Stereoselective Syntheses of 2-Deoxy-β-*C*-arabino- and ribopyranosides: 2-Deoxy-β-arabino- and ribopyranosyl Cyanides

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2-Deoxy-β -arabino- and ribopyranosyl cyanides, which should be suitable for the syntheses of biologically active products, were stereoselectively prepared from the reaction of the enones, 1,5-anhydro-2-deoxy-*erythro*-hex-1-en-3-ulose derivatives, with acetone cyanohydrin, followed by the stereoselective reduction of the producing ketones with $NaBH_4$-$CeCl_3 \cdot 7H_2O$ and L-Selectride, respectively.

The C-C bond formation at the anomeric center of carbohydrates has become an increasingly important area in synthetic oraganic chemistry. In particular, a wide variety of medicinally imporatant *C*-nucleosides[1] have been discovered as well as several *C*-glycosyl flavonoids[2] and other structurally diverse *C*-glycosides.[3] Although a lot of stereoselective routes exist for *C*-glycopyranosides,[4] little synthetic strategies have been reported for 2-deoxy-*C*-glycosides.[5] Efficient and stereocontrolled methods for the 2-deoxy-*C*-glycosidation remain an imporatant synthetic objective, not only for the preparation of biologically active 2-deoxy-*C*-glycosides including antiviral[6] *C*-nucleosides but also for the homologation of carbohydrates to serve as chiral sources for other synthetic targets.

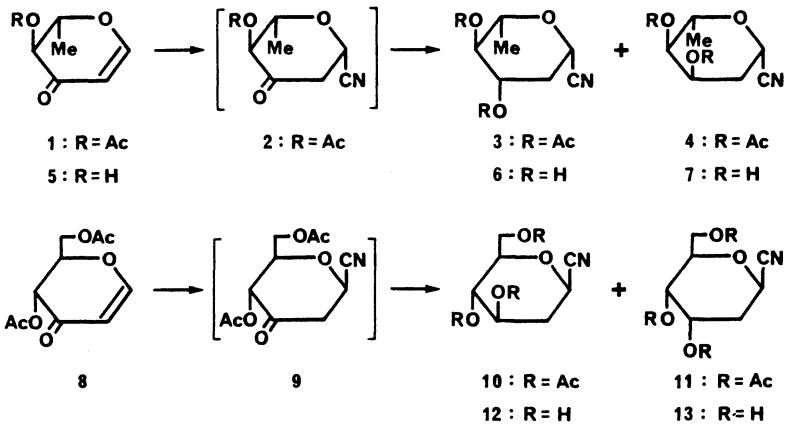
As part of an ongoing program in these and related areas, we wish to report the stereoselective syntheses of 2-deoxy-β-*C*-glycopyranosides: 2-deoxy-β-*C*-arabino- and ribopyranosyl cyanides by using acetone cyanohydrin, which is a tractable and inexpensive reagent.

Our strategy is based on the following considerations: i) the 1,4-addition of the cyanide ion[7] to the anomeric position of such enones as **1** and **8** in basic conditions to give thermodynamically the β-glycosyl cyanides; ii) the stereoselective reduction of the producing ketones such as **2** and **9** by $NaBH_4$-$CeCl_3 \cdot 7H_2O$[8] and bulky L-Selectride to give predominantly the arabino- and ribopyranosides, respectively, because of the significant influence of the C-4 substituent and the ring oxygen atom.[9]

Thus, reaction of acetone cyanohydrin[7] with the conjugated enone, 4-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*erythro*-hex-1-en-3-ulose[10] (**1**) was best realized by using *N*,*N*-diisopropylethylamine as a catalytic base in acetonitrile to afford the intermediary 1,4-adduct **2**, which in turn was exclusively converted into the 2-deoxy-β-*C*-glycosides **3** and **4**. The 1,4-addition was also done by use of Na_2CO_3 as a catalyst in aqueous acetonitrile, but in a lower yield.

