pentofuranoside (**16**, 2.39 g, 37%), $[\alpha]^{25}D$ +315.6° (*c* 1.08, $CHCl_3$) [lit.[2] $[\alpha]^{25}D$ +314° (*c* 1, $CHCl_3$)], and methyl 2-deoxy-4-thio-β-D-*erythro*-pentofuranoside (**15**, 3.86 g, 59.5%), $[\alpha]^{25}D$ −278° (*c* 1.02, $CHCl_3$) (lit.[2] $[\alpha]^{25}D$ −277.6°).

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Registry No.—**1**, 6254-69-9; **2**, 6207-00-7; **3**, 60295-22-9; **4**, 60295-23-0; **5**, 32589-06-3; **6**, 60295-24-1; **7**, 60295-25-2; **10**, 60295-26-3; **11a**, 60295-27-4; **11b**, 60295-28-5; **12**, 60295-29-6; **13**, 60295-30-9; **14**, 60295-31-0; **15**, 24707-95-7; **16**, 24707-94-6; 2-methoxypropene, 16519-32-7; benzyl bromide, 100-39-0; *p*-toluenesulfonyl chloride, 98-59-9; *p*-chlorobenzenesulfonyl chloride, 98-60-2; potassium thioacetate, 10387-40-3.

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Reduction of Ketones with Incorporation of Deuterium at the α Position. Anomalous Reduction of Keto Sugar Derivatives[1,2]

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Reduction of the 3-keto sugar methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (**1**) with sodium borohydride in moist methanol proceeded stereospecifically to the allose derivative (**2**) having the 3-hydroxyl group axially oriented. Use of sodium borodeuteride under similar conditions gave the corresponding labeled analogue (characterized as its diacetate **11**) deuterated completely and exclusively at C-3, indicating equatorial attack on **1** by the reductant. In contrast, when the reduction was performed in dry 2-propanol, there resulted a 1:1 mixture of the axial 3 alcohol (allo derivative **2**) nd the equatorial 3 alcohol (gluco derivative **3**). When the latter reduction was repeated with sodium borodeuteride in dry 2-propanol, the allo product was again found to be labeled completely and exclusively at C-3 (as shown by the NMR spectrum of its diacetate **11**), but the gluco product **3** (studied as its diacetate **12**) was found to be fully protiated at C-3 and fully deuterated at C-2. The labeling experiments thus show that the gluco product **3** arises not by axial attack of the reductant at the ketonic (C-3) position of the precursor (**1**), but by stereospecific attack at the α position (C-2) of a presumed enediolic intermediate derived from **1**. The ready generation of a 2,3-enediol from **1** is demonstrated by preparation of the enediol diacetate **4**. Lithium aluminum hydride in tetrahydrofuran and sodium borohydride in *N,N*-dimethylformamide both reduce **1** exclusively to the axial 3 alcohol **2**. Zinc borohydride in 1,2-dimethoxyethane reduced **1** without cleavage of the 2-*O*-acetyl group to give mainly the allo product (**8**), together with a small proportion of gluco derivative (**9**). These results indicate the need for caution in interpreting results of label incorporation through reduction as a means of locating carbonyl groups in sugar derivatives, at least when dry alcoholic media are used. The results also suggest useful possibilities for synthesis of specifically labeled sugars.

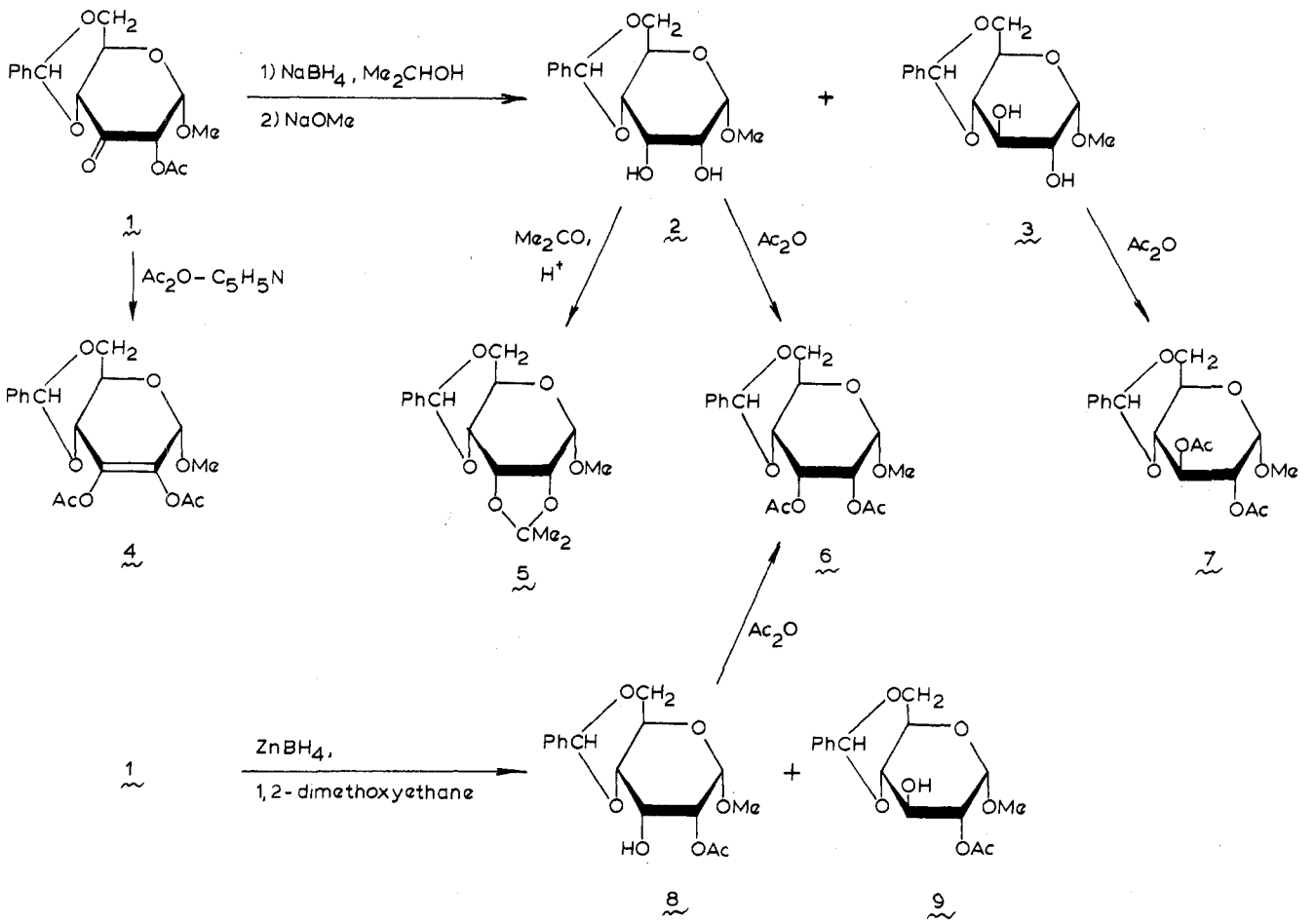
The reduction of sugar derivatives having one free ketonic group gives mixtures of two secondary alcohols, isomeric at the original carbonyl position, in relative proportions strongly controlled by steric factors. The sequence of oxidation–reduction is commonly used[3] to prepare alcohols of inverted stereochemistry from the precursor and for "marking" the site of oxidation with deuterium or tritium by use of appropriately labeled reductants.[4,5] The present report developed on the one hand from a program[6,7] designed to furnish specifically labeled sugars of use as biochemical probes and for interpretation of complex NMR and mass spectral patterns, and on the other from studies[8–10] concerning the mechanism whereby metal salts protect cellulose from oxidative degradation during bleaching.

