

## SYNTHESIS OF 2,3-DIDEOXY-D-HEX-2-ENOPYRANOSYL CYANIDES

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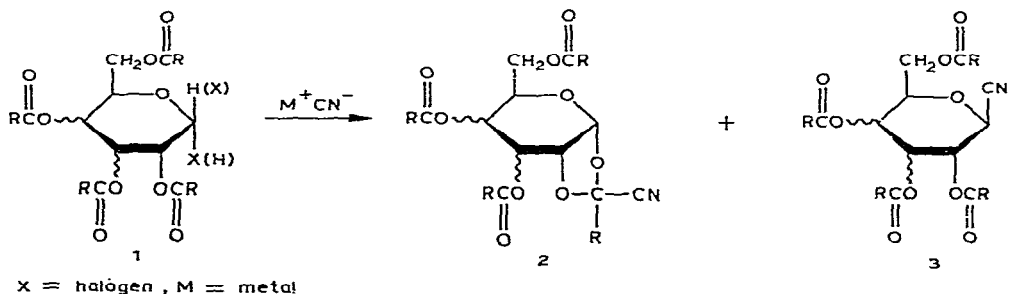
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### ABSTRACT

Treatment of D-glycals with trimethylsilyl cyanide in the presence of a catalytic amount of a Lewis acid gives 2,3-dideoxy-D-hex-2-enopyranosyl cyanides. 3,4,6-Tri-O-acetyl-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol rapidly gives, exclusively and almost quantitatively, the product having the  $\alpha$ -D configuration. 2,3,4,6-Tetra-O-acetyl-1,5-anhydro-D-arabino- and -D-lyxo-hex-1-enitol give anomeric mixtures of cyanides.

### INTRODUCTION

Monosaccharide derivatives in which the anomeric hydroxyl group is replaced by a cyano group have been recognized as versatile intermediates in the synthesis of a variety of C-glycosyl compounds, such as C-nucleosides<sup>1,2</sup>, but have not been readily available. Direct replacement of the halogen atom of per-O-acetylated alderyl halides (**1**) by cyanide ion to give **3** proved to be a complex process, leading to considerable proportions of **2**. Availability of anomeric cyanides is further limited to compounds having 1,2-trans geometry<sup>3,4</sup>.

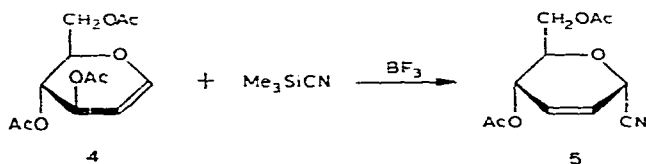


During our search for effective methods of synthesis of C-glycosyl compounds having the  $\alpha$ -D configuration, we found that D-glycals react with electron-rich alkenes, under Lewis-acid catalysis, to afford, with high selectivity<sup>5</sup>,  $\alpha$ -C-linked derivatives. We have now successfully applied the same principle for attaching a one-carbon-atom

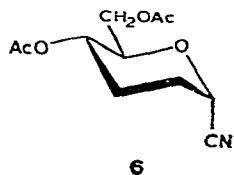
unit (a cyano group) to C-1 of an aldopyranoid ring. Reactions of glycals with sodium salts of various anions, including carbanions, in the presence of boron trifluoride etherate are known<sup>6-9</sup>, but reaction with cyanides has not heretofore been reported.

#### RESULTS AND DISCUSSION

The reaction of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-*D*-arabino-hex-1-enitol (**4**) with sodium cyanide in acetonitrile in the presence of boron trifluoride etherate, that is, under conditions successfully applied by Heyns and Park<sup>6</sup> for the reaction of **4** with the sodium salt of methyl dicyanoacetate, afforded a rather complex mixture of products from which one crystalline, nitrogen-containing compound was isolated in low yield by column chromatography. From analytical and spectral data, in particular from <sup>1</sup>H-n.m.r.-spectral data, this product was identified as 4,6-di-*O*-acetyl-2,3-dideoxy- $\alpha$ -*D*-erythro-hex-2-enopyranosyl cyanide (5,7-di-*O*-acetyl-2,6-anhydro-3,4-dideoxy-*D*-arabino-hept-3-enonitrile, **5**). Attempts to enhance formation of **5** by adding to the reaction mixture a tetraalkylammonium halide or tetrabutylammonium hydrogensulfate, to promote transfer of the nucleophile into solution, did not result in any significant change in the distribution of the products. Likewise, use of separately obtained tetrabutylammonium cyanide<sup>10</sup> failed to improve the yield of **5**.

