Carbohydrate Research, 104 (1982) 183–193
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

SYNTHESIS OF *gem*-DI-*C*-SUBSTITUTED DERIVATIVES OF CARBOHYDRATES BY WAY OF NUCLEOPHILIC-ADDITION REACTIONS OF ALDOHEXOFURANOID 3-*C*-METHYLENE DERIVATIVES*

YOUSIF ALI†, DOLATRAI M. VYAS††, ROBERT C. NABINGER§, AND WALTER A. SZAREK§§
Carbohydrate Research Institute and Department of Chemistry, Queen's University, Kingston, Ontario K7L 3N6 (Canada)

(Received June 12th, 1981; accepted for publication, September 16th, 1981)

ABSTRACT

Nucleophilic Michael-type additions to aldohexofuranoid 3-*C*-methylene derivatives, namely, 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-nitromethylene-α-D-*ribo*-hexofuranose and 3-*C*-[cyano(ethoxycarbonyl)methylene]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose employing phase-transfer catalysis, afforded novel *gem*-di-*C*-substituted sugars. The conversion of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-3-*C*-nitromethyl-α-D-*allo*-hexofuranose into a 3-*C*-hydroxymethyl-3-*C*-methyl derivative with titanium trichloride, and that of the nitromethyl groups of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-di-*C*-nitromethyl-α-D-*ribo*-hexofuranose, and 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-3-*C*-nitromethyl- and -3-*C*-nitromethyl-α-D-*allo*-hexofuranose into cyano groups with phosphorus trichloride in pyridine is also described.

INTRODUCTION

Our interest in exploring synthetic methods for the introduction of a *gem*-di-*C*-alkyl branch in carbohydrates stems from the presence, in some naturally occurring antibiotics, of a sugar compound having a *gem*-di-*C*-methyl group[2]. During the past few years, various synthetic approaches for carbon–carbon-bond formation at C-4′ in nucleosides and C-4 in aldopentofuranoid and aldohexofuranoid sugars have been reported; these include enamine alkylation[3], photoamidation reactions[4], and formose reactions[5]. Introduction of a *gem*-di-*C*-alkyl branch at C-5 in an aldopentofuranoid sugar has been accomplished by the addition of an organozinc reagent to an aldehyde[6], whereas introduction of such branching at C-5 of hexose derivatives has been accomplished by Grignard reactions with sugar 1,4-lactones and keto derivatives[7].

*For a preliminary report of part of this work, see ref. 1.
†On leave from the Department of Chemistry, University of Baghdad.
††Present address: Bristol Laboratories, Syracuse, New York, 13201.
§Present address: Sandoz Pharmaceuticals, East Hanover, New Jersey, 07936.
§§To whom inquiries should be addressed.

A few total syntheses of *gem*-di-*C*-alkyl carbohydrate derivatives involving Diels–Alder reactions[8], and employing furan or oxabicycloketone derivatives[9] have also been reported. Fraser-Reid *et al.*[10] employed photochemically-induced addition of oxycarbinyl species to hex-2-enopyranosid-4-uloses to produce a *gem*-di-*C*-alkyl branch at C-2. The only reported examples of such branching at C-3 are those described by Tronchet and Bourgeois[11], and by Rosenthal and Dodd[12], which involved nucleophilic Michael-type additions to 3-*C*-methylene aldofuranoid derivatives.

A previous communication[1] from this laboratory reported the synthesis of novel *gem*-di-*C*-alkyl carbohydrate derivatives by phase-transfer-catalyzed[13] addition reactions to 3-*C*-methylene derivatives, namely, 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-nitromethylene-α-D-*ribo*-hexofuranose[14] (**1**) and 3-*C*-[cyano(ethoxycarbonyl)-methylene]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose[12] (**2**). In the present work, the preliminary studies have been extended, and the synthesis from **1** and **2** of a variety of *gem*-di-*C*-alkyl carbohydrate derivatives has been achieved.

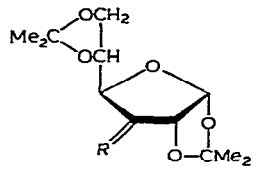
RESULTS AND DISCUSSION

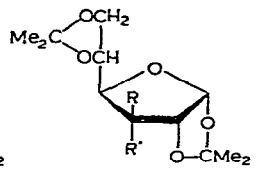
Addition of nitromethane to 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[15] (**3**) using phase-transfer conditions, namely, benzene–0.2M sodium hydroxide and tetrabutylammonium bromide as the catalyst, gave the known[14] 1,2:5,6-di-*O*-isopropylidene-3-*C*-nitromethyl-α-D-allofuranose (**4**) in 71% yield; no trace of the *gluco* epimer[16] was found. This result is consistent with that of Zhdanov *et al.*[17], who also obtained exclusively the *allo* epimer from the phase-transfer-catalyzed nitromethane addition to the 1,2:5,6-di-*O*-cyclohexylidene analog of **3**. Treatment of **4** with dimethyl sulfoxide–acetic anhydride, by the procedure described by Albrecht and Moffatt[14], gave the 3-*C*-methylene derivative **1**.

