Synthethic Routes to 3-*C*-Cyano-3-deoxy-D-galactopyranose Derivatives

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Routes to 3-*C*-cyano-3-deoxy-D-galactopyranose derivatives have been developed from methyl 3,4-anhydro-α-D-galactopyranoside and 1,6:3,4-dianhydro-β-D-galactopyranose. Upon treatment with diethylaluminum cyanide, both precursors give products of trans-diaxial opening although some diequatorial opening also occurs with the former. The axial *C*-cyano groups in both cases are readily epimerized by dilute sodium methoxide, giving 3-*C*-cyano-3-deoxy-D-galacto products. In neither case is there any evidence of β elimination or of skeletal rearrangements.

For certain studies underway in our laboratory we need supplies of a protected form of 3-*C*-cyano-3-deoxy-D-galactopyranose such as **5** or **12**, and in exploring synthetic routes to these derivatives, we have uncovered a number of factors that are of interest for the preparation of branched-chain sugars of this type.

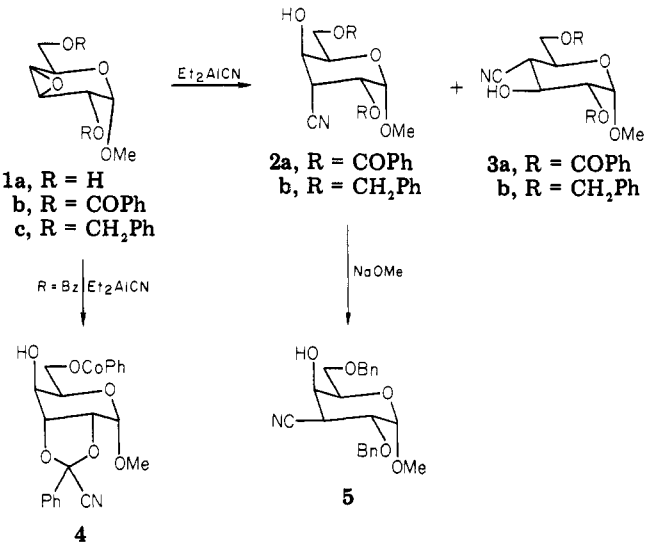
A C substituent on a pyranose ring can be introduced readily by opening an epoxide with a carbon nucleophile.[1] However, the favored mode of reaction gives the product of trans-diaxial cleavage,[2] which means that this process could not be applied either to a 2,3- or a 3,4-epoxide for the *direct* preparation of **5** or **12**. However, in view of the axial C4-oxygen, one plausible approach would be to open a 3,4-β-expoxide with cyanide ion, and subsequently epimerize at C3.

Accordingly, methyl 3,4-anhydro-α-D-galactopyranoside protected as its dibenzoate **1b** was treated with diethylaluminum cyanide[4] (Scheme I). However, the product obtained was clearly neither **2a** nor **3a** since the ^{1}H NMR spectrum did not contain a signal ~3 ppm assignable to H3 of **2a** or H4 of **3a** (vide infra). The ^{13}C NMR spectrum confirmed this conclusion, indicating the presence of only one C=O signal; however, a signal for a quatenary carbon at 102.4 ppm provided a clue for the presence of the ketal **4**. Such alkylidene derivatives are well-known in carbohydrate chemistry although usually they involve the anomeric carbon.[5]

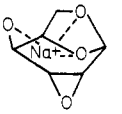
The benzoyl group of **1b** was obviously participating in the epoxide cleavage and hence we turned to the dibenzyl ether **1c**. Treatment with diethylaluminum cyanide[4] afforded an 80% yield of the mixture of the regioisomers **2b** and **3b** in the ratio 5:1, the major component being obtained as a crystalline material. Epimerization at C3 of **2b** was effected by treatment with a catalytic amount of sodium methoxide in methanol for 24 h. An equilibrium was thereby established in which the ratio of the galacto, **5**, and gulo, **2b**, epimers was 6:1 (vide infra). The combined, isolated yield after equilibration was only 64%; however, examination of the side products gave no evidence of the formation of elimination products nor for any epimerization of adjacent oxygen sites as had been noted in the work of Guthrie.[6]

The above-described route to **5** was compromised by the nonregiospecificity in the reaction of **1c**, and hence an alternate route was sought. The C2 and C3 substituents of **5** are transdiequatoral in the $^4C_1$ representation shown; however, they would be trans diaxial in the $^1C_4$ conformation, and thus an α oxirane of a 1,6-anhydro-β-D-pyranose ought to be opened in the desired sense.[7] The desired starting material for this alternative route was dianhydro gulose **7**. However, we were aware that Hardegger has examined the opening of **7a** with benzyl thiolate and found that nucleophilic attack occurred predominantly at C2, leading to the product of trans-diequatorial epoxide opening,[8] thereby causing us to have some doubts about the course of cyanolysis of **7**.

