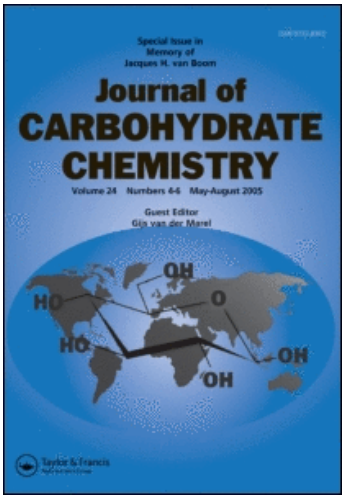


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Cyano Sugars: Synthesis by Opening of an Epoxide Ring in Pentofuranosides with Diethylaluminum Cyanide

Satoru Watanabe[a]; Ivan Kavai[a]; Miroslav Bobek[a]
[a] Grace Cancer Drug Center, Roswell Park Cancer Institute, Buffalo, New York, USA

To cite this Article Watanabe, Satoru , Kavai, Ivan and Bobek, Miroslav(1995) 'Cyano Sugars: Synthesis by Opening of an Epoxide Ring in Pentofuranosides with Diethylaluminum Cyanide', Journal of Carbohydrate Chemistry, 14: 6, 685 — 701
To link to this Article: DOI: 10.1080/07328309508005370
URL: http://dx.doi.org/10.1080/07328309508005370

J. CARBOHYDRATE CHEMISTRY, 14(6), 685-701 (1995)

CYANO SUGARS: SYNTHESIS BY OPENING OF AN EPOXIDE RING IN PENTOFURANOSIDES WITH DIETHYLALUMINUM CYANIDE.

Satoru Watanabe, Ivan Kavai and Miroslav Bobek*

Grace Cancer Drug Center, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, New York 14263, USA.

Received November 15, 1994 - Final Form February 7, 1995

ABSTRACT

Reaction of diethylaluminum cyanide (DEAC) with methyl 2,3-anhydroribofuranosides was examined as a potentially useful method for the introduction of the cyano group at C-2 and C-3 of furanosyl sugars. Thus, treatment of methyl 2,3-anhydro-5-*O*-benzyl-ß-D-ribofuranoside with DEAC provided methyl 5-*O*-benzyl-3-cyano-3-deoxy-ß-D-xylofuranoside (**2**), while similar treatment of methyl 2,3-anhydro-5-*O*-benzyl-α-D-ribofuranoside gave a mixture of methyl 5-*O*-benzyl-3-cyano-3-deoxy-α-D-xylofuranoside (**5**) and methyl 5-*O*-benzyl-2-cyano-2-deoxy-α-D-arabinofuranoside (**6**). Epimerization of **2** at C-3 was readily effected in the presence of base to give methyl 5-*O*-benzyl-3-cyano-3-deoxy-ß-D-ribofuranoside (**9**). In contrast, **5** and **6** were resistant to base-promoted epimerization. Sequential acetylation and acetolysis converted the cyano sugars **2** and **9** into the corresponding tri-*O*-acetyl derivatives **13**, **14** and **15**.

INTRODUCTION

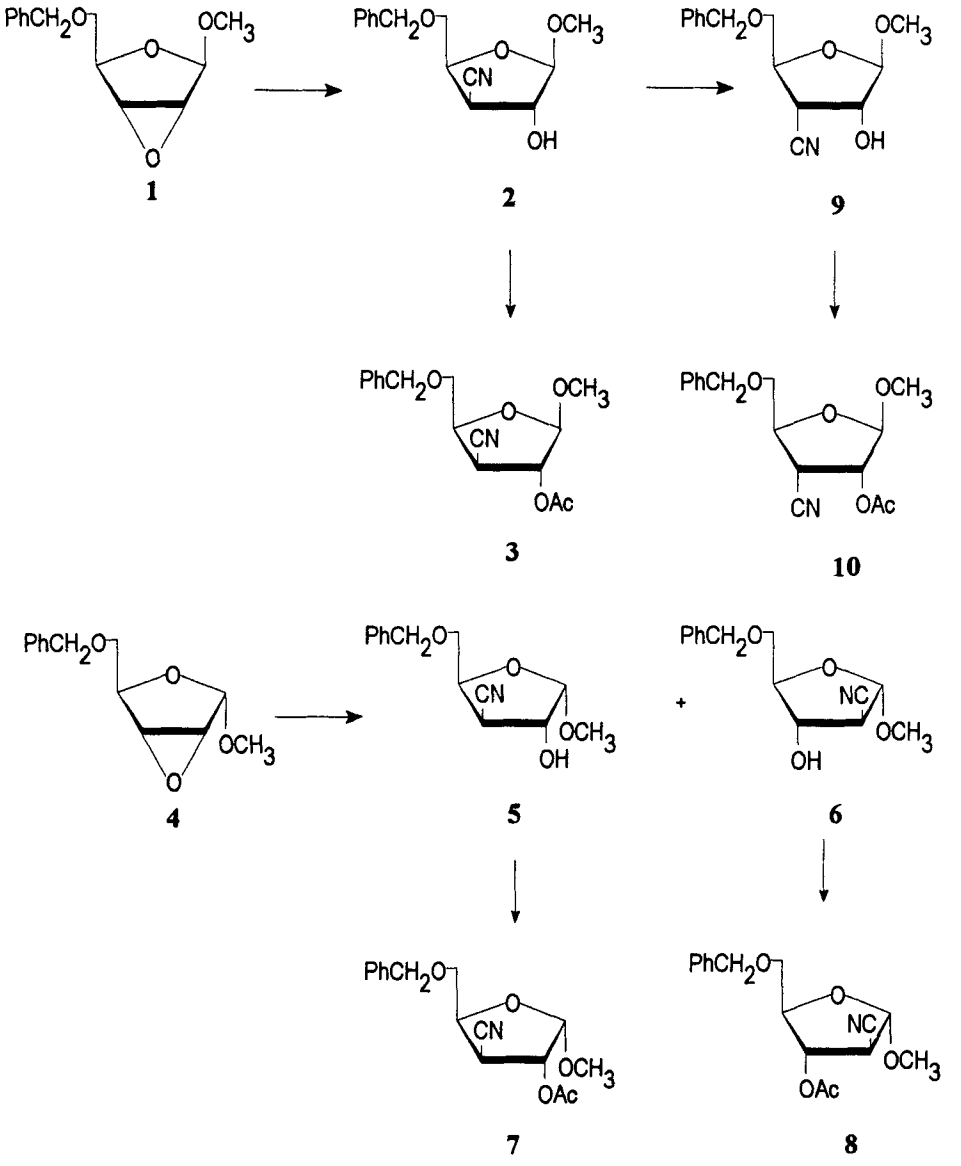
Cyano-sugars can serve as useful intermediates for the synthesis of potential chemotherapeutic cyanonucleosides[1,2] and of various C-branched-chain sugars.[3] The nitrile

function can be a synthon for the aminomethyl and aldehyde groups[4-6] which, in turn, can be readily converted to a variety of other functionalities. We now report that the reaction of diethylaluminum cyanide[7-9] (DEAC) with methyl 2,3-anhydro-5-*O*-benzyl-α,β-D-ribofuranosides constitutes a convenient approach for the synthesis of C-2- and C-3-nitrile substituted pentofuranosides.

