ture was kept in an nmr tube. The spectrum was observed at various time intervals during a 7-day period; at all times the ratios of the methoxyl-group integral to the acetyl-group integral remained constant at 1.0 to 4.0. No deuterium incorporation could be detected in 1 recovered after 7 days.

Change in Nmr Peak Positions with Concentration.—Spectra of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (1) were measured at concentrations of 1, 5, 10, and 20% (w/v) in chloroform-*d*, which also contained 5% (w/v) tetramethylsilane. The acetoxy-group signals did not vary in field position by more than 0.004 ppm.

Registry No.—**1**, 604-70-6; **1a**, 18031-45-3; **1b**, 18031-46-4; **1c**, 18031-47-5; **1d**, 18031-48-6; **2**, 18031-49-7; **3**, 7432-72-6; **4**, 18031-51-1; **5**, 3162-96-7; **6**, 4141-45-1; **6a**, 18031-54-4; **6b**, 18031-55-5; **7**, 18031-56-6; **8a**, 18031-57-7; **8b**, 18031-58-8.

The Structure and Properties of Some D-Arabino- and D-Xylopyranosyladenines[1]

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The anomeric pairs of both 9-D-arabino- and 9-D-xylopyranosyladenine have been prepared (**10a**, **10b** and **11a**, **11b**, respectively), together with the 7-α-D-arabino- and 7-β-D-xylopyranosyladenines. Evidence was obtained to show that all the arabinosides appeared to be in the 1*C* conformation; and all the xylosides, the *C*1 conformation. The arabinosides **10a** and **10b** violated Hudson's isorotation rules while the xylosides **11a** and **11b** obeyed them. The β-arabinoside **10b** was more conveniently prepared from the D-arabinopyranosyl halide blocked with *p*-nitrobenzoyl groups rather than with nonparticipating benzyl groups. The effect of other acyl blocking groups on anomer distribution of the nucleoside products was also examined.

The demonstrated anticancer activity of the furanose forms of 9-β-D-arabinosyl-[2a] and 9-β-D-xylosyladenine[2b] suggested that the pyranose forms be prepared in sufficient quantity for comparative studies. This manuscript describes the synthesis of the unknown α and β anomers of 9-D-arabinopyranosyladenine, the known 9-β-D-xylopyranosyladenine,[3] and its unknown α anomer. In addition, interesting observations bearing on the conformations of these compounds on Hudson's isorotation rules[4] and the *trans* rule[5] are recorded.

The known 9-β-D-xylopyranosyladenine[3] (**11b**) was prepared in good yield by condensation of chloromercuri-6-benzamidopurine with 2,3,4-tri-*O*-benzoyl-D-xylopyranosyl bromide[6] in refluxing xylene followed by deacylation with methanolic sodium methoxide (Scheme I). The properties of **11b** agreed well with those reported previously.[3] Because of the arabinose work discussed below, the α anomer, **11a**, was sought and found by chromatography of the crude product through a Dowex 1 (OH) column.[7] There was also isolated a minute amount of another xylopyranosyladenine (**Y**) which, on the evidence discussed later, was shown to be the 7-substituted nucleoside.

Preparation of 9-β-D-arabinopyranosyladenine **10b** from a halo sugar required that the arabinose be blocked by nonparticipating groups in order to maximize the yield of β anomer. The benzyl-blocked haloarabinose **4** was chosen because the corresponding furanose isomer was known to react with 6-benzamidopurine to afford, after deblocking, mainly 9-β-D-arabinofuranosyladenine.[8]

The halo sugar **4** was obtained from methyl β-D-arabinoside.[9] This was converted into **1** with sodium hydride and benzyl chloride in hot N,N-dimethylformamide (DMF).[10] This procedure required a smaller excess of reagents, a less laborious work-up and gave purer product in our hands than the literature procedure for the L isomer[11] of **1**. Hydrolysis of **1** afforded **2** which was treated with *p*-nitrobenzoyl chloride to afford **3** as a syrup that could be induced to crystallize partially. However, the entire syrup was generally converted into the halo sugar **4**. This was used immediately for the nucleoside condensation.

