crystallisation of the residue from ether afforded 1·0 g (88%) of compound *XXVIII*, m.p. 124—126°C, $[\alpha]_D^{25}$ −1·4° (*c* 0·50, chloroform). For $C_{33}H_{28}O_9$ (568·6) calculated: 69·71% C, 4·96% H; found: 69·91%, 4·96% H.

4-Methoxyphenyl β-D-Ribofuranoside (*XXIX*)

A suspension of the ester *XXVIII* (570 mg; 1·0 mmol) in methanolic 0·015M-$NaOCH_3$ (10 ml) was stirred at room temperature for 20 h, neutralised with acetic acid, and evaporated under diminished pressure. The residual sirup was chromatographed on a column of silica gel (30 g) in 9 : 1 ethyl acetate–2-propanol solvent mixture to afford 180 mg (70%) of the ribofuranoside *XXIX*, m.p. 97—97·5°C, $[\alpha]_D^{25}$ −7·1° (*c* 0·50, water). For $C_{12}H_{16}O_6$ (256·3) calculated: 56·24% C, 6·29% H; found: 56·46% C, 6·32% H.

4-Methoxyphenyl 2,3-O-Isopropylidene-β-D-ribofuranoside (*XXX*)

A mixture of the ribofuranoside *XXIX* (650 mg; 2·5 mmol), *p*-toluenesulfonic acid (50 mg), and acetone (10 ml) was kept at room temperature for 2·5 h, neutralised with saturated aqueous

sodium hydrogen carbonate, and evaporated under diminished pressure. The residue was chromatographed on a column of silica gel (30 g) in 9 : 1 benzene–acetone solvent mixture to afford 519 mg (87%) of the isopropylidene derivative *XXX*, m.p. 54—55°C, $[\alpha]_D^{25}$ −5·4° (*c* 0·50, chloroform). IR spectrum (*c* 5 . 10^{-3}M, tetrachloromethane): 3525 cm^{-1} (an intensive band of hydrogen bonding between the hydroxylic function and the glycosidic oxygen atom). For $C_{15}H_{20}O_6$: (296·3) calculated: 60·80% C, 6·80% H; found: 60·58% C, 6·80% H.

2-(2,3-O-Isopropylidene-α-D-ribofuranosyl)-1,4-benzoquinone (*XXVI*)

p-Toluenesulfonic acid (20 mg) was added to a suspension of the quinone *XXIII* (100 mg; 0·45 mmol) in acetone (10 ml), the mixture stirred at room temperature for 3·5 h, neutralised with silver oxide, and filtered. The filtrate was evaporated under diminished pressure and the residue chromatographed on a column of silica gel (5 g) in 9 : 1 benzene–acetone solvent mixture to afford 102 mg of the isopropylidene derivative *XXVI*, m.p. 47—49°C. Infrared spectrum (*c* 5 . 10^{-3}M, tetrachloromethane): 3637 cm^{-1} (an intensive band of the free hydroxylic function) and 3614 cm^{-1} (a poorly intensive hydrogen bonding between the hydroxylic function and the furanose ring oxygen atom, *cf.*[23]). For $C_{14}H_{16}O_6$ (280·3) calculated: 59·99% C, 5·75% H; found: 59·71% C, 5·89% H.

2-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-1,4-benzoquinone (*XXVII*)

The title isopropylidene derivative *XXVII*, a sirup, $[\alpha]_D^{25}$ −91·5° (*c* 0·50, chloroform), was prepared analogously to the anomer *XXVI*. Infrared spectrum of *XXVII* (*c* 5 . 10^{-3}M, tetrachloromethane): 3637 cm^{-1} (a poorly intensive band of the free hydroxylic function), 3614 cm^{-1} (a poorly intensive band of the hydroxylic function attached by hydrogen bonding to the furanose ring oxygen atom), and 3523 cm^{-1} (a strongly intensive band of the hydrogen bonding between the hydroxylic function and the quinonoid carbonyl group). For $C_{14}H_{16}O_6$ (280·3) calculated: 59·99% C, 5·75% H; found: 59·84% C, 5·59% H.

1-(β-D-Ribofuranosyl)-3,4-dimethylbenzene 2′,3′-O-Cyclophenylboronate (*XXXI*)

Phenylboronic anhydride (108 mg; 1·02 mmol) and anhydrous magnesium sulfate (500 mg) were added to a suspension of the glycosyl derivative *XI* (230 mg; 0·85 mmol) in ethyl acetate (10 ml), the mixture shaken at room temperature for 20 min, filtered, and the filtrate evaporated under diminished pressure. The residual sirup exhibited the expected mass spectrum (molecular peak at 356). Infrared spectrum of compound *XXXI* (*c* 5 . 10^{-3}M, tetrachloromethane): 3631 cm^{-1} (a poorly intensive band of the free hydroxylic function) and 3606 cm^{-1} (a strongly intensive band of the hydrogen bonding involving the hydroxylic function, the furanose ring oxygen atom, and π-electrons of the benzene ring).

1-(β-D-Ribofuranosyl)-3,4-dimethoxy-6-nitrobenzene 2′,3′-O-Cyclophenylboronate (*XXXII*)

The title cyclic phenylboronate *XXXII*, m.p. 156—158°C (diisopropyl ether–light petroleum), was prepared analogously to compound *XXXI*. Mass spectrum of compound *XXXII* exhibits a molecular peak at 401. Infrared spectrum (*c* 5 . 10^{-3}M, tetrachloromethane): 3636 cm^{-1} (band of the free hydroxylic function), 3606 cm^{-1} (an intensive band of the hydrogen bonding involving the hydroxylic function, the furanose ring oxygen atom, and π-electrons of the benzene ring) and 3585 cm^{-1} (band of the hydrogen bonding between the hydroxylic function and the nitro group oxygen atoms). For $C_{19}H_{20}BNO_8$ (401·2) calculated: 56·88% C, 5·03% H, 3·49% N; found: 56·69% C, 5·02% H, 3·41% N.

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