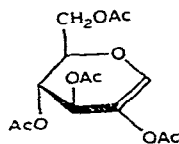


However, when **4** was treated with a slight excess of trimethylsilyl cyanide in the presence of a catalytic amount of boron trifluoride etherate in dichloromethane, examination of the reaction mixture revealed its rapid, and essentially quantitative, transformation into a single product (**5**). The  $\alpha$ -*D* configuration was assigned to this product, based on examination of the <sup>1</sup>H-n.m.r. spectrum of its saturated analog **6**.



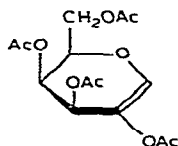
Palladium-catalyzed, atmospheric-pressure hydrogenation of **5** transformed it into an oily product (**6**) devoid of a carbon-carbon double bond. The <sup>1</sup>H-n.m.r. spectrum of **6** contained two low-field signals. The signal ascribed to the anomeric proton (H-1,  $\delta$  4.85) was a broad doublet,  $J \sim 4$  Hz (a singlet in the spectrum of **5**), indicating an axial position for the cyano group. The other low-field signal ( $\delta$  4.75) forms a six-

line multiplet displaying one medium ( $\sim 4$  Hz) and two large ( $\sim 10$  Hz) coupling constants. It corresponds to the doublet ( $J$  9.5 Hz) in the spectrum of the unsaturated compound **5**, and therefore is assigned to H-4. This configurational assignment is in keeping with the well-established tendency of **4** to form  $\alpha$ -D-glycosyl products in reactions with alcohols<sup>11</sup>, thiols<sup>12</sup>, and carbon<sup>5,13</sup> nucleophiles.



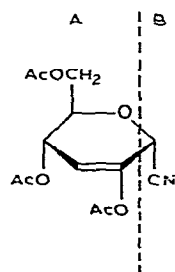
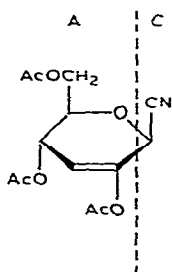
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Similarly, 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol (**7**) was found to react readily with trimethylsilyl cyanide in the presence of boron trifluoride; but, in this case, formation of approximately equal amounts of two products was observed. Isomeric, unsaturated hexopyranosyl cyanides were isolated from the reaction mixture by column chromatography, and were assigned structures **8** and **9** based upon analytical and spectral data.



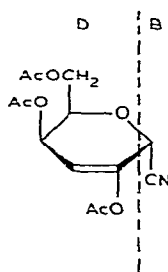
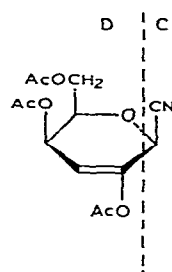
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2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-*lyxo*-hex-1-enitol (**10**) gave, under the same conditions, a 1:1 mixture of **11** and **12**. All hexopyranosyl cyanides thus obtained exhibited only a very weak band in the vicinity of  $2200\text{ cm}^{-1}$  in their infrared spectra. Their fragmentation upon electron-impact, mass spectrometry included formation of  $(M + 1)$  and  $(M - 16)$  ( $C-1^1-C-1$  bond-fission) ions, in general following established patterns<sup>14</sup>.