6-Benzamidopurine did not react with **4** under the mild conditions that were suitable for the furanose isomer.[8] However, chloromercuri-6-benzamidopurine reacted readily with **4** in refluxing xylene to give an anomeric mixture of **8** that was treated with sodium methoxide to give **9**. Some of the anomeric mixture of **9** was separated by preparative thin layer chromatography. The crystalline anomer of **9**, later found to be the α anomer, was readily debenzylated by sodium in liquid ammonia.[12] However, debenzylation of the gummy anomeric mixture of **9** was difficult and was successful only when the gummy **9** was suspended on coarse Celite.[13] The anomeric mixture was most conveniently separated at **10** using a Dowex-1 (OH) column.[7] An equal mixture of α and β anomers of **10** was obtained together with a minor, third component (**Z**) of mp 268–

(1) (a) The work was supported by the Cancer Chemotherapy National Service Center (CCNSC), National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Contract No. PH-43-64-500. The opinions are those of the authors and not necessarily those of the CCNSC. (b) A portion of this was presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(2) (a) J. G. Brink and G. A. LePage, *Can. J. Biochem.*, **43**, 1 (1965), and earlier papers; (b) D. B. Ellis and G. A. LePage, *ibid.*, **43**, 617 (1965).

(3) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 833 (1946), and earlier work.

(4) C. S. Hudson, *Advan. Carbohyd. Chem.*, **3**, 15 (1948).

(5) B. R. Baker, *Ciba Found. Symp., Chem. Biol. Purines*, 120 (1957).

(6) H. G. Fletcher, Jr., and C. S. Hudson, *J. Amer. Chem. Soc.*, **69**, 921 (1947).

(7) C. A. Dekker, *ibid.*, **87**, 4027 (1965).

(8) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 3004 (1963).

(9) (a) C. S. Hudson, *J. Amer. Chem. Soc.*, **47**, 265 (1925); (b) J. W. Pratt, *ibid.*, **74**, 2200 (1952).

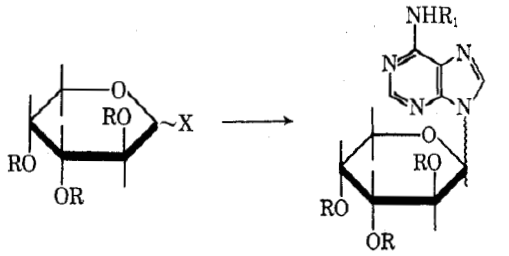
(10) For other alkylations of carbohydrates employing sodium hydride and an aprotic solvent, see (a) U. E. Diner, F. Sweet, and R. K. Brown, *Can. J. Chem.*, **44**, 1591 (1966); (b) D. M. W. Anderson and G. M. Cree, *Carbohyd. Res.*, **2**, 162 (1966), and (c) J. S. Brimacombe, B. D. Jones, M. Stacey, and J. J. Willard, *ibid.* **2**, 167 (1966).

(11) S. Tejima and H. G. Fletcher, Jr. [*J. Org. Chem.*, **28**, 2999 (1963)] have prepared the L isomer by benzylation with potassium hydroxide.

(12) E. J. Reist, V. J. Bartuska, and L. Goodman, *ibid.*, **29**, 3725 (1964).

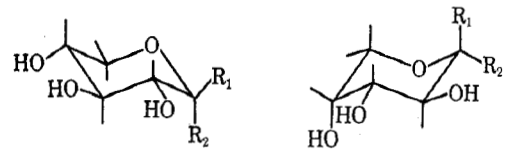
(13) A diatomaceous earth product of Johns-Manville; Celite Grade 560 was suitable.

SCHEME I



1, R = $CH_2C_6H_5$; X = OMe(β)
2, R = $CH_2C_6H_5$; X = OH
3, R = $CH_2C_6H_5$; X = $O_2CC_6H_4NO_2(p)$
4, R = $CH_2C_6H_5$; X = Cl
5, R = Bz; X = Br(β)
6, R = Ac; X = Br(β)
7, R = C(=O)$C_6H_4NO_2(p)$; X = Br(β)
12, R = X = C(=O)$C_6H_4NO_2(p)$

8, R = $CH_2C_6H_5$; R_1 = Bz
9, R = $CH_2C_6H_5$; R_1 = H
10, R = R_1 = H



11a, R_1 = H; R_2 = Ad
b, R_1 = Ad; R_2 = H

10a, R_1 = H; R_2 = Ad
b, R_1 = Ad; R_2 = H

270° dec. This was also an arabinosyladenine, according to its analysis.