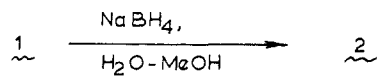
This study describes the use of a model ketone, methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose[10,11] (**1**), and related derivatives for evaluation of the regio- and stereoselectivity of its reduction with deuterated hydride reductants. It is shown that, according to the nature of the solvent used, reduction may take place exclusively (as is usually supposed) at the carbonyl group, or alternatively by attack at the position α to the carbonyl group, to give concurrently the corresponding α-labeled derivative.

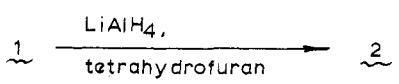
Results and Discussion

Reduction of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (**1**) with sodium borohydride in aqueous methanol gave methyl 4,6-*O*-benzylidene-α-D-allopyranoside (**2**), iolated in near-quantitative yield, as a chromatographically homogeneous dihydrate. The product was further characterized as the anhydrous compound by recrystallization from benzene. Conversion of **2** under essentially nonacidic conditions into methyl 4,6-*O*-benzylidene-2,3-*O*-isopropylidene-α-D-allopyranoside (**5**) served to establish the 2,3-cis geometry of the reduced product. Furthermore, hydrolysis of **2** led exclusively to D-allose, detected chromatographically on paper and clearly differentiated from either glucose, mannose, or galactose. The free sugar obtained by

Scheme I







hydrolysis was also firmly characterized as the crystalline phenylosazone. The syrupy 2,3-diacetate (**6**) of **2** gave an NMR spectrum in benzene-d_6 (see Tables I and II) consistent with the allo configuration; in particular the characteristic chemical shifts and spin couplings of H-1, H-2, and H-3 stand in clear contrast to values for the corresponding D-gluco product (**7**). It may be noted that **2** was quite difficult to acetylate to completion; conventional acetylation conditions gave mainly a monoacetate.

Similarly, when **1** was reduced with lithium aluminum hydride in tetrahydrofuran or with sodium borohydride in methanol–*N*,*N*-dimethylformamide,[11] the product was that (**2**) having the D-allo configuration. As would be expected, the sole product of these hydride reductions is that isomer which arises via quasi-equatorial attack of the hydride species from the apparent less hindered side of the carbonyl group. Sodium borohydride in either methanol or methanol–*N*,*N*-dimethylformamide[11] evidently exerts sufficient base strength to remove the 2-*O*-acetyl group.

In sharp contrast to the foregoing results, reduction of the ketone **1** in dry 2-propanol, a solvent frequently used in kinetic studies[12] of reductions by borohydride, gave (after removal of the acetyl groups) an approximately 1:1 mixture of two products that were found to be the D-allo derivative **2** and its 3 epimer, namely, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**). Each product was isolated and characterized on a crystalline basis. Conversion of these into their respective diacetates **6** and **7** permitted a first-order NMR spectral analysis of the ring-proton signals. The spectrum of **7** at 250 MHz in benzene-d_6 was identical with that of the product obtained upon acetylation of the reduction products described in the preceding paragraphs.

The use of zinc borohydride in dry 1,2-dimethoxyethane gave 64% of crystalline methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-allopyranoside (**8**), identified by NMR spectroscopy (see Tables I and II) and by conversion into the diacetate **6**, together with 14% of the known[14,15] methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**9**). Interestingly, this reduction procedure affords products in which the 2-*O*-acetyl group is retained. Thus it might be supposed at this point that the formation of both **2** (or **8**) and **3** (or **9**) could arise from attack of the hydride species on **1** from the equatorial and axial directions, respectively.

However, examination of the diacetates of the products from the reduction of **1** with sodium borodeuteride in dry 2-propanol revealed that, whereas the D-allo isomer **11** was labeled (as expected) exclusively at C-3, the D-gluco isomer **12** was monodeuterated in the 2 position, and not (as might be expected) at C-3. The crystalline diacetate **12** was identified by comparison of its melting point and optical rotation with those of the known[13] unlabeled compound **7**. The NMR spectrum of **12** in deuterated benzene (see Table I) was identical with that[13] of compound **7**, except that no H-2 resonance was observed, and the H-1 signal had become a singlet (loss of $J_{1,2}$ proton–proton coupling) and the H-3 signal was evident as a doublet (loss of $J_{2,3}$ proton–proton coupling), thus pinpointing the substitution by deuterium at C-2. A similar NMR analysis was conducted on the D-allo diacetate, where

Table I. NMR Chemical Shift Data[a]