RESULTS AND DISCUSSION

The starting methyl 2,3-anhydro-5-*O*-benzyl-β-D-ribofuranoside (**1**) and its α-anomer **4** were prepared from 1,2,3,5-di-*O*-isopropylidene-β-D-xylofuranose as reported previously.[10] Treatment of **1** with DEAC in toluene resulted in *trans* opening of the epoxide ring at C-3 to give methyl 5-*O*-benzyl-3-cyano-3-deoxy-β-D-xylofuranoside (**2**) (Scheme 1) as the only product. In the NMR spectrum of **2**, the signals for the anomeric proton and for H-2 appeared as a singlet and a doublet ($J_{2,3}$=1.5 Hz), respectively, establishing the *trans* relationship for H-1, H-2 and H-3. The signal for H-3 appeared upfield at δ 3.20-3.05 as a result of the shielding effect[11] of the cyano group. The regiospecific opening of the epoxide in **1** parallels similar opening[12-14] of this epoxide with other acid-type nucleophiles. The direction of the opening is believed to be governed by a combination of the steric and polar effects[15] of the groups adjacent to the epoxide ring. In the epoxide **1**, the polar effect favors the cleavage at C-3. The steric effect of the methoxy and benzyloxymethyl substituents oppose each other, but it has been suggested that the effect of the methoxy group at C-1 is likely to be stronger because of the anomeric effect.[12] In an attempt to enhance the attack by DEAC at C-2, by increasing the polar effect at C-3, the protecting benzyl group in **1** was replaced with an acetyl group. However, methyl 5-*O*-acetyl-2,3-anhydro-β-D-ribofuranoside[16] was resistant to cleavage of the epoxide by DEAC even under conditions more forceful than those used for cleavage of **1**.

Reaction of methyl 2,3-anhydro-5-*O*-benzyl-α-D-ribofuranoside (**4**) with DEAC gave a mixture of two products in an approximate 3:1 ratio. The major component was



SCHEME 1

shown to be methyl 5-*O*-benzyl-3-cyano-3-deoxy-α-D-xylofuranoside (**5**) while the second product was identified as methyl 5-*O*-benzyl-2-cyano-2-deoxy-α-D-arabinofuranoside (**6**). The NMR spectrum of **5** showed the anomeric proton as a doublet (δ 4.78, $J_{1,2}$=4.5 Hz), the coupling constant being consistent with the *cis* stereochemistry of H-1 and H-2. Because of the deshielding effect[11] of the 2-CN group, the signal for the anomeric proton of **6** appeared downfield (δ 5.17, $J_{1,2}$= 2.0 Hz) from that in **5**, the small coupling constant being consistent with the *trans* relationship of H-1 and H-2. Thus, as expected, removal of the steric effect at C-1 led to a competing attack by DEAC at C-2, which resulted in the formation of a significant amount of **6**. That the opening of the epoxide in **4** with DEAC occurred predominantly at C-3, while a similar reaction of this epoxide with KHF_2[17] or diborane[14] resulted in a predominant C-2 opening, may be rationalized by the strong proclivity of aluminum alkyls to form adducts with ethers.[18] The likely formation of such an adduct between DEAC and the 4-benzyloxymethyl group may, thus, enhance its attack at the adjacent (C-3) position.

In an attempt to obtain 2-cyano-2-deoxy- and 3-cyano-3-deoxy-D-ribopento-furanosides, the base promoted epimerization[8,19] of **2**, **5** and **6** was studied next. Treatment of **2** with KCN in pyridine-methanol at 50-55 °C resulted in epimerization at C-3 to give an equilibrium mixture of methyl 5-*O*-benzyl-3-cyano-3-deoxy-β-D-ribofuranoside (**9**) (70%) and **2** (22%). The NMR spectrum of **9** showed the signals of the anomeric proton and of H-2 as a singlet and a doublet ($J_{2,3}$=3.8 Hz), respectively, while the signal for H-3 appeared as a multiplet at δ 3.23. Similar results were obtained by using NaOH or Na_2CO_3 in methanol as the catalysts in the epimerization of **2**, but the yield of **9** and recovered **2** was lower. In contrast, treatment of **5** or **6** with these catalysts gave only the recovered starting compounds. When the reaction was performed at higher temperatures or for extended periods of time, only extensive decomposition of the starting compounds resulted.