The assignment of configuration to the anomers of **10** began with periodate oxidation experiments. Surprisingly, the oxidation product from the dextrorotatory anomer of **10** had a rotation of the same sign as that of the oxidation product from β-D-xylopyranosyladenine; that from the levorotatory anomer had the opposite sign. These results suggested that the anomers of **10** do not obey Hudson's isorotation rules.[4] This seems to be an exception to the generalization that purine nucleosides obey Hudson's rules[14a,b] while pyrimidine nucleosides disobey them.[14c] To establish firmly this exception, we obtained additional proof from nmr studies and application of the *trans* rule.[5]

The nmr results are given in Table I. The H-1′ protons of **10a**, **Z**, **11b** and **Y** exhibited the large $J_{1',2'}$ coupling constants that are only compatible with H-1′ and H-2′ being *trans* diaxial.[15] For 9-(D-arabinopyranosyladeninel), **10**, this *trans*-diaxial relationship between H-1′ and H-2′ was possible, if chair forms are considered,[16] only for the α anomer and only in the 1*C* conformation. This is depicted for **10a** in Scheme I. This result corroborates the periodate oxidation results. By the same argument, **Z** must have the same conformation as **10a**.

For 9-(D-xylopyranosyladenine), **11**, the *trans*-diaxial relationship is only possible for the β anomer, and only in the *C*1 conformation depicted in Scheme I for **11b**.

TABLE I

CHEMICAL SHIFTS OF SOME ARABINO- AND XYLOPYRANOSYLADENINES[a]

Compd	H-1′ δ, ppm	H-1′ $J_{1',2'}$, cps	Purine H's, δ, ppm
10a	5.50	9	8.31, 8.45
10b	6.09	1.5	8.24, 8.37
Z	5.32	9	8.18, 8.29[b]
11a	6.11	2	8.27, 8.47
11b	5.43	9	8.23, 8.34
Y	5.49	9	8.25, 8.35[b]
9a	5.50	9	7.84, 8.31
9b	6.14	2	8.09, 8.26

[a] Spectra were run on a Varian A-60 using a mixture of DMSO–D_2O as solvent and 6% TMS in $DCCl_3$ as external reference except for **9a** and **9b** which were run on a Varian HA-100 in $DCCl_3$ with TMS as internal reference. [b] The difference in chemical shift for the 2 and 8 protons (Δδ, cps) are 6.6 for **Z** and 6.0 for **Y**.

This corroborates the earlier assignment of configuration[3] to **11b**. By the same argument, **Y** has the same configuration and conformation as **11b**. Now **11a** is also expected to be in the *C*1 conformation with only the bulky adenine group in an axial position; in the 1*C* conformation, all three hydroxyl groups would be axial and the "Δ2 effect" [17] would be operative. The chemical shifts for H-1′ of **11a** and **11b** support this: H-1′ of **11a**, which is equatorial in the *C*1 conformation, is downfield from that of **11b** which is axial. This indicates that **11a** and **11b**, like the 9-D-glycopyranosyladenines,[16c,d] obey the generalization[18] that any equatorial proton is at lower field than an axial proton when the carbohydrate compounds considered are epimeric and both are in the same chair conformation. By the same argument, H-1′ of **10b** is also equatorial and has the 1*C* conformation as depicted in Scheme I. Analysis of instability factors[17] alone could not establish this. The 1*C* conformation has as instability factors the adenine and one hydroxyl group axial; the *C*1 conformation has two axial hydroxyl groups and the "Δ2 effect." [17] The weight to be assigned to the axial adenine group as an instability factor is not known, nor whether one should consider an "anomeric effect" [19] for the purine ring.

In the same way, the anomeric configuration and 1*C* conformation could be assigned to the anomers of the benzyl-blocked arabinosides **9a** and **9b** from the data in Table I. These assignments agreed with those obtained by debenzylation of each of these anomers to the corresponding anomer of **10**. Like **10**, the anomers of **9** disobeyed Hudson's rules, with **9b** being more dextrorotatory. The difference in chemical shift between the purine H-2 and H-8 protons of **9a** is considerably greater than those differences of the other compounds in Table I. One of the purine protons is shifted considerably upfield in **9a**. This proton may be shielded[20] by the ring current effect of the aromatic ring of the C-2′ benzyloxy group. Examination of models show greater

(14) (a) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochem. Biophys. Res. Commun.*, **22**, 505 (1966); (b) R. H. Iwamoto, E. M. Acton, and L. Goodman [*J. Med. Chem.*, **6**, 684 (1964)] reported a series of purine deoxyriboside anomers that obeyed Hudson's rules except for one pair containing sugar blocking groups—2-acetamido-6-chloro-9-(2-deoxy-3,5-di-*O*-*p*-tolyl-D-ribofuranosyl)adenine; (c) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochem.*, **6**, 843 (1967).