The keto cyanide **2** was submitted to the hydride reduction with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ in methanol, followed by acetylation to give predominantly 3,4-di-*O*-acetyl-2,6-dideoxy-β-L-arabinopyranosyl cyanide (**3**) in a 64% yield with the corresponding β-L-ribopyranosyl cyanide (**4**) in a 15% yield. The borohydride reduction without $CeCl_3$ gave a mixture of **3** and **4** in 23% and 22% yields without stereoselectivity. These selectivities suggested that $CeCl_3$ decreased the participation of the ring oxygen atom[9] and, relatively, $NaBH_4$ could approach to the C-3 carbonyl group from the same site of the C-4 acetoxyl group by the interaction.

In the transformation, other hydride reagents [$LiBH_4$, $Zn(BH_4)_2$, $LiBHEt_3$, $NaBH_3CN$, Bu_4NBH_4, Me_4NBH_4, $Me_4NBH(OAc)_3$, Red-Al, DIBAL, and $LiAlH_4$] were assayed in several solvents (MeOH, ether, THF, and dichloromethane), but they gave **3** and **4** in lower yields.



However, remarkably, the L-Selectride reduction in THF resulted the predominant formation of the ribopyranoside **4** in a 59% yield with only a 6% yield of the arabinopyranoside **3**. This result was reasonably supported by the consideration that the approach of the bulky hydride reagent to the C-3 carbonyl group would be restricted to the opposite site of the C-4 acetoxyl group by the steric hindrance as well as the aid of the ring oxygen atom[9] to give exclusively the cis-3,4-diol **4**.

The corresponding α-glycosyl cyanides were not recognized as detectable amounts in the aforesaid reactions.

The de-*O*-acetylated enone **5** was treated with the similar manner through borohydride reductions, but it gave **3** and **4** only in very low yields after acetylation.

The compounds **3** and **4** were de-*O*-acetylated by 7% methanolic ammonia solution to 2,6-dideoxy-β-L-arabino- and ribopyranosyl cyanides (**6** and **7**) in 95% and 87% yields, respectively, while the deacetylation with MeONa occurred in moderate yields.

When 4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-ulose[10] (**8**) was used for the aforesaid addition, the corresponding products, 3,4,6-tri-*O*-acetyl-2-deoxy-β-D-arabino-and β-D-ribopyranosyl cyanides (**10** and **11**) were provided in almost same yields as described above, after borohydride reduction and acetylation. Namely, through the $NaBH_4$-$CeCl_3$ reduction, **10** and **11** were produced in 60% and 20% yields, while, through the L-Selectride reduction, **10** and **11** were in 4% and 60% yields.

Both compounds **10** and **11** were similarly de-*O*-acetylated to **12** and **13** in high yields, respectively. The latter compound **13** was slightly labile even on keeping in a refrigerator.

In conclusion, an efficient and stereoselective preparation of 2-deoxy-β-*C*-glycosides: 2-deoxy-β-arabino- and ribopyranosyl cyanides has been developed, starting from 1,5-anhydro-2-deoxy-*erythro*-hex-1-en-3-ulose derivatives (**1** and **8**) by using the addition of acetone cyanohydrin followed by borohydride reduction.

Experimental

Melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. Optical rotations were measured with a JASCO DIP-360 photoelectric polarimeter in chloroform and methanol. IR spectra were recorded on a Hitachi Perkin-Elmer 225 spectrometer, and ^{1}H NMR spectra on a JEOL GX-400 spectrometer in $CDCl_3$ and CD_3OD using TMS as internal standard. Mass spectra were measured with a Hitachi M-80 mass spectrometer. TLC was carried out on Merck TLC plates (60F-254, 0.25 mm). Column chromatography was performed on silica gel, Merck Kieselgel 60. In general, organic solvents were purified and dried by the appropriate procedures, and evaporation was carried out under reduced pressure below 35 °C.