Nucleophilic additions to both endo- and exo-cyclic carbohydrate nitroolefins are known[18,19]. Phase-transfer-catalyzed additions of active methylene compounds to endocyclic carbohydrate nitroolefins have also been reported[20].

Treatment of **1** with potassium cyanide in benzene–0.2M sodium hydroxide using tetrabutylammonium bromide as the catalyst afforded crystalline 3-*C*-cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-nitromethyl-α-D-*gluco*-hexofuranose (**5**) in 73% yield. The i.r. spectrum confirmed the presence of both alkyl functions, showing a nitro absorption at 1545, and a weak nitrile-absorption at 2210 cm^{-1}. Previous workers have shown that, in contrast to the corresponding monophase systems, phase-transfer-catalyzed addition of hydrogen cyanide[17] or of nitromethane[21] to 1,2:5,6-di-*O*-cyclohexylidene-α-D-*ribo*-hexofuranos-3-ulose affords the kinetically controlled products. Additions to analogous 3-*C*-methylene derivatives have been shown also to occur from the less hindered, kinetically favored *exo*-side[11,14,22]. Accordingly, the *gluco* configuration was assigned to **5**.

Addition of nitromethane to **1** under the same conditions as just described afforded, in 82% yield, syrupy 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-di-*C*-nitromethyl-α-D-*ribo*-hexofuranose (**6**). During the course of the present study,





1 R = $CHNO_2$
2 R = CCO_2Et (CN)
3 R = O

4 R = CH_2NO_2, R' = OH
5 R = CN, R' = CH_2NO_2
6 R = R' = CH_2NO_2
7 R = $CHCO_2Et$ (CN), R' = CH_2NO_2
8 R = Me, R' = CH_2NO_2
9 R = Me, R' = CH_2OH
10 R = Me, R' = CH_2OTs
11 R = H, R' = CH_2NO_2
12 R = H, R' = CN
13 R = Me, R' = CN
14 R = R' = CN
15 R = CN, R' = CH_2CN
16 R = OH, R' = CN
17 R = CN, R' = $CHCO_2Et$ (CN)

the preparation of compound **6** was reported by Hall *et al.*[23] by Michael addition of nitromethane in the presence of triethylamine to the nitroolefin **1**. Likewise, the reaction of ethyl cyanoacetate and **1** afforded, in 73% yield, crystalline 3-*C*-[(*R*,*S*)-cyano(ethoxycarbonyl)methyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-nitromethyl-α-D-*allo*-hexofuranose (**7**). The i.r. spectrum of **7** showed a nitro absorption at 1560, and a carbonyl absorption at 1745 cm^{-1}.

In order to incorporate a methyl group as a component of a *gem*-di-*C*-alkyl branch, attempts were made to add a methyl Grignard reagent to nitroolefin **1**. Initial attempts using methylmagnesium iodide at 25, 0, and −25° were unsuccessful. However, upon lowering of the temperature to −50°, the reaction proceeded smoothly, to afford 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-3-*C*-nitromethyl-α-D-*allo*-hexofuranose (**8**) as a syrup, in 60% yield. The ^{1}H-n.m.r. spectrum of **8** showed a methyl singlet at δ 1.24, and the i.r. spectrum displayed a nitro absorption at 1550 cm^{-1}.

Nieuwenhuis and Jordaan reported[24] the conversion, in carbohydrates, of a nitromethyl into an aldehyde group by use of the titanium trichloride method originally developed by McMurry and Melton[25]. In the present work, **8** was converted into the nitronate salt with sodium methoxide, and the salt was treated with titanium trichloride to yield a syrup that was reduced immediately with sodium borohydride; syrupy 3-deoxy-3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-*allo*-hexofuranose (**9**) was obtained in 38% yield, and *p*-toluenesulfonylation in pyridine, afforded, in 77% yield, crystalline 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-3-*C*-(*p*-tolylsulfonyloxymethyl)-α-D-*allo*-hexofuranose (**10**).

The normal sequence used in the transformation of a nitromethyl into a nitrile group involves converting the nitromethyl into an aldehyde group, and oxime formation by use of hydroxylamine, followed by dehydration[26] of the oxime. Direct transformation of a nitromethyl into a nitrile group involves the use of either diethyl phosphorochloridite[27], or phosphorus oxychloride in *N,N*-dimethylformamide[28]. The former method resulted in low yields, while the latter required vigorous conditions. Wehrli and Schaer reported[29] a novel method for this transformation, which uses phosphoryl chloride in pyridine under mild conditions. Since no direct transformation of a nitromethyl into a nitrile group in the case of carbohydrates has been reported, it was felt that the method of Wehrli and Schaer[29] could be useful in the synthesis of novel, branched monosaccharide derivatives.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-nitromethyl-α-D-*allo*-hexofuranose (**11**), prepared by sodium borohydride reduction[14] of **1**, was chosen as the initial substrate for testing the conversion of a nitromethyl into a nitrile group. Treatment of **11** with phosphoryl chloride in pyridine for 1 h at 40° afforded crystalline 3-*C*-cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*allo*-hexofuranose (**12**) in 49% yield. In analogous fashion, treatment of **8** and **6** with phosphoryl chloride in pyridine, under the same conditions, afforded 3-*C*-cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-*allo*-hexofuranose (**13**) in 47% yield, and the *gem*-di-*C*-nitrile 3-deoxy-3,3-di-*C*-cyano-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**14**) in 52% yield, respectively.