(15) L. D. Hall, *Advan. Carbohyd. Chem.*, **19**, 51 (1964).

(16) The reasoning that leads to these conclusions is the same as that used for the ribopyranosyl nucleosides. See (a) Y. H. Pan, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, **4**, 246 (1967), and (b) Z. Samek and J. Farkas, *Collect. Czech. Chem. Commun.*, **30**, 2149 (1965). For hexopyranosyl nucleosides, see (c) A. F. Cook and W. G. Overend, *J. Chem. Soc., C*, 1549 (1966), and (d) T. Nishimura and B. Shimizu, *Agr. Biol. Chem.*, **28**, 224 (1964).

(17) (a) R. E. Reeves, *Advan. Carbohyd. Chem.*, **6**, 107 (1951); (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 371.

(18) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **44**, 249 (1966).

(19) (a) Reference 17b, p 376; (b) N. S. Bhacca and D. Horton [*J. Amer. Chem. Soc.*, **89**, 5993 (1967)] and N. S. Bhacca, D. Horton, and H. Paulsen [*J. Org. Chem.*, **33**, 2484 (1968)] report examples where the anomeric effect of a 1-*O*-acetyl group can outweigh the instability effects of several axial *O*-acetyl groups.

(20) A. D. Broom, M. P. Schweizer, and P. O. P. Ts'o [*ibid.*, **89**, 3612 (1967)] have described the shielding of purine ring protons on nucleosides by an adjacent purine ring when the nucleosides are stacked in solution.

opportunity for the phenyl and purine rings to be in close proximity when they are both equatorial–equatorial as in **9a** than when the purine ring is axial as in **9b**.

The data in Table I also establish the location of the glycosidic bond in **Z** and **Y**. The difference in chemical shift ($\Delta\delta$) between the 2 and 8 protons of **Z** and **Y** compare closely with those reported for 7-substituted (2–6 cps)[21] but differ from those for the 3-substituted isomers (26–48 cps).[21] The ultraviolet data (see Table II) are also in agreement with these results. Thus

TABLE II

ULTRAVIOLET SPECTRA OF SOME D-XYLO- AND D-ARABINOPYRANOSYLADENINES

	$\lambda_{m\mu}$ ($\epsilon \times 10^{-3}$)		
Compd	pH 1[a]	pH 7[a]	pH 13[a]
10a	256[b] (14.7)	258[b] (14.8)	258[b] (14.7)
10b	256[b] (14.0)	258[b] (14.3)	258[b] (14.6)
Z	272[b] (12.6)	267[b] (8.7)	267[b] (8.9)
	237[c]	231[c]	
11a	256[b] (15.3)	258[b] (16.0)	258[b] (15.2)
11b	256[b] (16.1)	258[b] (15.9)	258[b] (16.5)
Y	273[b] (13.7)	270[b] (9.0)	270[b] (9.2)
	238[c]	231[c]	
9a	257[b] (12.7)	260[b] (13.1)	260[b] (13.2)
9b	257[b] (13.3)	260[b] (13.6)	260 (13.5)

[a] Solvents were 0.1 *N* HCl for pH 1, Beckman 3581 buffer for pH 7 and 0.1 *N* NaOH for pH 13. [b] Maximum. [c] Minimum. For **Z**, $\lambda_{min}^{pH\ 1} - \lambda_{min}^{pH\ 7}$ is 6 mμ; for **Y**, 7 mμ.

$\lambda_{min}^{pH\ 1} - \lambda_{min}^{pH\ 7}$ are positive for both **Z** and **Y**, and the isobestic points for both are on the short side (between 250 and 260 mμ) of their maxima. These results agree with those reported for other 7-substituted isomers,[21] and disagree with those for the 3 isomers. The $\Delta\delta$ method[21] for assigning the position of the glycosidic bond must be used with caution. Other factors may influence these $\Delta\delta$ values, as exemplified by the shielding effect of the C-2′ benzyloxy group discussed in the previous paragraph.

