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THE SYNTHESIS OF D-RIBOFURANOSYL DERIVATIVES OF METHYL PROPIOLATE AND A STUDY OF THE ACTIVATING INFLUENCE OF THE ESTER GROUP IN CYCLOADDITION REACTIONS*†‡

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ABSTRACT

2,3,5-Tri-*O*-benzyl-D-ribofuranosyl bromide (**17**) has been converted into methyl 3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)propiolate (**8**) and its α anomer **10** in 21 and 42% yields, respectively, by reaction with the silver salt of methyl propiolate. Attempts to prepare **8** from (β-D-ribofuranosyl)ethyne (**1**) by standard methods were unsuccessful. The reactions of the esters **8** and **10** and the ethyne **1** with several 1,3-dipoles have been examined. With diazomethane, **8** and **10** gave the pyrazole esters **20** and **28**, respectively, whereas the ethyne **1** reacted more slowly to give a mixture of **23** (37%) and **26** (31%). The ester **10** was converted into the triazoles **32** (51%) and **36** (34%) by reaction with benzyl azide. Treatment of the ester **10** with phenylhydrazine gave the pyrazolone **38** in 71% yield. A number of the products of dipolar addition have been converted into new D-ribofuranosyl-pyrazoles and -triazoles by hydrogenolysis.

INTRODUCTION

In Part I we described[4] the synthesis of 2,3,5-tri-*O*-benzyl-β-D-ribofuranosylethyne (**1**) and its α anomer **9** as potential intermediates for the synthesis of *C*-nucleoside antibiotics[5] and their analogues. One of our aims was to convert the ethyne **1** into a functionalised derivative, for instance the propiolic acid **2** and its ester **3**, which would be susceptible to 1,3-dipolar and Michael additions, leading to pyrazoles and other heterocycles. Fox and his colleagues have described[6–8] complementary work with isopropylidene derivatives of D-ribose. Tronchet *et al.*[9] have synthesised an acetylenic acid related to a potential *C*-nucleoside precursor. The use of alkenic esters to achieve similar objectives has been reported by Moffatt[10], Just[11,12], and their co-workers. We now describe in detail our own approaches to this problem.

*Dedicated to the memory of Professor J. K. N. Jones, F.R.S.
†*C*-Nucleoside Studies: Part V. For Part IV, see Ref. 1.
‡Preliminary reports, see Refs. 2, 3.

DISCUSSION

The conversion of terminal acetylenes into acetylenic acids or esters, by treatment of the Grignard reagent or alkali metal salt with carbon dioxide or ethyl chloroformate, is well documented[13]. When the ethyne **1**, in tetrahydrofuran solution, was treated with ethylmagnesium bromide, a gas, presumably ethane, was evolved in quantitative yield. The intermediate Grignard reagent (**4**) was shown to be present by quenching the reaction with deuterium oxide. The resulting deuterioethyne **5** was isolated, showing a strong acetylenic C–D stretching frequency in its infrared spectrum as well as a C≡C stretching frequency modified by deuteration; a comparison of the ^{1}H-n.m.r. spectrum with that of **1** showed the loss of the acetylenic proton.

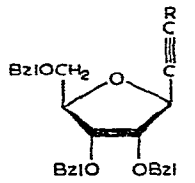
Many unsuccessful attempts were made to bring about reaction between **4** and carbon dioxide, tetramethyl orthocarbonate, and ethyl chloroformate. The parent ethyne **1** could be isolated, usually with high recovery. Similarly, **1** was converted into the lithium derivative **6** by means of phenyllithium. Again, attempts to convert **6** into **2** or **3** were unsuccessful, although the deuterioethyne **5** could be formed readily. The sodium salt **7** gave similar results. We have no convincing explanation for these observations, but it may be that the metallic reagents are stabilised by the proximity of a number of ether oxygen atoms. As another solution to the problem was discovered, we did not explore carbonation reactions in the α series. It is of interest that Tronchet *et al.*[9] apparently encountered no difficulty in converting the lithium salt of the ethyne **12** into the acid **13** by reaction with carbon dioxide.

We have successfully used[14] Heck's palladium-catalysed dicarboalkoxylation reaction[15] to convert the ethyne **1** into the maleate **14**, a potential precursor of the antibiotic showdomycin[16,17]. When the modified Heck reaction[15] for monocarboalkoxylation of an acetylene was examined, using **1** as substrate, none of the acetylene ester **8** was detected.

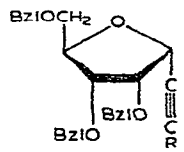
Moffatt has described[10] the reaction between 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide and the silver derivative of methyl propiolate, aimed at the synthesis of a D-ribofuranosyl derivative of methyl propiolate. The major product was, however, the acetal derivative **15**, arising from the 1,2-benzoxonium ion; others[18–20] have described a similar phenomenon. This problem would not arise in the absence of a participating group on C-2 of the ribose moiety, and we therefore studied the reaction of the D-ribofuranosyl chloride **16** with silver (methyl propiolate). The reaction was slow in boiling dichloromethane, but when the bromide **17** was used, reaction occurred at room temperature to give three main products, which were separated by chromatography.

The least-polar component was the enol ether **18*** (10%), whose structure followed from the mass spectrum (strong $M-C_7H_7$ peak), ^{1}H-n.m.r. spectrum, and elemental analysis. The next compound to be eluted from the column was the

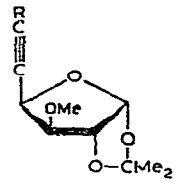
*We apologise that no mention was made in ref. 2 of the prior preparation of this compound by Dr. Michael W. Winkley[21].



