Carbohydrate Research, 159 (1987) 81–94
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

IMPROVED AND LARGE-SCALE SYNTHESIS OF CERTAIN GLYCOSYL CYANIDES. SYNTHESIS OF 2,5-ANHYDRO-5-THIO-D-ALLONONITRILE

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(Received April 22nd, 1986; accepted for publication in revised form, July 25th, 1986)

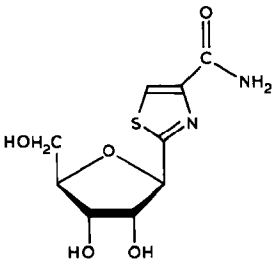
ABSTRACT

The first synthesis of 2,5-anhydro-5-thio-D-allononitrile starting with L-lyxose, *via* a trifluoromethanesulfonic ester intermediate, has been accomplished. Methods have been developed to achieve a large-scale synthesis of 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-D-*talo*-heptononitrile (**5**). An improved procedure has been developed to synthesize 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-gulononitrile (**9**). The structures of **5** and the thioamide derivative from **9**, 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-gulonothioamide, were confirmed by X-ray crystallographic analysis.

INTRODUCTION

Glycosyl cyanides are among the most useful carbon-linked derivatives of carbohydrates, and have been extensively used in the synthesis of novel, carbon-linked nucleosides[1] and enzyme antagonists[2].

We have synthesized both tiazofurin‡ (2-β-D-ribofuranosylthiazole-4-carboxamide[3]) (**1**), and selenazofurin‡ (2-β-D-ribofuranosylselenazole-4-carbox-



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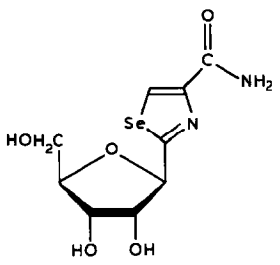

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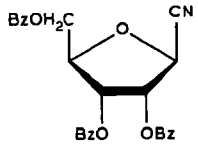

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‡Generic names given to compounds **1** and **2**, respectively.

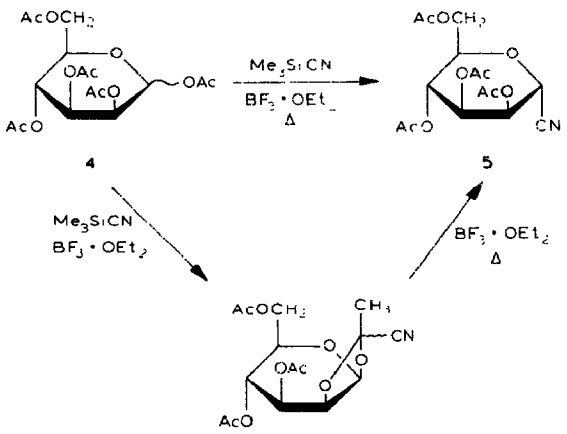
0008-6215/87/$ 03.50

amide[4]) (**2**) from 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allononitrile[5] (2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide) (**3**). Numerous analogs of **1** and **2** have been synthesized by us[6] and others[7].

These syntheses invariably began with the glycosyl cyanide **3**. A rapid, facile, large-scale synthesis of **3** has recently been reported by Cook and McNamara[8]. We have now developed methods for a large-scale synthesis of 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-D-*talo*-heptononitrile (**5**) (2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl cyanide). We have also developed improved procedures for synthesizing 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-gulononitrile (2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyl cyanide) (**9**). The first synthesis of 2,5-anhydro-5-thio-D-allononitrile (4-thio-β-D-ribofuranosyl cyanide) (**15**) from L-lyxose has been accomplished. These procedures and pertinent X-ray crystallographic data used in confirming the structures of compounds **5** and **9** are now reported.

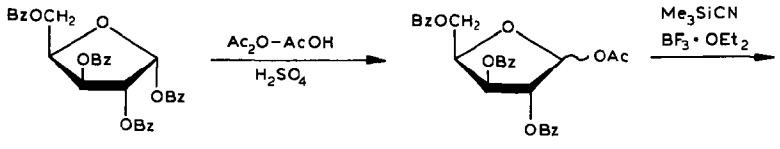
RESULTS AND DISCUSSION

The large-scale preparation of 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-D-*talo*-heptononitrile[9] (**5**) involved the reaction of three equivalents of trimethylsilyl cyanide with 1,2,3,4,6-penta-*O*-acetyl-D-mannopyranose (**4**). Use of the polar aprotic solvent, nitromethane and the stronger Lewis acid boron trifluoride in place of dichloromethane and stannic chloride, respectively, was consistent with previously reported observations for acetylated *versus* benzoylated substrates[9,10]. It was also found necessary to elevate the reaction temperature slightly (35–37°) in order to destabilize the cyanoethylidene by-products **6a,b** and hasten their conversion into the desired "α nitrile" **5**. Chromatographic purification of **5** yielded, after evaporation of solvent *in vacuo*, a clear syrup which, on standing, produced large crystals having a melting point different from that reported for this compound[9]. Recrystallization from ethanol did not change the melting point. Proton- and ^{13}C-



n.m.r. data, as well as optical rotation, were in agreement with those reported[9]. X-Ray analysis of the crystalline material *(vide infra)* unambiguously confirmed the structure in detail. This procedure provided a significantly higher yield (51% *vs.* 37%) than previously reported[9], and the product was not contaminated with any of the corresponding "β" isomer[9].