A variety of *gem*-di-*C*-substituted carbohydrates have been obtained also in the present work by nucleophilic addition reactions to 3-*C*-[cyano(ethoxycarbonyl)-methylene]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**2**). Compound **2** was obtained in crystalline form, in 85% yield, by treatment of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**3**) with ethyl cyanoacetate in benzene–0.2M sodium hydroxide in the presence of tetrabutylammonium bromide at room temperature; **2** had been obtained previously[12] as only a minor product (5% yield) from the condensation of **3** with ethyl cyanoacetate and ammonium acetate in *N,N*-dimethylformamide at room temperature. Treatment of **2** with potassium cyanide in ethanol at reflux, under the conditions described by Nallet *et al.*[30], afforded 3-*C*-cyano-3-*C*-cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-hexofuranose[11] (**15**) in 30% yield. Addition of cyanide ion to **2**, in benzene–0.2M sodium hydroxide in the presence of tetrabutylammonium hydrogensulfate, gave 3-*C*-cyano-3-*C*-[(*R,S*)-cyano(ethoxycarbonyl)methyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-hexofuranose (**17**), in 65% yield, and a small proportion of the known[31] cyanohydrin derivative **16**.

The *gem*-di-*C*-substituted derivatives described herein are of significant synthetic potential, since their modification should yield carbohydrates containing two different functional groups at the branch point. The structural assignments for some of the adducts are based on the assumption that the addition reactions to the substituted methylene derivatives had occurred in a manner similar to those previously reported

by other workers, namely, from the less hindered *exo*-side. The results of a ^{13}C-n.m.r. study of the adducts will be reported separately.

EXPERIMENTAL

General methods. — Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer model 141 automatic polarimeter at 23 ± 3°. I.r. spectra were recorded with a Unicam SP 1000 spectrophotometer. N.m.r. spectra were recorded at 60 MHz for solutions in chloroform-*d* with tetramethylsilane (Me_4Si) as the internal standard. The term "petroleum ether" refers to the fraction of b.p. 60–80°. Column chromatography was performed on Brinkmann silica gel 60 (70–230 mesh, E. Merck).

1,2:5,6-Di-O-isopropylidene-3-C-nitromethyl-α-D-allofuranose (**4**). — Compound **3** (ref. 15, 6.0 g), dissolved in benzene (60 mL), was treated with nitromethane (10 mL) for 12 h with constant stirring at room temperature in the presence of 0.2M sodium hydroxide (10 mL) and tetrabutylammonium bromide (0.6 g). The aqueous phase was separated and extracted twice with benzene (10 mL). The combined organic layers were dried (magnesium sulfate) and evaporated to afford a syrup that crystallized upon addition of 2-propanol. Recrystallization from 2-propanol afforded **4** (5.3 g, 71%), m.p. 103–104°, $[\alpha]_D^{23}$ +23.6° (*c* 0.8, chloroform); lit.[14] m.p. 109–110°, $[\alpha]_D$ +23.3° (*c* 1.1, chloroform).

3-C-Cyano-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-nitromethyl-α-D-gluco-hexofuranose (**5**). — A mixture of **1** (ref. 14, 3 g) and potassium cyanide (1 g) was stirred in benzene (70 mL)–0.2M sodium hydroxide (7 mL), in the presence of tetrabutylammonium bromide (0.3 g), for 3 h at room temperature. The aqueous phase was then separated and extracted twice with benzene (10 mL). The combined benzene layers were dried (magnesium sulfate) and evaporated to afford a syrup which crystallized upon the addition of 2-propanol (5 mL). The crude product was recrystallized from 2-propanol–petroleum ether to afford **5** (2.2 g, 73%), m.p. 120–121°, $[\alpha]_D^{23}$ +24.8° (*c* 0.8, chloroform); ν_{max}^{Nujol} 2210 weak (CN) and 1545 cm^{-1} (NO_2); ^{1}H-n.m.r.: δ 5.95 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.12 (d, 1 H, H-2), 5.06 (d, 1 H, $J_{1',1''}$ 16.0 Hz, H-1'), 4.66 (d, 1 H, H-1''), 4.49–3.60 (m, 4 H, H-4,-5,-6,6'), 1.54, 1.45, 1.35 (s, 12 H, intensity ratio 1:1:2, 2 CMe_2).

Anal. Calc. for $C_{14}H_{20}N_2O_7$: C, 51.2; H, 6.1; N, 8.5. Found: C, 51.0; H, 6.2; N, 8.5.