Registry no.	Compd	Solvent	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	PhCH	OAc	OMe	Aryl	Other
42400-52-2	1[b]	$CDCl_3$[c]	5.21 d	5.41 dd	*d*		3.80–4.48 m			5.56 s	2.20 s	3.44 s	7.38 m	
4153-17-7	2	C_6D_6[e]	4.47 d	3.41 t	4.08 t	2.93 dd	3.98 sx	4.16 m	3.44 m	5.29 s	*d*	2.91 s	6.18–6.64 m	
3162-96-7	3[f]	$(CD_3)_2SO$[c]	4.99 d	3.75	*g*	*g*	4.53	*g*		5.92 s	*d*	3.68 s	6.92 m	
59830-63-6	4	$CDCl_3$[e]	5.10 s	*d*	*d*	4.74 d	4.12 sx	4.32 dd	3.86 t	5.55 s	2.16 s, 2.21 s	3.49 s	7.36 m, 7.45 m	
59830-64-7	5	$CDCl_3$[e]	4.70 d	4.35 dd	4.58 dd	3.79 dd	4.20 sx	4.37 sx	3.69 t	5.56 s	*d*	3.42 s	7.32, 7.5 m	1.42, 1.62 s CMe_2
56687-82-2	6	C_6D_6[c]	4.61 d	4.94 dd	5.83 t	3.07 dd	4.12–4.49 m		3.31–3.59 m	5.29 s	1.76 s	3.05 s	7.58, 7.19 m	
57564-28-0	11	C_6D_6[h]	4.61 d	4.94 d	*d*	3.07 d	4.12–4.49 m		3.31–3.59 m	5.29 s	1.76 s	3.05 s	7.58, 7.19 m	
4141-45-1	7[f]	C_6D_6[e]	4.91 d	5.11 dd	6.02 t	3.48 t	3.85 sx	4.00 dd	3.47 dd	5.23 s	1.69, 1.72 s	2.95 s	7.16, 7.55 m	
57538-71-3	12	C_6D_6[e]	4.91 s	*d*	6.02 d	3.48 t	3.85 sx	4.00 dd	3.47 dd	5.23 s	1.69, 1.72 s	2.95 s	7.16, 7.55 m	
57538-70-2	8	$CDCl_3$[c]	4.83 d	4.89 dd	*i*	3.59 dd	4.16 m	4.39 dd	3.76 t	5.58 s	2.17 s	3.45 s	7.34 m	
59830-65-8	8-*3-d*	$CDCl_3$[h]	4.83 d	4.89 d	*i*	3.59 d	4.16 m	4.39 dd	3.76 t	5.58 s	2.17 s	3.45 s	7.34 m	
25577-40-6	9	$CDCl_3$[e]	4.74 d	5.66 t	*i*		3.36–4.46 m			5.32 s	2.15 s	3.46 s	7.34 m	
28642-65-1	10	$CDCl_3$[h]	5.32 d	5.62 d	*d*		3.88–4.53 m			5.59 s	*d*	3.50 s	7.42, 8.12 m	
55338-59-5	13	$CDCl_3$[e]	4.78 s	*d*	5.74 d	3.90 dd	4.31 sx	4.41 dd	3.82 dd	5.52 s	2.18 s	3.51 s	7.35–7.50 m	

[a] Chemical shifts are on the δ (ppm) scale: d, doublet; t, triplet; m, multiplet; dd, doublet of doublets; sx, sextet. [b] See ref 10. [c] At 100 MHz. [d] No signal. [e] At 250 MHz. [f] See ref 13. [g] Not determined because of second-order effects. [h] At 90 MHz. [i] Exact chemical shift not determined; obscured by other resonances.

no H-3 signal was observed, and H-2 resonated as a doublet (with loss of $J_{2,3}$ proton–proton coupling); the H-4 signal was not distinct because of overlap with other signals. The mass spectra of both **11** and **12** showed molecular ions at *m/e* 367, one unit higher than for their nondeuterated analogues.

In a further extension to a related example, the 2-*O*-benzoyl analogue of **1**, namely, methyl 2-*O*-benzoyl-α-D-*ribo*-hexopyranosid-3-ulose (**10**), was reduced under conditions identical with those used for the reduction of **1**. After O-debenzoylation and subsequent acetylation of the products, there was obtained an approximately 1:8 mixture of the D-allo (**11**) and D-gluco (**12**) diacetates. These were separated by column chromatography and identified by NMR spectroscopy. Apparently, relative to the acetoxy group, the benzoyloxy group at C-2 facilitates deuterium incorporation at that carbon atom.

Such anomalous incorporations of deuterium α to the ketone group appear to be novel. Related precedent is evident in at least two publications that have documented epimerizations, α to a ketone group, occurring during reduction with borohydride. One example[16] cites the epimerization, with sodium borohydride in methanol, of a bicyclic ketone having a very acidic α-hydrogen atom. A later publication[17] describes the epimerization of menthone, 3-thujone, and 3-isothujone at the α position as each is reduced by sodium borohydride in anhydrous solvents. Moreover, it was found[17] in the latter studies that the addition of at least 5% of water to the solvent was sufficient to inhibit the epimerization, an observation that led the investigators to conclude that a very strongly basic species exists in anhydrous alcoholic or ethereal solutions of sodium borohydride.

Prompted by the latter findings, both compounds **1** and **10** were reduced with sodium borodeuteride in 19:1 2-propanol–water. The product, isolated as its diacetate, was found to be entirely the D-allo derivative **11**, having deuterium incorporation exclusively at C-3. No D-gluco isomer (**12**) was evident, despite careful examination of the products by TLC and NMR spectroscopy.

The classical reduction mechanism readily accounts for the formation of **11**, but the D-gluco-*2-d* product **12** must arise via attack of the reductant at C-2. Possibly, in the dry solvent containing a base (such as BD_4^-), an enol A might become the substrate, with attack of the hydride from the upper face of the molecule to give, under product-development control, the D-gluco-*2-d* isomer B. Such a process would be favored in terms of release of steric strain in the species A, and may help to account for the fact that the 2-benzoate **10**, having a more bulky 2 substituent, gives rise to ~80% of the D-gluco-*2-d* product, compared with only ~50% with the 2-acetate **1**. That no D-manno product is found may be explained on steric grounds; the axial methoxyl group presumably offers sufficient hindrance to prevent approach of the hydride species from the underside of the molecule. The foregoing mechanism invokes a nucleophilic attack on an enediol intermediate, normally considered to be an unfavorable process, and other possible mechanisms should also be considered. Anchimeric participation by the 2-*O*-acyl group is one such possibility, but such a mechanism by way of a 2,3-ortho ester type of intermediate is difficult to reconcile with the observed D-gluco (and not D-allo) stereochemistry of the 2-deuterated product **12**. Further experimental work will be necessary to test the various possible mechanistic hypotheses.