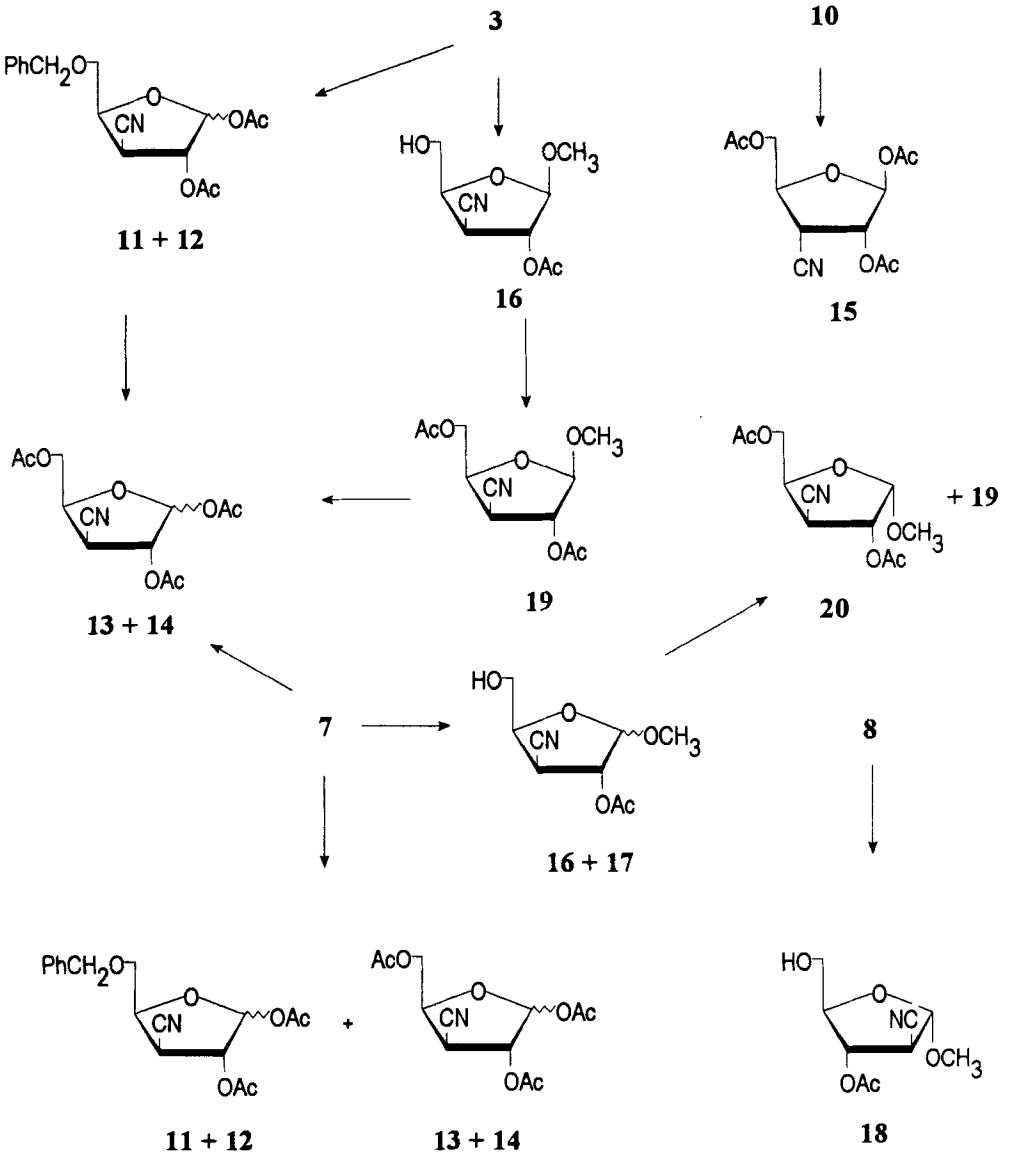
Acetylation of **2**, **5**, **6**, and **9** with acetic anhydride in pyridine or acetic anhydride-trifluoroacetic acid gave the corresponding monoacetyl derivatives **3**, **7**, **8**, and **10**, respectively. For preparation of the fully acetylated pentofuranosyl cyano sugars, which can serve as useful intermediates for the synthesis of the related cyanonucleosides, acetolysis appeared as a convenient method. Initially, selective acetolysis of compounds **3**,

7, **10** under controlled conditions was attempted to avoid a possible isomerization of **3**, **7**, **10** to their pyranosyl derivatives, but no suitable reaction conditions could be found for a selective replacement of 1-*O*-methyl with the acetyl. Thus, partial acetolysis of **3** or **7** gave 1,2-di-*O*-acetyl derivatives (**11**, **12**) contaminated with 1,2,5-tri-*O*-acetates (**13**, **14**) as mixtures of α and β anomers (Scheme 2). Complete acetolysis of **3** and **7** gave the α- and β-anomers of the 1,2,5-tri-*O*-acetates (**13**,**14**), while complete acetolysis of **10** furnished 1,2,5-tri-*O*-acetate **15** as the single β anomer. The anomeric configuration was established by the NMR spectrum of **15** which showed the signal of the anomeric proton as a singlet. That the furanosyl structure of the cyano derivatives was not changed during complete acetolysis was shown by the following series of experiments: the mixture of **11** and **12** obtained by partial acetolysis of **3** was sequentially treated with boron trichloride (1 M in dichloro-methane), to remove the benzyl groups, and acetylated to furnish a mixture of the tri-*O*-acetates **13** and **14**. Similarly, treatment of **3** and of **8** with boron trichloride at -70 °C gave methyl 2-*O*-acetyl-3-cyano-3-deoxy-β-D-ribofuranoside (**16**) and methyl 3-*O*-acetyl-2-cyano-2-deoxy-α-D-arabinofuranoside (**18**), respectively. Treatment of **7** with boron trichloride fostered, in addition to removal of the benzyl group, isomerization of the *O*-methyl group to give an anomeric mixture of **16** and **17**. Acetylation of **16** and of the mixture of **16** and **17** gave methyl 2,5-di-*O*-acetyl-3-cyano-3-deoxy-β-D-xylofuranoside (**19**) and a mixture of **19** and **20**, respectively. Acetolysis of **19** furnished a mixture of **13** and **14**.

Further support for the assigned configuration of the tri-*O*-acetates was obtained by comparing the proton coupling constants of **13** and **14** with those of the xylofuranosyl and xylopyranosyl tetra-*O*-acetates.[20] Similarly, the proton coupling constants of **15** were in good agreement with those of the β-ribofuranosyl tetra-*O*-acetate[21] as compared with those of the alternative ribopyranosyl tetra-*O*-acetates.[22]

EXPERIMENTAL

General procedures. Melting points were determined with a Mel-Temp capillary point block and are uncorrected. Elemental analyses were performed by Robertson



SCHEME 2

Laboratory, Morison, NJ. IR spectra were recorded with Perkin-Elmer Models 457 and 710B spectrophotometers. ^{1}H NMR spectra were recorded on a Varian 390 (90 MHz) and a Bruker WP-200 (200 MHz) spectrometers, and chemical shifts are given in ppm using Me_4Si as internal standard. Mass spectra were recorded with a Finnigan 4500 mass spectrometer. Thin-layer and column chromatography was performed on EM Science silica gel plates and on silica gel (230-400 mesh) from E. Merck Industries Co., respectively. Evaporations were conducted under diminished pressure at bath temperatures below 40 °C.