Synthesis of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-gulononitrile[11] (**9**) involved the preparation of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-xylofuranose (**8**). Here again, significant improvements were made over the procedures reported[12]. It was dis-



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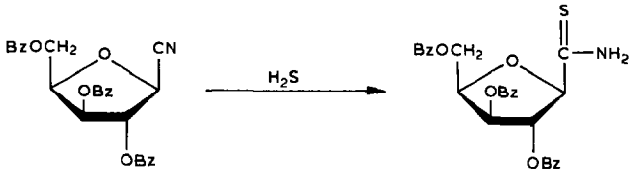


9 10

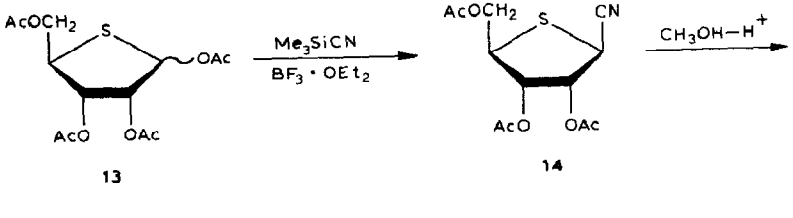
covered that commercially available 1,2,3,5-tetra-*O*-benzoyl-α-D-xylofuranose* (**7**) could also be converted, almost quantitatively into **8** by an acid-catalyzed transformation. Compound **8** was efficiently converted into **9** (90% yield) by cyanotrimethylsilane in nitromethane, with boron trifluoride as the catalyst. The previously reported procedure[11] gave a 35% yield of **9** from 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl bromide. The nitrile **9** could not be so crystallized as to yield crystals suitable for X-ray crystallographic studies. Hence, **9** was treated with hydrogen sulfide in 1,4-dioxane–ethanol, to provide the thioamide **10**, which yielded crystals suitable for X-ray analysis *(vide infra)*.

The hitherto unknown 2,5-anhydro-5-thio-D-allononitrile (**15**) was an intermediate needed in a concurrent project. Application of this method to the synthesis of **15** also permitted examination of the effect of a sulfur atom in the furanose ring on the cyanidation process. Methyl 4-*S*-acetyl-2,3-*O*-isopropylidene-4-thio-β-D-ribopyranoside (**12**) was synthesized by an improved procedure from methyl 2,3-*O*-isopropylidene-α-L-lyxopyranoside[13] *via* the trifluoromethanesulfonic (triflic) ester[14] **11**. Use of the triflate group to activate secondary hydroxyl groups in carbohydrates towards nucleophilic displacement has been shown to be very effective[15]. Displacement of the triflate group in **11** with potassium thioacetate occurred within

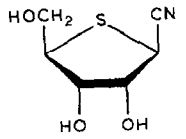
*Available from Sigma Chemical Company.