3-Deoxy-1,2:5,6-di-O-isopropylidene-3,3-di-C-nitromethyl-α-D-ribo-hexofuranose (**6**). — Compound **1** (ref. 14, 1 g), dissolved in benzene (10 mL), was treated with nitromethane (3 mL) in the presence of 0.6M sodium hydroxide (5 mL) and tetrabutylammonium bromide (150 mg), with stirring for 2 h at room temperature. The aqueous phase was then separated and extracted twice with benzene (10 mL). The combined organic layers were dried (magnesium sulfate) and evaporated to afford a syrup, which was purified by column chromatography with 10:1 (v/v) toluene–ethyl acetate as the eluent. Compound **6** was obtained as a colorless syrup (1 g,

83%), $[\alpha]_D^{23}$ +43.0° (*c* 0.8, chloroform); ν_{max}^{Nujol} 1555 (NO_2) cm^{-1}; ^{1}H-n.m.r.: δ 5.75 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 5.09 (d, 1 H, H-2), 4.09 (4 H, 2 CH_2NO_2), 4.49–3.52 (m, 4 H, H-4, -5, -6,6'), 1.52, 1.42, 1.32 (s, 12 H, intensity ratio 1:1:2, 2 CMe_2).

Anal. Calc. for $C_{14}H_{22}N_2O_9$: C, 46.4; H, 6.1; N, 7.7. Found: C, 46.6; H, 6.2; N, 7.6.

3-C-[(R,S)-Cyano(ethoxycarbonyl)methyl]-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-nitromethyl-α-D-allo-hexofuranose (**7**). — Compound **1** (ref. 14, 0.8 g) and ethyl cyanoacetate (0.5 mL) were stirred in benzene (20 mL)–0.2M sodium hydroxide (5 mL) in the presence of tetrabutylammonium bromide (80 mg) for 12 h at room temperature. The aqueous layer was then separated and extracted twice with benzene (5 mL). The combined organic layers were dried (potassium carbonate) and evaporated under reduced pressure to afford a syrup, which crystallized upon the addition of 2-propanol. Recrystallization from 2-propanol gave **7** (0.8 g, 73%), m.p. 136–138°; ν_{max}^{Nujol} 1745 (C=O) and 1560 cm^{-1} (NO_2); ^{1}H-n.m.r.: δ 6.10 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 5.17 (d, 1 H, $J_{1',1''}$ 16.6 Hz, H-1'), 4.90 (d, 1 H, H-2), 4.66 (d, 1 H, H-1''), 4.50–3.54 (m, 7 H, H-4, -5, -6,6', CHCN, CH_2CH_3), and 1.55–1.15 (m, 15 H, 2 CMe_2, CH_2CH_3).

Anal. Calc. for $C_{18}H_{26}N_2O_9$: C, 52.2; H, 6.3; N, 6.8. Found: C, 52.2; H, 6.3; N, 6.9.

3-Deoxy-1,2:5,6-di-O-isopropylidene-3-C-methyl-3-C-nitromethyl-α-D-allo-hexofuranose (**8**). — Methyl iodide (4.5 mL) was added, dropwise with stirring, to magnesium turnings (100 mg) in diethyl ether (20 mL) at room temperature. Upon consumption of the magnesium, the solution was diluted with diethyl ether (20 mL) and cooled to −50°. A solution of nitroolefin **1** (1 g) in diethyl ether (20 mL) was added dropwise to the methylmagnesium iodide solution, with the temperature being maintained at −50°. The reaction mixture was allowed to warm gradually to room temperature, and stirred for an additional 1 h. The reaction was quenched with saturated ammonium chloride solution (50 mL), and the aqueous layer was separated and washed three times with diethyl ether (50 mL). The combined organic layers were dried (magnesium sulfate) and the solvent was evaporated to afford a brown syrup. The product was purified by column chromatography with 20:1 (v/v) benzene–ethyl acetate as the eluent. Compound **8** was isolated as a colorless syrup (650 mg, 60%), $[\alpha]_D^{23}$ +27.3° (*c* 1.2, chloroform); ν_{max}^{film} 1550 cm^{-1} (NO_2); ^{1}H-n.m.r.: δ 5.80 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.70 (s, 2 H, H-1',1''), 4.56 (d, 1 H, H-2), 4.24–3.43 (m, 4 H, H-4, -5, -6,6'), 1.54, 1.45, 1.39 (s, 12 H, intensity ratio 1:1:2, 2 CMe_2), and 1.24 (s, 3 H, Me).

Anal. Calc. for $C_{14}H_{23}NO_7$: C, 53.0; H, 7.3; N, 4.4. Found: C, 52.9; H, 7.3; N, 4.3.

3-Deoxy-3-C-hydroxymethyl-1,2:5,6-di-O-isopropylidene-3-C-methyl-α-D-allo-hexofuranose (**9**). — Compound **8** (1 g) was dissolved in dry methanol (5 mL), and 0.32M sodium methoxide solution (10 mL, methanol) was added. After 10 min at room temperature, a freshly mixed, aqueous solution of 15% titanium trichloride (20 mL)–3.3M ammonium acetate (30 mL) was added rapidly to the reaction mixture,

and the resultant solution was stirred for 20 min at room temperature under nitrogen. The aqueous solution was extracted three times with diethyl ether (70 mL), and the combined ether extracts were washed with 5% sodium hydrogencarbonate (100 mL) and saturated sodium chloride solution (100 mL). The ethereal solution was dried (magnesium sulfate) and evaporated to afford a syrup (600 mg), which was used directly for borohydride reduction.