Scheme I



The synthetic route to **7** involves prior formation of the isomer **6a**, which upon treatment with sodium hydroxide in methanol leads to an equilibrium mixture of **7a** and **6a** in the ratio 4:1. We surmised that in an aprotic solvent the gulo form should predominate because of the chelation depicted in **14**. Accordingly, compound **6a** was treated



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with sodium hydride in tetrahydrofuran and allowed to come to equilibrium for 6 h, prior to the addition of benzyl

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(1) Hicks, D. R.; Fraser-Reid, B. O. *Can. J. Chem.* **1975**, *53*, 2017.
(2) Williams, N. R. *Adv. Carbohydr. Chem. Biochem.* **1970**, *25*, 109.
(3) Buchanan, J. G.; Fletcher, R. *J. Chem. Soc.* **1965**, 6316. Buchanan, J. G. *Ibid.* **1958**, 2511.
(4) Nagata, W.; Yoshioka, M.; Okumura, T. *J. Chem. Soc. C* **1970**, 2365.
(5) Coxon, B.; Fletcher, H. G., Jr. *J. Am. Chem. Soc.* **1963**, *85*, 2637; **1964**, *86*, 922.
(6) Davidson, B. E.; Guthrie, R. D.; McPhail, A. T. *J. Chem. Soc., Chem. Commun.* **1968**, 1273.
(7) Černý, M.; Stanek, J., Jr. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 24.
(8) Vegh, L.; Hardegger, E. *Helv. Chim. Acta* **1973**, *56*, 1961.

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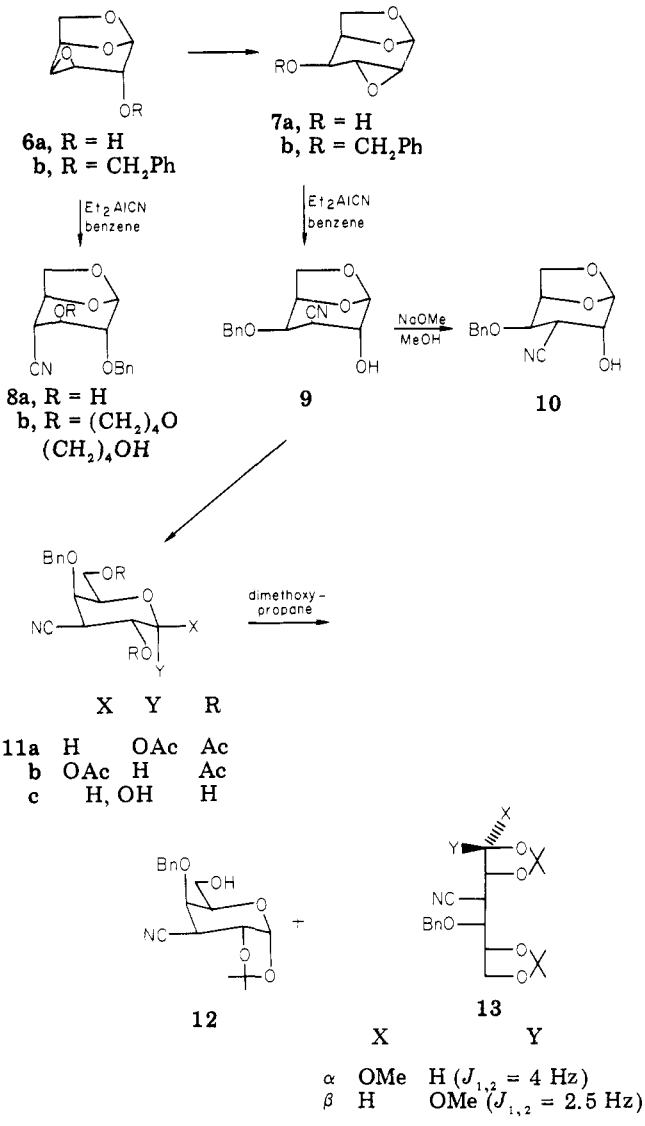
Scheme II



bromide. Under these conditions the ratio of **7b** and **6b** improved slightly to 6:1. Similar effects resulting from chelation of oxyanions have recently been reported for selective formation of α and β glycosides.[10]

We decided to carry out our pilot experiments on **6b** using diethyl aluminum cyanide. Under the conditions of Nagata using tetrahydrofuran as solvent,[4] the product was **8b**, resulting from etherification by the tetrahydrofuran dimer. A similar product had been isolated by Guthrie and co-workers in their experiments.[6] However, with benzene as solvent, the desired cyanohydrin **8a** was obtained in 80% yield. Similarly, with benzene as solvent, **7b** afforded **9** as the only product in 80% yield, as a crystalline material.