Methyl 5-*O*-Benzyl-3-cyano-3-deoxy-β-D-xylofuranoside (2). Diethylaluminum cyanide (DEAC, 180 mL, 0.27 mol, 1.5 M in toluene) was added to a solution of methyl 2,3-anhydro-5-*O*-benzyl-ß-D-ribofuranoside (**1**) (30.9 g, 0.131 mol) in toluene (420 mL, Na dried) and the reaction mixture was stirred at 50-60 °C under argon for 4 h. The mixture was cooled, diluted with ethyl acetate (900 mL), and, then poured into a stirred mixture of ice-water (1500 mL) and acetic acid (150 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 300 mL). The combined organic solution was sequentially washed with water, dried (Na_2SO_4), and concentrated to leave a syrup which was purified by chromatography on silica gel (740 g), using petroleum ether-ether (1:1) as the eluent, to give 2.6 g of **2** (65%) as a syrup: IR (neat) 2220 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (s, 5H, phenyl), 4.82 (s, 1H, H-1), 4.62 (s, 2H, CH_2Ph), 4.57 (d, 1H, $J_{2,3}$=1.5 Hz, H-2), 4.40 (m, 1H, H-4), 3.90-3.50 (m, 2H, H-5,5'), 3.32 (s, 3H, OCH_3), 3.20-3.05 (m, 1H, H-3); ^{1}H NMR (DMSO-d_6) δ 7.35 (s, 5H, phenyl), 6.03 (d, 1H, OH), 4.78 (s, 1H, H-1), 4.56 (s, 2H, CH_2Ph), 4.35-4.25 (m, 1H, H-4), 3.67, 3.60 (s,s, 2H, H-5,5'), 3.40 (m, 1H, H-3), 3.25 (s, 3H, OCH_3); MS M *m/z* 263; 231, M -$HOCH_3$; 91, $PhCH_2$.

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.72; H, 6.58; N, 5.18.

Methyl 2-*O*-Acetyl-5-*O*-benzyl-3-cyano-3-deoxy-β-D-xylofuranoside (3). To a solution of **2** (19.9 g, 0.075 mol) in dry pyridine (21 mL), cooled in an ice bath, was added acetic anhydride (16 mL) and the reaction mixture was stirred at 0-4 °C for 20 min and then at room temperature overnight. Xylene (40 mL) was added to the mixture which was then concentrated. The residue was coconcentrated with xylene (2 x 80 mL), triturated

with methanol (50 mL) and filtered. The filtered product (20.74 g; mp 123.0-123.5 °C) was washed with methanol and dried. Concentration of the combined filtrates to a small volume to induce crystallization gave additional **3** (0.64 g; mp 122.0 °C) for the total yield of 21.38 g (92%): mp 123.0-123.5 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 7.38 (s, 5H, phenyl), 5.32 (d, 1H, $J_{2,3}$=1.3 Hz, H-2), 4.98 (s, 1H, H-1), 4.62 (2s, m, 3H, CH_2Ph, H-4), 3.82 (m, 2H, H-5,5'), 3.38 (s, 3H, OCH_3), 3.32 (d,d, 1H, $J_{3,4}$=7.2 Hz, H-3), 2.08 (s, 3H, OAc); MS M *m/z* 305; 273, M -CH_3OH; 245, M -CH_3COOH; 214, M -$PhCH_2$; 184, M-CH_2OCH_2Ph; 91, $PhCH_2$.

Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.89; H, 6.31; N, 4.48.

Methyl 5-*O*-Benzyl-3-cyano-3-deoxy-α-D-xylofuranoside (5) and Methyl 5-*O*-Benzyl-2-cyano-2-deoxy-α-D-arabinofuranoside (6). A stirred solution of methyl 2,3-anhydro-5-*O*-benzyl-α-D-ribofuranoside (**4**) (38.3 g , 0.162 mol) in dry toluene (250 mL) was treated with DEAC (250 mL of the toluene solution, 0.38 mol) at 50-60 °C and under argon for 3 h. The reaction mixture was cooled, diluted with ethyl acetate (60 mL), and was slowly poured into a stirred mixture of ice-water (1600 mL) and acetic acid (200 mL). After 30-60 min of stirring, the organic phase was separated and the aqueous phase was extracted with dichloromethane (4 x 300 mL). The combined organic solution was sequentially washed with water, dried (Na_2SO_4), and concentrated. The residue was added to a similar residue, which was obtained from a second reaction batch of **4** (22.4 g, 0.095 mol) with DEAC, and the combined residue was separated by chromatography on silica gel (1500 g) using petroleum ether-ether (1:1) as the eluent. The appropriate fractions were combined and concentrated to give pure **6** (13.1 g, R_f = 0.40), a mixture of **5** and **6** (2.83 g) and **5** (39.70 g, R_f = 0.21). The mixture of **5** and **6** was rechromatographed to give additional **5** (0.12 g) and **6** (0.69 g) for the total yield of 13.79 g (20%) of **6** and 39.82 g (57.9%) of **5.**

For **5**: ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 5H, phenyl), 4.90 (d, 1H, $J_{1,2}$=4.5 Hz, H-1), 4.59, 4.57 (s,s, 2H, $PhCH_2$), 4.66-4.34 (m, 2H, H-2, H-4), 3.69 (d, 2H, $J_{4,5}$=3.7 Hz, H-5), 3.45 (s, 3H, OCH_3), 3.19 (t, 1H, $J_{2,3}$=$J_{3,4}$=8.0 Hz, H-3); ^{1}H NMR (DMSO-d_6) δ 7.35 (s, 5H, Ph), 5.67 (d, 1H, J=7.9 Hz, OH), 4.78 (d, 1H, $J_{1,2}$=4.2 Hz, H-1), 4.52 (s, 2H, CH_2Ph), 4.44-4.20 (m, 2H, H-2, H-4), 3.62 (d,d, 2H, J=3.2, 2.6 Hz, H-5,5'), 3.46-3.28

(m, 1H, H-3), 3.32 (s, 3H, OCH_3); MS M *m/z* 263; 264, M + 1; 91, $PhCH_2$; 77, Ph; 107, $PhCH_2O$.

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.61; H, 6.54; N, 5.28.

For **6**: IR (neat) 2220 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (s, 5H, Ph), 5.17 (d, 1H, $J_{1,2}$=2.0 Hz, H-1), 4.57 (s, 2H, CH_2Ph), 4.32 (m, 1H, H-4), 4.07 (m, 1H, H-3), 3.63 (d, 2H, $J_{4,5}$=4.8Hz, H-5), 3.39 (s, 3H, OCH_3), 3.03 (d,d, 1H, $J_{1,2}$=2.0 Hz, $J_{2,3}$=4.0 Hz, H-2); ^1H NMR (DMSO-d_6) δ 7.33 (s, 5H, Ph), 6.11 (d, 1H, J= 5.7 Hz, OH), 5.19 (d, 1H, $J_{1,2}$=3.2 Hz, H-1), 4.54 (s, 2H, CH_2Ph), 4.22 (m, 1H, H-4), 3.92 (m, 1H, H-3), 3.63 (d, 1H, $J_{4,5}$=2.6 Hz, H-5), 3.59 (d, 1H, $J_{4,5'}$ = 5.1 Hz, H-5'), 3.32 (s, 3H, OCH_3), 3.07 (d,d, 1H, $J_{1,2}$=3.2 Hz, $J_{2,3}$=3.3 Hz, H-2); MS M *m/z* 263, 91, $PhCH_2$; 107, $PhCH_2O$; 231, M - CH_3O.