According to the *trans* rule[5] the reaction of various haloacylarabinopyranoses with chloromercuri-6-benzamidopurine should afford, after deblocking, mainly the α anomer, **10a**. This reaction was investigated and the results, given in Table III, are as predicted.

TABLE III

YIELDS OF (D-ARABINOPYRANOSYL)ADENINE FROM VARIOUS HALOARABINOSES

	Anomer ratio[a]	Over-all yield,[b] %		
Compd	**10a**:**10b**	**10a**	**10b**	**Z**
4	50:50	11[c]	11[c]	0.39
5	89:11	56	7	1.3
6	84:16	66	12	3.5
7	77:23	54	16	0.07[c]

[a] Based on products isolated from Dowex columns. [b] Over-all yield from D-arabinose. [c] Value from another run.

Thus **4**, without a participating group at C-2, afforded an equal mixture of **10a** and **10b** while compounds **5**,[22] **6**,[23] and **7** all could react *via* a C-1, C-2 orthoester ion and all gave **10a** as the major product. The highest ratio of **10a**:**10b** is given by **5**, which is expected to have the greatest tendency to react *via* the orthoester ion. The halo sugar **7** gave the most favorable yield of **10b**. The route from **7** became the method of choice for preparing **10b** since it was much shorter, simpler and gave better yields than that from **4**. The use of **7** gave such an insoluble blocked nucleoside (**8**, R = *p*-nitrobenzoyl) that the usual nucleoside work-up had to be modified. This modified procedure may be useful for more soluble blocked nucleosides also. Table III shows that the yield of the **7** isomer, **Z**, also varied with the halo sugar used. No 3 isomer is found. Perhaps some 3 substitution[24] did occur, but the product rearranged to the 9 isomer in the hot reaction medium containing mercuric halide.[24b] Our results also show the power of the Dowex-1 (OH) column[7] for nucleoside anomer separations. It is capable of separating large batches of nucleoside mixture, as well as permitting the isolation of the very minute amounts of **Z**.

It is also interesting to note that the use of benzoyl blocking groups on the halo sugar gave about the same proportions of the various adenine nucleosides for both arabino- and xylopyranose. Thus the yields of C-1′–C-2′ *trans* nucleoside were about 55–60%; the other anomer, about 7–8%; and the 7 isomer about 1–2% (see **5**, Table III; see Experimental Section for **11a**, **11b** and **Y**).

The several lines of evidence discussed above clearly establish that the dextrorotatory anomer is **10b** and the levorotatory one, **10a**. Their specific rotations are recorded in Table IV together with values for other known pairs of pentosyladenines, all of which obey Hudson's isorotation rules. The rotations for the anomers of **10** and **11** were run in both DMF and water and show that the violation of Hudson's rules by **10** is not an isolated phenomenon for only one solvent. Since only two anomeric pairs of pentopyranosyladenines are known,[25] it is impossible to say whether the optical behavior of the arabinose or the xylose anomeric pairs is unusual. Possibly the arabinose behavior is if one may extrapolate from the fact that some known anomeric pairs of hexopyranosyladenines[26] do obey Hudson's rules. Information on this point may be available from ORD studies.

The ORD curves of **10a**, **10b**, **Z**, **11a**, and **11b**[27,28] were like those reported for many β-purine pentofuranosides[14a] and some hexopyranosides,[16c] and agreed with the generalization that β-purine nucleosides have negative Cotton effects and α-nucleosides, positive effects.[14a] The only unusual feature was that in rela-

(21) L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *J. Amer. Chem. Soc.*, **86**, 5320 (1964).

(22) (a) H. G. Fletcher and C. S. Hudson, *ibid.*, **72**, 4173 (1950); (b) J. O. Deferrari, M. A. Ondetti, and V. Deulofeu, *J. Org. Chem.*, **24**, 183 (1959).

(23) C. S. Hudson and F. P. Phelps, *J. Amer. Chem. Soc.*, **46**, 259 (1924).

(24) (a) See ref 21, footnotes 9–12; (b) B. Shimizu and M. Miyaki, *Chem. Ind.* (London), 664 (1966).