It is now appropriate to outline the structure proof for the cyanohydrins in Schemes I and II. In light of the above-mentioned abnormal results of Hardegger on the diequatorial opening of **7a**,[8] there could be doubts about the authenticity of **9**. However, these were readily dispelled by showing that treatment of **9** with sodium methoxide in methanol led quantitatively to a new product, **10**. (Indeed basic workup of **9** must be avoided.) The mere fact of this ready epimerization meant that the cyanohydrin obtained from **7b** could not have been the diequatorial product.

Independent confirmation was sought from the ^{1}H NMR spectrum. The positions of $H6_{exo}$ and $H6_{endo}$ in the various 1,6-anhydro sugars could be assigned by comparison with well-known analogues.[7] In going from **9** to **10**, H3 and $H6_{endo}$ are expected to be affected appreciably, the former because the orientation is changed from equatorial to axial, and the latter because the shielding effect of the nitrile group has been removed. Accordingly, from the parameters for these isomers (see Experimental Section) the $\Delta\delta$ values were found to be 0.4 and 0.5 ppm, respectively. The observed coupling constants for $J_{3,4}$ (7.0 Hz in **9**, and 10.75 Hz in **10**) are in keeping with these assignments.

Similar reasoning to the foregoing applies to the structures assigned to the epimers **2** and **5** (Scheme I). Thus, the ease of the epimerization of **2** to **5** coupled with the expected change in $J_{2,3}$ (from 5.75 to 11.2 Hz) is compelling evidence for the assignments made.

With the stereochemistry of **9** secure, we could now cleave the 1,6-anhydro ring and this was achieved with boron trifluoride etherate in acetic anhydride at room temperature for 30 min. The anomeric triacetates **11a** and **11b** were obtained quantitatively in the ratio 4:1. Column chromatography afforded the α-anomer **11a** as a crystalline material and comparison of the critical ^{1}H NMR data (see Experimental Section) for $J_{2,3}$ and $J_{3,4}$ in **11a** and **5** (12.0 vs. 11.2 Hz, and 2.5 vs. 2.5 Hz) indicated that both substances had the same configuration.

Deacetylation of the mixture of anomeric acetates gave the triol **11c**, which we now sought to protect differentially. Treatment with dimethoxy propane and *p*-toluenesulfonic acid in methylene chloride–dimethoxyethane gave **12** after chromatography as a crystalline material in 70% yield. However, two syrupy byproducts were also isolated whose elemental composition and molecular weights pointed to the structure **13**. The assignments of configuration are based on the values for $J_{1,2}$ (4.0 and 2.5 Hz, respectively).

The combined yields of **13a** and **13b** could be raised to 70% if the acetonation was carried out in neat, dry dimethoxypropane containing a small amount of methane. Compounds similar to **13** have been isolated from reactions of other sugars with dimethoxypropane.[11]

In summary, the route to 3-cyano-3-deoxy-D-galactopyranose shown in Scheme II is preferred to that shown in Scheme I. The preparation of the epoxide precursors **1c** and **7b** is also easier in the latter case, particularly if the required levoglucosan (1,6-anhydro-β-D-glucopyranose) can be obtained by pyrolysis[12] rather than the alternative four-step sequence.[13]

Experimental Section

Methyl 2,6-Di-*O*-benzyl-3-*C*-cyano-3-deoxy-α-D-gulopyranoside (2b) and Methyl 2,6-Di-*O*-benzyl-4-*C*-cyano-4-deoxy-α-D-glucopyranoside (3b). Methyl 3,4-anhydro-α-D-galactopyranoside[3] (**1a**; 1.76 g, 10 mmol) dissolved in dry dimethylformamide (20 mL) was treated with benzyl bromide (15 mL) and freshly prepared silver oxide (5.3 g). The mixture was stirred in the dark for 3 days after which it was filtered, and the filtrate was poured into ice water. Extraction with ether and the usual processing followed by column chromatography on silica gel afforded the dibenzyl ether **1c** as an oil (2.1 g, 62%). To a