CF3SO2O
OMe
AcS⁻ K⁺
DMF, 23°
AcS
CMe2

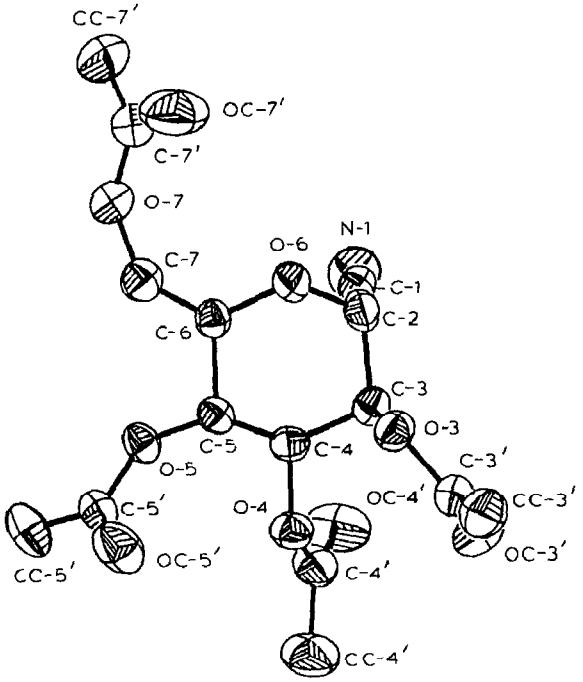
11 12


AcOCH2
OAc
Me3SiCN
BF3 · OEt2
CN
CH3OH—H⁺
AcO
OAc

13 14


HOCH2
CN
HO
OH

15


CC-7′
OC-7′
C-7′
O-7
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O-6
N-1
C-1
C-2
C-6
C-3
O-3
C-5
C-4
O-5
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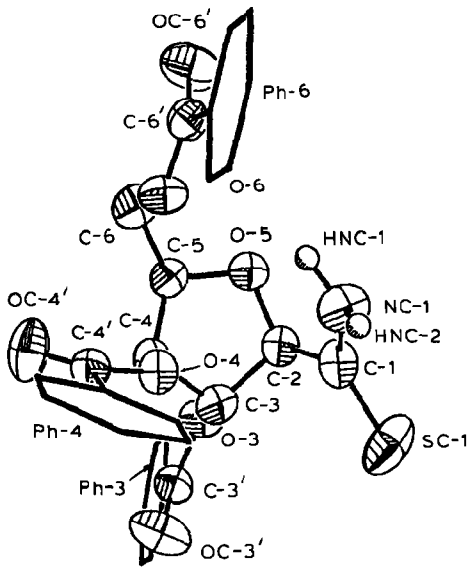
OC-3′
C-4′
CC-4′



2 h at 23° in *N,N*-dimethylformamide (DMF). In contrast, the corresponding *p*-toluenesulfonic ester[13] required 24 h at 105° to be displaced by potassium thioacetate. The methyl glycoside **12** was converted into 1,2,3,5-tetra-*O*-acetyl-4-thio-D-ribofuranose (**13**) by the procedure reported[13]. Conversion of ester **13** into 3,4,6-tri-*O*-acetyl-2,5-anhydro-5-thio-D-allononitrile (**14**) was accomplished in 79% yield with three equivalents of trimethylsilyl cyanide in nitromethane, with boron trifluoride as the catalyst. Deprotection of **14** with methanolic hydrogen chloride at 0° gave 2,5-anhydro-5-thio-D-allononitrile (**15**) in 46% yield.

Computer drawings of the structures of 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-D-*talo*-heptononitrile (**5**) and 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-gulonothioamide (**10**) are respectively shown in Figs. 1 and 2, which include the atom numbering. Tables I and II contain the positional parameters and the equivalent, isotropic, thermal parameters for the atoms of the two structures. It is clear from the Figures that the anomeric configuration of **5** is α, whereas that of **10** is β. The six-membered sugar ring of **5** is in the $^4C_1$ conformation. The five-membered sugar ring of **10** has the ^3E conformation. Selected bond-lengths and angles of **5** are given in Table III, and similar data for **10** in Table IV.

Compound **5** contains no hydrogen atoms that can participate in hydrogen bonds, and **10** contains only two such hydrogen atoms, HNC-1 and HNC-2. The atom HNC-2 is involved in an intermolecular hydrogen-bond with SC-1. The important hydrogen-bond parameters are NC-1 ... SC-1 (translation of SC-1 is $2 - x, y, 2 - z$) 3.416(5) Å HNC-2 ... SC-1, 2.519(4) Å, and NC-1–HNC-2 ... SC-1 forms an angle of 171.5(1)°. The uncertainties in the last two quantities are misleading as, during the refinement, the hydrogen atoms of NC-1 were allowed to ride on

TABLE I

POSITIONAL PARAMETERS ($\times 10^5$) AND THERMAL PARAMETERS ($\times 10^3$) FOR **5**, WITH E.S.D. VALUES IN PARENTHESES

Atom	x	y	z	U
C-1	2177(4)	8378(3)	2149(2)	53(1)[a]
N-1	904(4)	8411(3)	2276(2)	75(1)[a]
C-2	3865(3)	8394(2)	1957(2)	43(1)[a]
C-3	4227(3)	9441(2)	1490(2)	40(1)[a]
O-3	5872(2)	9540(1)	1472(1)	43(1)[a]
C-3′	6465(3)	10545(2)	1573(2)	48(1)[a]
OC-3′	5689(3)	11332(2)	1607(2)	67(1)[a]
CC-3′	8175(3)	10502(3)	1623(2)	60(1)[a]
HC-31	8601	11092	1932	58
HC-32	8483	10554	1046	58
HC-33	8545	9839	1854	58
C-4	3574(3)	9370(2)	604(2)	39(1)[a]
O-4	3964(2)	10287(1)	111(1)	46(1)[a]
C-4′	2940(4)	11109(2)	111(2)	54(1)[a]
OC-4′	1829(3)	11116(2)	547(2)	90(1)[a]
CC-4′	3448(5)	11970(3)	−468(3)	82(2)[a]
HC-41	2603	12430	−615	89
HC-42	3781	11582	−955	89
HC-43	4284	12396	−257	89
C-5	4152(3)	8381(2)	156(2)	36(1)[a]
O-5	3335(2)	8268(2)	−621(1)	40(1)[a]
C-5′	4062(3)	8554(2)	−1350(2)	42(1)[a]
OC-5′	5366(2)	8858(2)	−1356(1)	64(1)[a]
CC-5′	3015(4)	8428(3)	−2076(2)	64(1)[a]
HC-51	3473	8645	−2596	65
HC-52	2128	8865	−1964	65
HC-53	2709	7689	−2112	65
C-6	3754(3)	7386(2)	680(2)	36(1)[a]
C-7	4421(3)	6372(2)	302(2)	45(1)[a]
HC-71	5434	6255	526	47
HC-72	4483	6452	−296	47
O-7	3466(2)	5468(2)	498(1)	49(1)[a]
C-7′	3938(4)	4782(3)	1081(2)	57(1)[a]
OC-7′	5163(3)	4839(2)	1430(2)	96(1)[a]
CC-7′	2738(5)	3948(3)	1250(3)	82(2)[a]
HC-71	3220	3271	1367	86
HC-72	2058	3872	779	86
HC-73	2160	4176	1732	86
O-6	4363(2)	7482(1)	1505(1)	43(1)[a]
HC-2	4428	8366	2475	39
HC-3	3778	10056	1759	41
HC-4	2475	9336	666	38
HC-5	5242	8445	69	35
HC-6	2651	7341	691	35