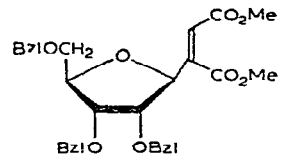
1 R = H
2 R = CO_2H
3 R = CO_2Et
4 R = MgBr
5 R = D
6 R = Li
7 R = Na
8 R = CO_2Me



9 R = H
10 R = CO_2Me
11 R = CO_2H



12 R = H
13 R = CO_2H



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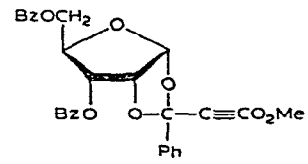
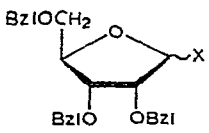
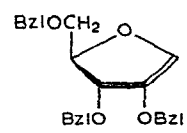


15



16 X = Cl
17 X = Br



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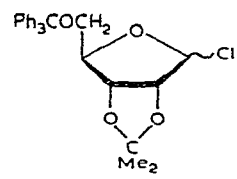


19

Bzl = $PhCH_2$

β-propiolic ester **8** as a syrup, $[\alpha]_D$ +16.0° (chloroform) in 21% yield. Finally, the crystalline α-propiolic ester **10**, m.p. 38–39°, $[\alpha]_D$ +84.3° (chloroform), was obtained in 42% yield.

To establish rigorously the anomeric configuration of the esters, each was subjected to hydrolysis with alkali and the resulting acids (**2** and **11**) were decarboxylated, by heating in benzene solution, to give the ethynes **1** and **9**.

In each case only one ethyne (**1** or **9**) was produced (t.l.c.) showing that no epimerisation had occurred at any stage. The assignment of configuration to the parent ethynes has been rigorously established[4,22]. The esters **8** and **10** obey Hudson's rule, as do the ethynes **1** and **9**, in contrast to the behaviour of some compounds in the isopropylidene series[22]. Fox[7] did not quote rotational data for his ester derivatives but their configurations are securely assigned by n.m.r. studies. The preponderance of the α anomer **10** in our ester products is to be expected in view of the good yield (63%) of the α-ethyne **9** isolated[4] from the reaction of the chloride **16** with ethynyl-

magnesium bromide. Interestingly, in the reaction of 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl chloride (**19**) with silver methyl (or ethyl) propiolate, the preponderant product is the β anomer[7]. Our own work directed to an improved synthesis of the β ester **8** will be reported in due course.

An ethereal solution of the ester **8** was treated with 1 mol equivalent of diazomethane, added slowly to avoid *N*-methylation of the pyrazole that was formed initially. The syrupy pyrazole **20** (or **25**) was obtained in 85% yield after chromatography, and there was no evidence for the formation of an isomer. The structure was assigned as **20** by analogy with a number of cycloadditions of diazomethane to activated acetylenes[7,23–26], where the methylene group of the diazomethane acts as the more nucleophilic end of the 1,3-dipole. The n.m.r. signal due to H-3(5) in **20** appeared at δ 7.84, as expected[27]. When the ester **8** was treated with an excess of diazomethane, two *N*-methyl compounds were formed, of which the major was isolated crystalline. The major isomer should be **21**, having the *N*-methyl group vicinal to the ester group[24,25,28]. The *N*-methyl resonance appeared as a singlet at δ 4.14.

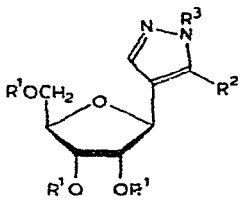
Although the other *N*-methyl isomer could only be obtained as a 2:1 mixture with **20**, its n.m.r. spectrum showed the *N*-methyl signal at δ 3.40, confirming that the major isomer had the *N*-methyl group as in **21**, deshielded by proximity to the methoxycarbonyl group. It is worth noting that, if **25** underwent *N*-methylation, neither of the *N*-methyl groups in the two isomers would have a vicinal relationship to the methoxycarbonyl group, and would therefore be expected to show very similar n.m.r. properties. This constitutes confirmatory evidence that **20** (and not **25**) is the product of addition of diazomethane to **8**.

When **20** was debenzylated by catalytic hydrogenolysis, the known crystalline triol **22** was obtained, whose m.p. corresponded approximately with literature values[7,10]. The n.m.r. spectrum (pyridine-d_5) showed the pyrazole-ring proton resonance as a singlet at δ 7.56; for the ethyl ester, Fox[7] found δ 7.90 (dimethyl sulphoxide-d_6).

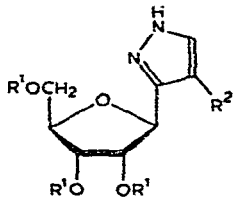
Similarly, the α-acetylenic ester **10** reacted rapidly with 1.2 mol equivalents of diazomethane to give the pyrazole ester **28** in 89% yield. Hydrogenolysis of **28** afforded the crystalline ribofuranosylpyrazole **29**. It is interesting that the α,β pairs **28**, **20**, and **29**, **22** do not obey Hudson's rule, but we have not studied this further.

In contrast with the behaviour of the esters **8** and **10**, the ethyne **1**, even at higher concentration, required several days to react with 1.1 mol equivalents of diazomethane. Chromatography of the products on silica gel gave, in order of elution from the column, unreacted **1** (29%), followed by the pyrazoles **26** (31%) and **23** (37%). The orientation of the two pyrazoles was established by ^{1}H-n.m.r. spectroscopy, particularly after removal of benzyl groups by hydrogenolysis.

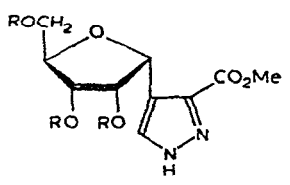
The n.m.r. spectrum of **26** in chloroform-*d* showed the pyrazole H-4 signal as a broad singlet at δ 6.04. (Moffatt[29] gave δ 5.86 for H-4 in the methyl derivative **30**). The H-3(5) signal in **26** was obscured by the aromatic signals, but **27**, obtained as a syrup by hydrogenolysis of **26**, showed H-3(5) and H-4 as doublets, J 2 Hz, at δ 7.83 and 6.65, respectively. The spectrum of **31** (ref. 29), in the same solvent (pyridine-d_5),



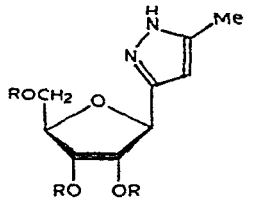
20 R^1 = Bzl, R^2 = CO_2Me, R^3 = H
21 R^1 = Bzl, R^2 = CO_2Me, R^3 = Me
22 R^1 = H, R^2 = CO_2Me, R^3 = H
23 R^1 = Bzl, R^2 = R^3 = H
24 R^1 = R^2 = R^3 = H