The syrup was dissolved in ethanol (20 mL), and, at 0°, sodium borohydride (100 mg) was added in portions. The reaction mixture was allowed to warm to room temperature, and stirred for an additional 1 h; t.l.c. (5:1, v/v, benzene–ethyl acetate) showed the presence of a major component, which had a much lower R_F (0.25) than that of the starting material, and of a minor component which migrated at the same rate as the starting material. The solution was evaporated to dryness, and methanol (30 mL) was added to and evaporated from the residue five times. The residue was dissolved in water (50 mL), and the aqueous solution was extracted three times with dichloromethane (30 mL). The combined organic extracts were dried (magnesium sulfate) and evaporated to afford a syrup. Column chromatography with 3:1 (v/v) toluene–ethyl acetate as the eluent afforded the starting material **8** (52 mg) and the desired product **9** (352 mg, 38% based on recovered starting material), $[\alpha]_D^{23}$ +25.0° (*c* 0.4, chloroform); ν_{max}^{film} 3450 cm^{-1} (OH); ^{1}H-n.m.r.: δ 5.73 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.27 (d, 1 H, H-2), 4.23–3.45 (m, 6 H, H-1′,1″ -4, -5, -6,6′), 2.96 (s, 1 H, OH), 1.55, 1.46, 1.37, 1.34 (s, 12 H, 2 CMe_2), and 1.07 (s, 3 H, Me).

Anal. Calc. for $C_{14}H_{23}O_6$: C, 58.3; H, 9.1. Found: C, 58.2; H, 9.0.

*3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-C-methyl-3-C-*(p-*tolylsulfonyloxymethyl*)-α-D-allo-*hexofuranose* (**10**). — Compound **9** (165 mg) was dissolved in pyridine (5 mL), and *p*-toluenesulfonyl chloride (165 mg) was added. The solution was stirred for 16 h at room temperature, and then poured into ice–water (25 mL). The mixture was extracted three times with dichloromethane (20 mL), and the combined organic extracts were dried (magnesium sulfate) and evaporated to afford a crystalline residue. Recrystallization of the residue from diethyl ether–petroleum ether afforded **10** (195 mg, 77%), m.p. 134.5–136°, $[\alpha]_D^{23}$ +39.5° (*c* 1.1, chloroform); ^{1}H-n.m.r.: δ 7.92–7.18 (m, 4 H, aryl), 5.64 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.31–3.75 (m, 7 H, H-1′,1″, -2, -4, -5, -6,6′), 2.44 (s, 3 H, aryl Me), 1.35, 1.31, 1.22 (s, 12 H, intensity ratio 2:1:1, 2 CMe_2), and 1.02 (s, 3 H, Me).

Anal. Calc. for $C_{21}H_{30}O_8S$: C, 57.0; H, 6.9; S, 7.2. Found: C, 57.0; H, 6.9; S, 7.1.

*3-C-Cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-*α-D-allo-*hexofuranose* (**12**). — Compound **11** (ref. 14) was dissolved in pyridine (7 mL) and the solution was treated with phosphoryl chloride (400 mg) at 40° for 18 h. The reaction was carefully quenched with ice–water (50 mL), and the aqueous solution was extracted three times with dichloromethane (30 mL). The combined organic extracts were dried (magnesium sulfate) and evaporated to a syrup that crystallized. Recrystallization from 2-propanol–petroleum ether afforded **12** (210 mg, 49%), m.p. 109–110°, $[\alpha]_D^{23}$ 74.5° (*c* 0.6, chloroform); $\nu_{max}^{CHCl_3}$ 2250 weak cm^{-1} (CN); ^{1}H-n.m.r.: δ 5.88 (d, 1 H,

$J_{1,2}$ 3.7 Hz, H-1), 4.85 (dd, 1 H, $J_{2,3}$ 3.8 Hz, H-2), 4.41–3.67 (m, 4 H, H-4, -5, -6,6'), 3.15–2.87 (m, 1 H, H-3), and 1.65, 1.54, 1.42 (s, 12 H, intensity ratio 1:1:2, 2 CMe_2).

Anal. Calc. for $C_{13}H_{19}NO_5$: C, 58.0; H, 7.1; N, 5.2. Found: C, 57.8; H, 7.2; N, 5.2.