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.64; H, 6.52, N, 4.93.

Methyl 2-*O*-Acetyl-5-*O*-benzyl-3-cyano-3-deoxy-α-D-xylofuranoside (7). To a cooled (0 °C) solution of **5** (31.18 g, 0.118 mol) in dry dichloromethane (240 mL) were added acetic anhydride (130 mL) and trifluoroacetic acid (99%, 6 mL) and the reaction mixture was kept at 3 °C for 60 h. Xylene (100 mL) was added to the mixture which was then evaporated. The residue was coconcentrated with xylene (2 x 100 mL) and the resulting crystalline residue was triturated with methanol, filtered and recrystallized (methanol) to give 32.79 g (90%) of **7**; mp 101.0-101.5 °C; IR (neat) 2220 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (s, 5H, phenyl), 5.17 (m, 2H, H-1, H-2), 4.62, 4.58 (s,s, 2H, CH_2Ph), 4.54-4.34 (m, 1H, H-4), 3.70 (d,d, 2H, $J_{4,5}$ = 0.7 Hz, $J_{4,5'}$ =3.6 Hz, H-5, H-5'), 3.68-3.42 (m, 1H, H-3), 3.36 (s, 3H, OCH_3), 2.10 (s, 3H, OAc); MS M *m/z* 305; 77, Ph; 91, $PhCH_2$; 107, $PhCH_2O$; 214, M -$PhCH_2$.

Anal. Calcd for $C_{16}H_{19}NO_5$: C 62.94 H 6.27 N 4.59. Found: C 63.14; H 6.22; N 4.59.

Methyl 3-*O*-Acetyl-5-*O*-benzyl-2-cyano-2-deoxy-α-D-arabinofuranoside (8). Similarly to acetylation of **5**, a solution of **6** (13.1 g, 0.05 mol) in dry dichloromethane (200 mL) was treated with acetic anhydride (80 mL) and trifluoroacetic acid (35 mL) and the reaction mixture worked-up to give a residue which was separated by chromatography

on silica gel (700 g, petroleum ether-ether, 2:1) to yield 4.0 g of **8** and a fraction of **8** contaminated with the starting material which was reacetylated and rechromatographed to provide additional 6.33 g of **8** as a syrup; IR (neat) 2220 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (s, 5H, phenyl), 5.30-5.22 (m, 2H, H-1, H-3), 4.60 (s, 2H, CH_2Ph), 4.29-4.16 (m, 1H, H-4), 3.69 (d, 2H, $J_{4,5}$ = 4.0 Hz, H-5), 3.39 (s, 3H, OCH_3), 3.08 (d,d, $J_{1,2}$ = 1.5, $J_{2,3}$ = 3.0 Hz, H-2), 2.06 (s, 3H, OAc,); MS M *m/z* 305; 71, Ph; 91, $PhCH_2$; 107, $PhCH_2O$.

Anal. Calcd for: $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.64; H, 6.09; N, 4.31.

Methyl 5-*O*-Benzyl-3-cyano-3-deoxy-β-D-ribofuranoside (9). *Method* A. *Isomerization of 2 with potassium cyanide in methanol-pyridine.* Potassium cyanide (2.832 g, 0.0434 mol) in methanol (150 mL) was added to a solution of **2** (10.938g, 0.0415 mol) in dry pyridine (80 mL) and the reaction mixture was stirred at 50-55 °C for 2 h. Additional potassium cyanide (1.273 g, 0.0215 mol) in methanol (70 mL) was added to the reaction mixture and stirring was continued for another hour when TLC (petroleum ether-ether, 1:1) showed that no further change had occurred. The mixture was cooled in ice-water and neutralized by acetic acid. Xylene (25 mL) was added to the mixture and the solvents were removed by evaporation. The residue was sequentially coconcentrated with xylene (3 x 50 mL), taken up in dichloromethane (100 mL), filtered, and again concentrated. The crude product was chromatographed twice on silica gel (260 g) using petroleum ether-ether (1:1) as the eluent to give **9** (7.03 g, 64%), a mixture of **2** and **9** (2.89 g, 26 %), and **2** (0.24 g, 2.0 %).

Method B. Isomerization of 2 with NaOH in methanol. To a solution of **2** (0.557 g, 0.0021 mol) in methanol (42 mL) was added dropwise a 1N solution of NaOH in methanol to adjust the pH of the reaction mixture to 9. The mixture was kept at room temperature for 5 h, neutralized with glacial acetic acid and concentrated. The oily residue was coconcentrated two times with toluene, taken up in chloroform, and filtered. After removal of chloroform by evaporation, the residual syrup was chromatographed on silica gel (50 g) using petroleum ether-ether (1:1) as the eluent to give 0.359 g (64%) of **9** and 0.014g (2.5%) of **2**.

Method C. Isomerization of 2 with anhydrous sodium carbonate in methanol. To a stirred solution of **2** (0.532 g, 0.002 mol) in methanol (50 mL) was added anhyd sodium

carbonate until a pH 9 was reached. The reaction mixture was stirred at room temperature for 5 h (monitored by TLC), neutralized by acetic acid and worked up as described in *method A* to give 0.12 g (22 %) of **2**, 0.015 g (3.5 %) of a mixture of **9** and **2** and 0.324 g (61%) of **9** as an oil. ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 5H, Ph), 4.86 (s, 1H, H-1), 4.62-4.57 (m, 1H, H-4), 4.59 (s, 2H, CH_2Ph), 4.30 (d, 1H, $J_{2,3}$ = 3.8 Hz, H-2), 3.61 (d, 2H, $J_{4,5}$ = 4.8 Hz, H-5), 3.25-3.21 (m, 1H, H-3), 3.28 (s, 3H, OCH_3); MS M *m/z* 263; 262, M -1; 231, M -CH_3OH; 91, $PhCH_2$; 107, $PhCH_2O$.

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.72; H, 6.58; N, 5.18.