(25) Some anomeric pairs of 2-deoxyribopyranosylpurines are known: E. E. Leutzinger, W. A. Bowles, R. K. Robins, and L. B. Townsend [*J. Amer. Chem. Soc.*, **90**, 127 (1967)] found that the anomers of 9-(2′-deoxy-D-ribopyranosyl)adenine obey Hudson's isorotation rules. (b) J. Davoll and B. Lythgoe [*J. Chem. Soc.*, 2526 (1949)] obtained the α and β anomers of the 2′-deoxyribopyranosyl derivatives of theophylline and noted that the relative values of the optical rotations of these two reversed upon acetylation.

(26) (a) K. Onodera, S. Hirano, and F. Masuda, *Tetrahedron Lett.*, 2189 (1966); (b) M. L. Wolfrom, H. G. Garg, and D. Horton, *J. Org. Chem.*, **30**, 1556 (1965).

(27) We are grateful to Dr. T. L. V. Ulbricht (Twyford Laboratories, Ltd., England), Dr. J. P. Verheyden (Institute of Molecular Biology, Syntex Research, Palo Alto), and Mr. R. Sproule (Durrum Instrument Corp., Palo Alto) for the ORD spectra of these compounds.

(28) D. W. Miles, R. K. Robins, and H. Eyring [*Proc. Nat. Acad. Sci. U. S.*, **57**, 1158 (1967)] have noted that purine nucleoside ORD spectra have very low signal-to-noise ratios. For this reason, the positions and amplitudes of the ORD extrema are inexact and we shall discuss these qualitatively only.

TABLE IV

OPTICAL ROTATIONS[a] OF THE PENTOSYLADENINES

Pentose	Anomer	Furanosyl	Pyranosyl
Ribose	α	+24[b]	
	β	−65.5[c]	−38[d]
Arabinose	α	+69[e]	−34 (−48)
	β	−5[f]	+36.5 (+50)
Xylose	α	−2	−6.9 (−30)
	β	−36[g]	−30[h] (−46)
Lyxose	α	+94[i]	
	β	−21[j]	
Arabinose	α-Z		−7.0
Xylose	β-Y		−60

[a] Both literature values and new values were determined in water except for those enclosed in parentheses which were determined in DMF. [b] R. S. Wright, G. M. Tener, and H. G. Khorana, *J. Amer. Chem. Soc.*, **80**, 2004 (1958). [c] J. Davoll and B. A. Lowry, *ibid.*, **73**, 1650 (1951). [d] J. Baddilley, G. W. Kenner, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 657 (1944), and ref 16a. [e] N. W. Bristow and B. Lythgoe, *ibid.*, 2306 (1949). [f] E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **27**, 327 (1963). [g] Unpublished data of V. J. Bartuska and E. J. Reist, these laboratories. The previous value (−22.5°) reported by W. W. Lee, A. P. Martinez, G. L. Tong, and L. Goodman, *Chem. Ind.* (London), 2007 (1963), is of a eutectic mixture of α and β anomers. The earliest value (−19°) was reported by P. Chang and B. Lythgoe, *J. Chem. Soc.*, 1992 (1950). [h] Reference 3 reported $[\alpha]_D$ −24 ± 4°. [i] P. Kohn, L. M. Lerner, and B. B. Kohn, *J. Org. Chem.*, **32**, 4076 (1967). [j] E. J. Reist, D. F. Calkins, and L. Goodman, *ibid.*, **32**, 169 (1967).

tion to the spectra of other β-nucleosides, the whole curve of **10b** was displaced in a dextrorotatory way above the base line by some background rotation. Hence **10b** was dextrorotatory at 589 mμ. Some attempts have been made to relate the signs of the Cotton effects in purine nucleosides with the angle of the base moiety.[14a,29,30] It is interesting to note that the sign of the Cotton effect of **Z** (the 7 isomer) and **10a** (the 9 isomer) are both positive.

Experimental Section[31]

The D-Xylopyranosyladenines (11a, 11b, and Y).—By the usual procedure,[32] the reaction of 14.1 g (19.6 mmol) of chloromercuri-6-benzamidopurine admixed with 36% Celite and 9.60 g (19.6 mmol) of 2,3,4-tri-*O*-benzoyl-D-xylopyranosyl bromide[6] in refluxing xylene for 2 hr afforded, after work-up, 14.0 g (over 100%) of crude benzoyl-blocked nucleoside. This was stirred in 300 ml of methanol containing 0.5 g of sodium methoxide at room temperature for 2 days. After removing the solvent, the residue was triturated with ether to remove the methyl benzoate and recrystallized from water to afford 3.24 g (58%) of **11b** (monohydrate) in two crops: mp 294–295° and 293–294° (lit.[3] mp 290°); R_f 0.18 in ME-20; R_f 0.36 in ME-30.

