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4-AMINO-3-(2,3,5-TRI-*O*-BENZYL-β-D-RIBOFURANOSYL)-5-PYRAZOLECARBONITRILE. SYNTHESIS AND CONVERSION INTO A SUGAR-BLOCKED 5,7-DISUBSTITUTED FORMYCIN ANALOG*

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ABSTRACT

The title compound, a potential intermediate to protected *C*-nucleoside analogs related to formycin A, was synthesized *via* a new route wherein 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrophenyl)-D-ribofuranose was converted to 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allonic acid, and further transformed into 4-(*tert*-butyloxycarbonyl)-5-ethoxycarbonyl-3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole. After amidation and dehydration to form the 4-(*tert*-butyloxycarbonyl)-5-pyrazolecarbonitrile, acidolysis followed by a Curtius-type sequence afforded the 4-amino-5-pyrazolecarbonitrile nucleoside. Treatment of the latter with nitrous acid and copper chloride in a Sandmeyer-type reaction gave a diazonitrile rather than a chloronitrile. Attempts to convert either the aminonitrile or the diazonitrile to 5,7-diamino-3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine (5-aminoformycin A) by condensation with guanidine or *N,N*-dimethylguanidine were unsuccessful. Condensation of the aminonitrile with carbon disulfide in pyridine provided access to the formycin system in the form of 3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine-5,7-dithione.

INTRODUCTION

4-Amino-3-(β-D-ribofuranosyl)-5-pyrazolecarbonitriles having protected sugar hydroxyl groups are key intermediates for the chemical preparation of the *C*-nucleoside antibiotic formycin A (Ref. 1). Three independent routes to these pyrazole intermediates have been described[2–4]. In the synthesis of the 2,3,5-tri-*O*-benzoyl derivative **1** according to Kalvoda[2], the ring was constructed from the acyl cyanide **4**. In the approach developed by Acton and Ryan[3] as an extension of earlier work by Farkaš and Šorm[4], the 2,3,5-tri-*O*-benzyl derivative **2** was prepared *via*

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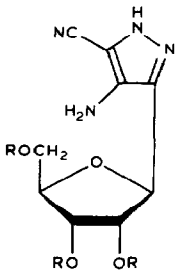
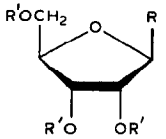


1 R = Bz
2 R = Bzl
3 R = Ac



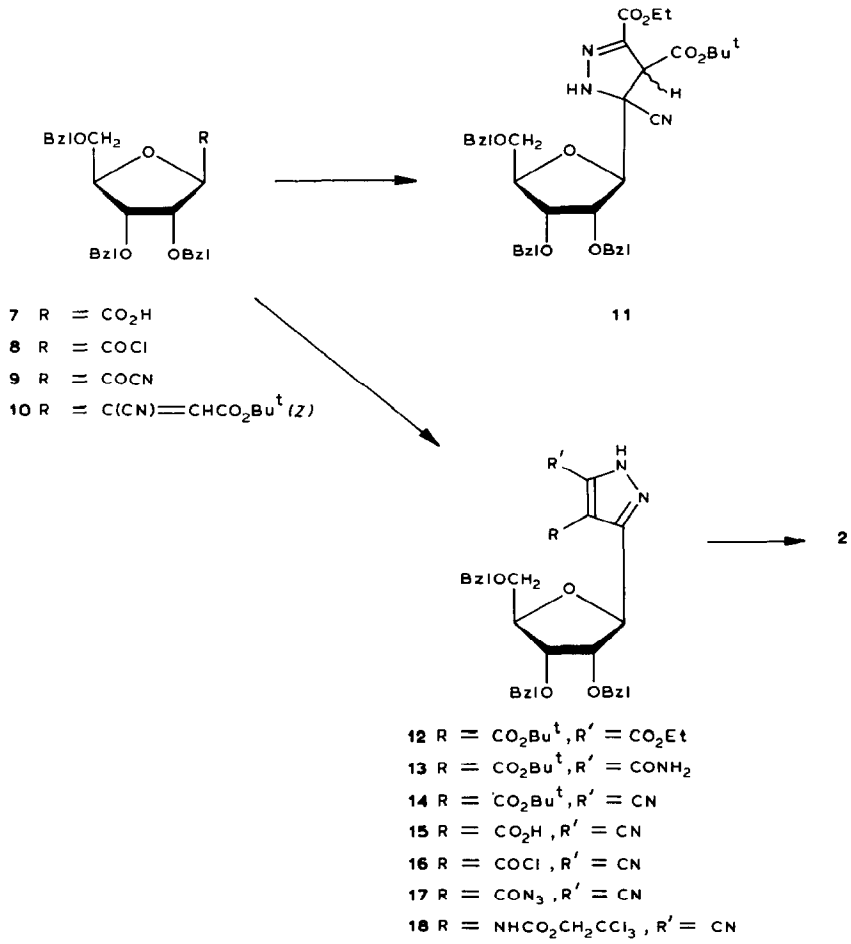
4 R = COCN, R' = Bz
5 R = CHN_2, R' = Bzl
6 R = C≡CCH$(OEt)_2$, R' = Bzl