(9) Černý, M.; Buban, I.; Pacak, J. *Collect. Czech. Chem. Commun.* **1963**, *28*, 1569.
(10) Schmidt, R. R.; Reichrath, M.; Moering, O. *Tetrahedron Lett.* **1980**, *21*, 3561.
(11) Stevens, J. D. *Carbohydr. Res.* **1972**, *21* 490. Ducruix, A.; Pascard, C.; David, S.; Fischer, J-C., *J. Chem. Soc., Perkin Trans. 2* **1976**, 1678.
(12) Ward, R. B. *Methods Carbohydr. Chem.* **1963**, *2*, 394. Shafizadeh, F.; Furneaux, R. H.; Cochran, T. G.; Scholl, J. P.; Sakai, Y. *J. Appl. Polymer. Sci.* **1979**, *25*, 3525.
(13) Coleman, G. H. *J. Appl. Polymer Sci.* **1963**, *2*, 397.

solution of **1c** (120 mg, 0.34 mmol) in dry benzene (5 mL) was added diethyl aluminum cyanide (1 mL, 1.8 M in toluene,[4] 1.8 mmol), and the mixture was refluxed under argon for 1 h and then poured into ice-cold 0.1 N hydrochloric acid solution with stirring. The benzene extract was washed with brine and water and then dried and evaporated to give an oily residue weighing 103 mg (80%), which showed two components **2b** and **3b** (R_f 0.2 and 0.38, respectively) on TLC in ethyl acetate–petroleum ether (30–60 °C; 7:3). Silica gel column chromatography with the same solvent mixture afforded the two components:

For **2b**: mp 87–88 °C $[\alpha]^{23}_D$ +39.4° (*c*, 1.2 in chloroform); IR ($CHCl_3$) 3400 (OH), 2240 (CN) cm^{-1}; ^1H NMR δ 3.17 (dd, 1, $J_{2,3}$ = 5.75 Hz, $J_{3,4}$ = 2.75 Hz, H3), 3.43 (s, 3, OCH_3), 3.79 (m, 2, H6, H6′), 3.97 (brq, 1, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 5.75 Hz, H2), 4.13 (m, 1, H4), 4.23 (m, 1, H5), 4.39 (q, 2, J_{AB} = 12 Hz, $PhCH_2$), 4.63 (q, 2, J_{AB} = 12 Hz, $PhCH_2$), 4.77 (d, 1, $J_{1,2}$ = 3.5 Hz, H1), 7.34 (m, 10, aromatic). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.9; H, 6.57; N, 3.65. Found: C, 69.2; H, 6.66; N, 3.63.

For **3b**: $[\alpha]^{23}_D$ +63.8° (*c*, 1 in chloroform); IR (neat) 3460 (OH), 2240 (CN) cm^{-1}; ^1H NMR δ 2.78 (d, 1, *J* = 3.2 Hz, OH), 2.95 (t, $J_{3,4}$ = $J_{4,3}$ = 10.5 Hz, H4), 3.28 (dd, 1, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, H2), 3.33 (s, 3, OCH_3), 3.70 (m, 2, H6, H6′), 3.96 (dt, 1, $J_{4,5}$ = 10.5 Hz, $J_{5,6}$ = $J_{5,6'}$ = 3 Hz, H5), 4.16 (brt, 1, $J_{3,4}$ = 10.5 Hz, H3), 4.63 (m, 5, H1, 2 $PhCH_2$), 7.33 (m, 10, aromatic). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.9; H, 6.57; N, 3.65. Found: C, 68.6; H, 6.61; N, 3.64.

Methyl 2,6-Di-*O*-benzyl-3-*C*-cyano-3-deoxy-α-D-galactopyranoside (5). The gulo cyanohydrin **2b** (1.0 g, 2.6 mmol) was dissolved in methanol (50 mL) and sodium (~100 mg) was added. After 24 h the solution was evaporated to dryness, and the products were separated on a silica gel column, using ethyl acetate petroleum ether (30–60 °C; 7:3), affording **2b** (80 mg) and **5** (550 mg; R_f 0.2 and 0.3, respectively in same solvent).

For **5** (an oil): $[\alpha]^{20}_D$ +62.0 (*c*, 1 in chloroform); IR (neat) 3440 (OH), 2240 (CN) cm^{-1}; ^1H NMR δ 3.18 (dd, 1, $J_{2,3}$ = 11.2 Hz, $J_{3,4}$ = 2.5 Hz, H3), 3.34 (s, 3, OCH_3), 3.70 (m, 3, H4, H6, H6′), 4.06 (dd, 1, $J_{1,2}$ = 3.2 Hz, $J_{2,3}$ = 11.2 Hz, H2), 4.20 (m, 1, H5) 4.4–4.8 (m, 4, $PhCH_2$), 4.61 (d, 1, H1), 7.34 (m, 10, aromatic). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.9; H, 6.57; N, 3.65. Found: C, 68.5, H, 6.58; N, 3.56.