The starting materials, 4-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*erythro*-hex-1-en-3-ulose (**1**), 1,5-anhydro-2,6-dideoxy-L-*erythro*-hex-1-en-3-ulose (**5**), and 4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-ulose (**8**), were prepared according to the Czernecki's procedures.[10]

3,4-Di-*O*-acetyl-2,6-dideoxy-β-L-arabinopyranosyl Cyanide (3) and 3,4-Di-*O*-acetyl-2,6-dideoxy-β-L-ribopyranosyl Cyanide (4). A) By $NaBH_4$-$CeCl_3$: A mixture of **1** (1.74 g), acetone cyanohydrin (2.8 ml) and *N*,*N*-diisopropylethylamine (0.36 ml) in acetonitrile (17 ml) was stirred at 70 °C for 3 days, and then evaporated to a residue (approximately 3.5 g) containing **2**. A solution of the residue in methanol (100 ml) was stirred with $CeCl_3 \cdot 7H_2O$ (4.18 g) at 5 °C for 20 min, and $NaBH_4$ (1.0 g) was added. The mixture was stirred at the same temperature for 1.5 h and then at room temperature for 18 h. The reaction mixture was neutralized with Amberlite CG-50 (H type), filtered and evaporated to a residue, which was stirred with acetic anhydride (10 ml) in pyridine (30 ml) at room temperature for 24 h. After addition of ethanol, the mixture was evaporated and co-evaporated with toluene to a residue, which was chromatographed on silica gel (100 g) with 15 : 1 chloroform-ethyl acetate to give **3** (1.58 g, 64%) and **4** (0.37 g, 15%) having the R_f-values 0.45 and 0.37 (10 : 1 chloroform-ethyl acetate).

3: Needles from ethyl acetate-hexane; mp 102 °C; $[\alpha]_D^{31}$ −100° (*c* 1.1, $CHCl_3$); IR (KBr): 1720, 1240, and 1220 cm^{-1} (OAc); ^{1}H NMR (400 MHz, $CDCl_3$); δ=1.25 (3H, d, Me-5, *J*=6.2 Hz), 2.03 (1H, m, H-2ax), 2.04 and 2.08 (each 3H, s, OAc), 2.40 (1H, ddd, H-2eq, *J*=13.2, 5.1, and 1.5 Hz), 3.94 (1H, dq, H-5, *J*=9.6 and 6.2 Hz), 4.76 (1H, t, H-4, *J*=9.6 and 9.5 Hz), 4.86 (1H, dd, H-1, *J*=5.8 and 1.5 Hz), and 5.22 (1H, ddd, H-3, *J*=11.7, 9.5 and 5.1 Hz); MS *m*/*z* 242 (M^++1).

Found: C, 54.89; H, 6.11%. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27%.

4: Syrup; $[\alpha]_D^{31}$ −157 ° (*c* 1.1, $CHCl_3$); IR (neat): 1740, 1245, and 1220 cm^{-1} (OAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24 (3H, d, Me-5, *J*=6.1 Hz), 2.07 and 2.19 (each 3H, s, OAc), 2.26 (2H, m, H-2ax and 2eq), 4.31 (1H, dq, H-5, *J*=9.6 and 6.1 Hz), 4.61 (1H, dd, H-4, *J*=9.6 and 3.0 Hz), 4.77 (1H, dd, H-1, *J*=5.6 and 2.7 Hz), and 5.37 (1H, dd, H-3, *J*=6.3, 3.0 and 0 Hz); MS *m*/*z* 242 (M^++1).

Found: C, 54.64; H, 6.34%. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27%.

B) By L-Selectride: A sample of **1** (1.70 g) was treated by the same procedure as described in the Section A. To a stirred solution of the residue (approximately 3.5 g) containing the adduct **2** in THF (100 ml) was added dropwise a 1 M L-Selectride solution in THF (25 ml) at −78 °C, and then stirring was continued for 1 h at the same temperature. After addition of 50% acetic acid, the mixture was partitioned between ethyl acetate and water. The combined organic layers were dried and evaporated to a residue, which was acetylated as described in the Section A. After silica-gel column chromatography, **3** (0.14 g, 6%) and **4** (1.42 g, 59%) were obtained.