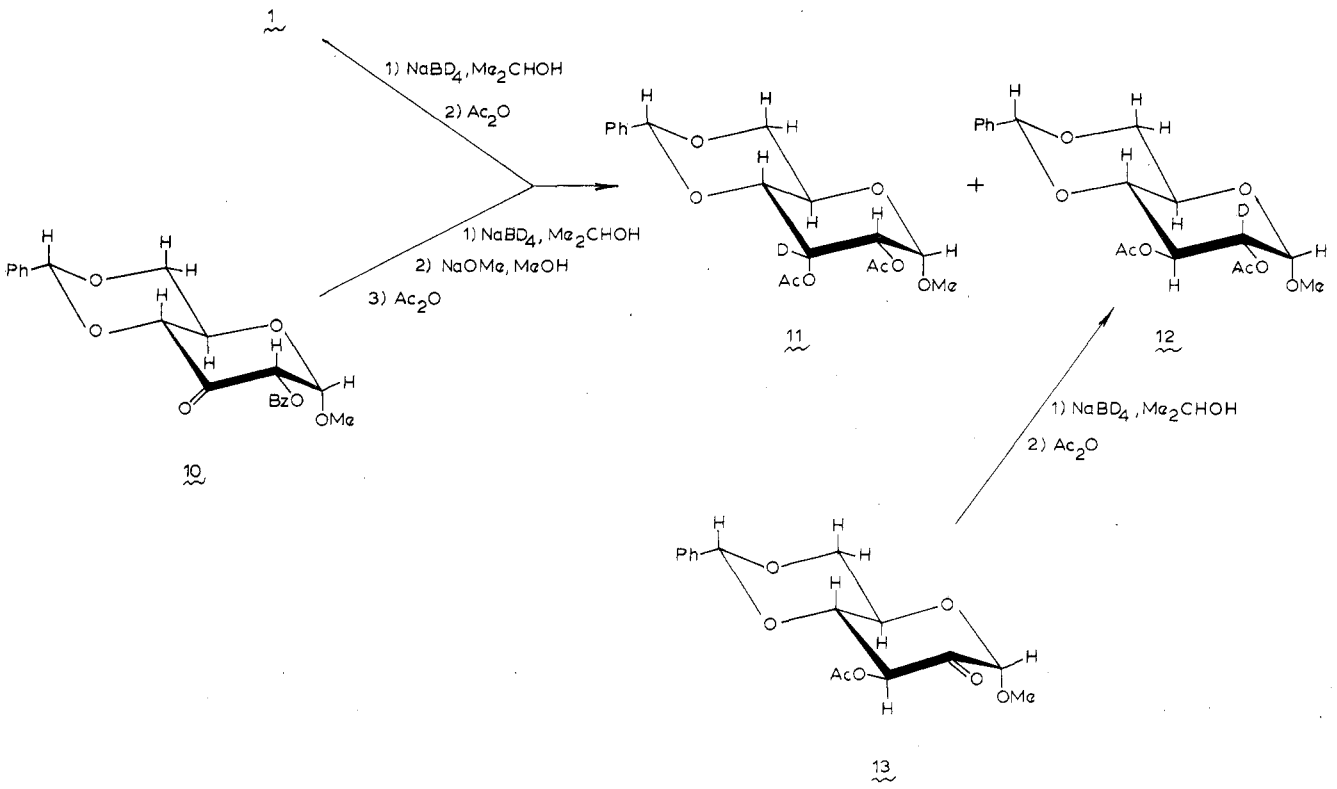
No enolization between C-3 and C-4 was evident in these reactions. Steric factors would probably exert some impedance to development of sp^2 hybridization at the ring-fusion position (C-4), but inductive stabilization by the 2-acyloxy group is probably the most important factor influencing formation of the 2,3-enol. The 2-benzoyloxy group would be the more effective intermediate of the two 2-acyloxy groups for such

Table II. First-Order Proton–Proton Coupling Constants[a]

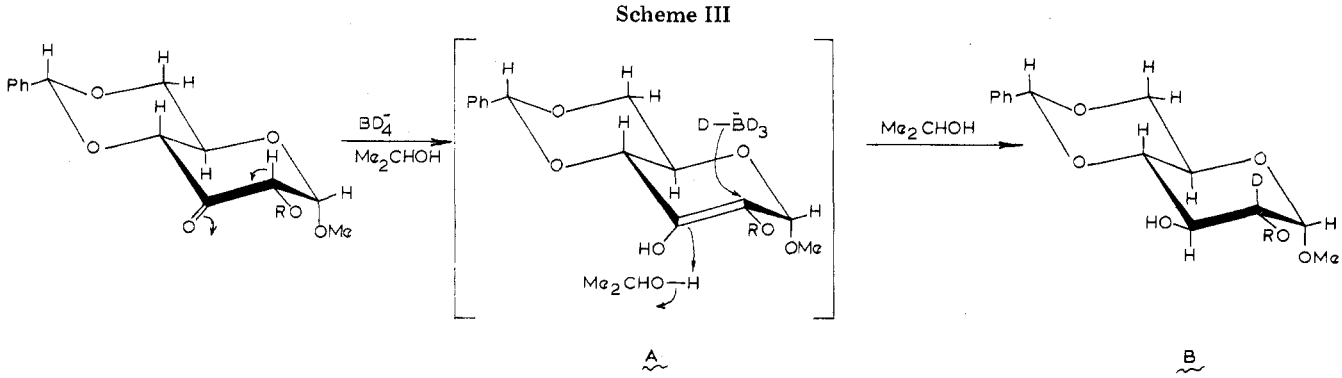
Compd	Solvent	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
1[b]	$CDCl_3$[c]	4.25	*d*	*d*	*e*	*e*	*e*	*e*
2	C_6D_6[f]	4	3.8	3.8	10	5	10	10
3	$(CD_3)_2SO$[c]	3.8	*e*	*e*	*e*	*e*	*e*	*e*
4	$CDCl_3$[f]				9.1	4.6	10.0	10.3
5	$CDCl_3$[c]	4.7	5.8	3.7	10.0	5.0	10.5	10.5
6	C_6D_6[c]	4.1	3.5	3.5	9.5	*e*	*e*	*e*
11	C_6D_6[h]	4.1	*d*	*d*	9.5	5.0	10.0	10.0
7[g]	C_6D_6[c]	4.0	10.0	10.0	10.0	5.0	10.0	11.2
12	C_6D_6[f]	*d*	*d*	10.0	10.0	5.0	10.0	11.2
8	$CDCl_3$[c]	4.0	4.5	2.6	9.5	5.0	9.4	9.4
8 (3-deut)	$CDCl_3$[h]	4.0	*d*	*d*	9.5	5.0	9.4	9.4
9	$CDCl_3$[c]	4.5	4.5	*e*	*e*	*e*	*e*	*e*
10	$CDCl_3$[h]	4.4	*d*	*d*	*e*	*e*	*e*	*e*
13	$CDCl_3$[f]	*d*	*d*	10.9	9.1	5.0	10.0	10.0

[a] Coupling constants are given in hertz. [b] Shows $J_{2,4} = 1.25$ Hz. [c] At 100 MHz. [d] Nonexistent proton for coupling. [e] Not measured because of second-order effects. [f] At 250 MHz. [g] See ref 13. [h] At 90 MHz.

