Synthesis of Pyrazofurin and its Analogues [1]

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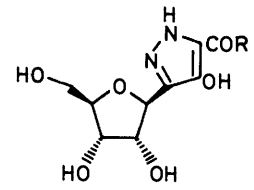
Pyrazofurin and its analogues have been synthesized from ribosyl β-keto acid derivatives, which can be readily prepared by Wittig reaction of the protected D-ribose with phosphoranes.

Reaction of 2,3-*O*-isopropylidene-5-*O*-trityl-α- and -β-D-ribose (6) with 3-ethoxycarbonyl-2-oxopropylidenetriphenylphosphorane (8a) gave ethyl 4-(2',3'-*O*-isopropylidene-5'-*O*-trityl-α- and -β-D-ribofuranosyl)-3-oxobutanoate (10a). The β-keto ester (10a) was treated with tosyl azide in the presence of triethylamine to afford ethyl 2-diazo-4-(2',3'-*O*-isopropylidene-5'-*O*-trityl-α- and -β-D-ribofuranosyl)-3-oxobutanoate (11a) which, on treatment with sodium hydride, cyclized to ethyl 4-hydroxy-3-(2',3'-*O*-isopropylidene-5'-*O*-trityl-β-D-ribofuranosyl)pyrazole-5-carboxylate (16β) and the α-anomer (16α). Ammonolysis of (16β) and (16α) afforded the corresponding amides (19β) and (19α) which, after removal of the protecting groups, gave pyrazofurin (1) and pyrazofurin B (2) respectively. Pyrazofurin analogues (3), (4), and (5) were also synthesized by analogous procedures.

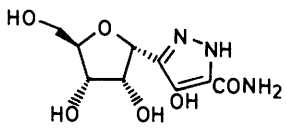
Pyrazofurin (pyrazomycin) (1),[2] a *C*-nucleoside having antitumour [3] and antiviral [4] activity, was isolated from fermentations of a strain of *Streptomyces candidus*.[5] Pyrazofurin B (2),[6] the α-anomer of (1), was also isolated from the same fermentations.

The chemical synthesis of (1) was first achieved by Farkas *et al.*[7] in 1972. DeBernardo and Weigele [8] reported the synthesis of compound (1) from the β-keto ester prepared by substitution of the protected 1-bromo-D-ribose with diethyl acetonedicarboxylate. Recently, Buchanan *et al.*[9] have reported the conversion of 3-cyano-4-nitro-5-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole into (1).

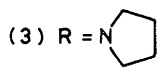
We now report a simple and novel synthesis of compound (1) and its analogues from ribosyl β-keto esters and amides which can be readily prepared by a Wittig reaction.



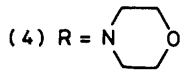
(1) R = NH_2 (Pyrazofurin)



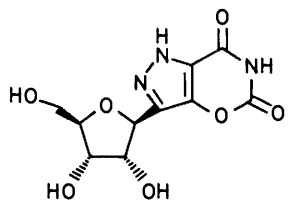
Pyrazofurin B (2)



(3) R = N



(4) R = N O



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Results and Discussion

It is reported that a stable ylide such as cyanomethylenetriphenylphosphorane reacts with the protected ribose (6) [10] to give a *C*-glycoside which serves as a precursor for the synthesis of *C*-nucleosides.[11] Previously, applying this reaction, we have synthesized homo-*C*-nucleosides from compound (6) and pyrimidinylmethylenephosphoranes.[12] Our starting material (10a), the analogue of which has already been prepared by Claisen condensation of methyl D-ribofuranosylacetate with lithio-t-butyl acetate,[13] was easily obtained by Wittig reaction of (6) with the phosphorane (8a). When a solution of compound (6) and the phosphorane (8a) [14] in acetonitrile was heated under reflux, an anomeric mixture (β : α *ca.* 2 : 1) of the *C*-glycoside (10a) was obtained in 95% yield. The ratio of the β- and α-anomers was determined by ^1H and ^{13}C n.m.r. spectroscopy. In the ^{13}C n.m.r. spectrum of (10a), signals due to two methyl carbons of the isopropylidene group of the β-anomer are observed at δ_C 25.60 and 27.60 p.p.m., within the range strongly indicative of the β configuration (25.5 ± 0.2 and 27.5 ± 0.2), whereas those of the α-anomer are observed at δ 24.95 and 26.24 p.p.m., clearly in the α range (24.9 ± 0.3 and 26.3 ± 0.2).[11] The intensity of these signals shows that the β-anomer is predominant. In the ^1H n.m.r. spectrum of (10a), a signal due to one of two isopropylidene methyl groups of the β-anomer is observed at δ 1.53, whereas that of the α-anomer is observed at δ 1.48. The signals due to the methylene protons at C-2 of the β- and α-anomers are observed at δ 3.47 and 3.52, respectively. The intensity of these signals showed that the ratio β : α was 2 : 1.

This reaction was also carried out in other solvents such as benzene, toluene, and nitromethane with the intention of clarifying the solvent effect on the yield and the ratio β : α. The results are summarized in Table 1. In every case, compared with acetonitrile, the reaction proceeded more rapidly, but the yield of (10a) as well as the β : α ratio was lower.

Table 1. Reaction of the protected D-ribose (6) with the phosphorane (8a) to give the *C*-glycoside (10a) [a]

Solvent	Reaction time (h)	Yield (%) of (10a)	Ratio β : α
Acetonitrile	90	95	2 : 1
Nitromethane	10	74	3 : 2
Benzene	20	54	1 : 1
Toluene	8	58	1 : 1

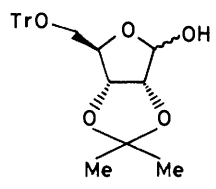
[a] The reaction was carried out under reflux.

Next, we investigated the synthesis of (10a) using the phosphonate (9) [15] instead of (8a). When a solution of

Table 2. ^1H and ^{13}C N.m.r. spectral data (δ values for isopropylidene methyl groups) for *C*-glycosides (10a—d)

Compd.	^1H ($CDCl_3$) α		β		^{13}C ($CDCl_3$) (p.p.m.) α		β	
(10a)	1.30	1.48	1.32	1.53	24.95	26.24	25.60	27.60
(10b)	1.29	1.45	1.33	1.54	24.89	26.18	25.60	27.48
(10c)	1.30	1.48	1.31	1.52	24.95	26.18	25.60	27.48
	(1.34	1.51) [a]			(24.30	25.89) [a]	(24.36	25.89) [a]
(10d)	1.28	1.46	1.32	1.52	25.01	26.30	25.54	27.48

[a] Enol form.