2,6-Dideoxy-β-L-arabinopyranosyl Cyanide (6). A sample of **3** (335 mg) was stirred in 7% methanolic ammonia solution (3.4 ml) at 5 °C for 3 h. The reaction mixture was evaporated to a residue, which was chromatographed on silica gel (10 g) with 1 : 2 benzene-ethyl acetate to give a syrup of **6** (207 mg, 95%): R_f 0.33 (2 : 1 chloroform-acetone); $[\alpha]_D^{29}$ −66° (*c* 1.0, MeOH); IR (neat): 2230 cm^{-1} (CN); ^{1}H NMR (400 MHz, CD_3OD): δ=1.29 (3H, d, Me-5, *J*=6.0 Hz), 1.85 (1H, ddd, H-2ax, *J*=14, 11.5, and 6.0 Hz), 2.15 (1H, ddd, H-2eq, *J*=14, 4.8, and 1.6 Hz), 2.93 (1H, t, H-4, *J*=9.2 and 9.0

Hz), 3.59 (1H, dq, H-5, J=9.2 and 6.0 Hz), 3.71 (1H, ddd, H-3, J=11.5, 9.0 and 4.8 Hz), and 4.96 (1H, dd, H-1, J=6.0 and 1.6 Hz); MS m/z 157 (M^+).

Found: C, 53.01; H, 6.91%. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05%.

2,6-Dideoxy-β-L-ribopyranosyl Cyanide (7). A sample of **4** (359 mg) was deacetylated by the procedure described in the preparation of **6**, and then worked up to give needles of **7** (203 mg, 87%) after recrystallization from ethyl acetate-hexane: R_f 0.32 (2:1 chloroform-acetone); mp 162 °C; $[\alpha]_D^{29}$: −107° (c 0.87, MeOH); IR (KBr): 2230 cm^{-1} (CN); ^1H NMR (400 MHz, CD_3OD): δ=1.25 (3H, d, Me-5, J=6.1 Hz), 2.1 (2H, m, H-2ax and 2eq), 3.17 (1H, dd, H-4, J=9.4 and 4.0 Hz), 4.03 (1H, dd, H-1, J=6.3 and 2.9 Hz), 4.04 (1H, dq, H-5, J=9.4 and 6.1 Hz), and 4.79 (1H, t, H-3, J=4.0 and 0 Hz); MS m/z 157 (M^+).

Found: C, 53.42; H, 7.11%. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05%.

3,4,6-Tri-*O*-acetyl-2-deoxy-β-D-arabinopyranosyl Cyanide (10) and 3,4,6-Tri-*O*-acetyl-2-deoxy-β-D-ribopyranosyl Cyanide (11). A) By $NaBH_4$-$CeCl_3$: A mixture of **8** (1.02 g), acetone cyanohydrin (1.85 ml) and *N,N*-diisopropylethylamine (0.16 ml) in acetonitrile (10 ml) was stirred at room temperature for 3 days, and then evaporated to a residue containing **9**. The residue was treated with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ followed by acetylation as described in the preparation (Section A) of **3** and **4**, and then worked up to give **10** (0.80 g, 60%) and **11** (0.26 g, 20%) having the R_f-values 0.37 and 0.32 (8:1 chloroform-ethyl acetate).

10: Needles from ethyl acetate-hexane; mp 156 °C; $[\alpha]_D^{26}$ +63° (c 0.93, $CHCl_3$); IR (KBr): 1730 and 1220 cm^{-1} (OAc); ^1H NMR (400 MHz, $CDCl_3$): δ=2.05, 2.07 and 2.10 (each 3H, s, OAc), 2.11 (1H, ddd, H-2ax, J=13.8, 11.7 and 5.9 Hz), 2.42 (1H, ddd, H-2eq, J=13.8, 5.0 and 1.5 Hz), 4.05 (1H, ddd, H-5, J=9.6, 4.8 and 1.8 Hz), 4.12 (1H, dd, H-6, J=12.8 and 1.8 Hz), 4.35 (1H, dd, H-6′, J=12.8 and 4.8 Hz), 4.94 (1H, dd, H-1′, J=5.9 and 1.5 Hz), 5.02 (1H, dd, H-4, J=9.6 and 9.2 Hz), and 5.27 (1H, ddd, H-3, J=11.7, 9.2, and 5.0 Hz); MS m/z 300 (M^++1).