Scheme II



Scheme III



1 R = $MeC(=O)-$

10 R = $PhC(=O)-$

stabilization. Acetylation of **1** under vigorous conditions (hot acetic anhydride–pyridine) gave 74% of the crystalline enediol diacetate **4**, whose NMR spectrum clearly indicated that the site of unsaturation was C-2–C-3 and not C-3–C-4.

In a further study related to the reduction of the glycos-3-uloses **1** and **10**, the borodeuteride reduction of methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose (**13**), prepared by oxidation of its alcohol precursor[15] with acetic anhydride–methyl sulfoxide, was examined. In both aqueous methanol and dry 2-propanol, only the D-gluco-2-*d* product was detected. Similar results have been observed[18] on reducing the ketone **13** with sodium borohydride in methanol–*N*,*N*-dimethylformamide. In this instance, the failure to detect any significant proportion of C-3-labeled product may arise from steric hindrance by the axial methoxyl group at C-1, which would be expected to inhibit axial attack by the reagent at C-3 of an enolic intermediate. Vigorous acetylation of **13** converted it into the enediol diacetate **4**.

The foregoing results point out the need for caution in assigning structures to products arising from the reduction of carbohydrate ketonic intermediates when dry solvents are employed. The use of solvents that contain at least 5% of water appears to be necessary to ensure labeling exclusively at the carbonyl carbon atom. On the other hand, the use of dry solvents may provide some new procedures for the synthesis of specifically labeled sugars heretofore accessible only with difficulty.

Experimental Section

General Methods. Evaporations were performed on a rotary evaporator at 45 ± 5 °C. Melting points were measured either on a microscope hotstage (Leitz) or in a capillary melting point apparatus (Hoover) and are not corrected. Optical rotations were determined either with a Quick-Polarimeter (Roussel and Jouan) or a Perkin-Elmer Model 141 spectropolarimeter. NMR spectra were recorded at either 90, 100, or 250 MHz with respectively Brüker WH-90, Varian HA-100, or Cameca-250 instruments; chemical shifts are reported on the δ scale (ppm) downfield from the internal standard of tetramethylsilane. Mass spectra (70 eV ionizing voltage) were determined with an AEI-MS9 instrument. Thin layer chromatography was performed with silica gel G (Merck), and column chromatography with silica gel 60 (Merck), 70–230 mesh (gravity flow) or <200 mesh (medium pressure in 316 stainless-steel columns at 6–10 atm). Solvents used were A, 3:1 dichloromethane–ether; B, 9:1 ether–hexane; C, 1:1 ether–hexane; or D, 7:3 chloroform–acetone.

General Procedure for Acetylation. To a solution of the alcohol in pyridine was added acetic anhydride with stirring. The mixture was stirred at room temperature, with protection from moisture, for the indicated time, after which the reaction was terminated by the addition of ice, with further stirring for 0.5–1 h. Volatile materials were evaporated off, and small portions of toluene were evaporated two to five times from the residue to remove traces of pyridine. The product was then dissolved in a small volume of chloroform or dichloromethane, washed sequentially with equal volumes of water, saturated aqueous sodium hydrogen carbonate, and water, and then dried (magnesium sulfate or sodium sulfate), to give, after evaporation of the solvent, a product that was processed, either by chromatography or crystallization, to give the pure acetate.

General Procedure for Processing Borohydride Reduction Reactions. After the reduction procedure indicated and decomposition of the excess reagent, the solvent was evaporated off, and methanol was repeatedly evaporated from the residue to remove boric acid as the volatile methyl borate. The product was thendissolved in chloroform or dichloromethane, washed with water, and the organic extract was dried (magnesium sulfate or sodium sulfate). The solvent was then evaporated and the product was either chromatographed or crystallized to give the pure compound.

Reduction of Methyl 2-*O*-Acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (1). A. With Sodium Borohydride in Aqueous Methanol. To a stirred solution of 800 mg (2.48 mmol) of the hexulose **1** in 90 ml of methanol was added 150 mg (3.58 mmol) of a solution of sodium borohydride in water. After 3 h, the solution was neutralized with a stream of carbon dioxide, and the methanol was evaporated off. Processing by the general method described gave 680 mg (97%) of an oil, homogeneous by TLC (R_f 0.31, solvent A). Crystallization from dichloromethane–hexane gave 934 mg (62%) of pure **2**: mp 58–60, 167–168 °C (anhydrous, from benzene); $[\alpha]^{21}D$ +128° (*c* 1, chloroform) [lit.[11] mp 60 °C, for the dihydrate, mp 148–149, mp[19] 175–177 °C, $[\alpha]D$ +126° (*N*,*N*-dimethylformamide[11])]; for NMR data see Tables I and II.

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.53; H, 6.29.

B. With Lithium Aluminum Hydride. A solution of 500 mg (13.5 mmol) of lithium aluminum hydride in 30 ml of tetrahydrofuran was added dropwise to a cold (0 °C), stirred solution of 1.03 g (3.10 mmol) of the hexulose **1** in 25 ml of the same solvent. After 2 h at 0 °C, the solution was heated under reflux for 1 h and cooled, and the excess reductant was decomposed with ethyl acetate. The resultant suspension was filtered through a bed of Celite, and the filtrate was evaporated to dryness. The residue was triturated in chloroform, and the remaining salts, which were precipitated upon addition of a few drops of saturated aqueous sodium hydrogen carbonate, were filtered off. The organic extract, after conventional processing, gave 700 mg (78%) of **2** as an oil that was homogeneous by TLC. Crystallization as in the preceding experiment gave product **2** (mp 58–59 °C) that was identical by $[\alpha]D$ and NMR spectrum with that from the preceding borohydride reduction of **1**.