Methyl 2-*O*-Acetyl-5-*O*-benzyl-3-cyano-3-deoxy-β-D-ribofuranoside (10). Compound **9** (0.613 g) was acetylated with acetic anhydride (3 mL) in pyridine (4 mL) at room temperature overnight. Methanol (10 mL) followed by xylene (10 mL) were added to the reaction mixture which was then concentrated. The residue was coconcentrated with xylene, and purified by chromatography on silica gel (petroleum ether- ether, 1:1) to give **10** (0.638 g, 90 %) as an oil: ^{1}H NMR ($CDCl_3$ δ 7.34 (s, 5H, Ph), 5.26 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 4.86 (s, 1H, H-1), 4.60 (s, 2H, $PhCH_2$), 4.68-4.50 (m, 1H, H-4), 3.63 (d, 2H, $J_{4,5}$ = 4.8 Hz, H-5), 3.40 (d,d, 1H, $J_{3,4}$ = 4.7 Hz, H-3), 3.30 (s, 3H, OCH_3), 2.10 (s, 3H, O-Ac); MS M *m/z* 305; 77, Ph; 91, $PhCH_2$; 107, $PhCH_2O$; 273, M-CH_3OH; 274, M-CH_3O.

Anal. Calcd for $C_6H_{19}NO_5$: C, 62.94; H, 6.27; N 4.59. Found: C, 63.01; H, 6.32; N, 4.48.

1,2-Di-*O*-acetyl-5-*O*-benzyl-3-cyano-3-deoxy-α-D-xylofuranose (11) and **1,2-Di-*O*-acetyl-5-*O*-benzyl-3-cyano-3-deoxy-ß-D-xylofuranose (12).** *Method A. From methyl 2-O-acetyl-5-O-benzyl-3-cyano-3-deoxy-α-D-xylofuranoside (7).* To a cold (3 °C) solution of **7** (2.141 g, 0.007 mol) in acetic anhydride (40 mL) was added a solution of H_2SO_4 in acetic anhydride (25 drops, v/v=1:5) . The reaction mixture was kept at 3-5 °C for 4 h (monitored by TLC) and 6 additional drops of the H_2SO_4 solution were added. After 4 h, TLC indicated that a triacetate began to form and, therefore, the reaction was stopped by the addition of anhyd sodium acetate. Xylene (60 mL) was stirred with the reaction mixture and the supernatant was decanted. The solid residue was stirred with

chloroform and filtered. The decanted solution was concentrated and the residue was sequentially coconcentrated with xylene (60 mL), combined with the chloroform filtrate, and concentrated again. The residue was combined with a similar residue obtained from a second acetolysis reaction of **7** (1.755 g, 0.0057 mol). The combined residue was flash chromatographed on silica gel (260 g, ether-petroleum ether, 2:1, and then ether-petroleum ether, 3:1), and the fractions which contained poorly separated products (1.53 g) were rechromatographed on silica gel (155 g, ether-petroleum ether, 9:5) to give 1.030 g (24%) of **12** (oil), 1.2 g (28%) of crystalline **11** (lower R_f) and 0.790 g (22%) of an anomeric mixture of the triacetates **13** and **14**.

Method B. From methyl 2-O-acetyl-5-O-benzyl-3-cyano-3-deoxy-β-D-xylofuranoside (3). To a cold (3 °C) solution of **3** (1.074 g, 0.0035 mol) in acetic anhydride (20 mL) was added H_2SO_4 (4 drops) over a period of 4 h. When a triacetate derivative began to appear (as shown by TLC), the reaction was terminated by the addition of anhyd sodium acetate, diluted with chloroform (50 mL) and filtered. The filter cake was washed with chloroform and the combined filtrate was concentrated. Coconcentration of the residue with xylene gave the crude product which was separated by chromatography on silica gel (40 g) using ether-petroleum ether (2:1) as the eluant to give recovered **3** (0.02 g, 1.8%), **12** (0.123 g, 10.5%), a mixture (2:1) of **11** and **12** (0.387 g, 33%), the triacetate **13** (0.266 g, 25%) contaminated with a trace of its α-anomer **14**, and a mixture of **13** and **14** (0.065 g, 6%).

For **11**: mp 111-2° C (ethanol); ^{1}H NMR ($CDCl_3$) δ 7.38 (s, 5H, Ph), 6.46 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1), 5.57 (d,d, 1H, $J_{2,3}$ = 11.5 Hz, H-2), 4.62, 4.60 (s,s, 2H, $PhCH_2$), 4.50-4.64 (m, 1H, H-4), 3.74, 3.72 (2d, 2H, $J_{4,5}$ = 4.0 Hz, $J_{4,5'}$=3.6 Hz, H-5,5'), 3.57 (t, 1H, $J_{3,4}$ = 11.0 Hz, H-3), 2.10, 2.07 (s,s, 6H, OAc).

For **12**: ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 5H, Ph), 6.15 (s, 1H, H-1), 5.42 (s, 1H, H-2), 4.59, 4.57 (s,s, 2H, $PhCH_2$), 4.65-4.51 (m, 1H, H-4), 3.88-3.66 (m, 2H, H-5,5'), 3.38 (d, 1H, $J_{3,4}$ = 6.9 Hz), H-3), 2.06, 2.03 (s,s, 6H, OAc).

Anal. (a 2:1 mixture of **11** and **12**) Calcd for: $C_{17}H_{19}NO_6$: C 61.25 H 5.74 N 4.20. Found: C 61.34 H 5.44 N 4.04.

1,2,5-Tri-*O*-acetyl-3-cyano-3-deoxy-β-D-xylofuranose (13) and **1,2,5-Tri-*O*-acetyl-3-cyano-3-deoxy-α-D-xylofuranose (14)**. To a cold (3-5 °C) solution of **7** (1.165

g, 0.038 mol) in acetic anhydride (24 mL) was added a solution of H_2SO_4 in acetic anhydride (20 drops, v/v=1:10) with stirring during 3 h, while the progression of the reaction was monitored by TLC. The reaction mixture was stirred for one h and anhyd sodium acetate (2 g) was added followed by addition of xylene (20-25 mL). The mixture was concentrated and the residue was coconcentrated with xylene (3 x 25 mL). The residue was then taken up in dichloromethane (50 mL), filtered and the filtered solid was washed with dichloromethane (50 mL). Concentration of the combined filtrate followed by chromatography of the residue on silica gel (124 g, ether-chloroform 1:1) gave a mixture of **13** and **14** (0.592 g) and pure **13** (0.128 g, low R_f isomer) as an oil. Repeated chromatography of the mixture gave **14** (oil, 0.236 g, high R_f), **13** (0.162 g) and a mixture (0.122 g) of **13** and **14**. For **13**: ^{1}H NMR ($CDCl_3$) δ 6.18 (s, 1H, H-1), 5.44 (s, 1H, H-2), 4.71-4.65 (m, 1H, H-4), 4.42-4.32 (m, 2H, H-5,5'), 3.52 (d, 1H, $J_{3,4}$ = 6.9 Hz, H-3), 2.14-2.12 (s,s,s, 9H, OAc); IR (neat or Nujol) 2220 (CN) cm^{-1}; MS M *m/z* 226; 166, 145, 93.