2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-diazo-D-allitol (**5**). In the scheme devised by Buchanan *et al.*[5], the blocked acetylenic sugar **6** was transformed into 1,4-dinitro-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole which, on further reaction with potassium cyanide, yielded the corresponding 4-nitro-5-pyrazolecarbonitrile by *cine* substitution. Catalytic hydrogenation gave the aminonitrile **3**. The sugar hydroxyl groups were initially protected as benzyl ethers, but the benzyl groups were removed at an early stage and replaced by the more easily cleaved *O*-acetyl group. Reaction of the aminonitriles **1–3** with formamidine, followed by treatment with sodium methoxide[2,4] or, in the case of the benzyl ethers, with boron trichloride[3], led to formycin A.

Large quantities of the tri-*O*-benzyl intermediate **2** were required in connection with work directed toward formycin analogs as potential T-cell-specific antileukemic agents[6]. However, certain aspects of the literature route to **2** prompted us to seek an alternative approach more suitable for large-scale synthesis. In particular, we judged large-scale reactions involving a diazo sugar intermediate[3,4] to be less attractive than those in which the pyrazole ring is elaborated *via* an acyl cyanide[2]. The latter approach seemed amenable to modifications that would permit us to obtain **2** rather than **1**, and we describe herein a new route to **2** based on this concept.

RESULTS AND DISCUSSION

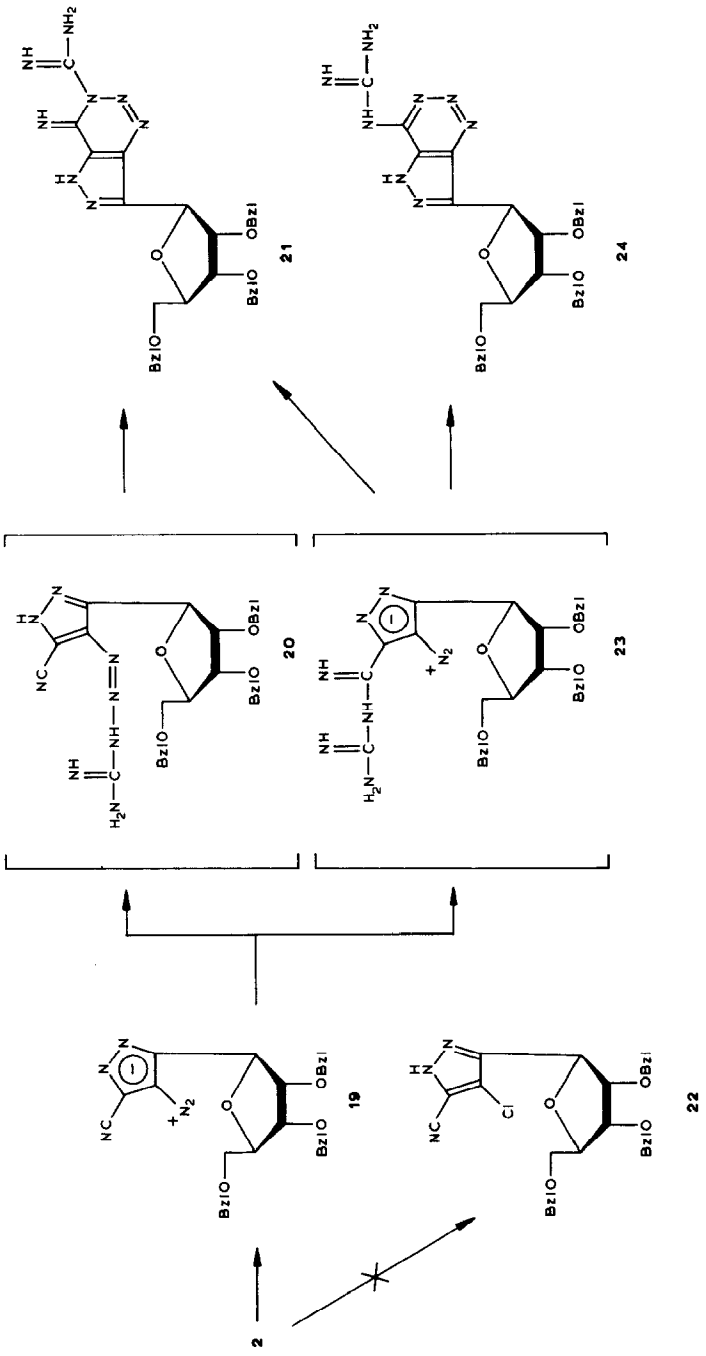
2,3,5-Tri-*O*-benzyl-1-*O*-(*p*-nitrobenzyl)-D-ribofuranose was prepared according to the literature method[7] and converted, *via* a series of standard steps, to the carboxylic acid **7**, acid chloride **8**, and acyl cyanide **9**. It may be noted that **7**, in the form of an ethyl ester, had been prepared previously[8], but by a method different from the one described here. Condensation of **9** with (*tert*-butyloxycarbonylmethylene)triphenylphosphorane afforded the Wittig adduct **10** as a colorless oil, in 75% overall yield after flash chromatography on silica gel. The identity of **10** was evident from its i.r. spectrum, which contained a weak nitrile peak at 2230 cm^{-1},