[a] U_{eq} is one-third the trace of the orthogonalized U_{ij} tensor.

NC-1. Another possible hydrogen bond involves the atoms NC-1–HNC-1 ... O-5. However, it is doubtful that there is a hydrogen bond involving these atoms, as the NC-1–HNC-1 ... O-5 angle is 102.9°.

EXPERIMENTAL

General methods. — Melting points were determined on a Thomas–Hoover, capillary melting-point apparatus and are uncorrected. Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ. Thin-layer chromatography (t.l.c.) was conducted on aluminum-backed plates of silica gel 60 F-254 (EM Reagents). Detection of components in t.l.c. was by u.v. light, and with 10% H_2SO_4 in MeOH spray, followed by heating. Preparative-scale chromatography was performed by flash-chromatography techniques, silica gel (J. T. Baker; ~40 μm) or Kiesel gel 60 (EM Reagents; 40–63 μm) being used. Evaporations were conducted under diminished pressure, with the bath temperature below 35°. 90-MHz ^{1}H-N.m.r. spectra were recorded with a JEOL FX-90Q spectrometer. ^{13}C-N.m.r. spectra were recorded at 22.5 MHz with the same instrument. The chemical-shift values are expressed in δ values relative to tetramethylsilane as the internal standard.

X-Ray crystallography. — Suitable crystals of 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-D-*talo*-heptononitrile (**5**) and 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-gulonothioamide (**10**) were selected to be studied by X-ray diffraction. Data were obtained by using a Nicolet R3 autodiffractometer with a graphite monochromator. Copper radiation (1.54178 Å) was used in the study of **5**, and molybdenum radiation (0.71073 Å) in the structure determination of **10**. In each case, the lattice parameters were obtained by a least-squares technique involving several, centered, 2θ values. Crystal and other experimental data are summarized in Table V. Single-crystal intensity-data were collected by using a variable-speed, $\theta - 2\theta$ scan procedure. Data for which $I < 2\sigma(I)$ were considered unobserved. Trial structures for the two compounds were obtained by using the direct-methods program SOLV of the SHELXTL[16] computer-program package. The structures were refined by using a cascading, least-squares method. All non-hydrogen atoms of the two structures were refined anisotropically. Positions for all hydrogen atoms of both structures, except the amide hydrogen atoms HNC-1 and HNC-2 of **10**, were calculated based on geometrical considerations. The hydrogen atoms of the terminal methyl groups of **5** were refined as rigid bodies and the other hydrogen atoms were allowed to "ride" on their neighboring carbon atoms during the refinement process. Positions of HNC-1 and HNC-2 of **10** were obtained from a difference map, and these two atoms were allowed to "ride" on NC-1 during refinement. HNC-1 and HNC-2 were refined isotropically, and the temperature factors of the other hydrogen atoms were set at values 1.2 times the initial U_{eq} of the neighboring carbon atoms. The resulting, residual values are included in Table I. Weights were based on counting statistics, and had the form $w = 1/2(F) + G(F2)$, with $G = 3.6 \times 10^{-4}$ and 2.5×10^{-4}

TABLE II

POSITIONAL PARAMETERS ($\times 10^4$) AND THERMAL PARAMETERS ($\times 10^3$) FOR **10**, WITH E.S.D VALUES IN PARENTHESES