Anal. Calcd for $C_{12}H_{15}NO_7$: C, 50.52; H, 5.30; N, 4.91. Found: C, 49.71; H, 5.19; N 4.55.

For **14**: ^{1}H NMR ($CDCl_3$) δ 6.45 (d, 1H, $J_{1,2}$ = 4.2 Hz, H-1), 5.45 (d,d, 1H, $J_{2,3}$ = 4.3, H-2), 4.76-4.70 (m, 1H, $J_{3,4}$ = 8.9 Hz, H-4), 4.42-4.27 (m, 2H, H-5,5'), 3.64 (t, 1H, H-3), 2.20-2.12 (s,s,s, 9H, OAc); IR (neat or Nujol) 2220 cm^{-1} (CN); MS M *m/z* 226; 166, 145, 93.

Anal. Calcd for: $C_{12}H_{15}NO_7$ .1/2 H_2O: C, 48.98; H, 5.48; N 4.76.
Found: C, 48.94; H, 5.13; N 4.50.

1,2,5-Tri-*O*-acetyl-3-cyano-3-deoxy-β-D-ribofuranose (15). To a cold (3 °C) solution of **10** (5.70 g, 0.0187 mol) in acetic anhydride and acetic acid (v/v=1:1, 80 mL) was added dropwise concd H_2SO_4 (2 mL) with stirring and the reaction mixture was stirred at 3 °C overnight. Anhyd sodium acetate (23 g) was added to the mixture which was then stirred at room temperature for 30 min. The mixture was poured into ice-water (250 mL) and extracted with chloroform (4 x 200 mL). The combined extract was dried (Na_2SO_4) and concentrated to give a syrup which was chromatographed on silica gel (170 g, ether-petroleum ether, 2:1). Concentration of the appropriate fractions gave **15** (4.52 g, 84%) contaminated with a trace of its α-anomer. Recrystallization of this product from ethanol gave pure **15**: mp 68-69 °C; ^{1}H NMR ($CDCl_3$) δ 6.18 (s, 1H, H-1), 5.44 (d, 1H,

$J_{2,3}$ = 4.74 Hz, H-2), 4.77-4.63 (m, 1H, H-4), 4.45-4.22 (m, 2H, H-5,5'), 3.61-3.42 (m, 1H, $J_{3,4}$ = 4.68, H-3), 2.10 (s,s,s, 9H, OAc); IR (neat or Nujol) 2220 (CN) cm^{-1}; MS *m/z* 226; 166; 145; 93.

Anal. Calcd for $C_{12}H_{15}NO_7$: C, 50.52; H, 5.30; N, 4.91. Found: C, 50.60; H, 5.37; N, 4.87.

Methyl 2-*O*-Acetyl-3-cyano-3-deoxy-β-D-xylofuranoside (16). Boron trichloride (7 mL, 0.0070 mol, 1 M in dichloromethane) was added under argon to a cold (-78 °C) solution of **3** (1.092 g, 0.0035 mol) in dry dichloromethane (50 mL) and the reaction mixture was stirred at -78 °C for 2 h. It was then warmed to 0 °C and poured into a stirred solution of sodium bicarbonate (10 g) in ice-water (100 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (50 mL). The combined organic solution was dried (Na_2SO_4) and concentrated to give an oil which was purified by chromatography on silica gel (40 g, 1:1 chloroform/ether) to give **16** (0.345 g, 46%) : ^{1}H NMR ($CDCl_3$) δ 5.30 (d, 1H, $J_{2,3}$ = 1.3 Hz, H-2), 4.98 (s, 1H, H-1), 4.80-4.35 (m, H-4), 3.85 (d, 2H, H-5,5'), 3.38 (s, 3H, OCH_3), 3.3-2.80 (m, 1H, H-3), 2.10 (s, 3H, OAc).

Anal. Calcd for: $C_9H_{13}NO_5$ .1/2 H_2O: C, 48.20; H, 6.29; N, 6.24. Found: C, 48.21; H, 6.24; N, 5.92.

Methyl 2-*O*-Acetyl-3-cyano-3-deoxy-α,β-D-xylofuranoside (16, 17). Methyl 2-*O*-acetyl-5-*O*-benzyl-3-cyano-3-deoxy-α-D-xylofuranoside (**7**) (0.878 g, 0.0028 mol) dissolved in dry dichloromethane (40 mL) was treated with boron trichloride (6 mL, 0.0060 mol, 1 M in dichloromethane) as described in the preparation of **16** to give an anomeric mixture (0.563 g, 92%) of **16** and methyl 2-*O*-acetyl-3-cyano-3-deoxy-α-D-xylofuranoside (**17**) (2:1) as an oil: ^{1}H NMR ($CDCl_3$) δ 5.30 (d, 1H, $J_{2,3}$ = 1.3 Hz, H-2, **16**), 5.15 (m, 2H, H-1, H-2, **17**), 4.90 (s, 1H, H-1, **16**), 4.75-4.20 (m, H-4, **16**, **17**), 3.80 (d, 4H, H-5,5', **16, 17**), 3.70-3.20 (m, H-3, **17**), 3.38 (s, 3H, OCH_3, **16**), 3.32 (s, 3H, OCH_3, **17**), 3.30-2.80 (m, 1H, H-3, **16**), 2.08 (s, 6H, OAc, **16, 17**).

Methyl 3-*O*-Acetyl-2-cyano-2-deoxy-α-D-arabinofuranoside (18). Boron trichloride (5.8 mL, 0.0058 mol, 1 M in dichloromethane) was added under argon to a cold (-78 °C) solution of **8** (0.74 g, 0.00242 mol) in dry dichloromethane (80 mL) and the reaction mixture was stirred at -78 °C for 2 h. It was then warmed to 0 °C and poured into

a stirred solution of sodium bicarbonate (9 g) in ice-water (25 mL). The reaction flask was rinsed with chloroform (80 mL) and the combined organic phase was separated, dried (Na_2SO_4), and concentrated to give a syrupy residue which was separated by chromatography on silica gel (35 g) in chloroform/ether (1:1) to give the starting material **8** (0.421 g, 56%) and solid **18** (0.216 g, 38%) : ^{1}H NMR ($CDCl_3$) δ 5.25-5.12 (m, 2H, H-1, H-3), 4.08 (m, 1H, H-4), 3.80-3.65 (m, 2H, H-5,5'), 3.28 (s, 3H, OCH_3), 3.05-2.08 (d,d, 2H, J = 1.2 and 3.0 Hz, H-2), 2.0 (s, 3H, O-acetyl).