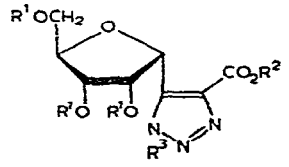
25 R^1 = Bzl, R^2 = CO_2Me
26 R^1 = Bzl, R^2 = H
27 R^1 = R^2 = H



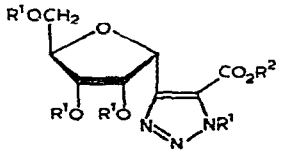
28 R = Bzl
29 R = H



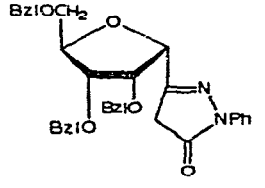
30 R = Bzl
31 R = H



32 R^1 = R^3 = Bzl, R^2 = Me
33 R^1 = R^3 = H, R^2 = Me
34 R^1 = R^3 = Bzl, R^2 = H
35 R^1 = Bzl, R^2 = Me, R^3 = H



36 R^1 = Bzl, R^2 = Me
37 R^1 = Bzl, R^2 = H



38

showed H-4 at δ 6.26. The effect of the 3(5)-methyl group on the H-4 signal[29] is as expected[27].

The pyrazole proton signals of **23** were completely obscured by those of the aromatic protons. Hydrogenolysis of **23** afforded the crystalline triol **24**, whose n.m.r. spectrum (pyridine-d_5) showed the pyrazole protons as a 2-proton singlet at δ 8.12. This is in agreement with the symmetrical pyrazole-substitution pattern in **24**, allowing for the rapid tautomeric exchange of the pyrazole NH proton.

The reaction of **1** with diazomethane is an acceptable route to the simple C-ribofuranosylpyrazoles **27** and **24**, particularly when account is taken of the recoverable starting-material. Of these, **27** is the more interesting, as it is related to pyrazofurin (pyrazomycin) and the formycins[5].

When the ethyne **1** was treated with ethyl diazoacetate under a variety of conditions (see Experimental), no useful product could be isolated. Reaction was very slow and a complex mixture of products was formed. These observations on cycloaddition of diazoalkanes to acetylenes are in full agreement with earlier work which showed that the most rapid reaction occurs when the acetylene is activated, as by an ester group, and the diazoalkane component does not contain an electron-withdrawing substituent[23,26].

In Part I, it was shown[4] that the ethyne **1** reacted with benzyl azide to give two isomeric *N*-benzyltriazoles. We have now found that the acetylenic ester **10** reacts with benzyl azide under milder conditions to give two triazole esters (in 51 and 34% yield), shown to have structures **32** and **36**, respectively. Both triazole esters underwent hydrogenolysis to the same crystalline compound, 4(5)-methoxycarbonyl-5(4)-α-D-ribofuranosyl-1,2,3-triazole (**33**), showing that they differed only in the location of the *N*-benzyl group. In order to assign individual structures to the two esters ("major" and "minor"), the chemical shifts of the NCH_2 signals of the esters and the corresponding acids were compared. The major ester and its related acid both showed the NCH_2 signals as an AB quartet, with the signal in the spectrum of the acid displaced upfield by 0.02 p.p.m. In the spectra of the minor ester and its acid, the NCH_2 groups resonated as singlets, the signal from the acid being deshielded by 0.24 p.p.m. This shows a closer spatial relationship of the NCH_2 and ester (and acid) group in the case of the minor product. The acid must therefore be **37** and the ester **36**. Structures **32** and **34** may then be assigned to the major ester and acid.

These assignments are confirmed by considering the multiplicity of the NCH_2 signals. The NCH_2 group in **32** and **34** is nearer to the asymmetric environment of the ribofuranosyl moiety than it is in **36** and **37**. The AB pattern shown for the NCH_2 signal by **32** and **34** is therefore to be expected, in contrast with the singlets given by **36** and **37**.

The formation of appreciable quantities of both possible isomers **32** and **36** from **10** and benzyl azide is interesting in view of a similar result with **1** and benzyl azide. Horton and coworkers[30,31] have shown that phenyl azide adds regioselectively to terminal ethynes derived from carbohydrates, to give mainly 1,4-substituted 1,2,3-triazoles, in keeping with steric considerations. In our own examples, the benzyl group may have a smaller steric requirement than phenyl, but electronic factors may also be involved.

The ester **10** reacted with trimethylsilyl azide, and removal of the trimethylsilyl group gave the crystalline triazole **35** in 39% yield. Several unsuccessful attempts were made to decarboxylate the acid **34** to obtain a ribofuranosyltriazole in the α series.

When the ester **10** was treated with phenylhydrazine, the pyrazolin-5-one **38** was isolated in 71% yield after chromatography. The i.r. spectrum showed bands at 1724 (C=O), 1602 (C=N), and 907 cm^{-1} (pyrazolinone ring[32]), in agreement with structure **38**, which was confirmed by the n.m.r. spectrum.

EXPERIMENTAL

General methods. — Melting points are corrected. I.r. spectra were measured for potassium bromide discs or for films, with a Perkin–Elmer 257 or 157G spectrophotometer. Mass spectra were recorded with an A.E.I. MS-902 or MS-30 spectrometer. N.m.r. spectra were measured on a Jeol MH-100 spectrometer at 100 MHz, with tetramethylsilane as internal standard. Chemical shifts (first order) are quoted on the δ scale and first-order couplings in Hz. Specific rotations were measured with a Bendix-NPL 143D automatic polarimeter (path length, 1 cm). Adsorption chromatography was conducted on silica gel (Merck; 70–230 mesh ASTM). For t.l.c., Kieselgel G (Merck) was used as the adsorbent; carbohydrates were detected with anisaldehyde–sulphuric acid[33]. Evaporations were performed under diminished pressure below 40° on a rotary evaporator.