8  $[\alpha]_D + 150^\circ$ 9  $[\alpha]_D + 18^\circ$ 

$$(A + B) - (A + C) = 150^\circ - 18^\circ$$

$$B - C = +132^\circ$$

11  $[\alpha]_D - 85^\circ$ 12  $[\alpha]_D - 210^\circ$ 

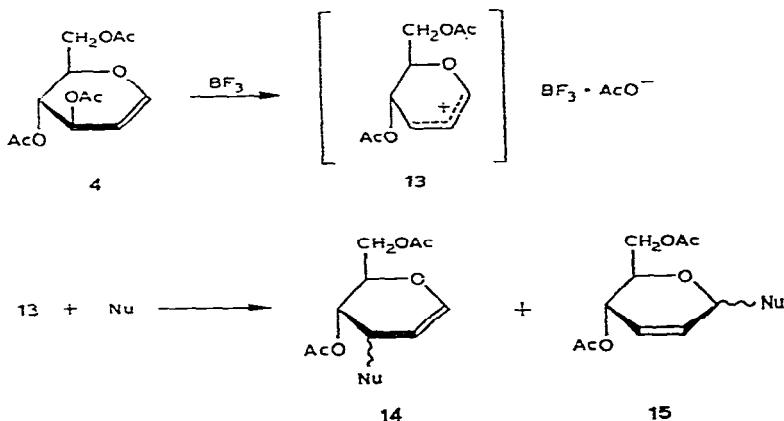
$$(D + B) - (D + C) = -85^\circ + 210^\circ$$

$$\therefore -C = +125^\circ$$

The anomeric configuration of the pair of cyanides (**8** and **9**) derived from glycal **7** was deduced from  $^1\text{H}$ -n.m.r.-spectral data, the member of an anomeric pair of 2,3-unsaturated pyranoses having the larger  $J_{1,3}$  value being that with the alpha configuration<sup>15-17</sup>. Also, the anomer assigned the  $\alpha$ -D configuration (**8** and **11**) had a more positive specific optical rotation than its counterpart (**9** and **12**, respectively). In the set of four cyanides obtained from glycals **7** and **10**, there are two pairs epimeric at C-1 (**8** and **9**, and **11** and **12**) and two pairs epimeric at C-4 (**8** and **11**, and **9** and **12**). Application of the rule of optical superposition to the measured values of the specific rotation gives results consistent with the assumption that differences between observed rotations of the isomers should be approximately the same for each pair.

The reaction of glycals with trimethylsilyl cyanide is apparently regiospecific, that is, the nucleophile bonds exclusively to the anomeric center. This finding has special significance in view of the generally accepted intermediacy of the bidentate cation **13** in Lewis acid-catalyzed reactions of glycals with nucleophiles.

The tendency of different substituents to react at C-1 or C-3 of the intermediate **13** has been explained<sup>12,18</sup> by using Pearson's principle<sup>19</sup> of hard and soft acids and bases, according to which the anomeric center of glycals is a relatively "hard" site for the binding of nucleophiles. Consequently, C-nucleophiles, which are typical "soft" bases, might be expected to add to C-3 to form products preponderantly of type **14**. However, apart from the reaction of glycal **4** with the sodium salt of methyl dicyanoacetate, which reportedly gives C-3 branched glugal derivatives<sup>6</sup> [**14**, Nu =  $\text{CH}(\text{CN})_2$ ], C-C bond-formation takes place only at the anomeric center. Nucleophilic addition reactions of glycals include dimerization<sup>20</sup> of **4** and reaction of glycals with aromatic compounds<sup>13</sup>, alkenes<sup>5</sup>, and, in this case, a cyano group. The apparent discrepancy between the supposedly soft character of the C-3 center in **13** and the observed binding of soft C-nucleophiles at the harder anomeric center may be explained in kinetic terms. If the rate of the reaction at C-1 is sufficiently greater than that at C-3, exclusive formation of **15** can be expected, because, in the cases discussed, there is no possibility of thermodynamic equilibration. This assump-



tion is in complete agreement with the finding that reaction of glycols with thiols leads primarily to 2,3-unsaturated thioglycosides (**15**, Nu = SR), although an equilibrium mixture was shown<sup>12,18</sup> to contain mainly 3-substituted glycols (**14**).

The regiospecific rearrangement-substitution of glycols described here, resulting in attachment of a versatile, one-carbon unit to the anomeric center, should be useful in the synthesis of C-glycosyl compounds, despite the lack of stereoselectivity observed in the case of 2-acetoxglycols.