1,6:2,3-Dianhydro-4-*O*-benzyl-β-D-gulopyranose (7b). 1,6:3,4-Dianhydro-β-D-galactopyranose (**6a**;[9] 4.0 g, 2.77 mmol) was dissolved in dry tetrahydrofuran (50 mL), and sodium hydride (1.0 g 4.1 mmol), which had been washed with petroleum ether, was added with stirring. After 5 h at room temperature, benzyl bromide (3.6 mL, 3.0 mmol) and tetra-*n*-butylammonium iodide (200 mg) were added, and stirring was continued for an additional 12 h. Customary workup followed by column chromatography afforded the gulo derivative **7b** (4.6 g, 70%) as a crystalline solid. Also isolated from the column was the galacto derivative **6b** (0.6 g, 10%).

For **7b**: $[\alpha]^{23}_D$ −10° (*c*, 1 in chloroform); R_f in 30% petroleum ether in ethyl acetate, 0.49; ^1H NMR δ 3.10 (dd, 1, $J_{2,3}$ = 1.5 Hz, $J_{3,4}$ = 4.4, H3), 3.45 (dd, 1, $J_{5,6}$ = 5.6, $J_{6exo,6endo}$ = 6.6 Hz, $H6_{exo}$), 3.51 (brs, 1, H2), 3.55 (brt, 1, $J_{4,5}$ = 5.0 Hz, H4), 3.90 (d, 1, $J_{5,6endo}$ = O Hz, $H6_{endo}$), 4.68 (s, 2, $PhCH_2$), 5.25 (m, 1, H1), 7.33 (m, 5, aromatic).

1,6-Anhydro-2-*O*-benzyl-4-*C*-cyano-4-deoxy-β-D-glucopyranose (8a). To a solution of the benzylated galacto epoxide **6b**[14] (150 mg, 0.64 mmol) in dry benzene (5 mL) was added diethyl aluminum cyanide (2 mL, 1.8 M in toluene, 3.6 mmol) and the solution was refluxed under argon for 2 h with stirring. Workup as described for **2b** above gave **8a** as a crystalline material (133 mg, 80%).

For **8a**: mp 143–144 °C; $[\alpha]^{23}_D$ −109° (*c*, 1 in chloroform); R_f in 50% petroleum ether in ethyl acetate, 0.24; IR (Nujol) 3560, 3420 (OH), 2235 (CN) cm^{-1}; ^1H NMR (acetone-d_6, Me_4Si) δ 2.8 (brs, 1, OH), 3.02 (m, 1, H4) 3.36 (m, 1, H2), 3.66 (dd, $J_{5,6exo}$ = 5.5 Hz, $J_{6exo,6endo}$ = 7.5 Hz, $H6_{exo}$), 4.12 (m, 1, H3), 4.19 (dd, $J_{5,6endo}$ = 1.0, $H6_{endo}$), 4.66 (q, 2, J_{AB} = 12.5 Hz, $PhCH_2$), 4.72 (m, 1, H5), 5.44 (brs, 1, H1) 7.36 (m, 5, aromatic). Anal. Calcd for $C_{14}H_{15}NO_4$: Calcd: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.06; H, 5.60; N, 5.60.

(14) Trnka, T.; Černý, M. *Collect. Czech. Chem. Commun.* **1971**, *36*, 2216.

1,6-Anhydro-4-*O*-benzyl-3-*C*-cyano-3-deoxy-β-D-galactopyranose (9). The benzylated gulo epoxide **7b** was subjected to cyanolysis as described above for the preparation of **8b** from **6b**, affording the product **9** in 80% yield.

For **9**: mp 95–96 °C; $[\alpha]^{23}_D$ −78.2° (*c*, 1 in chloroform); R_f in 50% petroleum ether in ethyl acetate, 0.28; IR ($CHCl_3$) 3560, 3430 (OH), 2235 (CN) cm^{-1}; ^1H NMR δ 2.3 (brs, 1, OH), 3.29 (brd, 1, J_{34} = 7.0 Hz, H3), 3.72 (dd, 1, $J_{5,6exo}$ = 5.0 Hz, $J_{6exo,6endo}$ = 8.5 Hz, $H6_{exo}$), 3.91 (dd, 1, $J_{4,5}$ = 4.1 Hz, H4), 4.04 (brs; 1, H2), 4.44 (brt, 1, H5), 4.56 (d, 1, $H6_{endo}$), 4.66 (q, 2, J_{AB} = 12.5 Hz, $PhCH_2$), 5.36 (d, 1, J_{12} = 2.0 Hz, H1), 7.36 (m, 5, aromatic). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found C, 64.34; H, 5.68; N, 5.07.