(2,3,5-Tri-O-benzyl-β-D-ribofuranosyl)ethynylmagnesium bromide (**4**). — A solution (10 ml) of the ethyne **1** (1.0 g) in dry tetrahydrofuran was added dropwise during 0.5 h to a stirred solution (25 ml) of 0.15M ethylmagnesium bromide in dry tetrahydrofuran at 65°. The liberated ethane (48 ml) was collected until evolution ceased. The resultant solution of **4** in tetrahydrofuran was 0.067 M.

1-Deuterio-(2,3,5-tri-O-benzyl-β-D-ribofuranosyl)ethyne (**5**). — A 0.067M solution of **4** in dry tetrahydrofuran (9 ml) was pipetted into deuterium oxide (1 ml). Chloroform (50 ml) was added, and the chloroform layer was washed successively with 4M sulphuric acid, saturated aqueous potassium hydrogencarbonate, and water. Evaporation of the dried (sodium sulphate) chloroform extract gave a crystalline solid (0.3 g). Recrystallisation from ethanol yielded the ethyne **5** (0.2 g, 78%), m.p. 62–64°; ν_{max}^{KBr} 3250 (w) (HC≡), 2570 (s) (DC≡), and 1965 cm^{-1} (s) (C≡C–D); n.m.r. data (100 MHz, chloroform-*d*): δ 3.6 (d, 2 H), 4.8–5.9 (m, 10 H) and 7.25 (m, 15 H, Ar).

Attempted carbonation of ethynylmagnesium bromide (**4**) *with carbon dioxide.* — The ethyne **1** (1.6 g) in dry tetrahydrofuran (20 ml) was added dropwise during 0.5 h to a stirred 0.22M solution of ethylmagnesium bromide in dry tetrahydrofuran (24.5 ml) at 65°. The ethane liberated was collected and heating continued until evolution of ethane (85 ml) ceased. The resulting solution of **4** was treated with gaseous carbon dioxide (30 atm.) in an autoclave for 36 h. Isolation with chloroform yielded the unchanged ethyne **1** (1.59 g, 99%) m.p. 62–64°.

(2,3,5-Tri-O-benzyl-β-D-ribofuranosyl)ethynyllithium (**6**) *and its reactions.* — An ethereal solution of the ethyne **1** was treated with phenyllithium, prepared by Gilman's method[34], to give a 0.082M solution of **6**.

A. Reaction with deuterium oxide. The foregoing solution (5 ml) was added to deuterium oxide (1 ml). Isolation with chloroform gave the deuterioethyne **5**, identical to the earlier preparation from **4**.

B. Treatment with ethyl chloroformate. The foregoing solution of **6** (12 ml) was added to ethyl chloroformate (0.21 g, 2 equiv.) in dry ether (10 ml) during 0.5 h. After 3 h at room temperature, t.l.c. (1:1 light petroleum–ether) showed no reaction.

The solution was heated for 6 h under reflux. T.l.c. indicated that some unspecific decomposition of **1** took place.

Reaction of the bromide **17** *with silver (methyl propiolate).* — The bromide[35] **17** (2.5 g) in dry dichloromethane (15 ml) was stirred, in the absence of light, for 50 min with silver (methyl propiolate)[10] (1.17 g, 1.2 equiv.). Filtration and evaporation yielded a syrup that was chromatographed on silica gel (90 g). Light petroleum–ether (9:2) eluted the enol ether **18** (204 mg, 10%), $[\alpha]_D^{22}$ −1.8° (*c* 3.25, chloroform); n.m.r. data (100 MHz, chloroform-*d*): δ 3.46–4.84 (m, 10 H), 5.08 (s, 1 H, H-1), and 6.98–7.48 (m, 15 H, Ar); *m/e* 311 s (M − CH_2Ph).

Anal. Calc. for $C_{26}H_{26}O_4$: C, 77.61; H, 6.47. Found: C, 77.48; H, 6.80.

Elution with 4:1 light petroleum–ether yielded syrupy methyl 3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)propiolate (**8**, 533 mg, 21%), $[\alpha]_D^{22}$ +16.0° (*c* 1.0, chloroform); ν_{max}^{film} 2240 (C≡C), 1718 (C=O), and 1260 cm^{-1} (C–O); n.m.r. data (100 MHz, chloroform-*d*): δ 3.68 (s, 3 H, OMe); *m/e* 486 w (M), 455 w (M − OMe), 409 w (M − Ph), 395 m (M − CH_2Ph), and 365 m (M − CH_2OCH_2Ph).

Anal. Calc. for $C_{30}H_{30}O_6$: C, 74.07; H, 6.17. Found: C, 74.30; H, 6.46.

Light petroleum–ether (3:1) eluted methyl 3-(2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl)propiolate (**10**, 1.080 g, 42%) as a crystalline solid. Recrystallised from ether–light petroleum, it had m.p. 38–39°, $[\alpha]_D^{22}$ +84.3° (*c* 1.72, chloroform); ν_{max} 2240 (C≡C), 1712 (C=O), and 1250 cm^{-1} (C–O); n.m.r. data (100 MHz, chloroform-*d*): δ 3.74 (s, 3 H, OMe); *m/e* 486 w (M), 455 w (M − OMe), 409 w (M − Ph), 395 s (M − CH_2Ph), and 365 m (M − CH_2OCH_2Ph).

Anal. Calc. for $C_{30}H_{30}O_6$: C, 74.07; H, 6.17. Found: C, 73.89; H, 6.24.

*Degradation of methyl 3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)propiolate* (**8**) *to ethyne* **1**. — The ester **6** (49 mg) was dissolved in 1,4-dioxane (2 ml) and water (0.5 ml) containing potassium hydroxide (6 mg, 1.04 equiv.), and the solution was stirred for 1 h at room temperature. Additional potassium hydroxide (4 mg, 0.7 equiv) was then added, and stirring was continued for a further 40 min. The solution was then acidified (0.1M hydrochloric acid), and the product extracted with chloroform. The residue obtained by evaporation of the chloroform extracts was heated in benzene (10 ml) for 18 h. Evaporation yielded (2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)ethyne[4] (**1**, 26 mg, 60%), m.p. 62–63°, $[\alpha]_D$ +7.3° (*c* 0.5, chloroform).