Atom	x	y	z	*U*
C-1	9191(1)	6037(6)	8996(3)	50(1)[a]
SC-1	9656(1)	6059(3)	8256(1)	86(1)[a]
NC-1	9216(1)	6442(5)	10077(2)	67(1)[a]
HNC-1	8911	6340	10514	119(17)
HNC-2	9506	6219	10528	88(14)
C-2	8676(1)	5533(5)	8403(3)	44(1)[a]
C-3	8653(1)	3651(5)	8022(2)	45(1)[a]
O-3	8343(1)	3566(4)	6926(2)	50(1)[a]
C-3′	8441(1)	2267(6)	6233(3)	49(1)[a]
OC-3′	8762(1)	1234(5)	6502(2)	85(1)[a]
CB-31	8116(1)	2316(5)	5109(3)	41(1)[a]
CB-32	8241(1)	1289(6)	4237(3)	52(1)[a]
HB-32	8532	590	4361	57
CB-33	7940(1)	1287(6)	3185(3)	59(1)[a]
HB-33	8026	591	2574	63
CB-34	7522(1)	2262(6)	3008(3)	55(1)[a]
HB-34	7315	2243	2278	61
CB-35	7399(1)	3267(6)	3873(3)	57(1)[a]
HB-35	7102	3943	3746	60
CB-36	7696(1)	3319(6)	4927(3)	50(1)[a]
HB-36	7612	4045	5526	53
C-4	8397(1)	2774(5)	8916(3)	45(1)[a]
O-4	8789(1)	2385(4)	9843(2)	45(1)[a]
C-4′	8724(1)	1035(5)	10525(3)	45(1)[a]
OC-4′	8347(1)	231(4)	10448(2)	73(1)[a]
CB-41	9170(1)	718(5)	11378(3)	44(1)[a]
CB-42	9610(1)	1543(7)	11348(4)	75(2)[a]
HB-42	9644	2352	10751	87
CB-43	10005(2)	1193(8)	12187(4)	103(2)[a]
HB-43	10310	1792	12178	103
CB-44	9972(2)	12(6)	13034(4)	88(2)[a]
HB-44	10252	−243	13597	92
CB-45	9533(2)	−791(8)	13057(3)	74(2)[a]
HB-45	9502	−1594	13659	81
CB-46	9133(1)	−475(6)	12239(3)	56(1)[a]
HB-46	8828	−1074	12259	59
C-5	8052(1)	4181(6)	9212(3)	44(1)[a]
C-6	7844(1)	4155(7)	10316(3)	56(1)[a]
HC-61	7684	3074	10388	54
HC-62	7608	5067	10310	54
O-6	8229(1)	4382(4)	11284(2)	51(1)[a]
C-6′	8145(1)	5530(6)	12085(3)	49(1)[a]
OC-6′	7787(1)	6430(4)	12005(2)	77(1)[a]
CB-61	8547(1)	5518(5)	13092(3)	43(1)[a]
CB-62	8965(1)	4513(7)	13125(3)	63(2)[a]
HB-62	9013	3831	12473	72
CB-63	9315(2)	4496(8)	14103(3)	78(2)[a]
HB-63	9606	3801	14130	86
CB-64	9245(2)	5478(7)	15036(4)	79(2)[a]
HB-64	9485	5457	15717	82

Table II (continued)

Atom	x	y	z	*U*
CB-65	8834(2)	6483(7)	14992(3)	78(2)[a]
HB-65	8790	7181	15639	83
CB-66	8481(1)	6504(6)	14026(3)	61(2)[a]
HB-66	8191	7202	14006	72
O-5	8315(1)	5765	9136(2)	49(1)[a]
HC-2	8610	6270	7746	48
HC-3	8967	3148	7957	48
HC-4	8218	1735	8709	47
HC-5	7757	4005	8678	50

[a]U_{eq} value is one-third the trace of the orthogonalized U_{ij} tensor.

TABLE III

SELECTED BOND-LENGTHS (Å) AND ANGLES (DEG) IN **5**. VALUES IN PARENTHESES FOR INDIVIDUAL BOND-LENGTHS AND ANGLES ARE E.S.D. VALUES; VALUES IN PARENTHESES FOR AVERAGE BOND-DISTANCES ARE CALCULATED, STANDARD DEVIATIONS

1	*2*	*3*	*1-2 (Å)*	*1-2-3 (deg)*
N-1	C-1	C-2	1.124(5)	176.8(3)
C-1	C-2	C-3	1.497(5)	108.1(2)
C-2	C-3	C-4	1.535(4)	108.9(2)
O-3	C-3	C-2	1.434(4)	106.6(2)
O-3	C-3	C-4	[a]	110.9(2)
C-3	C-4	C-5	1.524(4)	111.2(2)
O-4	C-4	C-3	1.428(3)	112.0(2)
O-4	C-4	C-5	[a]	108.3(2)
C-4	C-5	C-6	1.511(4)	109.1(2)
O-5	C-5	C-4	1.434(3)	108.9(2)
O-5	C-5	C-6	[a]	106.3(2)
C-5	C-6	O-6	1.533(4)	110.6(2)
C-7	C-6	C-5	1.515(4)	111.8(2)
C-7	C-6	O-6	[a]	107.2(2)
O-7	C-7	C-6	1.433(4)	110.4(2)
C-6	O-6	C-2	1.423(3)	115.1(2)
O-6	C-2	C-1	1.414(4)	113.2(2)
O-6	C-2	C-3	[a]	112.0(2)
Average bond-distances				
OX	CX′		1.354(18)	
CX′	OCX′		1.194(6)	
CX′	CCX′		1.487(7)	
X = 3, 4, 5 and 7				

[a]Previously listed in Table I.