## EXPERIMENTAL

*General methods.* — Melting points were determined with a Thomas-Hoover Uni-melt apparatus and are uncorrected. Optical rotations were determined with a Bendix ETL-NPL automatic polarimeter. Infrared spectra were recorded with a Beckman IR-10 spectrometer. <sup>1</sup>H-N.m.r. spectra were recorded for CDCl<sub>3</sub> solutions (internal standard, tetramethylsilane) with a Nicolet NT-200 spectrometer. Mass spectra were recorded with a Finnigan 3600 spectrometer (lucos data-system). Thin-layer chromatography was performed on Kieselgel 60 silica gel (E. Merck). Column chromatography was conducted on silica gel 60 (230–400 mesh; E. Merck) by gravity elution. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Compounds **7** and **10** were obtained according to the procedure of Lemieux and Lineback<sup>21</sup>.

*4,6-Di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl cyanide (5,7-di-O-acetyl-2,6-anhydro-3,4-dideoxy-D-arabino-hept-3-enonitrile, 5).* — To a mixture of 3,4,6-tri-O-acetyl-D-glucal (**4**; 300 mg, 1.1 mmol) and trimethylsilyl cyanide (120 mg, 1.2 mmol), stirred in dichloromethane (5 mL) at room temperature, was added boron trifluoride etherate (one drop). After 5 min, the starting material was absent [t.l.c., 1:1 (v/v) hexane–ethyl acetate]. The mixture was diluted with ether (30 mL), successively washed with aqueous sodium hydrogencarbonate (5 mL) and water (10 mL), dried (anhydrous magnesium sulfate), and filtered through a 1-cm layer of silica gel. Evaporation of the filtrate gave **5** (208 mg, 79%); m.p. 91° (from hexane–ethyl acetate),  $[\alpha]_D -16^\circ$  (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}^{\text{KBr}}$  1720 and 1240 cm<sup>-1</sup> (ester); <sup>1</sup>H-n.m.r. (CDCl<sub>3</sub>): δ 5.94 (d, *J*<sub>2,3</sub> 10.0 Hz, 1 H, H-2), 5.81 (m, 1 H, H-3), 5.43 (bs, 1 H, H-1), 5.32 (pd, *J*<sub>4,5</sub> 9.5, *J*<sub>3,4</sub> 1.2 Hz, 1 H, H-4), 4.20 (m, 2 H, H-6,6'), 4.10 (m, 1 H, H-5), and 2.10 (s, 6 H, 2 Ac); mass spectrum (70 eV), *m/z* (%): 240(1.5), 213(1), 196(1), 180(8), 166(4), 152(9), 145(40), 137(15), 122(32), 110(28), 103(100), 94(5), and 43(95).

*Anal.* Calc. for C<sub>11</sub>H<sub>13</sub>NO<sub>5</sub>: C, 55.2; H, 5.4; N, 5.9. Found: C, 55.1; H, 5.6; N, 5.8.

*4,6-Di-O-acetyl-2,3-dideoxy-α-D-erythro-hexopyranosyl cyanide (5,7-di-O-acetyl-2,6-anhydro-3,4-dideoxy-D-arabino-heptonitrile, 6).* — Cyanide **5** (30 mg) and 5% palladium-on-charcoal (100 mg) were shaken overnight in ethanol (10 mL) under hydrogen at atmospheric pressure. Filtration through Celite, and evaporation of the filtrate, afforded **6** as an oil;  $[\alpha]_D +37^\circ$  (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-n.m.r. (CDCl<sub>3</sub>):

$\delta$  4.85 (bd,  $J \sim 4$  Hz, 1 H, H-1), 4.75 (m,  $J \sim 10$  and  $\sim 4$  Hz, 1 H, H-4), 4.20 (m, 2 H, H-6,6'), 3.95 (m, 1 H, H-5), 2.09 and 2.11 (2 s, 6 H, 2 Ac), and 1.7–2.3 (m, 4 H, H-2,3,2',3').