C. With Sodium Borohydride in 2-Propanol. To a solution of 644 mg (2.00 mmol) of the glycos-3-ulose **1** in 250 ml of dry 2-propanol (reagent grade) was added 76 mg (4 equiv) of sodium borohydride, portionwise, with stirring and protection from moisture. After 0.5 h, the excess of reagent was decomposed by addition of a few drops of acetic acid. Processing by the general method described gave an oil that was dried and dissolved in 50 ml of dry methanol to which a 10-mg pellet of sodium had been added. After 1 h the solution was neutralized with carbon dioxide, and the solvent was evaporated off. The crude, deacetylated product was applied to a column of silica gel (45 g) and eluted successively with chloroform and then 9:1, 8:2, and 7:3 chloroform–methano (250 ml each) to give 186 mg (33%) of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**), mp 164–165 °C, $[\alpha]D$ +112° (*c* 1, chloroform) [lit.[20] mp 163–164 °C, $[\alpha]D$ +110° (*c* 2, chloroform)], and 198 mg (35%) of methyl 4,6-*O*-benzylidene-α-D-allopyranoside dihydrate, identical by melting point and $[\alpha]D$ with the products from the foregoing reductions A and B. An additional 43 mg (8.5%) of **2** and **3** was obtained as a mixture.

D. With Zinc Borohydride. To a solution of 363 mg (1.12 mmol) of **1** in 8 ml of dry 1,2-dimethoxyethane was added 4 ml (~2 mmol) of a solution of zinc borohydride[21] in the same solvent. After 0.5 h, TLC indicated complete reduction of **1**, and the excess of borohydride was decomposed by the addition of a 1 M solution of sodium hydrogen tartrate. The solvent was evaporated, and the residue was processed to give 290 mg of an oil that by TLC (solvent A) revealed two components (R_f 0.70 and 0.56). Chromatography on a column (1.4 × 60 cm) of silica gel (solvent A, 250 ml) gave 232 mg (64%) of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-allopyranoside (**8**) that was crystallized from ethyl acetate–hexane: mp 69–71 °C; $[\alpha]^{25}D$ +59.5° (*c* 0.8, chloroform); for NMR data see Tables I and II.

Anal. Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.28; H, 6.08.

With an additional 120 ml of solvent, 51 mg (14%) of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**9**) was obtained: mp 133–134 °C; $[\alpha]^{25}D$ +112° (*c* 1.2, chloroform) [lit.[22] mp 133–134 °C, $[\alpha]^{29}D$ +112° (*c* 0.9, chloroform)].

Methyl 2,3-Di-*O*-acetyl-4,6-*O*-benzylidene-α-D-allopyranoside (6). By the general procedure described, 200 mg (0.71 mmol) of **2** in 2 ml of pyridine was acetylated for 3 days with 2 ml (2.16 g, 21 mmol) of acetic anhydride. The oily product was applied to a column of silica gel (15 g) which was eluted with 65 ml of solvent A to give 256 mg (99%) of pure **6** as a syrup, $[\alpha]^{23}D$ +54° (*c* 1, chloroform), *m/e* 366 [M·+]. For NMR data see Tables I and II.

Anal. Calcd for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C, 59.02; H, 5.95.

Acetylation of Methyl 2-*O*-Acetyl-4,6-*O*-benzylidene-α-D-allopyranoside (8). A solution of 100 mg (0.31 mmol) of **8** in 5 ml of pyridine was acetylated during 20 h with 1 ml (an excess) of acetic anhydride. TLC (solvent B) of the oily product showed two zones (R_f 0.58, identical with **6**) and unreacted **2** (R_f 0.28). Column chromatography (solvent C, 100–200 psi, 1 × 50 cm) resolved the mixture to give 71 mg (68%) of **6**, $[\alpha]^{23}D$ +54° (*c* 1, chloroform), identical with authentic **6** by NMR spectroscopy; also obtained was 21 mg (19%) of unreacted **8**, mp 69–70 °C.

Methyl 4,6-*O*-Benzylidene-2,3-*O*-isopropylidene-α-D-allopyranoside (5). To a solution of 1.33 g (4.71 mmol) of **2** in 15 ml of dry acetone was added 1.5 g of anhydrous copper(II) sulfate. After stirring for 50 h at 20 °C, the suspension was filtered, and the filtrate

was evaporated to dryness to give an oil that by TLC (solvent A) was shown to be a mixture of starting material **2** (R_f 0.31) and a new product (R_f 0.94). Chromatography over a column (1.4 × 60 cm) of silica gel with solvent A gave 256 mg (19%) of an oil that eluted in 65 ml of solvent. Crystallization from dichloromethane–hexane gave 124 mg (8%) of pure **5**, mp 119–121 °C, $[\alpha]^{25}D$ +131° (*c* 1.4, chloroform).

Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.33; H, 6.89.

Nonreacted **2** was recovered by eluting the column with an additional 235 ml of the solvent, yield 930 mg (69.9%), mp 59 °C.

Hydrolysis of Methyl 4,6-*O*-Benzylidene α-D-allopyranoside (2) and Identification of the Product as D-Allose. A. Hydrolysis. A solution of 50 mg (0.18 mmol) of **2**, obtained from either of the proceeding experiments (A or B), in 10 ml of 0.1 M hydrochloric acid was heated for 1 h under reflux. After cooling, the acid was neutralized by passing the solution through a small column of Amberlite MB-3 resin. Concentration of the aqueous eluate gave 19 mg of a crystalline product that was indistinguishable on paper chromatography (R_f 0.29, 1:4:1 pyridine–ethyl acetate–water, detection with aniline phthalate and sodium metaperiodate–benzidine) from allose and clearly distinguishable from glucose (R_f 0.26), mannose (R_f 0.32), and galactose (R_f 0.20).

B. Conversion into the Phenylosazone. To a solution of 400 mg of crude hydrolysate from **2** in 60 ml of water was added a solution of phenylhydrazine (0.5 ml) in acetic acid (0.5 ml), and the mixture was heated for 2 h at 100 °C. Cooling to 5 °C produced 359 mg of a yellow, semicrystalline product which, after nine crystallizations from 1:1 ethanol–water, gave yellow needles, mp 166–169 °C (lit.[23] mp 167–168 °C), $[\alpha]^{25}D$ −38° (*c* 0.44, 2:3 pyridine–ethanol) [lit.[23] $[\alpha]D$ −36.7° → (3 h) −48.4° (*c* 0.4, pyridine–ethanol)].