TABLE IV

SELECTED BOND-LENGTHS (Å) AND ANGLES (DEG) IN **10**. VALUES IN PARENTHESES ARE AS IN TABLE III

1	*2*	*3*	*1-2 (Å)*	*1-2-3 (deg)*
SC-1	C-1	C-2	1.642(4)	119.8(2)
NC-1	C-1	C-2	1.307(4)	114.9(3)
SC-1	C-1	NC-1	[a]	125.3(3)
C-1	C-2	C-3	1.530(5)	112.1(3)
C-1	C-2	O-5	[a]	111.6(3)
C-2	C-3	C-4	1.532(6)	103.4(3)
O-3	C-3	C-2	1.440(4)	107.5(3)
O-3	C-3	C-4	[a]	109.5(3)
C-3	C-4	C-5	1.514(5)	101.7(3)
O-4	C-4	C-3	1.447(4)	104.7(3)
O-4	C-4	C-5	[a]	113.1(3)
C-4	C-5	O-5	1.522(6)	105.6(3)
C-6	C-5	C-4	1.500(5)	121.4(3)
C-6	C-5	O-5	[a]	108.9(3)
O-5	C-6	C-5	1.447(4)	111.0(3)
C-5	O-5	C-2	1.438(5)	109.3(2)
O-5	C-2	C-3	1.422(4)	107.3(3)
Average bond-distances				
OX	CX′		1.351(3)	
CX′	OCX′		1.199(2)	
CX′	CBX1		1.488(6)	
X = 3, 4, and 6				
C–C (phenyl 3)			1.378(10)	
C–C (phenyl 4)			1.375(11)	
C–C (phenyl 6)			1.380(7)	

[a]Previously listed in Table II.

for **5** and **10**, respectively. Atomic-scattering factors were obtained from the International Tables for X-ray crystallography[17]. All computer programs used in the solution of these structures are included in the SHELXTL program package which is part of the Nicolet R3 system.

3,4,5,7-Tetra-O-acetyl-2,6-anhydro-D-glycero-D-talo-*heptononitrile* (**5**). — D-Mannopyranose (100 g, 0.56 mol) was acetylated by the procedure of Irani and Bose[18]. The crude reaction-mixture was evaporated to dryness, and the residue co-evaporated with three 600-mL portions of toluene. The residual syrup was dissolved in dry nitromethane (1 L), and trimethylsilyl cyanide (225 mL) was added. The mixture was warmed to 35–37°, and redistilled boron trifluoride etherate[19] (138 mL) was added. After 2 h, the mixture was evaporated to a solid foam which was dissolved in dichloromethane (800 mL), and the solution successively washed with saturated, aqueous sodium hydrogencarbonate (2 × 250 mL) and water (1 × 250 mL), and dried (sodium sulfate). The product was adsorbed onto silica gel by

TABLE V

CRYSTAL AND OTHER EXPERIMENTAL DATA

	5	**10**
Formula	$C_{15}H_{19}NO_9$	$C_{27}H_{23}NO_7S$
M_r	357.3	505.5
$F(000)$	744	1056
Size (mm)	0.6 × 0.5 × 0.3	0.4 × 0.4 × 0.3
Space group	$P2_12_12_1$	C_2
a (Å)	8.683(2)	27.415(18)
b (Å)	12.457(3)	7.792(4)
c (Å)	15.932(4)	11.812(9)
α (deg)	90	90
β (deg)	90	98.52(6)
r (deg)	90	90
V (Å^3)	1729.3(7)	2494(2.7)
Z	4	4
D_x g.cm^{-3}	1.37	1.35
Radiation	Cu	Mo
m (cm^{-1})	9.46	1.68
sin θ/λ	0.54	0.65
Unique observed data	1298	2081
Unobserved data	76	1032
R	0.032	0.047
R_w	0.044	0.044

addition of silica gel (300 g; 60–200 mesh), and evaporation of the solvents. The residual powder was slurried in hexane, and the slurry added to the top of a column (8 cm × 80 cm) packed in hexane. The column was developed with dichloromethane, and the pooled fractions of product were evaporated to a golden syrup which crystallized spontaneously on standing at room temperature, to yield 101.2 g (51%) of **5**. Recrystallization from ethanol gave white crystals; m.p. 91.5–92.5°; lit.[9] 58–60°; $[\alpha]_D^{22}$ +27.8° (*c* 3.32, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 2.01, 2.07, 2.10, 2.18 (4 s, 12 H), 4.07 (m, 1 H), 4.14 (dd, 1 H, *J* 12.6 Hz), 4.32 (dd, 1 H), 4.91 (d, 1 H, *J* 2.1 Hz, H-1), 5.28 (m, 1 H), 5.34 (dd, 1 H), and 5.42 (dd, 1 H, *J* 2.99 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ 20.5, 61.6, 65.0, 65.5, 74.2, and 113.4 (α-CN). X-Ray recrystallography confirmed the structure in detail.