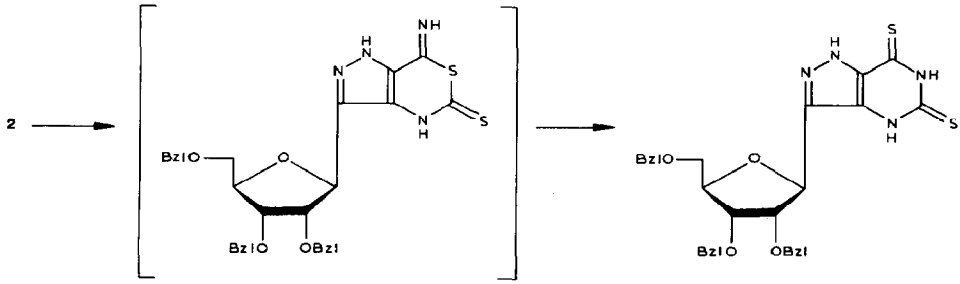
and a strong α,β-unsaturated ester peak at 1720 cm^{-1}. The vinylic proton in **10** was visible in the ^{1}H-n.m.r. spectrum as a broad peak at δ 6.68. The *cis* configuration of ester and nitrile groups was assumed for the double bond on the basis of the earlier finding of Kalvoda[2] that the corresponding 2,3,5-tri-*O*-benzoyl derivative could be converted to a maleimide. Treatment of **10** with ethyl diazoacetate in toluene for 48 h at 60–65° afforded, after silica gel flash-chromatography, a 64% yield of the dihydropyrazole **11** as an apparent mixture of two isomers. Evidence of isomerism was provided by the ^{1}H-n.m.r. spectrum of the analytical sample, which showed overlapping triplets at δ 1.20 and δ 1.23 for the OCH_2CH_3 groups, singlets at δ 2.20 and δ 2.27 for the $CHCO_2R$ protons on the dihydropyrazole ring, and doublets at δ 4.75 (J 4 Hz) and 4.97 (J 4 Hz) for the sugar C-1 protons. The possible presence also of a small proportion of the isomer with the α-D configuration relative to the sugar ring was suggested by a small singlet at δ 5.68. These data were consistent with regioselective but nonstereoselective ring closure in the reaction of **10** with ethyl diazoacetate. Elimination of hydrogen cyanide from **11** occurred readily

in the presence of triethylamine to form the pyrazole diester **12**. Treatment of **12** with ethanolic ammonia afforded the ester amide **13**, which was dehydrated directly with trifluoroacetic anhydride–pyridine in 1,4-dioxane solution to give the ester nitrile **14** (67%). Removal of the *tert*-butyl ester group of **14** was accomplished quantitatively in 20 min by heating in 95–97% formic acid at 60–65°. The acid **15** was converted directly to the acid chloride **16** with oxalyl chloride at 0°, and thereupon to the acyl azide **16** with sodium azide in the presence of tetrabutylammonium iodide, also at 0°. The identity of the acyl azide was evident from the i.r. spectrum which contained the expected peaks at 2260 (CN), 2140 (N_3), and 1750 cm^{-1} (CO_2Et). The azide was heated in toluene at 125° in the presence of 2,2,2-trichloroethanol to obtain, after flash chromatography on silica gel, a 60% overall yield (from **14**) of the carbamate **18** as an oil. Removal of the 2,2,2-trichloroethoxycarbonyl group of **18** was readily accomplished by treatment with zinc dust and ammonium chloride in methanol to obtain the desired amino nitrile **2**. The product was an oil as reported by Acton and Ryan[3], but could be obtained in analytical purity by silica gel flash chromatography using mixtures of ethyl acetate and hexanes as eluents. The presence of a nitrile group was evident in the i.r. spectrum as a strong peak at 2230 cm^{-1}. The β-D configuration was indicated by the presence, in the ^{1}H-n.m.r. spectrum, of a broad doublet at δ 4.99 (J ~3 Hz), with no other signal in this region that could be assigned to an α-D anomer. It appeared that most, if not all, of the α-D anomer present during the synthesis (see above) was removed during the several flash-chromatographic purifications performed along the way.