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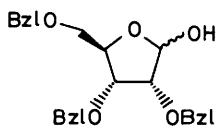

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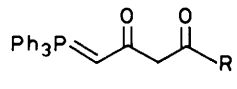
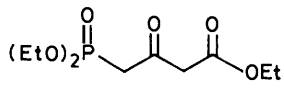


(8) a ; R = OEt
b ; R = NHPh
c ; R = N
d ; R = N O



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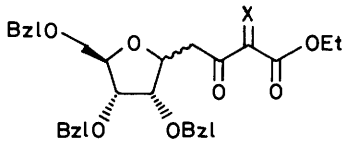
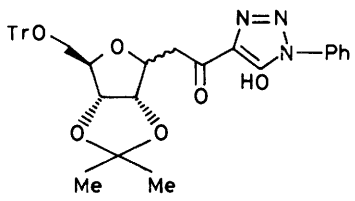


(13) X = H_2
(14) X = N_2



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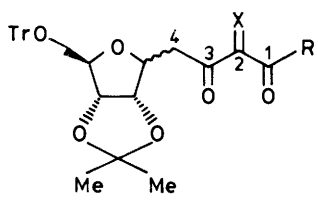
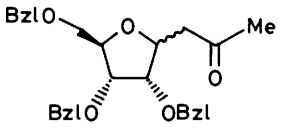


(10) a; R = OEt, X = H_2
b; R = NHPh, X = H_2
c; R = N , X = H_2
d; R = N O, X = H_2
(11) a; R = OEt, X = N_2
b; R = NHPh, X = N_2
c; R = N , X = N_2
d; R = N O, X = N_2



(15)

Tr = Ph_3C
Bzl = $PhCH_2$

compounds (6) and (9) containing sodium hydride in 1,2-dimethoxyethane (DME) was heated under reflux for 90 h, an anomeric mixture of (10a) (β : α *ca.* 1 : 2) was obtained in 63% yield. From a consideration of this result, it is found that use of (8a) for the synthesis of (10a) is more practical.

Similarly, reaction of compound (6) with the phosphoranes (8b—d), which were obtained from triphenylphosphine and the corresponding γ-chloroacetoacetamides, in nitromethane gave the corresponding *C*-glycosides (10b—d) in good yield. The careful separation of an anomeric mixture of (10c) by silica gel column chromatography gave the β-*C*-glycoside (foam) and the α-anomer (m.p. 175 °C). Similar treatment of compound (10d) afforded the β-*C*-glycoside (foam) and the α-anomer (m.p. 125—127 °C). ^1H and ^{13}C N.m.r. spectral data of the glycosides (10a—d) are shown in Table 2.

2,3,5-Tri-*O*-benzyl-D-ribose (7) [16] also reacted with the phosphorane (8a) in acetonitrile to give the *C*-glycoside (13) (β : α *ca.* 3 : 1) in 51% yield. The ratio of β : α was determined from the ^1H n.m.r. spectrum, in which two signals due to methylene protons at C-4 of the β- and α-anomers are observed at δ 2.69 (m, ABX type) and δ 2.97 (m, ABX type), respectively.

The signal of the α-anomer was shifted to lower field because of the benzyl group at O-2′. However, Moffatt and his co-workers [11] reported that the β-anomer of a *C*-glycoside protected with benzyl groups is thermodynamically more stable than the α-anomer. Moreover, the α-anomer, on treatment with base, is transformed into the β-anomer.[17] Thus, the glycoside (13) was treated with 0.1M sodium ethoxide in ethanol to give an anomeric mixture, the ^1H n.m.r. spectrum of which showed an increase of the β : α ratio.

Again, this reaction of compounds (7) and (8a) was also carried out in other solvents such as nitromethane, *N*,*N*-dimethylformamide (DMF), and toluene. The results are summarized in Table 3. The yield of (13) was rather low when these solvents were used, and 1-(2′,3′,5′-tri-*O*-benzyl-α- and -β-D-ribofuranosyl)propan-2-one (15) was obtained as a by-product.

Next, we carried out the conversion of *C*-glycosides (10a—d) into *C*-nucleosides. The *C*-glycoside (10a) was treated with tosyl azide in the presence of triethylamine to afford the diazo compound (11a) (β : α *ca.* 1 : 1) in 94% yield. Similar treatment of (10c) and (10d) gave the compounds (11c) and (11d) in quantitative yield. The *C*-glycoside (10b) was treated with tosyl azide under similar conditions to give the desired compound (11b), together with the 1,2,3-triazole (12) as a by-product. A deep brown colouration in the iron(III) chloride test indicated the presence of the enol form of (12). The ^1H and ^{13}C n.m.r. spectral data of compounds (11a—d) are shown in Table 4. The *C*-glycoside (13), protected with benzyl groups, was also treated with tosyl azide in the presence of triethylamine to give the diazo compound (14) in 91% yield.

Next, the intramolecular cyclization of the diazo ester (11a) to give the pyrazole (1b) was investigated. When compound (11a) was treated with sodium hydride in anhydrous DME at 20 °C for 3 h, the pyrazole (16β) (m.p. 159—160 °C) and the α-anomer (16α) (foam) were obtained in 42 and 21% yield, respectively. The assignment of their respective stereochemistries was again established by observing the isopropylidene methyl ^{13}C n.m.r. signals, which appeared at δ 25.48 and 27.30 p.p.m. in (16β), and at δ_C 24.60 and 26.18 p.p.m. in (16α). The i.r. spectra of both compounds contain an absorption band at 3 440 cm^{-1} due to the NH group of the pyrazole ring.

Similar treatment of compound (11c) with sodium hydride gave a mixture of compounds (17β) and (17α) in 53% yield, which was chromatographically inseparable. On the other hand, the *C*-glycoside (10d), when treated with sodium hydride, gave a 15% yield of the β-*C*-nucleoside (18β) as the sole product. Reaction of compound (11b) under similar conditions did not give the corresponding pyrazole, but resulted in the recovery of the starting material (α-anomer only) accompanied by the formation of the 1,2,3-triazole (12) (β : α *ca.* 3 : 1). The β-*C*-nucleosides (17β) and (18β) were also obtained in good yield by heating compound (16β) with pyrrolidine and morpholine, respectively.

Similar cyclization of compound (14) gave a 65% yield of the *C*-nucleoside (22β) and (22α) (β : α *ca.* 5 : 1), which, on being heated with morpholine, was exclusively transformed into the amide (23β), with concomitant epimerization of the α-isomer. The (22β) : (22α) ratio was determined by ^1H n.m.r. spectroscopy. Namely, signals due to the 5′-methylene protons of (22β) are observed at δ 3.56 (dd) and 3.86 (dd) owing to the effect of pyrazole ring whereas those of (22α) are observed at δ 3.51 (d).

Heating compound (16β) with ammonia in methanol gave the amide (19β) and the methyl ester (20β) in 73 and 22% yield, respectively. Prolonged heating (7 h) of compound (16β) with ammonia gave a 94% yield of the amide (19β) as the sole product. The i.r. spectrum of (19β) shows an absorption band due to the amido carbonyl at 1 665 cm^{-1}. In a similar manner, compound (16α) was transformed into the amide (19α) and the methyl ester (20α) in 46 and 25% yield, respectively.