1,6-Anhydro-4-*O*-benzyl-3-*C*-cyano-3-deoxy-β-D-gulopyranose (10). The galacto cyanohydrin **9** was epimerized as described above for the conversion of **2b** into **5**. Compound **10** was obtained as an oil.

For **10**: $[\alpha]^{23}_D$ −23.2° (*c*, 1.2 in chloroform); R_f in 50% petroleum ether in ethyl acetate, 0.36; IR (neat) 3520, 3460 (OH), 2235 (CN) cm^{-1}; ^1H NMR δ 1.8 (brs, 1, OH), 2.89 (dd, 1, $J_{2,3}$ = 4.0 Hz, $J_{3,4}$ = 10.75 Hz, H3), 3.62 (dd, 1, $J_{5,6exo}$ = 4.8 Hz, $J_{6exo,\ 6endo}$ = 8.5 Hz, $H6_{exo}$), 3.86 (dd, 1, $J_{1,2}$ = 2.3 Hz, H2), 3.99 (dd, 1, $J_{4,5}$ = 4.5 Hz, H4), 4.03 (d, 1, $H6_{endo}$), 4.37 (brt, 1, H5), 4.67 (q, 1, J_{AB} = 11.0 Hz, $PhCH_2$), 5.37 (d, 1, H1), 7.32 (m, 5, aromatic).

4-*O*-Benzyl-3-*C*-cyano-3-deoxy-α- and -β-D-galactopyranose Triacetate (11a and 11b). To a solution of the cyanohydrin **10** (750 mg, 2.8 mmol) in acetic anhydride (3 mL) was added boron trifluoride etherate (0.12 mL) with stirring. After 30 min, the reaction mixture was diluted with water and extracted with benzene. The organic layer was washed with dilute ammonium hydroxide and water and dried. Evaporation afforded a crystalline mass whose ^1H NMR spectrum indicated the presence of **11a** and **11b** in the ratio 4:1. Column chromatography using methylene chloride–petroleum ether (9:1) effected separation of the anomers (R_f 0.54 and 0.36, respectively).

For **11a**: mp 105–106 °C; $[\alpha]^{23}_D$ +72.5° (*c*, 1 in chloroform); IR ($CHCl_3$) 2230 (CN), 1740 (COOR) cm^{-1}; ^1H NMR δ 2.03 (s, 3, CH_3CO), 2.09 (s, 3, CH_3CO), 2.14 (s, 3, CH_3CO), 3.33 (dd, 1, $J_{2,3}$ = 12.0 Hz, $J_{3,4}$ = 2.5 Hz, H3), 3.98–4.22 (m, 4, H4, H5, H6, H6′), 5.86 (q, 2, J_{AB} = 11.0 Hz, $PhCH_2$), 5.52 (dd, 1, $J_{1,2}$ = 3.2 Hz, H2), 6.33 (d, 1, H1), 7.4 (m, 5, aromatic). Anal. Calcd for $C_{20}H_{23}NO_8$: C, 59.26; H, 5.72; N, 3.45. Found: C, 59.17; H, 5.74; N, 3.24.

4-*O*-Benzyl-3-*C*-cyano-3-deoxy-1,2-*O*-isopropylidene-α-D-galactopyranose (12). The mixture of acetates **11a,b** was deacetylated with sodium methoxide in methanol. A portion (1.2 g 4.3 mmol) of the resulting trial **11c** was dissolved in methylene chloride (100 mL) and dimethoxyethene (40 mL), and dry dimethoxypropane (0.6 mL, 4.3 mmol) and *p*-toluenesulfonic acid (200 mg) were added. After 4 h a further portion of dimethoxypropane (0.4 mL) was added, and this process was repeated until the starting material (**11c**) had disappeared. Neutralization with triethylamine followed by column chromatography using methylene chloride–ethyl ether (9:1) afforded compound **12**. (1.35 mg, 70%), R_f 0.2.

For **12**: mp 89–90 °C; $[\alpha]^{23}_D$ −24.5° (*c*, 1 in chloroform); IR ($CHCl_3$) 3580 (OH), 2240 (CN) cm^{-1}; ^1H NMR δ 1.86 (m,1, OH), 3.27 (t, 1, $J_{2,3} \approx J_{3,4}$) $\simeq$ 5.0 Hz,H3), 3.69 (dd, 1, $J_{5,6'}$ = 4.2 Hz, $J_{6,6'}$ = 11.0 Hz, H6′), 3.85 (dd, 1, $J_{5,6}$ = 6.0 Hz, H6), 4.03 (m, 2, H4, H5), 4.47 (t, 1, $J_{1,2}$ = 4.5 Hz, $J_{2,3}$ = 5.0 Hz, H2), 4.57 and 4.79 (AB q, 2, J_{AB} = 11.5, $PhCH_2$), 5.62 (d, 1, H1), 7.35 (m, 5, aromatic). Anal. Calcd for $C_{17}H_{21}O_5N$: C, 63.94; H, 6.63; N, 4.38. Found: C, 63.88; H, 6.67; N, 4.28.