Since we were interested in converting **2** into 5,7-diamino-1-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazolo[4.3-*d*]pyrimidine, the non-protected form of which had been independently prepared by other routes while this work was in progress[9,10], we attempted to condense the amino nitrile with guanidine but were unsuccessful. Under a variety of reaction conditions, unchanged starting material was recovered or extensive resinification took place. Also unsuccessful, in this case because of extensive acid-catalyzed debenzylation, was the reaction of **2** with chloroformamidine hydrochloride, which we had used earlier with 2-aminothiophene-3-carbonitrile[11]. Similar failure was experienced in attempts to substitute the more reactive synthon *N,N*-dimethylguanidine for guanidine, as described recently by Taylor *et al.*[12] for the transformation of 2-amino-3-cyanopyridine into 2,4-diaminopyrido[2,3-*d*]pyrimidine. It is evident that the amino nitrile system embodied in **2** is not sufficiently reactive to allow a one-step cyclization with guanidines. In light of this finding, we next considered the possibility of converting **2** into the chloronitrile **22**, with the intent of condensing the latter with guanidine as we had successfully done with a 2-chloro-3-cyanopyridine[13]. However, when **2** was treated with *tert*-butyl nitrite in the presence of cupric chloride[14], the only product was an oil, isolated in 74% yield after flash chromatography on silica gel, which proved to be the diazonitrile **19**. The identity of **19** was established from the microanalytical data which showed only a trace of chlorine, and from the i.r. spectrum which contained peaks



at 2250 (CN) and 2200 cm^{-1} (N_2^+). Buchanan *et al.*[15] also observed recently that the action of nitrous acid on a 3-alkyl-4-aminopyrazole-5-carbonitrile can lead to a reasonably stable diazonitrile. Although the lack of formation of a chloronitrile from **2** under Sandmeyer-type conditions was discouraging, we still hoped that **19** could be used to construct the 5,7-diaminopyrazolo[4,3-*d*]pyrimidine system, with molecular nitrogen serving as the leaving group. When equimolar amounts of **19**, guanidine hydrochloride, and potassium *tert*-butoxide were stirred in dry *N,N*-dimethylformamide at room temperature, a red color formed almost immediately. After 45 min, when t.l.c. showed no more starting material, the reaction mixture was worked up, and the major product was purified by flash chromatography to obtain a solid (48% yield) whose u.v. absorption spectrum contained a strong maximum at 321 nm, as compared with the spectrum of **19** which had maxima at 248 and 280 nm, respectively. Elemental analysis was consistent with the molecular formula $C_{31}H_{32}N_8O_4$, whereas the hoped for product required the formula $C_{30}H_{32}N_6O_4$. The apparent presence of two extra nitrogen atoms and one extra carbon atom can be explained if one assumes that guanidine reacted initially with **19** to form a short-lived triazene **20**, which then cyclized into the pyrazolo[4,3-*d*][1,2,3]triazine **21**, or that guanidine first attacked the nitrile group to form the intermediate **23**, which then cyclized to either **21** or the isomeric pyrazolo[4,3-*d*][1,2,3]triazine **24**. Although we favor structure **24** because of the absorbance at 321 nm, no effort to unambiguously assign this structure to the product was made as it clearly was not the compound we had intended to prepare. It was concluded that direct reaction of guanidine with **2** could not provide easy access to 5,7-disubstituted formycin analogs, and that an alternative method had to be used. Successful ring closure was achieved by replacing guanidine with carbon disulfide in refluxing pyridine[15], which led to the sugar-blocked formycin derivative 3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine-5,7-dithione (**26**) in 55% yield. The identity of **26** was established by elemental analysis and on the basis of the u.v. spectrum which contained, as expected from recent data on the corresponding nonprotected nucleoside[10], a long-wavelength absorbance peak at λ_{max} 360 nm for the alkaline solution. The probable mechanism of formation of **26** from **2** involved the intermediate **25** and is analogous to the one proposed by Taylor *et*



al.[16] for the formation of pyrazolo[3,4-*d*]pyrimidine-4,6-dithiones from 5-amino-4-pyrazolecarbonitriles. Studies on the elaboration of **26** to other 5,7-disubstituted formycin derivatives are in progress and will be reported separately.