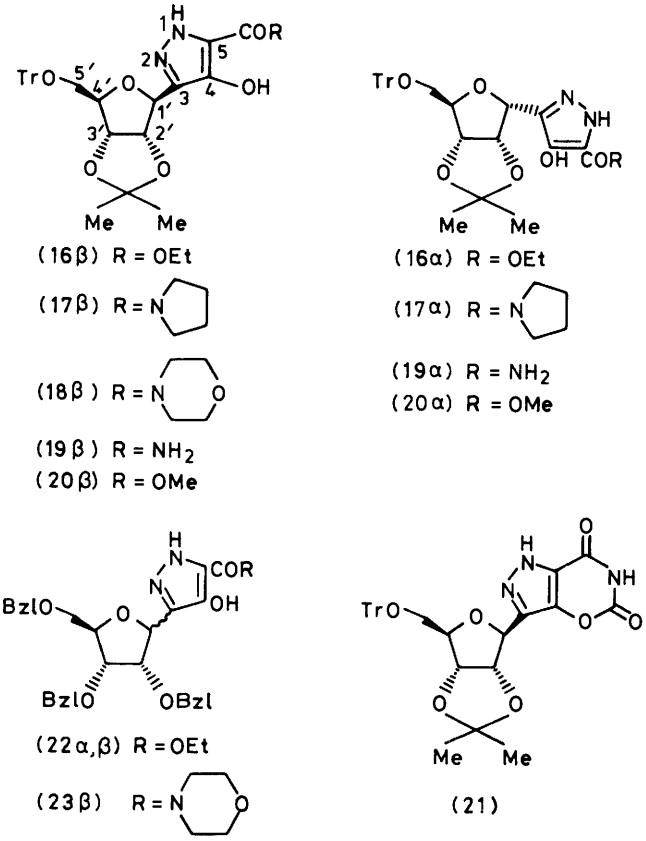


Table 3. Reaction of the protected D-ribose (7) with the phosphorane (8a) to give the *C*-glycoside (13)

Solvent	Reaction time (h)	Reaction temp. (°C)	Yield (%) of (13) [Yield (%) of (15)]	Ratio β : α
Acetonitrile	120	reflux	51 [0]	3 : 1
Nitromethane	75	90	43 [14]	3 : 1 [10 : 1]
DMF	100	90	7 [13]	5 : 1 [10 : 1]
Toluene	100	90	47 [26]	2 : 1 [5 : 1]

Table 4. ^1H and ^{13}C N.m.r. spectral data (δ values for isopropylidene methyl groups) for diazo compounds (11a—d)

Compd.	^1H ($CDCl_3$) α		^1H ($CDCl_3$) β		^{13}C ($CDCl_3$) (p.p.m.) α		^{13}C ($CDCl_3$) (p.p.m.) β	
(11a)	1.32	1.49	1.32	1.54	25.12	26.30	25.66	27.53
(11b)	1.33	1.50	1.33	1.55	24.95	26.30	25.62	27.48
(11c)	1.32	1.49	1.32	1.53	25.07	26.30	25.60	27.53
(11d)	1.30	1.48	1.32	1.53	24.95	26.30	25.60	27.48

Table 5. ^{1}H N.m.r. spectral data for protected *C*-nucleosides (16β)—(20β), (16α), (19α), and (20α) in $CDCl_3$

	δ						*J* (Hz)					
Compd.	1′-H	2′-H	3′-H	4′-H	5′-H_a	5′-H_b	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$
(16β) [a]	5.36 (d)	5.27 (dd)	4.71 (dd)	4.50 (dt)	3.29 (d)		3.5	6	3.5	5	—	—
(17β)	5.16 (d)	5.13 (dd)	4.68 (dd)	4.36 (m)	3.12 (dd)	3.25 (dd)	3.5	6	3.5	5	4	10
(18β)	5.18 (d)	5.06 (dd)	4.68 (dd)	4.35 (m)	3.14 (dd)	3.31 (dd)	3.5	6	3.5	5	4	10
(19β)	5.22 (d)	5.11 (dd)	4.65 (dd)	4.37 (m)	3.11 (dd)	3.24 (dd)	3.5	6	3.5	5	4	10
(20β)	5.37 (d)	5.28 (dd)	4.73 (dd)	4.51 (dt)	3.29 (d)		3.5	6	3.5	5	—	—
(16α)	5.42 (d)	4.92 (dd)	4.76 (d)	4.16 (dd)	3.20 (dd)	3.34 (dd)	4	6	0	4	4	10
(19α)	5.40 (d)	4.93 (dd)	4.78 (d)	4.29 (dd)	3.23 (dd)	3.32 (dd)	3.5	6	0	4	4	10
(20α)	5.44 (d)	4.94 (dd)	4.78 (d)	4.27 (dd)	3.22 (dd)	3.35 (dd)	4	6	0	4	4	10

[a] In C_6D_6 solution.

Table 6. ^{13}C N.m.r. spectral data [δ_C values (p.p.m.) for isopropylidene groups] for protected *C*-nucleosides (16β)—(20β), (16α), (17α), (19α), and (20α) in $CDCl_3$

Compd.	Me	Me	C
(16β)	25.48	27.30	113.84
(17β)	25.48	27.30	113.60
(18β)	25.48	27.30	113.72
(19β)	25.42	27.24	113.78
(20β)	25.54	27.36	114.02
(16α)	24.60	26.18	112.78
(17α)	24.60	26.30	112.61
(19α)	24.42	26.18	112.78
(20α)	24.66	26.37	112.96

Compound (20α) was treated again with ammonia to give compound (19α) in 71% yield. Reaction of compound (19β) with *N,N′*-carbonyldi-imidazole in DME, in the presence of a catalytic amount of sodium hydride, furnished the pyrazolo-[1,3]oxazine (21) in 56% yield. The ^{1}H n.m.r. and ^{13}C n.m.r. spectral data for the protected *C*-nucleosides (16)—(20) are summarized in Tables 5 and 6.

Deprotection of the amides (19β) and (19α) with 90% trifluoroacetic acid at 20 °C for 45 min gave pyrazofurin (1) (85%), m.p. 108—110 °C ($C_9H_{13}N_3O_6\cdot H_2O$), and pyrazofurin B (2) (84%), m.p. 69—70 °C ($C_9H_{13}N_3O_6\cdot 2H_2O$), respectively. The i.r. spectra of our synthetic compounds (1) and (2) were identical in every respect with those of authentic samples of pyrazofurin and pyrazofurin B, respectively. Analogous treatment of compounds (17), (18), and (21) gave the pyrazofurin derivatives (3), (4), and (5), respectively. The results are shown in Tables 7—9. On the other hand, removal of the benzyl group from (23β) proceeds readily in a solution of boron trichloride [18] in methylene dichloride at −78 °C to give a 77% yield of compound (4), which is identical with the compound derived from (18β).

Experimental

M.p.s were determined on a Yanaco model MP melting-point apparatus, and are uncorrected. ^{1}H N.m.r. and ^{13}C n.m.r. spectra were recorded using tetramethylsilane as internal standard on a JEOL JNM FX-100 spectrometer at 100 MHz and 25 MHz, respectively. ^{13}C-^{1}H Attachments were confirmed by off-resonance experiments. I.r. spectra were recorded on a JASCO A-101 spectrophotometer. High-performance liquid chromatography (h.p.l.c.) was carried out on a Waters Associate instrument (M 6000 pump; U6K injector) using a 254 nm u.v. detector. Wakogel (C-200) was employed for silica gel column chromatography. Merck Kieselgel 60F 254 was employed for t.l.c. Solvents used were purified by redistillation; *e.g.* acetonitrile and nitromethane were distilled from P_2O_5, DME from $LiAlH_4$, and DMF from BaO.