Reduction of Methyl 2-*O*-Acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (1) with Sodium Borodeuteride. A. In Dry 2-Propanol. To a solution of 533 mg (1.65 mmol) of **1** in 90 ml of anhydrous 2-propanol [dried over 3A molecular sieves (Linde)] was added portionwise 60 mg (3.46 equiv) of sodium borodeuteride with stirring and protection from moisture. After 0.5 h, 2–3 drops of acetic acid were added to decompose the excess of hydride, and the solution was evaporated to dryness. Analysis by TLC (solvent D) of the product obtained by the general processing procedure described revealed that the starting ketone **1** was absent, and that two closely migrating zones (R_f 0.70–0.75) were present. Acetylation of the crude product with 2 ml (an excess) of acetic anhydride and 10 ml of pyridine for 8 h at 25 °C gave a product containing three components (R_f 0.74, 0.58, and 0.28, solvent B). Subsequent pressure-column chromatography as in the preceding experiment gave sequentially as follows: (a) 195 mg (32%) of methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside-*2-d* (**12**), mp 106.5–107 °C (lit.[24] for the nondeuterated product mp 108–109 °C), $[\alpha]^{23}D$ +74° (*c* 1, chloroform) (lit.[23] $[\alpha]D$ +75.5° in chloroform), *m/e* 367 [M·+], R_f 0.74; (b) 139 mg (23%) of methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-allopyranoside-*3-d* (**11**), $[\alpha]D$ +54° (*c* 1, chloroform), *m/e* 367 [M·+], R_f 0.58, and (c) 148 mg (28%) of unreacted monoacetate (as the *3-d* analogue of **8**), mp 69–70 °C, R_f 0.29. In addition 62 mg (10%) of a mixture of **11** and **12** was obtained.

B. In 19:1 2-Propanol–Water. The foregoing reduction was repeated using 250 mg (0.78 mmol) of **1**, 30 mg (3.6 equiv) of sodium borodeuteride, and 60 ml of 19:1 2-propanol–water. Processing and acetylation as in procedure A revealed a product that showed two zones by TLC analysis (solvent B), R_f 0.58 and 0.29, corresponding to the allo diacetate **6** (**11**, 3-deuterated isomer) and the allo monoacetate **8** (as the 3-deuterated analogue), respectively. Column chromatography as in A gave 231 mg (81%) of **11**, $[\alpha]D$ +54° (*c* 1, chloroform), identical with **11** from A by NMR spectroscopy, together with 24 mg (8%) of the 3-deuterated monoacetate identical with **8** by melting point.

Reduction of Methyl 2-*O*-Benzoyl-4,6-O-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (10) with Sodium Borodeuteride. A. In Dry 2-Propanol. As in the reduction of **1**, 384 mg (1 mmol) of **10**[25] was reduced with 42 mg (4 equiv) of sodium borodeuteride with 100 ml of anhydrous 2-propanol as solvent. The product obtained by the general procedure described was dissolved in 50 ml of anhydrous methanol. A 20-mg pellet of sodium was added, and the solution was stirred for 1 h, at which time the solution was neutralized with acetic acid, and the solvent was evaporated off. The crude product was acetylated with 2 ml (an excess) of acetic anhydride in 10 ml of pyridine for 8 h at 25 °C to give a product that by TLC (solvent B) showed three carbohydrate components (R_f 0.74, 0.58, and 0.29) identical with those from reduction of **1**. Chromatography as in the foregoing example resolved the mixture as follows: (1) 302 mg (83%) of the D-gluco derivative **12**, mp 106–107 °C, $[\alpha]D$ +74° (*c* 1, chloroform); (2) 38 mg (10%) of the D-allo derivative **11**, $[\alpha]^{23}D$ +4° (*c* 1, chloroform), R_f 0.58; (3) a trace of the D-allo monoacetate **8** (as its 3-deuterated analogue), R_f 0.29.

B. In 19:1 2-Propanol–Water. As in the preceding reduction, 77 mg (0.2 mmol) of **10** in 30 ml of 19:1 2-propanol–water was reduced with 10 mg (5.8 equiv) of sodium borodeuteride. The products, after acetylation (30 h), were examined by TLC (solvent B). Only the zones having R_f 0.58 (major) and 0.29 (trace) were present. Column chromatography as in part A gave 56 mg (75%) of the allo diacetate-*3-d* (**11**), $[\alpha]D$ +54° (*c* 1, chloroform), identical with the product from the identical reduction of **1** by NMR spectroscopy. No gluco product (**12**) was detected.

Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose (13). To a solution of 8 ml of acetic anhydride and 16 ml of methyl sulfoxide was added 1.63 g (5.06 mmol) of methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside,[15] and the mixture was stirred for 24 h, with protection from moisture. The mixture was evaporated to an oil that was applied to a column of silica gel (45 g) which was eluted with solvent A to afford 1.12 g (61%) of **13** that crystallized from chloroform–hexane, mp 104–106 °C, $[\alpha]^{25}D$ +74° (*c* 0.9 chloroform), R_f 0.78 (solvent A).

Anal. Calcd for $C_{16}H_{18}O_4 \cdot H_2O$: C, 56.48; H, 5.92. Found: C, 56.62; H, 6.18.

For the anhydrous compound, Kondo et al.[18] reported mp 103–104 °C, $[\alpha]^{14}D$ +36° (*c* 0.6, chloroform).

Reduction of Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-α-D-*xylo*-hexopyranosid-2-ulose (13). A. With Sodium Borodeuteride in Aqueous Methanol. To a solution of 200 mg (0.59 mmol) of the glycosulose **13** in 20 ml of 1:1 water–methanol was added portionwise, with stirring, 200 mg (5.28 mmol) of sodium borodeuteride. After ~30 min, carbon dioxide was added and the solvents were evaporated off. The residue was processed by the general procedure described to give a product (R_f 0.23, solvent A) that was acetylated in 2 ml of pyridine with 2 ml of acetic anhydride for 48 h to yield 210 mg of an oil (R_f 0.91, solvent A) that crystallized from chloroform–hexane to give 133 mg (55%) of **12**, identical with authentic 2-deuterated **12** by NMR spectroscopy, mp 106 °C, $[\alpha]^{25}D$ +70° (*c* 1, chloroform).