EXPERIMENTAL

General methods. — I.r. spectra were recorded with a Perkin–Elmer Model 781 double-beam spectrophotometer, u.v. absorption spectra with a Varian Cary Model 210 instrument, and ^{1}H-n.m.r. spectra with a Varian T60A instrument and Me_4Si as the reference. T.l.c. was performed on Whatman MK6F silica gel and Baker 250F silica gel plates containing a fluorescent indicator. Column chromatography was performed on Baker 3405 and Baker "Flash" silica gel. Reagent grade solvents were redistilled and routinely stored over Davison 4A molecular sieves (Fisher Scientific, Boston, MA). Where necessary, dichloromethane and benzene were dried over CaH_2 before being distilled. $Hg(CN)_2$ was oven-dried under reduced pressure before use. Chemicals were purchased from Aldrich (Milwaukee, WI) and Alfa (Beverly, MA). Microchemical analyses were carried out by Galbraith Laboratories, Knoxville, TN.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-*D*-allonic acid* (**7**). — An ice-cold solution of HBr (7.46 g, 0.092 mol) in dichloromethane (186 mL) was added to an ice-cold solution of 2,3,5-tri-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-α,β-D-ribofuranose[7] (48.0 g, 0.084 mol) in dichloromethane (409 mL). The mixture was stirred for 2 min at 0°, the ice bath was removed, and after another 5 min the precipitated *p*-nitrobenzoic acid was quickly filtered and washed on the funnel with dichloromethane (100 mL). The combined filtrate and wash solution were evaporated, and the syrupy residue was taken up in benzene (600 mL). To this solution was added $Hg(CN)_2$ (59.6 g, 0.24 mol) at room temperature, and the mixture was stirred for 3.5 h and filtered. The filtrate was concentrated to dryness, the residue taken up in dichloromethane (750 mL), an additional quantity of inorganic salt removed, and the filtrate washed with 30% KI (3 × 300 mL), rinsed with water, dried (Na_2SO_4), and evaporated to a syrup. Flash chromatography on a silica gel column (75 mm × 450 mm) with 3:2 hexane–ethyl acetate as the eluent gave a fraction containing >90% pure 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allononitrile (22.1 g, 61% yield); ν_{max}^{film} 3100, 3090, 2920, 2870, 1730, 1605, 1590, 1530, 1500, 1450, 1400, 1360, 1330, 1315, 1260, and 1210 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 3.46 (d, 2 H, *J* 4 Hz), 3.86–4.89 (10 H, m), 7.28, 7.34, and 7.36 (15 H, overlapping s). The minor α-D isomer, which was eluted slightly ahead of the β-D isomer, could not readily be distinguished from it on the basis of the chemical shift of the sugar C-1 proton. However, the signals of the aromatic protons of the *O*-benzyl groups in the β-D isomer were all shifted downfield by 0.10–0.15 p.p.m. in comparison with those of the α-D isomer. There were also several important differences in the i.r. fingerprint region, where the three peaks at 1730, 1525, and 1270 cm^{-1} were of markedly higher intensity in the β-D isomer spectrum. The mostly pure β-D isomer (20 g, 0.046 mol) was dissolved

in methanol (30 mL) and the solution stirred while 20% KOH in methanol (125 mL) was added. The mixture was heated to reflux for 3 h, cooled, concentrated under reduced pressure to a volume of 15 mL, and made neutral to pH paper with 6M HCl. After dilution with water (250 mL), the product was extracted into ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to give **7** as a colorless syrup (16.5 g, 79% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 3.34–4.88 (12 H, m), and 7.33 (15 H, apparent s). A portion of the acid was esterified with diazomethane to give the methyl ester; ^{1}H-n.m.r. ($CDCl_3$): δ 3.66 (s, 3 H), 3.33–4.14 (7 H), 4.53 (s, 2 H), 4.59 (s, 2 H), 7.26, and 7.28 (15 H, apparent s). The carboxylic acid was used for the next step without further purification.

tert-*Butyl* (E)-*3-cyano-3-(2,3,5-tri*-O-*benzyl-β*-D-*ribofuranosyl)propenoate* (**10**). — To acid **7** (9.03 g, 0.02 mol) were added consecutively dry ether (80 mL), $SOCl_2$ (19 mL), and dry *N,N*-dimethylformamide (0.05 mL), and the mixture was heated at reflux for 1 h, cooled, and evaporated to dryness under reduced pressure. After removal of trace moisture by codistillation with toluene (3 × 15 mL), cyanotrimethylsilane (12.2 mL, 0.09 mol) was added to the residue, and the mixture was heated in an oil bath for 1.5 h at 70–80°. Volatile materials were removed by rotary evaporation at 80°, and dry benzene (64 mL) was added. The solution was cooled to 0°, and (*tert*-butyloxycarbonylmethylene)triphenylphosphorane (15.3 g, 0.04 mol) was added. After being stirred for 5 min at 0°, the mixture was left to come to room temperature and then stirred for 3 h. The mixture was washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography on silica gel with 7:3 hexane–ethyl acetate to give **10** as an oil (8.4 g, 75%); ν_{max}^{film} 3100–2880, 2230 (weak CN), 1720 (ester C=O), 1640, 1500, 1450, 1395, 1370, 1300, and 1250 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.49 (s, 9 H), 3.58 (br. d, 2 H, *J* 4 Hz), 3.8–4.7 (m, 10 H), 6.68 (br. s, 1 H), and 7.29, 7.33 (2 apparent s, 15 H).