*2,4,6-Tri-O-acetyl-3-deoxy- $\alpha$ -D-erythro- and - $\beta$ -D-erythro-hex-2-enopyranosyl cyanides (3,5,7-tri-O-acetyl-2,6-anhydro-4-deoxy-D-arabino- and -D-ribo-hept-3-enonitriles, 8 and 9).* — Glycal **7** (400 mg, 1.2 mmol) and trimethylsilyl cyanide (140 mg, 1.4 mmol) were dissolved in dichloromethane (6 mL) and treated with boron trifluoride etherate (1 drop) at room temperature. After 30 min [t.l.c., 1:1 (v/v) toluene–ethyl acetate], the mixture was processed as described for **5**, to give an oily mixture of **8** and **9** (278 mg, 78%);  $\nu_{\max}^{\text{film}}$  1720 and 1240  $\text{cm}^{-1}$  (ester).

*Anal.* Calc. for  $\text{C}_{13}\text{H}_{15}\text{NO}_7$ : C, 52.5; H, 5.1; N, 4.7. Found: C, 52.4; H, 5.1; N, 4.5.

Chromatography on a column of silica gel with 2:1 (v/v) petroleum ether–ethyl acetate gave equal amounts of **8** and **9**. Compound **8**: an oil;  $[\alpha]_{\text{D}} +18^\circ$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H-n.m.r.}$  ( $\text{CDCl}_3$ ):  $\delta$  5.93 (m, 1 H, H-3), 5.47 (pt,  $J$  9.0, 22, and  $\sim 2$  Hz, 1 H, H-5), 5.11 (bs, 1 H, H-1), 4.28 (m, 2 H, H-6,6'), 4.06 (m, 1 H, H-5), 2.10, and 2.22 (2 s, 9 H, 3 Ac). Compound **9**: an oil;  $[\alpha]_{\text{D}} +150^\circ$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H-n.m.r.}$  ( $\text{CDCl}_3$ ):  $\delta$  5.89 (t,  $J \sim 2.8$  and 3.0 Hz, 1 H, H-3), 5.42 (pt,  $J$  8.0, 3.0, and 3.0 Hz, 1 H, H-4), 5.34 (t,  $J \sim 2.8$  and 3.0 Hz, 1 H, H-1), 4.27 (m, 2 H, H-6,6'), 3.95 (m, 1 H, H-5), and 2.08, 2.10, and 2.22 (3 s, 9 H, 3 Ac).

*2,4,6-Tri-O-acetyl-3-deoxy- $\alpha$ -D-threo- and - $\beta$ -D-threo-hex-2-enopyranosyl cyanides (3,5,7-tri-O-acetyl-2,6-anhydro-4-deoxy-D-lyxo- and -D-xylo-hept-3-enonitriles, 11 and 12).* — Glycal **10** (400 mg, 1.2 mmol), treated with trimethylsilyl cyanide as before, gave a crystalline mixture of **11** and **12** (260 mg, 73%);  $\nu_{\max}^{\text{KBr}}$  1720 and 1240  $\text{cm}^{-1}$  (ester).

*Anal.* Calc. for  $\text{C}_{13}\text{H}_{15}\text{NO}_7$ : C, 52.5; H, 5.1; N, 4.7. Found: C, 52.5; H, 5.2; N, 4.6.

Chromatography on a column of silica gel with 2:1 (v/v) petroleum ether–ethyl acetate gave nearly equal amounts of **11** and **12**. Compound **11**: m.p.  $86^\circ$ ,  $[\alpha]_{\text{D}} -210^\circ$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H-n.m.r.}$  ( $\text{CDCl}_3$ ):  $\delta$  6.15 (pd,  $J_{3,4}$  6.2,  $J_{1,3}$  1.5 Hz, 1 H, H-3), 5.34 (d,  $J$  6.2 Hz, 1 H, H-4), 5.17 (d,  $J$  1.5 Hz, 1 H, H-1), 4.2–4.3 (m, 1 H, H-5), 4.26 (s, 2 H, H-6,6'), and 2.07, 2.08, and 2.22 (3 s, 9 H, 3 Ac). Compound **12**: m.p.  $84^\circ$ ,  $[\alpha]_{\text{D}} -85^\circ$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H-n.m.r.}$  ( $\text{CDCl}_3$ ):  $\delta$  6.09 (m, 1 H, H-3), 5.3–5.4 (m, 2 H, H-1,4), 4.09 (m, 1 H, H-5), 4.30 (m, 2 H, H-6,6'), and 2.09, 2.11, and 2.22 (3 s, 9 H, 3 Ac).

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