*Degradation of methyl 3-(2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl)propiolate* (**10**) *to ethyne* **9**. — The ester **10** (63 mg) was stirred for 55 min at room temperature with a solution of potassium hydroxide (12 mg, 1.63 equiv.) in 1,4-dioxane (2 ml) and water (0.5 ml). The solution was then acidified (0.1M hydrochloric acid) and the product extracted with chloroform. The residue obtained by evaporation of the chloroform extract was heated under reflux with benzene (10 ml) for 18 h. Evaporation yielded (2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl)ethyne[4] (**9**, 43 mg, 77%), m.p. 50–51°, $[\alpha]_D$ +80.6° (*c* 0.98, chloroform).

*3(5)-Methoxycarbonyl-4-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole* (**20**). — An ethereal solution (8 ml) of diazomethane (~1 equiv.) was added during 4 h to a solution of the ester **8** (67 mg) in ether (1 ml) at room temperature. Evaporation

afforded a syrup that was chromatographed on silica gel (4 g) to yield the pyrazole **20** (62 mg, 85%) as a syrup, $[\alpha]_D^{22}$ +100.9° (*c* 1.12, chloroform); ν_{max}^{film} 3152 (NH), 1728 (C=O), and 1244 cm^{-1} (C–O); n.m.r. data (100 MHz, chloroform-*d*) δ 3.78 (s, 3 H, OCH_3), 5.56 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1'), 7.06–7.42 (m, 15 H, Ar), 7.84 (s, 1 H, pyrazole H-5(3), and 13.60–14.12 (broad, 1 H, NH, visible at −60°, collapsed on warming the solution to room temperature); *m/e* 528 w (M), 497 (w (M−OCH_3), 451 w (M−Ph), 437 s (M−CH_2Ph), and 155 s (heterocycle+30); accurate mass (M−CH_2Ph) 437.1688, calc. for $C_{24}H_{25}N_2O_6$: 437.1712.

Anal. Calc. for $C_{31}H_{32}N_2O_6$: C, 70.46; H, 6.06; N, 5.30. Found: C, 70.04; H, 6.17; N, 5.26.

5-Methoxycarbonyl-1-methyl-4-(2,3,5-tri-O-benzyl-β-D-ribofuranosyl)pyrazole (**21**). — The ester **8** (272 mg) was stirred with a solution of diazomethane (4.3 equiv.) in ether (8 ml) overnight at room temperature. The mixture was evaporated *in vacuo* and the residue chromatographed on silica gel (5 g). Light petroleum–ether (3:2) eluted the *N*-methylpyrazole **21** as a crystalline solid (104 mg, 34%). Recrystallised from ethanol, it had m.p. 104.5–105.5°, $[\alpha]_D^{25}$ +62.0° (*c* 1.0, chloroform); ν_{max}^{KBr} 1726 (C=O) and 1278 cm^{-1} (C–O); n.m.r. data (100 MHz, chloroform-*d*): δ 3.88 (s, 3 H, OCH_3), 4.14 (s, 3 H, NCH_3), 5.48 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1'), 7.08–7.40 (m, 15 H, Ar), and 7.56 (3, 1 H, pyrazole H-3); *m/e* 542 m (M), 511 m (M−OCH_3), 465 w (M−Ph), 451 s (M−CH_2Ph), and 169 s (heterocycle+30).

Anal. Calc. for $C_{32}H_{34}N_2O_6$: C, 70.85; H, 6.27; N, 5.17. Found: C, 70.58; H, 6.30; N, 5.14.

Ether eluted a syrup (51 mg) that was apparently chromatographically homogeneous. Spectroscopic analysis indicated, however, that it was a mixture of 3-methoxycarbonyl-1-methyl-4-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole and the pyrazole **20** in the approximate ratio 2:1.

3(5)-Methoxycarbonyl-4-(β-D-ribofuranosyl)pyrazole (**22**). — The benzyl ether **20** (151 mg) in methanol (10 ml) was hydrogenated at 1 atm. for 28 h over 5% palladium on charcoal (40 mg). Filtration and evaporation *in vacuo* yielded the crystalline pyrazole **22** (62 mg, 84%). Recrystallised from ethanol, **22** had m.p. 175–176°, $[\alpha]_D^{22}$ +10.6° (*c* 0.56, water) (lit.[10]: m.p. 186–188°, m.p.[7] 181–182.5°). ν_{max}^{KBr} 3364, 3160, 3108 (all OH, NH), 1694 (C=O), and 1248 cm^{-1} (C–O); n.m.r. data (100 MHz, dimethyl sulphoxide-d_6): δ 3.64 (s, 3 H, OCH_3), 4.88 (d, 1 H, *J* 4 Hz, H-1'), and 7.56 [s, 1 H, pyrazole H-5(3)]; *m/e* 257 w (M−1), 227 m (M−OCH_3) and/or (M−CH_2OH), 199 m (M−CO_2CH_3), and 155 s (heterocycle+30).

Anal. Calc. for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.43; N, 10.85. Found: C, 46.61; H, 5.42; N, 10.74.

3(5)-Methoxycarbonyl-4-(2,3,5-tri-O-benzyl-α-D-ribofuranosyl)pyrazole (**28**). — The ester **10** (179 mg) was stirred with a solution of diazomethane (1.2 equiv.) in ether (5 ml) for 1 h at room temperature. After evaporation of the solvent, the residue was chromatographed on silica gel (5 g). Ether eluted the pyrazole **28** as a syrup (173 mg, 89%), $[\alpha]_D^{20}$ −25.3° (*c* 0.75 chloroform); ν_{max}^{film} 3160 (NH), 1724 (C=O), and 1248 cm^{-1} (C–O); n.m.r. data (100 MHz, chloroform-*d*): δ 3.76 (s, 3 H, OCH_3),

5.54 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1'), 6.86–7.16 (m, 5 H, Ar), 7.16–7.38 (m, 10 H, Ar), 7.82 [s, 1 H, pyrazole H-5(3)], and 14.56 (broad s, 1 H, NH); *m/e* 529 m (M+1) 528 w (M), 527 w (M−1), 437 s (M−CH_2Ph), 407 m (M−CH_2OCH_2Ph), and 155 m (heterocycle+30).