2-Oxo-3-(phenylcarbamoyl)propylidenetriphenylphosphorane (8b).—A mixture of γ-chloroacetoacetanilide [19] (10.6 g, 50 mmol) and triphenylphosphine (13.1 g, 50 mmol) in anhydrous nitromethane (50 ml) was heated at 90 °C for 10 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in chloroform (100 ml). The chloroform solution was washed with 10% aqueous sodium carbonate (50 ml × 2) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and benzene was added to the resulting residue. The crystals which separated were filtered off. Recrystallization from benzene gave the *product* (8b) as a pale yellow powder (11.5 g, 53%), m.p. 215 °C (decomp.) (Found: C, 77.0; H, 5.55; N, 3.25. $C_{28}H_{24}NO_2P$ requires C, 76.85; H, 5.55; N, 3.2%); $\nu_{max.}$ ($CHCl_3$) 1 665 and 1 505 cm^{-1}.

2-Oxo-3-(pyrrolidin-1-ylcarbonyl)propylidenetriphenylphosphorane (8c).—A mixture of *N*-(γ-chloroacetoacetyl)pyrrolidine * (9.5 g, 50 mmol) and triphenylphosphine (13.1 g, 50 mmol) in anhydrous nitromethane (50 ml) was heated at 90 °C for 4 h. The solvent was evaporated under reduced pressure and the residue was dissolved in benzene (100 ml). The benzene solution was washed with 10% aqueous sodium carbonate (50 ml × 2) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography (adsorbent 400 g). Elution with ethyl acetate–methanol (10 : 1) gave a viscous oil, which was dissolved in chloroform. The chloroform solution was poured into hexane to give the product (8c) as a pale yellow powder (10.0 g, 48%), m.p. 144 °C (Found: C, 74.3; H, 6.5;

* *N*-(γ-Chloroacetoacetyl)pyrrolidine and *N*-(γ-chloroacetoacetyl)-morpholine were prepared by the reaction of diketene with chlorine, followed by treatment with pyrrolidine and morpholine, respectively.

Table 7. Deprotection of protected *C*-nucleosides (17β)—(19β), (19α), and (21) with trifluoroacetic acid

Protected compound		90% CF_3CO_2H	Reaction	Products			
	g (mmol)	(ml)	time (h)	Compd.	Eluant proportions for column, ethyl acetate–acetone–methanol–water	Yield (g) [%]	M.p. (°C) [solvent for recrystallization]
(17β)	1.1 (1.8)	20	1	(3)	—	0.40 [74]	117—123 [Acetone–methanol]
(18β)	1.0 (1.6)	20	0.75	(4)	50 : 1 : 1 : 1	0.35 [65]	165—167 [Ethanol]
(19β)	1.76 (3)	40	0.75	(1)	6 : 1 : 1 : 1	0.34 [85]	108—110 [a] [Water]
(19α)	0.6 (1)	14	1	(2)	6 : 1 : 1 : 1	0.24 [84]	69—70 [b] [Water]
(21)	0.6 (0.9)	12	1	(5)	47 : 1 : 1 : 1	0.25 [84]	foam

[a] Lit.,[7] m.p. 112—115 °C,[8] 112—115 °C,[9] 111—113 °C. [b] Lit.,[6] m.p. 69—70 °C,[8] 76 °C.

Table 8. Elemental analyses and i.r. spectra of *C*-nucleosides (1)—(5)

Compd.	Found (%)			Formula	Requires (%)			$\nu_{C=O}$ (KBr)
	C	H	N		C	H	N	
(1)	38.95	5.35	15.2	$C_9H_{13}N_3O_6 \cdot H_2O$	39.0	5.45	15.15	1 640
(2)	36.3	5.9	14.35	$C_9H_{13}N_3O_6 \cdot 2H_2O$	36.6	5.8	14.25	1 650
(3)	51.45	6.7	11.2	$C_{13}H_{19}N_3O_6 \cdot CH_3COCH_3$	51.75	6.8	11.3	1 630 [a] 1 710 [b]
(4)	47.4	5.85	12.5	$C_{13}H_{19}N_3O_7$	47.4	5.8	12.75	1 630
(5)	42.15	4.35	13.3	$C_{10}H_{11}N_3O_7 \cdot 0.7CH_3COCH_3$	41.8	4.5	13.65	1 770, 1 720

[a] In $CHCl_3$. [b] Due to acetone.

Table 9. ^1H and ^{13}C N.m.r. spectra (δ values) for *C*-nucleosides (3)—(5)

Compd.	^1H [$(CD_3)_2SO$]			^{13}C (CD_3OD)				
	1′-H ($J_{1',2'}$/Hz)	NH or OH		1′-, 2′-, 3′-, and 4′-C				C-5′
(3)	4.65 (6)	9.43	12.85	72.56	75.91	77.67	85.77	63.17
(4)	4.72 (6)	8.55	12.38	72.04	75.74	77.20	85.25	62.47
(5)	4.76 (6)	11.95	14.00	72.51	76.15	77.03	86.48	63.23

N, 3.5. $C_{26}H_{26}NO_2P \cdot \frac{1}{2}H_2O$ requires C, 73.95; H, 6.3; N, 3.3%); $\nu_{max.}$ ($CHCl_3$) 1 620 and 1 530 cm^{-1}.

2-Oxo-3-(morpholinocarbonyl)propylidenetriphenylphosphorane (8d).—A mixture of *N*-(γ-chloroacetoacetyl)morpholine * (12 g, 58 mmol) and triphenylphosphine (15.3 g, 58 mmol) in anhydrous nitromethane (50 ml) was heated at 90 °C for 4 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in chloroform (100 ml). The chloroform solution was washed with 10% aqueous sodium carbonate (50 ml × 2) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography (400 g). Elution with ethyl acetate–methanol (10 : 1) gave the product (8d) as a pale yellow syrup (15 g, 60%) (Found: C, 68.6; H, 6.05; N, 3.45. $C_{26}H_{26}NO_2P \cdot 1\frac{1}{2}H_2O$ requires C, 68.1; H, 6.4; N, 3.05%); $\nu_{max.}$ ($CHCl_3$) 1 625, 1 585, and 1 540 cm^{-1}.

* *N*-(γ-Chloroacetoacetyl)pyrrolidine and *N*-(γ-chloroacetoacetyl)-morpholine were prepared by the reaction of diketene with chlorine, followed by treatment with pyrrolidine and morpholine, respectively.

Ethyl 4-(2′,3′-O-Isopropylidene-5′-O-trityl-α- and -β-D-ribofuranosyl)-3-oxobutanoate (10a).—(a) A mixture of 2,3-*O*-isopropylidene-5-*O*-trityl-α- and -β-D-ribose (6) [10] (10.9 g, 25 mmol) and 3-ethoxycarbonyl-2-oxopropylidenetriphenylphosphorane (8a) [14] (11.8 g, 30 mmol) in anhydrous acetonitrile (30 ml) was refluxed for 90 h. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography (400 g). Elution with hexane–ethyl acetate (9 : 1) gave the *product* (10a) (β : α *ca.* 2 : 1) as a foam (13.0 g, 95%) (Found: C, 72.85; H, 6.7. $C_{33}H_{36}O_7$ requires C, 72.75; H, 6.65%); $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 720 cm^{-1}. Similarly, use of nitromethane, benzene, or toluene as solvent, instead of acetonitrile, gave the product (10a) in 74, 54, and 58% yield, respectively. The results are summarized in Table 1.