Anal. Calc. for $C_{34}H_{37}NO_6$: C, 73.48; H, 6.72; N, 2.52. Found: C, 73.98; H, 6.81; N, 2.08.

*4-*tert-*Butyloxycarbonyl-5-cyano-3-ethoxycarbonyl-4,5-dihydro-5-(2,3,5-tri*-O-*benzyl-β*-D-*ribofuranosyl)pyrazole* (**11**). — To nitrile ester **10** (5.2 g, 9.36 mmol) were added dry toluene (35 mL) and ethyl diazoacetate (6.2 mL). The mixture was heated for 48 h at 60–65°, and concentrated to dryness by rotary evaporation. Volatile materials were removed by codistillation with xylene (3 × 20 mL), and the residue was purified by flash chromatography on silica gel with 7:3 hexane–ethyl acetate to give **11** as a thick oil (4.04 g, 64%); ν_{max}^{film} 3300, 3100–2800, 2250 (very weak CN), 1740 (ester C=O), 1590, 1500, 1450, 1370, and 1250–1220 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.20 1.23 (2 overlapping t, 3 H), 1.49 (s, 9 H), 2.20, 2.27 (2 s, 1 H), 3.64 (br. d, 2 H, *J* 5 Hz), 3.9–4.7 (m, 11 H), 4.75, 4.97 (2 d, 1 H), and 7.28, 7.29 (2 apparent d, 15 H).

Anal. Calc. for $C_{38}H_{43}N_3O_8 \cdot 0.5\ H_2O$: C, 67.24; H, 6.53; N, 6.19. Found: C, 67.32; H, 6.42; N, 5.87.

*4-*tert-*Butyloxycarbonyl-5-ethoxycarbonyl-3-(2,3,5-tri*-O-*benzyl-β*-D-*ribofuranosyl)pyrazole* (**12**). — Triethylamine (2.18 mL) was added to a solution of

nitrile **11** (4.04 g, 6.03 mmol) in toluene (7.2 mL), and the mixture was stirred for 3 h at room temperature and concentrated to dryness. The last traces of volatile materials were coevaporated with toluene (3 × 20 mL) to give an oil (3.8 g, 98% yield). Analytically pure **12** was obtained by flash chromatography on silica gel with 3:2 hexane–ethyl acetate; ν_{max}^{film} 3320, 3120–2890, 1750 (ester C=O), 1700, 1560, 1490, 1400, and 1370 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.49 (t, 3 H), 1.56 (s, 9 H), 3.2–4.7 (m, 11 H), 4.89 (s, 2 H), 5.66 (s, 1 H), and 6.9–7.6 (br. s, 15 H).

Anal. Calc. for $C_{34}H_{37}NO_6$: C, 69.15; H, 6.54; N, 4.36. Found: C, 69.10; H, 6.71; N, 4.31.

*4-*tert*-Butyloxycarbonyl-5-cyano-3-(2,3,5-tri-*O*-benzyl-β-*D*-ribofuranosyl)pyrazole* (**14**). — To diester **12** (3.7 g, 5.7 mmol) were added dry methanol (20 mL) and liquid NH_3 (40 mL), and the mixture was kept in a Teflon-lined pressure autoclave (Berghof-America, Raymond, NH) for 5 days. After the NH_3 was allowed to evaporate in the hood, the methanol was removed under reduced pressure to give amide **13** (3.5 g, 99% yield) as a low-melting solid, m.p. 45–53°; ν_{max}^{KBr} 3400–2860, 1680, 1600, 1495, 1450, 1390, 1370, 1320, 1250, and 1205 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.56 (s, 9 H), 3.28–4.96 (m, 12 H), 5.58 (d, 1 H, *J* 4 Hz), 6.66 (br. s, 2 H), and 7.24 (s, 15 H). The amide (2.9 g, 4.7 mmol) was dissolved directly in 1,4-dioxan (10 mL) containing pyridine (2.5 mL), and the solution cooled in an ice–salt bath. Trifluoroacetic anhydride (1.9 mL, 13 mmol) was added dropwise over 25 min, so that the internal temperature remained at 0–5°. The mixture was stirred for 1 h at 0°, and then kept overnight at room temperature. A few chips of ice were added, followed by ethyl acetate (100 mL). The organic layer was washed with saturated NaCl, dried (Na_2SO_4), and evaporated. Flash chromatography on silica gel with 7:3 hexane–ethyl acetate gave **14** as an oil (1.9 g, 67% yield); ν_{max}^{film} 3410, 3200, 3060–2865, 2250 (CN), 1700, 1570, 1500, 1455, 1400, 1370, 1360, 1345, 1300, 1260, and 1210 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 3.49–4.43 (m, 7 H), 4.53 (d, 2 H, *J* 3 Hz), 4.89 (s, 2 H), 5.66 (s, 1 H), and 6.79–7.53 (m, 15 H).