Anal. Calc. for $C_{31}H_{32}N_2O_6$: C, 70.46; H, 6.06; N, 5.30. Found: C, 70.22; H, 6.27; N, 5.31.

3(5)-Methoxycarbonyl-4-(α-D-ribofuranosyl)pyrazole (**29**). — The benzyl ether **28** (155 mg) in methanol (10 ml) was hydrogenated for 16 h over 5% palladium on charcoal (35 mg). Filtration, followed by evaporation, yielded the crystalline pyrazole **29** (58 mg, 77%), which was recrystallised from ethanol; m.p. 195–198°, $[\alpha]_D^{23}$ −74.0° (*c* 1.0, deuterium oxide); ν_{max}^{KBr} 3520, 3470, 3358, 3260 (all OH, NH), 1720 (C=O), and 1278 cm^{-1} (C–O); n.m.r. data (100 MHz, dimethyl sulphoxide-d_6): δ 3.80 (s, 3 H, OCH_3), 5.28 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1'), 7.58 [s, 1 H, pyrazole H-5(3)]; *m/e* 259 w (M+1), 227 m (M−OCH_3) or (M−CH_2OH), 199 w (M−CO_2CH_3), and 155 s (heterocycle+30).

Anal. Calc. for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.43; N, 10.85. Found: C, 46.29; H, 5.63; N, 10.69.

Reaction of (2,3,5-tri-O-benzyl-β-D-ribofuranosyl)ethyne (**1**) *with diazomethane.* — The ethyne **1** (1.483 g) was treated with diazomethane (1.1 equiv.) in ether (21 ml) for 112 h at room temperature. The residue, after removal of solvent, was chromatographed on silica gel (40 g). Light petroleum–ether (1:1) eluted unchanged **1** (424 mg, 29%). Elution with light petroleum–ether (1:2, 1:3, 1:4) gave first 3(5)-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole (**26**, 501 mg, 31%). Recrystallised from ether–hexane, it had m.p. 81.5–83°, $[\alpha]_D^{26}$ +6.9° (*c* 1.31, chloroform)*; ν_{max}^{KBr} 3305 cm^{-1} (br) (NH); n.m.r. data (100 MHz, chloroform-*d*): δ 3.40–4.76 (m, 11 H), 5.16 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1'), 6.04 (broad s, 1 H, pyrazole H-4), and 7.12–7.44 [m, 16 H, Ar, pyrazole H-5(3)]; *m/e* 470 w (M), 393 w (M−Ph), 379 s (M−CH_2Ph), 97 m (heterocycle+30), and 91 s ($PhCH_2$).

Anal. Calc. for $C_{29}H_{30}N_2O_4$: C, 74.04; H, 6.38; N, 5.96. Found: C, 74.13; H, 6.55; N, 5.96.

4-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole (**23**) was next eluted (599 mg, 37%). Recrystallised from ether–hexane, it had m.p. 112–113.5°, $[\alpha]_D^{26}$ −21.8° (*c* 1.14, chloroform)*; ν_{max}^{KBr} 3306 cm^{-1} (br) (NH); n.m.r. data (100 MHz, chloroform-*d*): δ 3.32–4.72 (m, 11 H), 5.02 (d, 1 H, $J_{1',2'}$ 7 Hz, H-1'), and 7.04–7.56 (m, 17 H, Ar, pyrazole H-3, H-5); *m/e* 470 w (M), 379 m (M−CH_2Ph), 97 s (heterocycle+30), and 91 s ($PhCH_2$).

Anal. Calc. for $C_{29}H_{30}N_2O_4$: C, 74.04; H, 6.38; N, 5.96. Found: C, 74.05; H, 6.45; N, 5.83.

3(5)-β-D-Ribofuranosylpyrazole (**27**). — The benzyl ether **26** (348 mg) in methanol (10 ml) was hydrogenated for 21 h at 1 atm. over 5% palladium on charcoal (302 mg). The mixture was filtered and evaporated to yield the syrupy

*The value given in ref. 3 is in error.

pyrazole **27** (148 mg, 100%), $[\alpha]_D^{24}$ −22.3° (*c* 1.16, water); λ_{max}^{MeOH} 221 nm (ε 2000); ν_{max}^{film} 3223 cm^{-1} (br) (OH, NH); n.m.r. data (100 MHz, pyridine-d_5): δ 4.14–4.40 (m, 2 H, H-5'a, H-5'b), 4.54–5.07 (m, 3 H, H-2',3',4'), 5.68 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1'), 6.65 (d, 1 H, *J* 2 Hz, pyrazole H-4), and 7.83 [d, 1 H, *J* 2 Hz, pyrazole H-5(3)]; *m/e* 200 m (M), 169 m (M−CH_2OH), and 97 s (heterocycle+30).

Anal. Calc. for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.00; N, 14.00. Found: C, 47.68; H, 6.10; N, 13.86.

4-β-D-Ribofuranosylpyrazole (**24**). — The benzyl ether **23** (454 mg) in methanol (10 ml) was hydrogenated for 19 h at 1 atm. over 5% palladium on charcoal (350 mg). The solution was filtered and evaporated to yield the crystalline pyrazole **24** (181 mg, 94%). Recrystallised from ethanol, **24** had m.p. 156–157°, $[\alpha]_D^{24}$ −43.0° (*c* 1.1 water); λ_{max}^{MeOH} 219 nm (ε 3100); ν_{max}^{KBr} 3400, 3350, and 3240 cm^{-1} (OH, NH); n.m.r. data (100 MHz, pyridine-d_5): δ 4.08–4.36 (m, 2 H, H-5'a, H-5'b), 4.52–4.88 (m, 3 H, H-2', H-3', H-4'), 5.47 (d, 1 H, $J_{1',2'}$ 6.5 Hz, H-1'), 6.20–7.00 (broad s, 3 H, 3 OH, exchangeable with D_2O), 8.12 (s, 2 H, pyrazole H-3, H-5), and 13.48–14.12 (broad, 1 H, pyrazole NH, exchangeable with D_2O); *m/e* 200 m (M), 169 s (M−CH_2OH), and 97 s (heterocycle+30).