B. With Sodium Borodeuteride in Dry 2-Propanol. To a solution of 302 mg (0.89 mmol) of the 2-ulose **13** in 5 ml of dry 2-propanol was added portionwise 110 mg (2.60 mmol) of sodium borodeuteride. The reaction was processed exactly as in A, to give, after column chromatography (15 g of silica gel, solvent A) of the acetylated product, 227 mg (70%) of pure **12**, identical with 2-deuterated **12** by NMR spectroscopy, mp 105 °C, $[\alpha]^{25}D$ +70° (*c* 1, chloroform).

Methyl 2,3-i-*O*-acetyl-4,6-*O*-benzylidene-α-D-*erythro*-hex-2-enopyranoside (4). To a solution of 500 mg (1.55 mmol) of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (**1**) in 10 ml of dry pyridine was added 2.5 ml of acetic anhydride, and the mixture was heated with stirring for 3 days at 70 °C, at which time TLC revealed a new zone having R_f 0.85 (solvent A, R_f 0.78 for **1**). The solution was evaporated, and toluene (5 × 10 ml) was evaporated from the residue, which was finally dissolved in benzene (30 ml) and decolorized (animal charcoal). The oil (717 mg) obtained upon solvent evaporation was chromatographed on a column of silica gel (35 g) with solvent A to give, in 45 ml of eluent, 415 mg (74%) of the product having R_f 0.85. Crystallization from dichloromethane–heptane gave **4**: mp 187–190 °C; $[\alpha]^{25}D$ +117° (*c* 1.34, chloroform); NMR data, see Tables I and II.

Anal. Calcd for $C_{18}H_{20}O_8$: C, 59.33; H, 5.53. Found: C, 59.56; H, 5.78.

Further elution of the column gave 168 mg of unreacted **1**.

The same product was obtained by similar acetylation of methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose (**13**).

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Registry No.—2-Phenylosazone, 59830-66-9; phenylhydrazine, 100-63-0; methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside, 18031-57-7.

References and Notes

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Synthesis of the ABC Ring System of Batrachotoxin and Several Related Highly Functionalized Cholane Derivatives[1]

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The objective of this work is the synthesis of the ABC ring system of the powerful neuropoison batrachotoxin (1) from cholic acid (2), utilizing intermediates which permit subsequent elaboration to the entire toxin molecule. Thus, stereoselective routes to a series of highly functionalized cholane derivatives are described, culminating with an efficient synthesis of **58** as follows: **2** → **5** → **38** → **51** → **53** → **58**. It was also shown that earlier established side-chain degradation procedures are applicable in this series, **7** → **22** and **40** → **45**, as potential entries to the D,E ring system of **1**. Unsuccessful approaches to the ABC ring system of **1** included the synthesis from **2** of epoxides **8** and **9**. Whereas earlier the oxidative cyclization of **18** → **20** had been described, epoxides **8** and **9** afforded ketones **12** and **13** under the cyclization conditions without formation of the desired **21**. In another approach, rather than 3α,9α-oxide **24**, dione **23** was obtained in high yield by treatment of epoxide **17** with methoxide ion. While **23** was convertible into ketone **25**, this last substance afforded neither hydrazone **28** nor epoxide **34**, two key intermediates required for a fragmentation approach to the ABC ring system. In another attempt **25** was reduced to an epimeric mixture **29** of C-7 alcohols. Mild MeOH–acid treatment of **29** led to a mixture of unsaturated keto steroids rather than to the desired 3α,9α-oxido ketal **33**.

Batrachotoxin (1) is one of four rare, powerfully toxic steroid alkaloids found in the skin of a small, brightly colored Colombian frog of the genus *Phyllobates*.[3] The molecule has proven important as a tool for the study of ion movements in electrogenic membranes.[4] Following the elegant structural elucidation studies of Witkop,[3] batrachotoxin has been the target of synthetic studies, those of Wehrli culminating in the formal total synthesis of the molecule from other steroids.[5] We have already described in preliminary form the synthesis of the ABC ring system of **1** from the readily available cholic acid (**2**).[1] We now present the details of this work together with the stereoselective synthesis and some reactions of several highly functionalized cholane derivatives which have proven useful in our initial evaluation of practical synthetic routes to the ABC ring system of batrachotoxin.

Our initial plan called for the synthesis of an intermediate possessing functional groups in the ABC portion of the molecule which would be relatively inert toward reagents required for the elaboration of the DE portion of the molecule, yet be readily convertible into the ABC system after the DE synthetic operations were completed. Methyl 3α,7α-diacetoxy-9α,11α-oxidocholanate (**6**) seemed ideal in view of the remarkable chemical stability exhibited by the 9α,11α-oxido grouping in several AB-cis steroids.[6] Moreover, Fieser[7] showed that the closely related alcohol **18** could be converted directly into the 11-oxo-3β-hydroxy 3α,9α-oxide **20** by oxidation with CrO_3.

Accordingly, epoxide **6** was synthesized from cholic acid as follows. Cholic acid (**2**) was converted into enone **3** by the method of Fieser.[8] Desulfurization of the corresponding dithioketal **4** afforded olefin **5**, epoxidation of which with *m*-chloroperoxybenzoic acid (MCPA) led to the desired epoxide **6**. The oxide ring was assigned the α orientation in accordance with the rule of rear attack,[9] the distinctive NMR splitting pattern of the C_{11} axial proton,[10] and the chemical shifts of the protons attached to C-18 and 19.[11] The overall process afforded 50 g of **6** starting with 200 g of cholic acid.

As a first step toward construction of the DE ring system of batrachotoxin, the acid **7** was prepared from epoxide **6** by selective hydrolysis of **6** with aqueous K_2CO_3–MeOH, affording acid alcohol **8** in 96% yield. Acetylation of **8** produced **7**. Treatment of **7** with $Pb(OAc)_4$[12] gave olefin **22** in high yield. Δ^{22}-Steroids have been employed by others[13] for efficient production of either bisnor acids or C-20 ketones.

Before proceeding further with the DE ring elaboration it seemed prudent to demonstrate the synthesis of the ABC system from epoxide **6** using Fieser's[7] oxidative cyclization procedure (**18** → **20**). Unfortunately, all attempts to oxidize acid **8** or its methyl ester **9** employing variations of Fieser's method uniformly led in near-quantitative yield to keto epoxides **12** and **13** with no hint of the desired oxide **21**. At the time it seemed likely that in **8** the 7α (axial) acetoxy group sterically prevented formation of the 3α,9α-oxide linkage present in **20**. In the light of our synthesis of ester **54** by an-