Anal. Calc. for $C_{35}H_{37}N_3O_6$: C, 70.58; H, 6.21; N, 7.08. Found: C, 70.15; H, 6.25; N, 6.93.

*5-Cyano-3-(2,3,5-tri-*O*-benzyl-β-*D*-ribofuranosyl)-4-(2,2,2-trichloroethoxycarbanoyl)pyrazole* (**18**). — To nitrile **14** (2.57 g, 4.31 mmol) was added 95–97% formic acid (12.3 mL), and the solution heated for 20 min at 60–65°. After evaporation of the mixture to dryness under reduced pressure, water (50 mL) was added, and the product extracted with ethyl acetate (2 × 75 mL). The organic layer was washed with concentrated NaCl, dried ($MgSO_4$), and evaporated to give **15** (2.3 g, 99% yield); ν_{max}^{film} 3190–2860, 2240 (CN), 1730, 1570, 1490, 1450, 1360, 1250, and 1210 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 3.3–5.0 (m, 13 H), 5.60 (s, 1 H), and 7.19 (2 apparent s, 15 H). To a magnetically stirred solution of **15** (2.42 g, 4.48 mmol) in dry benzene (29 mL) was added oxalyl chloride (2.9 mL). The mixture was heated for 2 h at reflux and concentrated to dryness by rotary evaporation. To the residue (**16**) was added dichloromethane (29 mL) and the solution cooled to 0°. To this cold solution were then added tetrabutylammonium iodide (10 mg) and a solution of

NaN_3 (0.36 g, 5.38 mmol) in water (4.9 mL) at 0°. The resulting heterogeneous mixture was stirred for 2 h at 0°, and the organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to give azide **17** (2.14 g); ν_{max}^{film} 3200–2900, 2260 (CN), 2180, 2140 (N_3), 1730 (ester C=O), 1690, 1560, 1500, 1460, 1360, and 1250 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 3.4–5.0 (m, 12 H), 5.63 (s, 1 H), and 7.18, 7.24 (2 apparent s, 15 H). The crude azide was taken up in toluene (30 mL) and trichloroethanol (7 mL) was added. The mixture was heated for 3.5 h at 125°, cooled, washed with water, dried ($MgSO_4$), and evaporated to dryness. The product was purified by flash chromatography on silica gel with 4:1, followed by 7:3 hexane–ethyl acetate to give **18** as an oil (1.82, 60% yield); ν_{max}^{film} 3240–2860, 2240 (strong CN), 1750 (carbamate C=O), 1600, 1490, 1450, 1360, and 1220 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 3.3–4.5 (m, 9 H), 4.56 (s, 4 H), 4.74 (br. s, 2 H), 5.18 (br. d, 1 H), and 7.26, 7.29 (2 apparent s, 15 H).

Anal. Calc. for $C_{33}H_{31}Cl_3N_4O_6$: C, 57.63; H, 4.52; Cl, 15.53; N, 8.16. Found: C, 57.63; H, 4.75; Cl, 15.37; N, 7.89.

*4-Amino-5-cyano-3-(2,3,5-tri-*O*-benzyl-β-*D*-ribofuranosyl)pyrazole* (**2**). — To a solution of carbamate **18** (2.9 g, 4.23 mmol) in methanol (122 mL) were added Zn dust (20.5 g) and NH_4Cl (6.83 g). The mixture was heated for 1.5 h at reflux, and the unreacted Zn was filtered and washed several times with methanol. The combined filtrate and washed solutions were concentrated to dryness, and to the residue were added water (154 mL), conc. NH_4OH (58 mL), and benzene (232 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated to an oil (2.13 g, 98% yield); ν_{max}^{film} 3500–2700, 2230 (CN), 1730, 1640–1590, 1530, 1490, 1450, and 1360 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 3.26 (br. s, 2 H), 3.39–4.31 (br. d, 6 H), 4.99 (br. d, 1 H), and 7.24, 7.26 (2 apparent s, 15 H). An analytical sample was prepared by flash chromatography on silica gel with 1:1 hexane–ethyl acetate.

Anal. Calc. for $C_{30}H_{30}N_4O_4$: C, 70.58; H, 5.88; N, 10.98. Found: C, 70.79; H, 5.93; N, 11.04.