Anal. Calc. for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.00; N, 14.00. Found: C, 48.14; H, 6.04; N, 14.05.

Treatment of **1** *with ethyl diazoacetate.* — The ethyne **1** (200 mg) in dichloromethane (15 ml) was heated under reflux, in the absence of light, with ethyl diazoacetate (7 equiv.) for 5 h. T.l.c. showed negligible reaction.

The reaction was repeated using carbon tetrachloride (25 ml) as solvent. After heating for 7 h under reflux, t.l.c. showed no significant reaction.

The reaction was then repeated with heating for 40 h under reflux in 1,4-dioxane (25 ml). T.l.c. indicated the mixture to consist predominantly of **1** and six minor components of greater polarity. After evaporation, the residue was chromatographed on silica gel (10 g). Light petroleum–ether (6:1) eluted unchanged **1** (80 mg, 40% recovery). Further elution with 5:1 light petroleum–ether, chloroform, and 5:1 ethyl acetate–methanol yielded six minor components, none of which were the expected pyrazoles, as shown by analytical and spectroscopic data.

1-Benzyl-4-methoxycarbonyl-5-(2,3,5-tri-O-benzyl-α-D-ribofuranosyl)-1,2,3-triazole (**32**) *and 1-benzyl-5-methoxycarbonyl-4-(2,3,5-tri-O-benzyl-α-D-ribofuranosyl)-1,2,3-triazole* (**36**). — The ester **10** (322 mg) in benzene (2 ml) was heated for 5.5 h under reflux with freshly distilled benzyl azide (352 mg, 4 equiv.). The solution was then evaporated and the residue chromatographed on silica gel (7 g). Light petroleum–ether (3:2) eluted unchanged ester **10** (32 mg, 10%). Light petroleum–ether (1:1) eluted the triazole **32** (209 mg, 51%) as a syrup, $[\alpha]_D^{25}$ +12.8° (*c* 3.52, chloroform); ν_{max}^{KBr} 1712 (C=O) and 1242 cm^{-1} (C–O); n.m.r. data (100 MHz, chloroform-*d*): δ 3.90 (s, 3 H, OCH_3), 5.55 (d, 1 H, *J* 16 Hz, $PhCH_aH_bN$), 5.73 (d, 1 H, *J* 16 Hz, $PhCH_aH_bN$), 5.92 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1'), and 6.80–7.48 (m, 20 H, Ar); *m/e* 619 w (M), 591 w (M−N_2), 588 w (M−OCH_3), 542 w (M−Ph), 528 s (M−CH_2Ph), and 246 s (heterocycle+30).

Anal. Calc. for $C_{37}H_{37}N_3O_6$: C, 71.73; H, 5.98; N, 6.78. Found: C, 71.75; H, 6.15; N, 6.71.

Light petroleum–ether (1:2) eluted the syrupy, isomeric triazole **36** (139 mg, 34%), $[\alpha]_D^{26}$ −44.3° (*c* 2.35, chloroform); ν_{max}^{film} 1723 (C=O) and 1258 cm^{-1} (C–O); n.m.r. data (100 MHz, chloroform-*d*), δ 3.58 (s, 3 H, OCH_3), 5.53 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1'), 5.82 (s, 2 H, Ph CH_2N), and 6.80–7.40 (m, 20 H, Ar); *m/e* 619 w (M), 591 w (M−N_2), 588 w (M−OCH_3), 542 w (M−Ph), 528 s (M−CH_2Ph), and 246 s (heterocycle+30).

Anal. Calc. for $C_{37}H_{37}N_3O_6$: C, 71.73; H, 5.98; N, 6.78. Found: C, 71.66; H, 6.12; N, 6.61.

4(5)-Methoxycarbonyl-5(4)-(α-D-ribofuranosyl)-1,2,3-triazole (**33**). — *A.* The benzyl ether **32** (310 mg) in methanol (10 ml) was hydrogenated at 1 atm. for 42 h over 5% palladium on charcoal (400 mg). Filtration, followed by evaporation, yielded the crystalline triazole **33** (114 mg, 88%) which, recrystallised from methanol–ethyl acetate had m.p. 176–178°, $[\alpha]_D^{25}$ −105.9° (*c* 0.9 methanol), λ_{max}^{MeOH} 229 nm (ε 6400); ν_{max}^{film} 3340 (br) (OH, NH), 1726 (C=O), and 1230 cm^{-1} (C–O); n.m.r. data (100 MHz, dimethyl sulphoxide-d_6): δ 3.80 (s, 3 H, OCH_3) and 5.48 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1'); *m/e* [of tetrakis(trimethylsilyl) derivative] 547 w (M) and 532 w (M−CH_3).

Anal. Calc. for $C_9H_{13}N_3O_6$: C, 41.70; H, 5.02; N, 16.22. Found: C, 41.56; H, 5.12; N, 16.35.

B. The benzyl ether **36** (212 mg) in methanol (10 ml) was hydrogenated at 1 atm. for 26 h over 5% palladium on charcoal (306 mg). Isolation as before yielded the triazole **33** (83 mg, 94%), m.p. 176–178°, identical to the sample prepared in by method *A*.