(1*R*)- and (1*S*)-4-*O*-Benzyl-3-*C*-cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-1-*O*-methyl-D-galactose (13a and 13b, Respectively). The triol **11c** (50 mg, mmol) was dissolved in dry dimethoxypropane (5 mL) and *p*-toluenesulfonic acid (5 mg) and a small amount of methanol (~10 drops) were added. After 5 h at room temperature, TLC in methylene chloride–diethyl ether (9:1) indicated the formation of **13a** (R_f 0.66) and **13b** (R_f 0.55). Column chromatography using the same solvent system afforded the anomers in the combined yield of 70%.

For **13a**: syrup $[\alpha]^{23}_D$ −17.6° (*c*, 0.5 in chloroform); IR ($CHCl_3$) 2240 (CN) cm^{-1}; ^1H NMR δ 1.31, 1.33, 1.40, 1.54 (2 $(CH_3)_2C$), 3.21 (dd, 1, $J_{2,3}$ = 4.8, $J_{3,4}$ = 8.0 Hz, H3), 3.31 (s, 3, OCH_3), 3.75 (dd, 1, $J_{4,5}$ = 4.0, H4), 3.85 (dd, 1, $J_{5,6'}$ = 6.6, $J_{6,6'}$ = 8.0 Hz, H6′), 4.01

(dd, 1, $J_{5,6}$ = 6.9, H6), 4.28 (t, 1, $J_{1,2}$ = 4.0 Hz, H 2), 4.33 (dt, 1, H5), 4.66 and 4.70 (AB q, 2, J_{AB} = 11.5, $PhCH_2$), 4.91 (d, 1, H1), 7.34 (s, 5, aromatic). Anal. Calcd for $C_{21}H_{29}O_6N$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.10; H, 7.51; N, 3.80.

For **13b**: syrup $[\alpha]^{23}_D$ +85.1° (c, 0.6 in chloroform); IR ($CHCl_3$) 2240 (CN) cm^{-1}; ^1H NMR δ 1.33, 1.42, 1.47, 1.54 (2 $(CH_3)_2C$), 3.19 (dd, 1, $J_{2,3}$ = 2.8, $J_{3,4}$ = 10.0, H3), 3.39 (s, 3, OCH_3), 3.78 (dd, 1, $J_{4,5}$ = 3.0, H4), 3.82 (dd, 1, $J_{5,6'}$ = 6.8, $J_{6,6'}$ = 8.2 Hz, H6'), 4.03 (dd, 1, $J_{5,6}$ = 6.6 Hz, H6), 4.37 (t, 1, $J_{1,2}$ = 2.5 Hz, H2), 4.40 (dt, 1, H5), 4.64 and 4.72 (AB q, 2, J_{AB} = 11.0 Hz, $PhCH_2$), 5.03 (d, 1, H1), 7.3 (s, 5, aromatic). Anal. Calcd for $C_{21}H_{29}O_6N$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.58; H, 7.61; N, 3.73.

Acknowledgment. We are grateful to the University of Maryland for financial assistance.

Registry No. 1a, 24578-12-9; **1b**, 82742-11-8; **1c**, 82742-12-9; **2b**, 82742-13-0; **3b**, 82742-14-1; **4**, 82752-59-8; **5**, 82742-15-2; **6a**, 16939-77-8; **6b**, 33208-46-7; **7a**, 34147-05-2; **7b**, 82742-16-3; **8a**, 82742-17-4; **8b**, 82742-18-5; **9**, 82742-19-6; **10**, 82742-20-9; **11a**, 82742-21-0; **11b**, 82752-60-1; **11c**, 82742-22-1; **12**, 82742-23-2; **13a**, 82742-24-3; **13b**, 82795-70-8.

Regio- and Stereoselective Remote Hydroxylations of the A Ring of Steroids. A Novel Route to 5α Steroids with Cis-Coupled A and B Rings[1]

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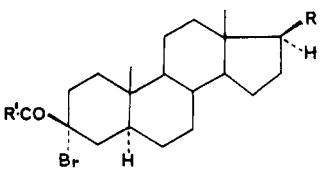
Under nonnucleophilic conditions, the $AgSbF_6$ dehalogenation of steroidal α-bromo ketones derived from cholestan-3-one and (5α)- and (5β)-17-hydroxyandrostan-3-one leads, after hydrolysis, to hydroxylation of the A ring. In compounds with A/B trans ring fusion, hydroxylation takes place at the 10α position (35–45% yield), leading to 5α, A/B cis steroids. In compound with A/B cis ring fusion, hydroxylation takes place at the 5β-position (45% yield). These results are discussed with reference to α-acyl carbenium ions and oxonium salts as intermediates.