Anal. Calcd for $C_9H_{13}NO_5.H_2O$: C, 46.34; H, 6.48; N, 6.00. Found: C, 46.03; H, 6.00; N, 5.70.

Methyl 2,5-Di-*O*-acetyl-3-cyano-3-deoxy-β-D-xylofuranoside (19). To a cold (0-4° C) solution of **16** (0.090 g, 0.0004 mole) in pyridine (7 mL) was added 4 mL of acetic anhydride and the reaction mixture was kept at room temperature overnight. Evaporation of the solvents followed by sequential coconcentration of the residue with xylene (3 x 30 mL), toluene (2 x 30 mL) and purification by chromatography on silica gel (2:1, ether-petroleum ether) gave **19** (0.048g, 47%) as an oil: ^{1}H NMR δ 5.35 (d, 1H, H-2), 5.0 (s, 1H, H-1), 4.82-4.52 (m, 1H, H-4), 4.40-4.32 (s,s, 2H, H-5,5'), 3.42-3.30 (m, 1H, H-3), 3.46 (s, 3H, OCH_3) 2.18 (s, 6H, OAc).

Methyl 2,5-Di-*O*-Acetyl-3-cyano-3-deoxy-α-D-xylofuranoside (20). Acetylation of a 2:1 mixture of **16** and **17** (0.254 g) with acetic anhydride in pyridine gave the crude product which was separated by chromatography on silica gel (ether-petroleum ether, 2/1) to give 0.050 g (16.4%) of **20** and 0.048 g (15.8%) of **19**. For **20**: ^{1}H NMR ($CDCl_3$) δ 5.10 (d, 2H, H-1, H-2), 4.44-4.20 (m, 1H, H-4), 3.83-3.80 (d, 2H, H-5,5'), 3.68-3.60 (m, 1H, H-3), 3.32 (s, 3H, OCH_3), 2.08 (s, 6H, OAc).

Acetolysis of **19**: To a cold (3 °C) solution of **19** (48 mg, 0.186 mmol) in acetic acid (20 mL) and acetic anhydride (20 mL) was added 0.2 mL of concd H_2SO_4 and the reaction mixture was stirred at 0 °C for 20 h. The mixture was poured into a stirred solution of sodium acetate (15 g) in ice water (150 mL) with continuing stirring for 30 min at room temperature. The mixture was then extracted with chloroform (4 x 100 mL) and the organic phase was sequentially washed with water, dried, and concentrated to give 0.03 g (56 %) of the product. The NMR of this product was identical with that of the product obtained from acetolysis of **3**.

Compounds **13** *and* **14** *from* **11** *and* **12**: Boron trichloride (4 mL of 1 M solution in dichloromethane, 4 mmol) was added to a cold (-78 °C) solution of **11** (272 mg, 0.8 mmol) and **12** (281 mg, 0.9 mmol) in dry dichloromethane (30 mL) under argon. The mixture was stirred at -76 °C for two h, warmed to room temperature and poured into a stirred mixture of sodium bicarbonate (6 g) and ice-water (60 mL). After 30 min of stirring, the organic phase was separated and the aqueous phase was extracted with dichloromethane (30 mL). The combined organic solution was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel (280 g, ether-petroleum ether, 2:1) to give 168 mg of an oil which was acetylated with acetic anhydride (0.5 mL) in pyridine (1 mL) at room temperature overnight. The NMR spectrum of the product, 1,2,5-tri-*O*-acetyl-3-cyano-3-deoxy-α,β-D-xylofuranose (**13**, **14**), was identical with that of the product from acetolysis of **7**.

ACKNOWLEDGMENT

This investigation was supported in part by Grant CA13038 from the National Cancer Institute.

REFERENCES

1. A. Azuma, Y. Nakajima, N. Nishizono, N. Minakawa, M. Suzuki, K. Hanaoka, T. Kobayashi, M. Tanaka, T. Sasaki, and A. Matsuda *J. Med. Chem.*, **36**, 4183 (1993).
2. C. O. Yang, H.Y. Wu, E.B. Fraser-Smith, K.A.M. Walker, *Tetrahedron Lett.*, **33**, 37 (1992).
3. N. R. Williams and J. D. Wander in *The Carbohydrates*, Vol. 1B; W. Pigman And D. Horton, Eds.; Academic Press: New York, 1980, p 761.
4. M. Rabinovitz in *The Chemistry of the Cyano Group*, Z. Rappoport, Ed.; Interscience Publishers: 1970, p 307.
5. T. F. Gallagher and J. L. Adams, *J. Org. Chem.* **57**, 3347 (1992).
6. D. Yu and M. D'Alarcao, *J. Org. Chem.* **54**, 3240 (1989).
7. W. Nagata, M. Yoshioka, and T. Okumura, *Tetrahedron Lett.*, 847 (1966).
8. A. Mubarak and B. Fraser-Reid, *J. Org. Chem.* **47**, 4265 (1982).
9. D. Habich and W. Barth, *Synthesis*, 943 (1988).

10. A. Yamashita and A. Rosowsky, *J. Org. Chem.* **41**, 3422 (1976).
11 W. A. Sheppard in *The Chemistry of the Cyano Group*, Z. Rappoport, Ed.; Interscience Publishers: 1970, p 233.
12. E. J. Reist and S. Holton, *Carbohydr. Res.*, **9**, 71 (1969).
13. J. A. Wright and N. F. Taylor, *Carbohydr. Res.*, **6**, 347 (1968).
14. Y.-L. Fu. and M. Bobek, *J. Org. Chem.*, **45**, 3836 (1980).
15. N. R. Williams in *Adv. Carbohydr. Chem. Biochem.*, **25**, 109 (1970).
16. C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 5247 (1958).
17. J. A. Wright, N. T. Taylor, and J. J. Fox, *J. Org. Chem.*, **34**, 2632 (1969).
18. R. Koster and P. Binger in *Adv. in Inorg. Chem. Radiol.*, 7, 284 (1965).
19. A. Calvo-Mateo, M. J. Camarasa, A. Diaz-Ortiz, and F. G. De las Heras, *Tetrahedron Lett.*, **29**, 941 (1988).
20. J. P. Utille and P. Vottero, *Bull. Soc. Chim. (France)*, 387, 1101 (1976).
21. B. L. Kam, J.-L. Barascut, and J.-L. Imbach, *Carbohydr. Res.* **69**,135 (1979).
22. S. C. Sharma and B. M. Lynch, *J. Carbohydr. Nucleosides Nucleotides*, **3**, 347 (1976).