Anal. Calc. for $C_{15}H_{19}NO_9$: C, 50.42; H, 5.36; N, 3.92. Found: C, 50.22; H, 5.27; N, 3.62.

*1-O-Acetyl-2,3,5-tri-O-benzoyl-*D*-xylofuranose* (**8**). — To a solution of 1,2,3,5-tetra-*O*-benzoyl-D-xylofuranose (**7**; 5 g, 8.8 mmol) in glacial acetic acid (150 mL) were added acetic anhydride (35 mL) and concentrated sulfuric acid (7 mL), with ice-cooling. After 8 h at room temperature, the starting material was absent, as indicated by thin-layer chromatography using 4:1 chloroform–acetone. The clear, yellow solution was poured into ice (300 g) and extracted with dichloromethane (3 × 250 mL). The extracts were combined, washed successively with water (3 × 250 mL), saturated aqueous sodium hydrogencarbonate (3 × 250

mL), dried (sodium sulfate), and evaporated, to yield **8** as a chromatographically pure, stiff syrup, 4.2 g (94%); ^{1}H-n.m.r. ($CDCl_3$): δ 2.06 (s, α-OAc), 2.12 (s, β-OAc), 4.48–4.64 (m, 2 H), 4.84–5.08 (m, 1 H), 5.78 (dd, 1 H, J 6.4, 4.6 Hz), 6.08 (t, 1 H, J 6.4 Hz), 6.39 (bd s, 0.1 H, β), and 6.69 (d, 0.9 H, J 4.6, Hz, α).

*2,5-Anhydro-3,4,6-tri-*O*-benzoyl-*D*-gulononitrile* (**9**). — To a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-xylofuranose (**8**; 5 g, 10 mmol) and trimethylsilyl cyanide (2 mL) in nitromethane (100 mL) was added boron trifluoride etherate (1.23 mL). After stirring the solution for 1.5 h at room temperature, it was evaporated to dryness *in vacuo*. The residue was dissolved in dichloromethane (100 mL). The solution washed with saturated, aqueous sodium hydrogencarbonate (3 × 250 mL), dried (sodium sulfate), and evaporated to dryness, and the residue triturated with absolute ethanol; after standing overnight, it gave 4.2 g (90%) of **9** as white crystals; m.p. 106–107°; lit.[11] 98°; ^{1}H-n.m.r. ($CDCl_3$): δ 4.62–4.73 (m, 2 H), 4.73–4.85 (m, 1 H), 4.83–5.02 (m, 1 H), 5.72–5.83 (m, 1 H), 6.02 (d, 1 H, J 3.8 Hz, H-2), 7.30–7.78 (m, 9 H), and 7.90–8.28 (m, 6 H).

Anal. Calc. for $C_{27}H_{21}NO_7$: C, 68.78; H, 4.49; N, 2.97. Found: C, 68.59; H, 4.24; N, 2.71.

*2,5-Anhydro-3,4,6-tri-*O*-benzoyl-*D*-gulonothioamide* (**10**). — A slow stream of hydrogen sulfide gas was passed into a rapidly stirred solution of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-gulononitrile (**9**; 2.0 g, 4 mmol) in 1:1 1,4-dioxane–ethanol (40 mL) for 6 h at room temperature. The reaction flask was then tightly stoppered, and the solution stirred overnight at room temperature; no starting material then remained. The solution was evaporated to dryness, and the residual syrup was triturated with absolute ethanol, to produce 2.1 g (98%) of analytically pure **10**; m.p. 165–167°, $[\alpha]_D^{25}$ +135.8° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 4.4 (m, 1 H), 5.0 (m, 3 H), 5.8 (d, 1 H), 6.3 (s, 1 H), 7.2–8.3 (m, 16 H), and 9.0 (d, 1 H).

Anal. Calc. for $C_{27}H_{23}NO_7S$: C, 64.15; H, 4.59; N, 2.77; S, 6.34. Found: C, 63.98; H, 4.44; N, 2.69; S, 6.34.

*1,2,3,5-Tetra-*O*-acetyl-4-thio-*D*-ribofuranose* (**13**). — In a flame-dried, 1-L, three-necked flask fitted with two 125-mL addition-funnels were placed dry dichloromethane (350 mL), dry pyridine (11.5 mL), and 4-(dimethylamino)pyridine (70 mg, 0.5 mmol). The solution was cooled to −20° in a Dry Ice–carbon tetrachloride bath, and trifluoromethanesulfonic anhydride (13.3 mL, 79 mmol) was added dropwise, with stirring. The resulting, white suspension was stirred for 20 min at −20°, and a solution of methyl 2,3-*O*-isopropylidene-α-L-lyxopyranoside[13] (10 g, 49 mmol) in dry dichloromethane (90 mL) was added dropwise, with stirring, at −20° during 1 h. The resulting, pale-yellow solution was stirred for 15 min at −20°, and poured into cold water (600 mL). The organic phase was separated, and the aqueous phases were extracted with dichloromethane (3 × 200 mL). The extract were combined, dried (sodium sulfate), and evaporated *in vacuo*. The residue was dissolved in dry *N,N*-dimethylformamide (420 mL), and potassium thioacetate (17 g, 149 mmol) and 1,1,3,3-tetramethylurea (4 mL) were added. The mixture was stirred for 2 h, the solvent removed *in vacuo*, and the residue dissolved