(b) A solution of ethyl 4-diethylphosphono-3-oxobutanoate (9) [15] (0.87 g, 3.3 mmol) in anhydrous DME (2 ml) was added dropwise to an ice-cooled suspension of sodium hydride (50% dispersion; 0.126 g, 2.6 mmol) in DME (5 ml). To the mixture was added a solution of (6) (0.94 g, 2.2 mmol) in DME (5 ml). The resulting mixture was refluxed for 90 h. A solution of acetic acid (0.158 g, 2.6 mmol) in DME (2 ml) was added dropwise to the stirred, ice-cooled reaction mixture.

The solvent was evaporated under reduced pressure, and water (10 ml) was added to the residue. The mixture was extracted with benzene (10 ml), and the extract was dried over anhydrous sodium sulphate and evaporated under reduced pressure. The resulting residue was subjected to column chromatography (30 g). Elution with hexane–ethyl acetate (9 : 1) gave the product (10a) (β : α *ca.* 1 : 2) as a foam (0.74 g, 63%).

4-(2′,3′-O-*Isopropylidene*-5′-O-*trityl*-α- *and* -β-D-*ribofuranosyl*)-3-*oxobutananilide* (10b).—A mixture of compound (6) (0.5 g, 1.2 mmol) and the phosphorane (8b) (1 g, 2.3 mmol) in anhydrous nitromethane (15 ml) was refluxed for 12 h. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography. Elution with hexane–ethyl acetate (8 : 1) gave the starting material (6) (0.1 g, 20% recovery). Subsequent elution with hexane–ethyl acetate (3 : 1) gave the product (10b) (β : α *ca.* 3 : 2) as a foam (0.5 g, 71%) (Found: C, 73.4; H, 6.25; N, 2.2. $C_{37}H_{37}NO_6 \cdot \frac{2}{3}H_2O$ requires C, 73.6; H, 6.4; N, 2.3%); $\nu_{max.}$ ($CHCl_3$) 3 300, 1 705, and 1 675 cm^{-1}.

N-[4-(2′,3′-O-*Isopropylidene*-5′-O-*trityl*-α- *and* -β-D-*ribofuranosyl*)-3-*oxobutanoyl*]*pyrrolidine* (10c).—A mixture of compound (6) (5 g, 11 mmol) and the phosphorane (8c) (5.8 g, 13.2 mmol) in anhydrous nitromethane (60 ml) was refluxed for 24 h. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography. Elution with hexane–ethyl acetate (2 : 1) gave the product (10c) (β : α *ca.* 3 : 2) as a foam (5.3 g, 87%). Rechromatography of the product with hexane–ethyl acetate (2 : 1) gave β-(10c) as a foam and α-(10c) as needles (from hexane–methanol), m.p. 175 °C. Compound β-(10c) (Found: C, 70.85; H, 7.0; N, 2.2. $C_{34}H_{37}NO_6 \cdot CH_3CO_2C_2H_5$ requires C, 70.4; H, 7.25; N, 2.05%); $\nu_{max.}$ ($CHCl_3$) 1 710 and 1 635 cm^{-1}; *compound* α-(10c) (Found: C, 73.5; H, 6.7; N, 2.5. $C_{34}H_{37}NO_6$ requires C, 73.3; H, 7.2; N, 2.5%); $\nu_{max.}$ ($CHCl_3$) 1 710 and 1 635 cm^{-1}.

N-[4-(2′,3′-O-*Isopropylidene*-5′-O-*trityl*-α- *and* -β-D-*ribofuranosyl*)-3-*oxobutanoyl*]*morpholine* (10d).—A mixture of compound (6) (3 g, 6.9 mmol) and the phosphorane (8d) (4 g, 9.3 mmol) in anhydrous nitromethane (30 ml) was heated at 95—100 °C for 32 h. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography. Elution with hexane–ethyl acetate (2 : 1) gave the product (10d) as a foam (3 g, 75%). Rechromatography of the product with hexane–ethyl acetate (2 : 1) gave β-(10d) as a foam and α-(10d) as needles (from hexane–methanol), m.p. 125—127 °C. *Compound* β-(10d) (Found: C, 71.45; H, 6.5; N, 2.45. $C_{34}H_{37}NO_7$ requires C, 71.05; H, 6.9; N, 2.15%); $\nu_{max.}$ ($CHCl_3$) 1 710 and 1 640 cm^{-1}. *Compound* α-(10d) (Found: C, 71.45; H, 6.5; N, 2.45); $\nu_{max.}$ ($CHCl_3$) 1 710 and 1 635 cm^{-1}.

Ethyl 2-*Diazo*-4-(2′,3′-O-*isopropylidene*-5′-O-*trityl*-α- *and* -β-D-*ribofuranosyl*)-3-*oxobutanoate* (11a).—Triethylamine (2.23 g, 22 mmol) and toluene-*p*-sulphonyl azide (12 ml) were sequentially added to a solution of the ester (10a) (12.0 g, 22 mmol) in anhydrous acetonitrile (100 ml). The mixture was kept at room temperature for 30 min. The solvent was then evaporated under reduced pressure, and the residue was subjected to column chromatography (500 g). Elution with hexane–ethyl acetate (9 : 1) gave the product (11a) (β : α *ca.* 1 : 1) as a foam (12.2 g, 94%) (Found: C, 70.05; H, 6.15; N, 5.0. $C_{33}H_{34}N_2O_7 \cdot \frac{1}{5}C_6H_{14}$ requires C, 69.85; H, 6.3; N, 4.75%); $\nu_{max.}$ ($CHCl_3$) 2 150, 1 710, and 1 645.

2-*Diazo*-4-(2′,3′-O-*isopropylidene*-5′-O-*trityl*-α- *and* -β-D-*ribofuranosyl*)-3-*oxobutananilide* (11b).—Triethylamine (0.3 g, 3 mmol) and toluene-*p*-sulphonyl azide (1.5 ml) were added to a solution of the anilide (10b) (1.8 g, 3 mmol) in anhydrous acetonitrile (20 ml). The mixture was kept at room temperature for 1 h. The solvent then was evaporated under reduced pressure, and the residue was subjected to column chromatography. Elution with hexane–ethyl acetate (4 : 1) gave the product (11b) (β : α *ca.* 1 : 2) as a foam (0.5 g, 26%) (Found: C, 71.3; H, 6.1; N, 6.3. $C_{37}H_{35}N_3O_6 \cdot \frac{1}{3}H_2O$ requires C, 71.25; H, 5.75; N, 6.75%); $\nu_{max.}$ ($CHCl_3$) 3 250, 2 150, and 1 670 cm^{-1}. Subsequent elution with ethyl acetate gave the triazole (12) as a foam (1.3 g, 70%) (Found: C, 64.45; H, 6.55; N, 6.4. $C_{37}H_{35}N_3O_6 \cdot 4H_2O$ requires C, 64.45; H, 6.3; N, 6.1%); $\nu_{max.}$ ($CHCl_3$) 1 730w and 1 650 cm^{-1}.

N-[2-*Diazo*-4-(2′,3′-O-*isopropylidene*-5′-O-*trityl*-α- *and* -β-D-*ribofuranosyl*)-3-*oxobutanoyl*]*pyrrolidine* (11c).—Triethylamine (1 g, 9.5 mmol) and toluene-*p*-sulphonyl azide (5 ml) were added to a solution of compound (10c) (5.3 g, 9.5 mmol) in anhydrous acetonitrile (40 ml). The mixture was kept at room temperature for 2 h. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography. Elution with hexane–ethyl acetate (4 : 1) gave the product (11c) as a foam (5.5 g, 100%) (Found: C, 68.2; H, 6.5; N, 7.3. $C_{34}H_{35}N_3O_6 \cdot H_2O$ requires C, 68.05; H, 6.15; N, 7.0%); $\nu_{max.}$ ($CHCl_3$) 2 100 and 1 620 cm^{-1}.