1-Benzyl-5-(2,3,5-tri-O-benzyl-α-D-ribofuranosyl)-1,2,3-triazole-4-carboxylic acid (**34**). — The ester **32** (166 mg) was stirred for 1 h at room temperature with a solution of potassium hydroxide (31 mg, 2 equiv.) in 1,4-dioxane (1 ml) and water (0.5 ml). The solution was then acidified (0.1M hydrochloric acid), diluted with brine (10 ml), and extracted with chloroform (4×30 ml). The chloroform extracts were dried (magnesium sulfate) and evaporated, yielding the syrupy acid **34**, $[\alpha]_D^{21}$ +19.0° (*c* 4.1, chloroform); ν_{max}^{film} 3600–2300 (CO*OH*) and 1710 cm^{-1} (C=O); n.m.r. data (100 MHz, chloroform-*d*): δ 3.48–4.76 (m, 11 H), 5.53 (d, 1 H, *J* 16 Hz, $PhCH_aH_bN$), 5.71 (d, 1 H, *J* 16 Hz, $PhCH_aH_bN$), 5.94 (d, 1 H, $J_{1',2'}$ 2 Hz, H-1'), 6.76–7.44 (m, 20 H, Ar), and 9.48 (broad s, 1 H, CO_2H); *m/e* 605 m (M), 514 s (M−CH_2Ph), 232 m (heterocycle+30), and 44 s (CO_2).

Anal. Calc. for $C_{36}H_{35}N_3O_6$: C, 71.40; H, 5.78; N, 6.94. Found: C, 71.49; H, 6.00; N, 6.91.

1-Benzyl-4-(2,3,5-tri-O-benzyl-α-D-ribofuranosyl)-1,2,3-triazole-5-carboxylic acid (**37**). — The triazole ester **36** (128 mg), potassium hydroxide (24 mg, 2 equiv.), 1,4-dioxane (2 ml), and water (1 ml) were stirred for 1 h at room temperature. The solution was acidified with 2M hydrochloric acid, diluted with brine (30 ml), and extracted with chloroform (3×40 ml). The chloroform extracts were dried (magnesium

sulfate), and evaporated to yield the syrupy acid **37** (125 mg, 100%); $[\alpha]_D^{23}$ +28.2° (*c* 1.31, chloroform); ν_{max}^{film} 3660–2100 (CO*OH*) and 1712 cm^{-1} (C=O); n.m.r. data (100 MHz, chloroform-*d*): δ 3.54–4.80 (m, 11 H), 5.64 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1'), 6.06 (s, 2 H, PhCH_2N), 6.94–7.80 (m, 20 H, Ar), and 10.20 (broad s, 1 H, CO_2H).

Anal. Calc. for $C_{36}H_{35}N_3O_6$: C, 71.40; H, 5.78; N, 6.94. Found: C, 71.15; H, 5.95; N, 7.06.

*4(5)-Methoxycarbonyl-5(4)-(2,3,5-tri-*O*-benzyl-α-*D*-ribofuranosyl)-1,2,3-triazole* (**35**). — The ester **10** (161 mg) in trimethylsilyl azide (1.45 g, 38 equiv.) was heated for 43 h under reflux. The excess of azide was evaporated off, and the residue was heated for 2 h under reflux in methanol (6 ml). The solution was evaporated, and the residue chromatographed on silica gel (4 g). Light petroleum–ether (1:1) eluted the triazole **35** (69 mg, 39%), which crystallised after one month. Recrystallised from ether–hexane, it had m.p. 107–109°, $[\alpha]_D^{24}$ −16.7° (*c* 1.14 chloroform); ν_{max}^{film} 3200 (broad NH), 1722 (C=O), and 1240 cm^{-1} (C–O); n.m.r. data (100 MHz chloroform-*d*): δ 3.78 (s, 3 H, OCH_3), 5.68 (d, 1 H, $J_{1',2'}$ 5 Hz, H-1'), 6.58–7.22 (m, 15 H, Ar), and 13.56–14.00 (broad, 1 H, NH, broad at −60° which collapses on warming to room temperature); *m/e* 529 w (M), 498 m (M−OCH_3), 452 m (M−Ph), 438 s (M−CH_2Ph), and 156 s (heterocycle+30).

Anal. Calc. for $C_{30}H_{31}N_3O_6$: C, 68.05; H, 5.86; N, 7.94. Found: C, 67.36; H, 5.78; N, 7.68.

Attempted decarboxylation of acid **34**. — *A*. The acid **34** (20 mg) in benzene (5 ml) was heated for 4 h under reflux. T.l.c. indicated that no reaction had taken place. Triethylamine (2 drops) was added and the solution was heated for 2 h under reflux. T.l.c. again indicated that no decarboxylation had taken place. The solution was evaporated and the residue was dissolved in toluene (4 ml) and heated for 4 h under reflux. T.l.c. again indicated that no decarboxylation had taken place.

B. The acid **34** (86 mg) in *N,N*-dimethylformamide (4 ml) and water (0.5 ml) containing potassium hydroxide (16 mg, 2 equiv.), was heated for 20 h under reflux. The mixture was cooled, diluted with ether (40 ml), and washed with 2M hydrochloric acid (25 ml), and then water (6×40 ml). Examination of the ether layer by t.l.c. indicated that only unchanged **34** was present.

*1-Phenyl-3-(2,3,5-tri-*O*-benzyl-α-*D*-ribofuranosyl)pyrazolin-5-one* (**38**). — The ester **10** (110 mg) in benzene (2 ml) was heated for 10 h under reflux with phenylhydrazine (25 mg, 1.02 equiv.). After evaporation the residue was chromatographed on silica gel (4 g). Benzene–ether (49:1) eluted the syrupy pyrazolinone **38** (90 mg, 71%), $[\alpha]_D^{25}$ +30.3° (*c* 1.78 chloroform); ν_{max}^{film} 1724 (C=O), 1602 (C=N), and 907 cm^{-1} (pyrazolinone ring); n.m.r. data (100 MHz, chloroform-*d*): δ 3.36–4.80 (m, 13 H), 4.96 (d, 1 H, $J_{1',2'}$ 6 Hz, H-1'), 7.04–7.48 (m, 18 H, Ar), and 7.68–7.92 (m, 2 H, Ar); *m/e* 562 m (M), 471 m (M−CH_2Ph), 441 w (M−CH_2OCH_2Ph), and 189 m (heterocycle+30).

Anal. Calc. for $C_{35}H_{34}N_2O_5$: C, 74.73; H, 6.05; N, 4.98. Found: C, 74.45; H, 6.03; N, 4.90.

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