in water (300 mL). The aqueous solution was extracted with chloroform (3 × 100 mL) and the extracts were combined, washed successively with water (100 mL), saturated aqueous sodium hydrogencarbonate (2 × 100 mL), and saturated aqueous sodium chloride (100 mL) dried (sodium sulfate), and evaporated *in vacuo*, to yield methyl 4-*S*-acetyl-2,3-*O*-isopropylidene-4-thio-β-D-ribofuranoside (**12**) as a dark-brown syrup which was directly converted into **13** by the procedure reported[13]; 8.5 g (54% from methyl 2,3-*O*-isopropylidene-α-L-lyxopyranoside) of **13** was isolated as an oil after chromatography on silica gel with 6:1 benzene–ethyl acetate as the eluant; ^{1}H-n.m.r. ($CDCl_3$): δ 2.0–2.2 (m, 12 H), 3.8 (m, 1 H), 4.2 (m, 2 H), 5.4 (dd, 1 H), 5.5 (m, 1 H), and 5.8 (d, 1 H).

3,4,6-Tri-O-acetyl-2,5-anhydro-5-thio-D-allononitrile (**14**). — A solution of 1,2,3,5-tetra-*O*-acetyl-4-thio-D-ribofuranose (**13**; 13.73 g, 36.4 mmol) in dry nitromethane (450 mL) was rapidly stirred, and purged with argon gas for 15 min. Freshly distilled trimethylsilyl cyanide (16.92 mL, 126 mmol) and boron trifluoride etherate (16 mL, 130 mmol) were added, and the mixture was stirred for 2 h at room temperature. Solvent was removed *in vacuo*, and the residue partitioned between dichloromethane (200 mL) and saturated, aqueous sodium hydrogencarbonate (150 mL). The organic phase was separated, and the aqueous phase was extracted with dichloromethane (3 × 100 mL). The extracts were combined, successively washed with water (100 mL), saturated aqueous sodium hydrogencarbonate (100 mL), and saturated aqueous sodium chloride (75 mL), dried (sodium sulfate), and evaporated *in vacuo*, to yield an oil which was chromatographed on silica gel with 4:1 benzene–ethyl acetate as eluant, to yield 8.76 g (79.8%) of **14** as an oil; $[\alpha]_D^{22}$ +138.6° (*c* 2.85, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 2.04–2.2 (3 s, 9 H), 3.8 (m, 1 H), 4.02–4.5 (m, 3 H), and 5.4–5.7 (m, 2 H); ^{13}C-n.m.r. ($CDCl_3$): δ 116.17 (β-CN); t.l.c. (1:4 ethyl acetate–benzene) R_F 0.37.

Anal. Calc. for $C_{12}H_{15}NO_6S$: C, 47.84; H, 4.98; N, 4.65; S, 10.63. Found: C, 47.63; H, 5.17; N, 4.48; S, 10.55.

2,5-Anhydro-5-thio-D-allononitrile (**15**). — A solution of 3,4,6-tri-*O*-acetyl-2,5-anhydro-5-thio-D-allononitrile (**14**; 5.91 g, 19.6 mmol) in ice-cold, 0.5M methanolic hydrogen chloride (225 mL) was stirred for 1 h at 0° and kept overnight at 4°. Solvent was removed *in vacuo*, and the residue chromatographed on silica gel with 1:19 methanol–ethyl acetate as eluant to yield 1.59 g (46%) of pure **15**; $[\alpha]_D^{22}$ +181.66° (*c* 1.37, CH_3OH); ^{1}H-n.m.r. (Me_2SO-d_6): δ 3.3–3.6 (m, 3 H), 4–4.2 (m, 1 H), 4.3 (d, 1 H), 4.9 (m, 1 H), 5.2 (d, 1 H), and 5.9 (d, 1 H); ^{13}C-n.m.r. (Me_2SO-d_6): δ 34.6, 53.7, 63.9, 74.9, 76.1, and 120.1; t.l.c. (1:4 CH_3OH–ethyl acetate) R_F 0.61.

Anal. Calc. for $C_6H_9NO_3S$: C, 41.40; H, 5.14; N, 8.00; S, 18.29. Found: C, 41.17; H, 5.33; N, 7.99; S, 18.03.

ACKNOWLEDGMENT

We thank the National Institutes of Health (Grants 1 RO1 CA 31783 and 1 RO1 CA 34284) for their support of this work.

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