N-[2-*Diazo*-4-(2′,3′-O-*isopropylidene*-5′-O-*trityl*-α- *and* -β-D-*ribofuranosyl*)-3-*oxobutanoyl*]*morpholine* (11d).—Triethylamine (0.67 g, 6.6 mmol) and toluene-*p*-sulphonyl azide (4 ml) were added to a solution of compound (10d) (3.5 g, 6 mmol) in anhydrous acetonitrile (30 ml). The mixture was kept at room temperature for 2 h. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography. Elution with hexane–ethyl acetate (2 : 1) gave the product (11d) as a foam (3.58 g, 100%) (Found: C, 70.3; H, 6.3; N, 6.1. $C_{34}H_{35}N_3O_7 \cdot \frac{1}{2}C_6H_6$ requires C, 69.85; H, 6.0; N, 6.6%); $\nu_{max.}$ ($CHCl_3$) 2 100 and 1 640 cm^{-1}.

Ethyl 3-*Oxo*-4-(2′,3′,5′-*tri*-O-*benzyl*-α- *and* -β-D-*ribofuranosyl*)*butanoate* (13).—(a) A solution of the protected ribofuranose (7) (1.85 g, 4.4 mmol) and the phosphorane (8a) (3.90 g, 10 mmol) in anhydrous acetonitrile (25 ml) was refluxed for 120 h. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography (100 g). Elution with hexane–ethyl acetate (5 : 1) gave the product (13) (β : α *ca.* 3 : 1) as a viscous oil (1.2 g, 51%) (Found: C, 71.85; H, 6.9. $C_{32}H_{36}O_7$ requires C, 72.15; H, 6.8%); $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 715 cm^{-1}; δ_H ($CDCl_3$) 1.24 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.69 (2 H × $\frac{3}{4}$, m, 4-H_2, β-anomer), 2.97 (2 H × $\frac{1}{4}$, m, 4-H_2, α-anomer), 3.37 (2 H × $\frac{1}{4}$, s, 2-H_2, α-anomer), 3.44 (2 H × $\frac{3}{4}$, s, 2-H_2, β-anomer), 3.40—3.53 (2 H, m, 5′-H_2), 4.49—4.55 (6 H, m, $PhCH_2$ × 3), and 7.16—7.32 (15 H, m, ArH).

(b) A solution of compound (7) (1.85 g, 4.4 mmol) and the phosphorane (8a) (3.90 g, 10 mmol) in nitromethane (25 ml) was heated at 90 °C for 75 h. Work-up as above gave compound (13) (1.0 g, 43%) and 1-(2′,3′,5′-tri-*O*-benzyl-α- and -β-D-ribofuranosyl)propan-2-one (15) (β : α *ca.* 10 : 1) as a viscous oil (0.28 g, 14%) (Found: C, 75.5; H, 7.15. $C_{29}H_{32}O_5$ requires C, 75.65; H, 7.0%); $\nu_{max.}$ 1 715 cm^{-1}; δ_H ($CDCl_3$) 2.03 (3 H × $\frac{1}{11}$, s, CH_3, α-anomer), 2.12 (3 H × $\frac{10}{11}$, s, CH_3, β-anomer), 2.56 (2 H × $\frac{10}{11}$, d, $J_{1,1'}$ 6 Hz, 1-H_2, β-anomer), 2.86 (2 H × $\frac{1}{11}$, m, 1-H_2, α-anomer), 3.36—3.55 (2 H, m, 5′-H_2), 4.44—4.56 (6 H, m, $PhCH_2$ × 3), and 7.16—7.32 (15 H, m, ArH).

(c) A solution of compound (7) (1.85 g, 4.4 mmol) and the phosphorane (8a) (3.90 g, 10 mmol) in anhydrous DMF (25 ml) was heated at 90 °C for 100 h. Work-up as above gave compound (13) (0.16 g, 7%) and compound (15) (0.26 g, 13%).

(d) A solution of compound (7) (1.85 g, 4.4 mmol) and the

phosphorane (8a) (3.90 g, 10 mmol) in anhydrous toluene (25 ml) was heated at 90 °C for 100 h. Work-up as above gave compound (13) (1.1 g, 47%) and compound (15) (0.53 g, 26%).

Ethyl 2-Diazo-3-oxo-4-(2′,3′,5′-tri-O-benzyl-α- and -β-D-ribofuranosyl)butanoate (14).—Triethylamine (0.57 g, 5.6 mmol) and toluene-*p*-sulphonyl azide (3.07 ml) were added to a solution of compound (13) (3.0 g, 5.6 mmol) in anhydrous acetonitrile (25 ml). The mixture was kept at 15 °C for 30 min. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography (100 g). Elution with hexane–ethyl acetate (5 : 1) gave the product (14) (β : α *ca.* 5 : 1) as a viscous oil (2.86 g, 91%) (Found: C, 67.9; H, 6.25; N, 5.0. $C_{32}H_{34}N_2O_7 \cdot \frac{1}{2}H_2O$ requires C, 67.7; H, 6.4; N, 4.95%); $\nu_{max.}$ 2 150, 1 710, and 1 650; δ_H ($CDCl_3$) 1.29 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.10 (2 H × $\frac{5}{6}$, m, 4-H_2, β-anomer), 3.29 (2 H × $\frac{1}{6}$, m, 4-H_2, α-anomer), 3.44—3.56 (2 H, m, 5′-H_2), 4.50—4.54 (6 H, m, $PhCH_2$ × 3), and 7.24—7.27 (15 H, m, ArH).

Cyclization of Compound (11a).—A solution of compound (11a) (6.50 g, 11 mmol) in pure dry DME (60 ml) was added dropwise to a stirred, ice-cooled suspension of sodium hydride (NaH) (50% dispersion; 2.64 g, 55 mmol) in pure dry DME (60 ml) under nitrogen during 30 min. The reaction temperature was raised gradually to 20 °C, and the mixture was stirred for a further 3 h. A solution of acetic acid (3.30 g, 55 mmol) in DME (10 ml) was then added dropwise to the stirred, ice-cooled reaction mixture. The solvent was evaporated under reduced pressure to give a residue, to which water and diethyl ether were added. The ethereal solution was dried over anhydrous sodium sulphate and concentrated. The residue was subjected to column chromatography (800 g). Elution with hexane–ethyl acetate (3 : 1) gave *ethyl 4-hydroxy-3-(2′,3′-O-isopropylidene-5′-O-trityl-β-D-ribofuranosyl)pyrazole-5-carboxylate* (16β) (2.66 g, 42%) as prisms (from diethyl ether), m.p. 159—160 °C (Found: C, 69.3; H, 6.05; N, 4.65. $C_{33}H_{34}N_2O_7$ requires C, 69.45; H, 6.0; N, 4.9%); $\nu_{max.}$ 3 440, 1 720, and 1 685 cm^{-1}. Further elution with the same solvent mixture gave ethyl 4-hydroxy-3-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-α-D-ribofuranosyl)pyrazole-5-carboxylate (16α) as a foam (1.34 g, 21%) (Found: C, 67.7; H, 6.05; N, 4.6. $C_{33}H_{34}N_2O_7 \cdot \frac{3}{4}CH_3CO_2C_2H_5$ requires C, 67.9; H, 6.35; N, 4.4%); $\nu_{max.}$ 3 440, 1 720, and 1 685 cm^{-1}.