Found: C, 52.13; H, 5.54%. Calcd for $C_{13}H_{17}NO_7$: C, 52.17; H, 5.73%.

11: Needles from ethyl acetate-hexane; mp 92 °C; $[\alpha]_D^{26}$ +102° (c 1.0, $CHCl_3$); IR (KBr): 1730 and 1220 cm^{-1} (OAc); ^1H NMR (400 MHz, $CDCl_3$): δ=2.05, 2.09, and 2.21 (each 3H, s, OAc), 2.28 (2H, m, H-2ax and 2eq), 4.20 (1H, dd, H-6, J=12.7 and 1.9 Hz), 4.35 (1H, dd, H-6′, J=12.7 and 4.6 Hz), 4.42 (1H, ddd, H-5, J=9.8, 4.6, and 1.9 Hz), 4.85 (1H, dd, H-1, J=4.3 and 3.2 Hz), 4.89 (1H, dd, H-4, J=9.8 and 2.8 Hz), and 5.43 (1H, dd, H-3, J=6.0, 2.8 and 0 Hz); MS m/z 300 (M^++1).

Found: C, 51.90; H, 5.51%. Calcd for $C_{13}H_{17}NO_7$: C, 52.17; H, 5.73%.

B) By L-Selectride: A mixture of **8** (1.14 g), acetone cyanohydrin (2.05 ml), and *N,N*-diisopropylethylamine (0.17 ml) in acetonitrile (11 ml) was stirred at room temperature for 3 days, and then evaporated to a residue. The residue was treated with L-Selectride followed by acetylation as described in the preparation (Section B) of **3** and **4** to give **10** (0.060 g, 4%) and **11** (0.89 g, 60%).

2-Deoxy-β-D-arabinopyranosyl Cyanide (12). A sample of **10** (550 mg) was de-*O*-acetylated by the procedure described in the preparation of **6**, and then worked up to give needles of **12** (282 mg, 89%) after recrystallization from ethyl acetate-hexane: R_f 0.37 (6:1 chloroform-methanol); mp 129 °C; $[\alpha]_D^{29}$ +90° (c 1.0, MeOH); IR (KBr): 2340 cm^{-1} (CN); ^1H NMR (400 MHz, CD_3OD): δ=1.86 (1H, ddd, H-2ax, J=13.6, 11.6, and 5.3 Hz), 2.16 (1H, ddd, H-2eq, J=13.6, 4.8, and 1.4 Hz), 3.27 (1H, t, H-4, J=9.2 Hz), 3.55 (1H, ddd, H-5, J=9.20, 5.0 and 2.0 Hz), 3.71 (1H, dd, H-6, J=12 and 5.0 Hz), 3.77 (1H, ddd, H-3, J=11.6, 9.20, and 4.8 Hz), 3.85 (1H, dd, H-6′, J=12 and 2.0 Hz), and 5.04 (1H, dd, H-1, J=5.3 and 1.4 Hz); MS m/z 173 (M^+).

Found: C, 48.32; H, 6.39%. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40%.

2-Deoxy-β-D-ribopyranosyl Cyanide (13). A sample of **11** (510 mg) was de-*O*-acetylated by the procedure described in the preparation of **6**, and then worked up to give a syrup of **13** (236 mg, 80%): R_f 0.34 (6:1 chloroform-methanol); $[\alpha]_D^{29}$ +83° (c 0.56, MeOH); IR (neat): 2330 cm^{-1} (CN); ^1H NMR (400 MHz, CD_3OD): δ=2.10 (2H, m, H-2ax and 2eq), 3.50 (1H, dd, H-4, J=9.6 and 3.2 Hz), 3.70 (1H, dd, H-6, J=12.2 and 5.3 Hz), 3.84 (1H, dd, H-6′, J=12.2 and 2.3 Hz), 3.98 (1H, ddd, H-5, J=9.6, 5.3, and 2.3 Hz), 4.07 (1H, dd, H-3, J=6.1, 3.2, and 0 Hz), and 4.85 (1H, d, H-1, J=4.3 and 0 Hz); MS m/z 174 (M^++1).

Found: C, 48.74; H, 6.42%. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40%.

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