3-C-Cyano-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-methyl-α-D-allo-hexofuranose (**13**). — Compound **8** (380 mg) was dissolved in pyridine (5 mL), and the solution was treated with phosphoryl chloride (400 mg) for 1 h at 50°. The reaction mixture was poured carefully into ice–water (20 mL), and the mixture was extracted twice with dichloromethane (20 mL). The combined organic extracts were dried (potassium carbonate) and evaporated to afford a crystalline residue. Recrystallization from 2-propanol–petroleum ether afforded **13** (153 mg, 45%) m.p. 127.5–128°, $[\alpha]_D^{23}$ +27.4° (*c* 0.8, chloroform); $\nu_{max}^{CHCl_3}$ 2240 weak cm^{-1} (CN); ^{1}H-n.m.r.: δ 5.76 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.40 (d, 1 H, H-2), 4.25–3.60 (m, 4 H, H-4, -5, -6,6'), and 1.64–1.13 (m, 15 H, 2 CMe_2, Me).

Anal. Calc. for $C_{14}H_{21}NO_5$: C, 59.3; H, 7.5; N, 4.9. Found: C, 59.4; H, 7.3; N, 5.0.

3,3-Di-C-cyano-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranose (**14**). — To a solution of **6** (500 mg) in pyridine (10 mL) was added phosphoryl chloride (900 mg), and the solution was heated for 1.5 h at 50°. The mixture was poured carefully into ice–water (25 mL), and the aqueous solution was extracted three times with dichloromethane (30 mL). The combined organic extracts were dried (magnesium sulfate) and evaporated to afford a crystalline residue. Recrystallization from 2-propanol–petroleum ether afforded **15** (210 mg, 52%) m.p. 113–115°, $[\alpha]_D^{23}$ +25.8° (*c* 0.6, chloroform); $\nu_{max}^{CHCl_3}$ 2250 weak cm^{-1} (CN); ^{1}H-n.m.r.: δ 6.00 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.96 (d, 1 H, H-2), 4.51–4.01 (m, 4 H, H-4, -5, -6,6'), and 1.66, 1.55, 1.45 (s, 12 H, intensity ratio 1:1:2, 2 CMe_2).

Anal. Calc. for $C_{14}H_{18}N_2O_5$: C, 57.1; H, 6.2; N, 9.5. Found: C, 57.2; H, 6.4; N, 9.4.

3-C-[Cyano(ethoxycarbonyl)methylene]-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranose (**2**). — Compound **3** (7 g), dissolved in benzene (100 mL), was treated with ethyl cyanoacetate (3.1 mL) for 20 h with constant stirring at room temperature, in the presence of 0.2M sodium hydroxide (12 mL) and tetrabutylammonium bromide (0.7 g). The aqueous layer was extracted three times with benzene (10 mL). The combined benzene layers were dried (magnesium sulfate) and evaporated to afford a brown syrup. The syrup was passed through a short column of silica gel with 20:1 (v/v) benzene–ethyl acetate as the eluent. The solvent was removed under reduced pressure to afford **2** as a syrup that crystallized (8.5 g, 85%). A sample was recrystallized from 2-propanol–hexane to afford white needles, m.p. 90–91°, $[\alpha]_D^{23}$ +79.0° (*c* 1.1, chloroform); ^{1}H-n.m.r.: δ 5.93 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.60 (d, 1 H, H-2), 4.53–4.02 (m, 6 H, H-4, -5, -6,6', CH_2CH_3), and 1.75–1.25 (m, 15 H, 2 CMe_2, CH_2CH_3).

Anal. Calc. for $C_{17}H_{23}NO_7$: C, 57.8; H, 6.5; N, 4.0. Found: C, 57.7; H, 6.7; N, 3.8.

3-C-Cyano-3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-gluco-hexofuranose (**15**). — Compound **2** (2 g) was dissolved in ethanol (25 mL) and treated with potassium cyanide (1.2 g) for 12 h at reflux temperature. The solvent was then removed, and the residue was extracted twice with dichloromethane (50 mL). The combined organic extracts were washed twice with water (25 mL), dried (magnesium sulfate), and evaporated to a syrup. Column chromatography with 10:1 (v/v) benzene–ethyl acetate as the eluent gave a syrup that crystallized. Recrystallization from 2-propanol afforded **15** as white crystals (0.52 g, 30%), m.p. 116–118°, $[\alpha]_D^{23}$ +21.6° (*c* 0.8, chloroform) {lit.[11] m.p. 121.5–123°, $[\alpha]_D$ +21.0° (*c* 0.8, chloroform)}; ν_{max}^{Nujol} 2250 weak cm^{-1} (CN); ^{1}H-n.m.r.: δ 6.03 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.93 (d, 1 H, H-2), 4.58–3.54 (m, 4 H, H-4, -5, -6,6'), 3.30 (d, $J_{1,1'}$ 16.6 Hz, H-1'), 2.80 (d, 1 H, H-1''), and 1.60, 1.46, 1.40 (s, 12 H, intensity ratio 1:1:2, 2 CMe_2).

Anal. Calc. for $C_{15}H_{20}N_2O_5$: C, 58.4; H, 6.5; N, 9.1. Found: C, 58.4; H, 6.5; N, 8.9.