4-Hydroxy-3-(2′,3′-O-isopropylidene-5′-O-trityl-α- and -β-D-ribofuranosyl)-5-pyrrolidin-1-ylcarbonylpyrazole (17α) *and* (17β).—(a) A solution of compound (11c) (1.7 g, 2.8 mmol) in pure dry DME (10 ml) was added dropwise to a stirred, ice-cooled suspension of sodium hydride (50% dispersion; 0.68 g, 14.2 mmol) in pure dry DME (10 ml). The mixture was stirred at room temperature for 3 h. A solution of acetic acid (0.85 g, 14.2 mmol) in DME (5 ml) was then added dropwise to the stirred, ice-cooled reaction mixture. The solvent was evaporated under reduced pressure to give a residue, to which water and chloroform were added. The chloroform layer was washed with water, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The resulting residue (2.6 g) was subjected to column chromatography. Elution with hexane–ethyl acetate (4 : 1) gave a mixture of compounds (17β) and (17α) (β : α *ca.* 2 : 1) as a foam (0.9 g, 53%); $\nu_{max.}$ ($CHCl_3$) 3 440, 3 340, and 1 620 cm^{-1}.

(b) A solution of the ester (16β) (0.73 g, 1.25 mmol) in pyrrolidine (15 ml) was refluxed for 6 h. Excess of pyrrolidine was evaporated under reduced pressure, and the residue was subjected to column chromatography (70 g). Elution with hexane–ethyl acetate (7 : 3) gave the product (17β) as a glass (0.64 g, 86%) (Found: C, 69.1; H, 6.75; N, 6.6. $C_{35}H_{37}N_3O_6 \cdot \frac{1}{2}H_2O$ requires C, 69.5; H, 6.35; N, 6.95%); $\nu_{max.}$ ($CHCl_3$) 3 440, 3 340, and 1 620 cm^{-1}.

4-Hydroxy-3-(2′,3′-O-isopropylidene-5′-O-trityl-α- and -β-D-ribofuranosyl)-5-morpholinocarbonylpyrazole (18β).—(a) A solution of compound (11d) (2.0 g, 3.3 mmol) in pure dry DME (20 ml) was added dropwise to a stirred suspension of sodium hydride (50% dispersion; 0.79 g, 16.5 mmol) in pure dry DME (10 ml) at −10 °C. The mixture was stirred at −10 °C for 30 min, and then at room temperature for 3 h. A solution of acetic acid (1 g, 16.5 mmol) in pure dry DME (5 ml) was then added dropwise to the stirred, ice-cooled reaction mixture. The solvent was evaporated under reduced pressure. The residue was dissolved in chloroform and the solution was washed with water, dried over anhydrous sodium sulphate, and evaporated under reduced pressure. The residue (3 g) was subjected to column chromatography. Elution with hexane–ethyl acetate (3 : 1) gave the product (18β) as a foam (0.3 g, 15%) (Found: C, 67.3; H, 6.35; N, 6.2. $C_{35}H_{37}N_3O_7 \cdot CH_3CO_2C_2H_5$ requires C, 66.95; H, 6.5; N, 6.0%); $\nu_{max.}$ ($CHCl_3$) 3 450, 3 250, and 1 630 cm^{-1}.

(b) A solution of the ester (16β) (0.73 g, 1.25 mmol) in morpholine (15 ml) was heated at 105—110 °C for 6 h. Excess of morpholine was evaporated under reduced pressure, and the residue was subjected to column chromatography (70 g). Elution with hexane–ethyl acetate (7 : 3) gave the product (18β) as a glass (0.72 g, 83%).

4-Hydroxy-3-(2′,3′-O-isopropylidene-5′-O-trityl-β-D-ribofuranosyl)pyrazole-5-carboxamide (19β).—A solution of the ester (16β) (2.30 g, 4 mmol) in pure dry methanol (70 ml) was saturated with ammonia gas at 0 °C. The mixture was heated at 90—95 °C in a sealed tube for 7 h. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography (60 g). Elution with hexane–ethyl acetate (3 : 2) gave the product (19β) as a glass (2.22 g, 94%) (Found: C, 67.6; H, 5.9; N, 7.3. $C_{31}H_{31}N_3O_6 \cdot \frac{1}{2}CH_3CO_2C_2H_5$ requires C, 67.7; H, 6.0; N, 7.15%); $\nu_{max.}$ ($CHCl_3$) 1 665 cm^{-1}. Shortened heating (3 h) of the mixture gave the product (19β) (73%) and methyl 4-hydroxy-3-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)pyrazole-5-carboxylate (20β) as a foam (22%) (Found: C, 68.5; H, 6.4; N, 4.45. $C_{32}H_{32}N_2O_7 \cdot \frac{2}{5}CH_3CO_2C_2H_5$ requires C, 68.2; H, 6.0; N, 4.75%); $\nu_{max.}$ ($CDCl_3$) 3 420 and 1 690 cm^{-1}.

4-Hydroxy-3-(2′,3′-O-isopropylidene-5′-O-trityl-α-D-ribofuranosyl)pyrazole-5-carboxamide (19α).—A solution of the ester (16α) (1.20 g, 1.9 mmol) in pure dry methanol (35 ml) was saturated with ammonia gas at 0 °C. The mixture was heated at 90—95 °C in a sealed tube for 2 h. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography (30 g). Elution with hexane–ethyl acetate (3 : 1) gave the starting material (16α) (0.18 g, 15% recovery) and methyl 4-hydroxy-3-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-α-D-ribofuranosyl)pyrazole-5-carboxylate (20α) as a glass (0.30 g, 25%) (Found: C, 66.75; H, 6.1; N, 4.25. $C_{32}H_{32}N_2O_7 \cdot CH_3CO_2C_2H_5$ requires C, 67.05; H, 6.25; N, 4.35%); $\nu_{max.}$ 3 420 and 1 690 cm^{-1}. Subsequent elution with hexane–ethyl acetate (3 : 2) gave the product (19α) as a glass (0.53 g, 46%) (Found: C, 66.95; H, 6.2; N, 7.1. $C_{31}H_{31}N_3O_6 \cdot \frac{3}{4}CH_3CO_2CH_2CH_3$ requires C, 67.2; H, 6.15; N, 6.9%); $\nu_{max.}$ 1 665 cm^{-1}. Similar treatment of compound (20α) gave the product (19α) in 71% yield.