*5-Cyano-4-diazo-3-(2,3,5-tri-*O*-benzyl-β-*D*-ribofuranosyl)pyrazole* (**19**). — To a magnetically stirred suspension of anhydrous $CuCl_2$ (280 mg, 2.14 mmol; dried for 18 h at 100° prior to use) in acetonitrile (3.1 mL) was added *tert*-butyl nitrite (0.31 mL, 2.52 mmol). The mixture was heated at 55–60°, and to the hot solution was added a solution of aminonitrile **2** (650 mg, 1.28 mmol) in acetonitrile (3.1 mL) over 10 min. The reaction was monitored by t.l.c. (silica gel, 7:3 hexane–ethyl acetate) until disappearance of the aminonitrile was complete. The reaction mixture was cooled to room temperature, poured into M HCl (15 mL), and extracted with ethyl acetate. The organic layer was washed with saturated NaCl, dried ($MgSO_4$), and evaporated to dryness. The residue was purified by flash chromatography on silica gel (1:1 hexane–ethyl acetate) to give **19** as a pale-yellow syrup (470 mg, 74% yield); ν_{max}^{film} 3100–2850, 2250 (CN), 2200 (N_2^+), 1610, 1590, 1500, 1450, and 1370 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 3.3–4.6 (m, 10 H), 4.73 (s, 2 H), 5.31 (d, 1 H, *J* 2 Hz), and 7.23, 7.31 (2 apparent s, 15 H).

Anal. Calc. for $C_{30}H_{27}N_5O_4$: C, 69.06; H, 5.23; N, 13.44. Found: C, 68.54; H, 5.22; N, 13.22.

Condensation of **19** *with guanidine.* — To a mixture of diazonitrile **19** (142 mg, 0.27 mmol) and guanidine hydrochloride (25 mg, 0.26 mmol) in dry *N,N*-dimethylformamide (1.5 mL) was added dry potassium *tert*-butoxide (30 mg, 0.26 mmol), and the mixture was stirred for 45 min at room temperature. The solvent was removed by rotary evaporation, and water (100 mL) was added to the residue. After extraction with chloroform (2 × 50 mL), the organic layer was dried ($MgSO_4$) and evaporated. The product was purified by flash chromatography on silica gel with chloroform, then 19:1, and finally 9:1 chloroform–methanol; yield 69 mg (48%); ν_{max}^{KBr} 3320–3100, 1690, 1600, 1550–1450, 1400, and 1200 cm^{-1}; λ_{max}^{MeOH} 321 nm (ε 24 640), and 244 sh (4 800); ^{1}H-n.m.r. ($CDCl_3$): δ 3.5–4.8 (m, 15 H), 5.29 (br. d, 1 H, *J* 4 Hz), 7.04, and 7.33 (2 apparent s, 15 H).

Anal. Calc. for $C_{31}H_{32}N_8O_4 \cdot 0.25\ H_2O$: C, 63.62; H, 5.61; N, 19.15. Found: C, 63.80; H, 5.74; N, 19.12.

*3-(2,3,5-Tri-*O*-benzyl-β-*D*-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine-5,7-thione* (**26**). — A mixture of the aminonitrile **2** (261 mg, 0.5 mmol), CS_2 (5 mL), 4-(*N,N*-dimethylamino)pyridine (20 mg), and anhydrous pyridine (5 mL) was heated for 4 days under reflux, at which time t.l.c. (silica gel, 49:1 chloroform–methanol) indicated complete disappearance of the starting material (R_F 0.45) and formation of a single, new yellow spot (R_F 0.55). Solvents were removed by rotary evaporation at 40° to give a yellow solid, which was taken up directly in M NaOH (8 mL) with a small amount of methanol being added to bring about complete solution. The solution was refluxed for 2 h, and then evaporated to dryness under reduced pressure. Chromatography of the residue on silica gel with chloroform as the eluent afforded a yellow solid (161 mg, 55%), m.p. 265–266° (methanol); ν_{max}^{KBr} 3420, 3160, 1610, 1580, 1520, 1495, 1455, 1400, 1360, 1300, 1225, and 1200 cm^{-1}; λ_{max} 270 (pH 11) (ε 23 200), 318 sh (11 100), and 365 nm (6980); ^{1}H-n.m.r. ($CDCl_3$): δ 3.2–4.6 (complex m, 11 H), 5.23 (s, 1 H, *J* 6.5 Hz), and 7.2, 7.3 (2 apparent s, 15 H).

Anal. Calc. for $C_{31}H_{30}N_4O_4S_2$: C, 63.46; H, 5.15; N, 9.55; S, 10.92. Found: C, 63.55; H, 5.41; N, 9.65; S, 11.16.

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