3-C-Cyano-3-C-[(R,S)-cyano(ethoxycarbonyl)methyl]-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-gluco-hexofuranose (**17**). — A solution of **2** (500 mg) in benzene (20 mL) was treated with potassium cyanide (200 mg) for 2 h with stirring at room temperature, in the presence of 0.2M sodium hydroxide (4 mL) and tetrabutylammonium hydrogensulfate (100 mg). The aqueous layer was extracted twice with benzene (5 mL), and the combined organic layers were dried (magnesium sulfate) and evaporated to a syrup. Fractionation of the syrup by column chromatography with 20:1 (v/v) benzene–ethyl acetate as the eluent afforded a trace amount of 3-*C*-cyano-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[31] (**16**), and a less-polar component that crystallized. Recrystallization of the less-polar component from 2-propanol–hexane afforded **17** as white crystals (350 mg, 65%), m.p. 92–93°, ^{1}H-n.m.r.: δ 5.96 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.16 (d, 1 H, H-2), 4.64–3.96 (m, 7 H, H-1', -4, -5, -6,6', CH_2CH_3), and 1.76–1.21 (m, 15 H, 2 CMe_2, CH_2CH_3).

Anal. Calc. for $C_{18}H_{24}N_2O_7$: C, 58.4; H, 6.4; N, 5.2. Found: C, 58.3; H, 6.5; N, 5.2.

ACKNOWLEDGMENTS

The authors are grateful to the Natural Sciences and Engineering Research Council Canada for a grant (to W.A.S.) and to the University of Baghdad for a sabbatical leave (Y.A.).

REFERENCES

1 Y. Ali and W. A. Szarek, *Carbohydr. Res.*, 67 (1978) c17–c19.
2 C. H. Shunk, C. H. Stammer, E. A. Kaczka, E. Walton, C. F. Spencer, A. N. Wilson, J. W. Richter, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.*, 78 (1956) 1770–1771; L. Ninet, F. Benazet, Y. Charpentte, M. Dubost, J. Florent, D. Mancy, J. Preud'homme, T. L. Therlfall, B. Vuillemin, D. E. Wright, A. Abraham, M. Cartier, N. de Chezelles, C. Godard, and J. Theilleux, *C.R. Hebd. Seances Acad. Sci., Ser. C*, 275 (1972) 455–458; L. Dolak, *J. Antibiot.*, 26 (1973) 121–125; H. Kawaguchi, T. Naito, and H. Tsukiura, *J. Antibiot.*,

Ser. A, 18 (1965) 11–25; H. KAWAGUCHI, T. MIYAKI, AND H. TSUKIURA, *ibid.*, 18 (1965) 220–221; H. MAEHR, T. H. WILLIAMS, M. LEACH, AND A. STEMPEL, *Helv. Chim. Acta*, 57 (1974) 212–213; H. MAEHR, M. LEACH, T. H. WILLIAMS, W. BENZ, J. F. BLOUNT, AND A. STEMPEL, *J. Am. Chem. Soc.*, 95 (1973) 8448–8449; H. MAEHR, J. F. BLOUNT, R. H. EVANS, JR., M. LEACH, J. W. WESTLEY, T. H. WILLIAMS, A. STEMPEL, AND G. BUECHI, *Helv. Chim. Acta*, 55 (1972) 3051–3054; H. MAEHR, M. LEACH, L. YARMCHUK, AND A. STEMPEL, *J. Am. Chem. Soc.*, 95 (1973) 8449–8450; R. WAX, W. MAIESE, R. WESTON, AND J. BIRNBAUM, *J. Antibiot.*, 29 (1976) 670–673.

3 J. A. SECRIST, 3RD, AND W. J. WINTER, JR., *J. Am. Chem. Soc.*, 100 (1978) 2554–2555.

4 A. ROSENTHAL AND K. SHUDO, *J. Org. Chem.*, 37 (1971) 1608–1612; A. ROSENTHAL AND M. RATCLIFFE, *Carbohydr. Res.*, 54 (1977) 61–73.

5 D. L. LELAND AND M. P. KOTICK, *Carbohydr. Res.*, 38 (1974) c9–c11; R. SCHAFFER, *J. Am. Chem. Soc.*, 81 (1959) 5452–5454; D. J. WARD, Ph.D. Thesis, Queen's University, Kingston, 1976; R. D. YOUSSEFYEH, J. P. H. VERHEYDEN, AND J. G. MOFFATT, *J. Org. Chem.*, 44 (1979) 1301–1309; G. H. JONES, M. TANIGUCH, D. TEGG, AND J. G. MOFFATT, *ibid.*, 44 (1979) 1309–1317.

6 YU. A. ZHDANOV, YU. E. ALEKSEEV, AND S. S. DOROSHENKO, *Dokl. Akad. Nauk SSSR*, 238 (1978) 868–869.

7 T. D. INCH, R. V. LEY, AND P. RICH, *J. Chem. Soc., C*, (1968) 1683–1692; M. FUNABASHI, H. SATO, AND J. YOSHIMURA, *Chem. Lett.*, (1974) 803–804; B. P. VATERLAUS AND H. SPIEGELBERG, *Helv. Chim. Acta*, 47 (1964) 381–390; W. A. SZAREK, D. M. VYAS, AND L.-Y. CHEN, *Carbohydr. Res.*, 53 (1977) c1–c4; E. WALTON, J. O. RODIN, C. H. STANNER, F. W. HOLLEY, AND K. FOLKERS, *J. Am. Chem. Soc.*, 80 (1958) 5168–5173.