3-(2′,3′-O-Isopropylidene-5′-O-trityl-β-D-ribofuranosyl)-1H,6H-pyrazolo[3,4-e][1,3]oxazine-5,7-dione (21).—A solution of the amide (19β) (1.76 g, 3 mmol) in pure dry DME (20 ml) was added dropwise to a stirred, ice-cooled suspension of sodium hydride (50% dispersion; 72 mg, 1.5 mmol) in pure

dry DME (15 ml) under nitrogen. To the mixture was added a solution of 1,1′-carbonyldi-imidazole (0.97 g, 6 mmol) in pure dry DME (5 ml). The resulting mixture was stirred for 10 h at room temperature. A solution of acetic acid (90 mg, 1.5 mmol) in DME (1 ml) was then added dropwise to the stirred, ice-cooled reaction mixture. The solvent was evaporated under reduced pressure to give a residue, to which was added a mixture of water (20 ml) and diethyl ether (20 ml). The ethereal layer was dried over anhydrous sodium sulphate and concentrated, and the residue was subjected to column chromatography (60 g). Elution with hexane–ethyl acetate (2 : 1) gave the product (21) as a foam (1.1 g, 56%) (Found: C, 65.7; H, 5.65; N, 6.4. $C_{32}H_{29}N_3O_7{\cdot}CH_3CO_2C_2H_5$ requires C, 65.95; H, 5.7; N, 6.4%); $\nu_{max.}$ ($CHCl_3$) 3 400, 1 775, and 1 740 cm^{-1}; δ_H ($CDCl_3$) 1.38 and 1.60 (6 H, br s × 2, CMe_2), 3.22 (2 H, d, $J_{4',5'}$ 4 Hz, 5′-H_2), 4.40 (1 H, dt, $J_{3',4'}$ 3, $J_{4',5'}$ 4 Hz, 4′-H), 4.73 (1 H, dd, $J_{2',3'}$ 5, $J_{3',4'}$ 3 Hz, 3′-H), 5.10 (1 H, dd, $J_{1',2'}$ 4, $J_{2',3'}$ 5 Hz, 2′-H), 5.17 (1 H, d, $J_{1',2'}$ 4 Hz, 1′-H), 7.3 (15 H, m, CPh_3), and 9.0 (1 H, s, NH); δ_C ($CDCl_3$) 25.48 and 27.30 (CMe_2) and 114.66 p.p.m. (CMe_2). Further elution with hexane–ethyl acetate (3 : 2) gave the starting material (19β) (0.6 g, 34% recovery).

Ethyl 4-Hydroxy-3-(2′,3′,5′-tri-O-benzyl-α- and -β-D-ribofuranosyl)pyrazole-5-carboxylate (22α) *and* (22β).—A solution of compound (14) (2.36 g, 4.3 mmol) in pure dry DME (20 ml) was added dropwise to a stirred, ice-cooled suspension of sodium hydride (60% dispersion; 0.86 g, 21 mmol) in pure dry DME (20 ml) under nitrogen. The mixture was stirred at room temperature for 24 h. A solution of acetic acid (1.26 g, 21 mmol) in DME (10 ml) was then added dropwise to the stirred, ice-cooled reaction mixture. The solvent was evaporated under reduced pressure to give a residue, to which were added water (30 ml) and diethyl ether (30 ml). The ethereal layer was dried over anhydrous sodium sulphate and concentrated, and the residue was subjected to column chromatography (100 g). Elution with hexane–ethyl acetate (3 : 1) gave the product (22α) *and* (22β) (β : α *ca.* 5 : 1) as a foam (1.53 g, 65%) (Found: C, 69.75; H, 6.25; N, 4.45. $C_{32}H_{34}N_2O_7{\cdot}\frac{1}{3}C_6H_{14}$ requires C, 69.55; H, 6.65; N, 4.75%); $\nu_{max.}$ ($CHCl_3$) 3 430, 3 270, 1 730, and 1 685 cm^{-1}; δ_H ($CDCl_3$) 1.42 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.51 (2 H × $\frac{1}{6}$, d, $J_{4',5'}$ 6 Hz, 5′-H_2, α-anomer), 3.56 (1 H × $\frac{5}{6}$, dd, $J_{5'a,5'b}$ 10, $J_{4',5'a}$ 2 Hz, 5′-H_2, β-anomer), 3.86 (1 H × $\frac{5}{6}$, dd, $J_{5a',5'b}$ 10, $J_{4',5'b}$ 3 Hz, 5′-H_2, β-anomer), 5.30—5.40 (1 H, m, 1′-H), and 7.00—7.44 (15 H, m, ArH). The β : α ratio was determined by high-performance liquid chromatography (h.p.l.c.) with a μ Bondapak C_{18} column (7.8 mm × 30 cm); eluant: methanol–water (3 : 1); flow rate: 2 ml min^{-1}; retention time: α 6.5 min; β 7.1 min.

4-Hydroxy-5-morpholinocarbonyl-3-(2′,3′,5′-tri-O-benzyl-β-D-ribofuranosyl)pyrazole (23β).—A solution of compounds (22α) *and* (22β) (2.80 g, 5 mmol) in morpholine (60 ml) was heated at 100 °C for 6 h. Excess of morpholine was evaporated under reduced pressure, and the residue was subjected to column chromatography (120 g). Elution with hexane–ethyl acetate (1 : 1) gave the product (23β) as a foam (2.35 g, 78%) (Found: C, 67.3; H, 6.25; N, 6.6. $C_{34}H_{37}N_3O_7{\cdot}\frac{1}{2}H_2O$ requires C, 67.1; H, 6.3; N, 6.9%); $\nu_{max.}$ ($CHCl_3$) 3 430, 3 270, and 1 640 cm^{-1}; δ_H ($CDCl_3$) 3.73 (8 H, br s, morpholine protons), 5.41 (1 H, s, 1′-H), 7.23—7.34 (15 H, m, ArH), 9.10 (1 H, s, OH), and 11.08 (1 H, br, NH).

General Procedure for Deprotection of Protected C-Nucleosides (17β), (18β), (19α) *and* (19β), *and* (21).—A solution of the protected *C*-nucleoside (1—3 mmol) in 90% trifluoroacetic acid (14—40 ml) was set aside at room temperature for 45 min—1 h. The solvent was evaporated under reduced pressure below 5 °C, and the residue was subjected to column chromatography. Elution with acetone–methanol–water gave the *C*-nucleoside (1)—(5); the results are summarized in Table 7.

Deprotection of the Protected C-Nucleoside (23β).—A solution of boron trichloride (1.97 g, 16.7 mmol) in pure dry methylene dichloride (7 ml) was added dropwise to a stirred solution of compound (23β) (0.1 g, 0.2 mmol) in pure dry methylene dichloride (2 ml) at −78 °C. The solution was kept at −78 °C for 24 h. A mixture of pure dry methanol (8.3 ml) and pure dry methylene dichloride (8.3 ml) was then added dropwise to the stirred solution at −78 °C. The mixture was kept at −20 °C for 24 h. The solvent was evaporated under reduced pressure at 30 °C and the residue was co-evaporated with pure dry methanol four times at 30 °C. The resulting residue was subjected to column chromatography (10 g). Elution with ethyl acetate–acetone–methanol–water (50 : 1 : 1 : 1) gave the product (4) (40 mg, 77%).

Acknowledgements

We thank Dr. R. L. Hamill (Eli Lilly, Indianapolis) for samples of pyrazofurin and pyrazofurin B, Mrs. C. Koyanagi, Miss K. Mushiake, and Miss K. Koike of the Central Analysis Room of this Institute for elemental analyses and spectral measurements, and the Ministry of Education, Japan, for partial financial support.

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Received 4th *August* 1983; *Paper* 3/1371