The remote functionalization of unactivated ring carbon atoms has generally been achieved by using radical initiators.[2] This paper describes an extension of such strategy to carbocationic initiation[3] by using the now well-established properties of α-acyl carbenium ions.[4-10]

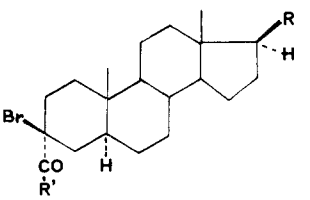
As depicted in Scheme I, these species, generated by dehalogenation of an α-bromo ketone with $AgSbF_6$ in a nonnucleophilic solvent, are converted by a series of hydride shifts to cyclic oxonium salts. Hydrolysis of such salts then leads to an effective remote hydroxylation. The formation of these oxonium salts inhibits skeletal rearrangement, so that selective hydroxylation of a steroidal A ring could be anticipated, following the generation of a C-3 acyl carbenium ion.

Results and Discussion

The bromo ketones **1a** and **2a** were prepared from cholestanone by a classical route. The bromoacetyl compounds **2b** and **3** were obtained from (5α)- and (5β)-17β-hydroxyandrostan-3-one.[8,9]



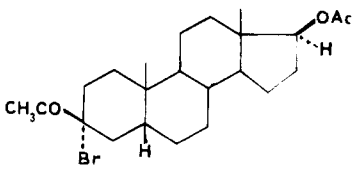
1



2

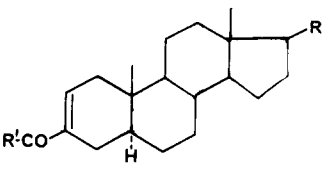
a R = C_8H_{17} R' = C_6H_5

b R = OAc R' = CH_3

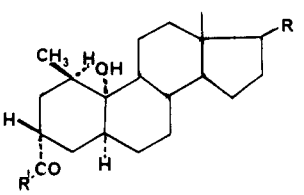


3

Dehalogenation of **1a** or **2a** in CH_2Cl_2 at −20 °C led, after hydrolysis, to the hydroxy ketone **4a** and the unsaturated ketone **5a** (**4a**, 45% yield from **1a**, 33% yield from **2a**; **5a**,



5



4

a R = C_8H_{17} R' = C_6H_5

b R = OAc R' = CH_3

35% yield from **1a**, 25% yield from **2a**). Ketone **4a** is

(1) Presented in part at the 2th European Symposium of Organic Chemistry, 1981.

(2) Kirk, D. N.; Hartshorn, M. P. "Steroid Reaction Mechanisms"; Elsevier: Amsterdam, 1969; p 394. Heusler, K.; Kalvoda, J. "Organic Reactions in Steroids Chemistry"; Fried, J., Edwards, J. A., Eds.; Van Nostrand-Reinhold: New York, 1972; p 237. Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170.

(3) Coustard, J. M.; Jacquesy, J. C. *J. Chem. Res., Synop.* **1977**, 280; *J. Chem. Res., Miniprint* **1977**, 3274. Kanischev, M. I.; Schegolev, A. A.; Smit, W. A.; Caple, R.; Kelner, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 5660. Olah, G. A.; Yoneda, N.; Ohnishi, R. *J. Am. Chem. Soc.* **1976**, *98*, 7341.

(4) Bégué, J. P.; Charpentier-Morize, M.; Bonnet-Delpon, D.; Sansoulet, J. *J. Org. Chem.* **1980**, *45*, 3357.

(5) Bégué, J. P.; Charpentier-Morize, M.; Pardo, C. *Tetrahedron* **1975**, *31*, 1919.

(6) Bégué, J. P.; Charpentier-Morize, M. *Acc. Chem. Res.* **1980**, *13*, 207.

(7) Bégué, J. P.; Malissard, M. *Tetrahedron* **1978**, *34*, 2095.

(8) Bégué, J. P.; Charpentier-Morize, M.; Bonnet-Delpon, D.; Sansoulet, J. *Can. J. Chem.* **1982**, *60*, 2087.

(9) Bégué, J. P.; Bonnet-Delpon, D. *Org. Magn. Reson.* **1982**, *18*, 190.

(10) Preliminary communication in: Bégué, J. P. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 610.

0022-3263/82/1947-4268$01.25/0