8 A. KONOWAL, J. JURCZAK, AND A. ZAMOJSKI, *Rocz. Chem.*, 42 (1968) 2048–2058; 44 (1970) 1981–1986.

9 O. ACHMATOWICZ, JR., P. BUKOWSKI, B. SZECHNER, Z. ZWIERZCHOWSKA, AND A. ZAMOJSKI, *Tetrahedron*, 27 (1971) 1973–1996; O. ACHMATOWICZ, JR., G. GRYNKIEWICZ, AND B. SZECHNER, *ibid.*, 32 (1976) 1051–1054; T. SATO, M. WATANABE, AND R. NOYORI, *Chem. Lett.*, (1978) 1297–1300.

10 B. FRASER-REID, N. L. HOLDER, D. R. HICKS, AND D. L. WALKER, *Can. J. Chem.*, 55 (1977) 3978–3985.

11 J. M. J. TRONCHET AND J. BOURGEOIS, *Carbohydr. Res.*, 29 (1973) 373–385.

12 A. ROSENTHAL AND R. H. DODD, *J. Carbohydr. Nucleos. Nucleot.*, 5 (1978) 545–557.

13 E. V. DEHMLOW, *Angew. Chem., Int. Ed. Engl.*, 16 (1977) 493–505.

14 H. P. ALBRECHT AND J. G. MOFFATT, *Tetrahedron Lett.*, (1970) 1063–1066.

15 B. T. LAWTON, W. A. SZAREK, AND J. K. N. JONES, *Carbohydr. Res.*, 10 (1969) 456–458.

16 A. ROSENTHAL, K.-S. ONG, AND D. BAKER, *Carbohydr. Res.*, 13 (1970) 113–125.

17 YU. A. ZHDANOV, YU. E. ALEKSEEV, I. N. SIILIS, AND S. G. KUREN, *Dokl. Akad. Nauk SSSR*, 238 (1978) 1355–1357.

18 H. H. BAER AND F. KIENZLE, *J. Org. Chem.*, 34 (1969) 3848–3853; G. B. HOWARTH, W. A. SZAREK, AND J. K. N. JONES, *J. Chem. Soc., C*, (1970) 2218–2224; H. PAULSEN AND W. GRIEVE, *Chem. Ber.*, 107 (1974) 3013–3019; H. H. BAER AND W. RANK, *Can. J. Chem.*, 52 (1974) 2257–2267; H. H. BAER AND K.-S. ONG, *ibid.*, 46 (1968) 2511–2517.

19 H. H. BAER AND W. RANK, *Can. J. Chem.*, 43 (1965) 3330–3339.

20 T. SAKAKIBARA AND R. SUDOH, *Chem. Commun.*, (1974) 69–70; T. SAKAKIBARA, M. YAMADA, AND R. SUDOH, *J. Org. Chem.*, 41 (1976) 736–737.

21 YU. A. ZHDANOV, YU. E. ALEKSEEV, I. N. SIILIS, AND S. S. DOROSHENKO, *Dokl. Akad. Nauk SSSR*, 231 (1978) 1355–1357.

22 A. ROSENTHAL AND D. BAKER, *J. Org. Chem.*, 38 (1973) 193–197; J. M. J. TRONCHET, J. M. BOURGEOIS, R. GRAF, AND J. TRONCHET, *C.R. Hebd. Seances Acad. Sci., Ser. C*, 269 (1969) 420–423; A. ROSENTHAL AND M. RATCLIFFE, *Carbohydr. Res.*, 60 (1978) 39–49.

23 R. H. HALL, A. JORDAAN, AND M. MALHERBE, *J. Chem. Soc., Perkin Trans. 1*, (1980) 126–128.

24 J. J. NIEUWENHUIS AND J. H. JORDAAN, *Tetrahedron Lett.*, (1977) 369–370.

25 J. E. MCMURRY AND J. MELTON, *J. Org. Chem.*, 38 (1973) 4367–4373.

26 G. P. ELLIS AND I. L. THOMAS, *Prog. Med. Chem.*, 10 (1974) 245–251.
27 T. MUKAIYAMA AND H. NAMBU, *J. Org. Chem.*, 27 (1962) 2201–2204.
28 J. SKRAMSTAD, *Acta Chem. Scand.*, 24 (1970) 3424–3428.
29 P. A. WEHRLI AND B. SCHAER, *J. Org. Chem.*, 42 (1977) 3956–3958.
30 J. P. NALLET, R. BARRET, C. ARNAUD, AND J. HUET, *Tetrahedron Lett.*, (1975) 1843–1844.
31 J. M. BOURGEOIS, *Helv. Chim. Acta*, 58 (1975) 363–372; A. ROSENTHAL AND B. L. CLIFF, *Can. J. Chem.*, 54 (1976) 543–547.