The crystallization liquors, from the above and another run (from which 58% of the theoretical yield of 6.00 g of **11b** had already been removed) were charged to a 125-g Dowex 1 (OH) column. Elution with 500 ml each of water, 30% methanol and 60% methanol removed traces of impurities. The elution was monitored by an ultraviolet absorption recorder and by tlc in solvent ME-30. The next 150 ml of 60% methanol afforded 310 mg (5.6%) of **11b**. The following 400 ml of 60% methanol (fraction 4) eluted 140 mg of **11b** and **Y**. Fraction 5 of 500 ml 60% methanol contained no nucleoside. The final fraction of 1 l. of 60% methanol afforded 500 mg (8.3%) of **11a**, mp 256–257°, R_f 0.50 in ME-30. Recolumning fraction 4 through 100 g of Dowex 1 (OH) afforded in successive 60% methanol fractions 30 mg of **11b** and 105 mg (1.75%) of **Y**, mp 270–271°, R_f 0.21 in ME-30.

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.9; H, 4.90; N, 26.2. Found for **11a**: C, 45.0; H, 4.90; N, 26.0. Found for **Y**: C, 44.7; H, 5.03; N, 25.9.

Methyl 2,3,4-Tri-*O*-benzyl-β-D-arabinopyranoside (1).—To a stirred mixture of 10.0 g (60.9 mmol) of methyl β-D-arabinopyranoside[9] in 100 ml of DMF was added 10.0 g (0.231 mol) of 58% sodium hydride suspended in oil (prewashed with petroleum ether, bp 30–60°). The stirred mixture was heated to 60° (internal temperature), treated with 28.0 ml (0.269 mol) of benzyl chloride and further heated (to about 75°) until a vigorous exothermic reaction (*caution*! suspend heating) ensued. After stirring and heating at reflux temperature for 45 min, the mixture was evaporated *in vacuo* to dryness. The residue was partitioned between 300 ml of methylene chloride and 200 ml of water. The organic phase was washed with 150 ml of water, dried and evaporated. The residue was then steam distilled until no more organic material passed over in the steam distillate. Evaporation of the pot residue afforded 24.1 g (91.4% yield) of **1**, a syrup; ir (neat) free of OH at 3.0 μ; R_f 0.35 with minor spots at 0.0, 0.78 and 1.0 in solvent EC–O. This is suitable material for the next step. Preparative chromatography on a silica gel plate with chloroform afforded the analytical sample **1**: ir (neat) free of OH at 3.0 μ; R_f 0.35 in solvent EC–O; $[\alpha]^{24}_D$ −90° (*c* 0.51, CH_2Cl_2).

Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.6; H, 6.96. Found: C, 74.3; H, 7.19.

High-vacuum distillation to remove the excess benzyl chloride and by-products did not yield as pure a product as steam distillation.

2,3,4-Tri-*O*-benzyl-β-D-arabinopyranose (2).—A solution of 24.1 g (55.5 mmol) of **1**, 414 ml of HOAc, and 165 ml (0.33 mol) of 2 *N* HCl was heated at 55–58° with stirring for 4 days, then 2 days at 30°, at which time the reaction was complete according to tlc. The reaction mixture was treated with 35 g of NaOAc (anhydrous) and evaporated. The residue was dissolved in 300 ml of CH_2Cl_2, washed with 200 ml of aqueous $NaHCO_3$ (saturated), 300 ml of water, dried, treated with charcoal, filtered and evaporated to afford 23.0 g (98.5%) of product, mp 50–60°, that crystallized immediately on seeding, and had R_f 0.24 in solvent EC–O. This product is suitable for the next step. Recrystallization from Skellysolve B of material from an earlier run afforded **2**: mp 68–78°; R_f 0.24 in solvent EC–O; $[\alpha]^{23}_D$ −63.4° → −56.8° after 68 hr (*c* 1.4, CH_2Cl_2) [lit.[11] mp of L isomer 83–86°, $[\alpha]^{20}_D$ +66.5 → +51.1° (2 days) (*c* 1.76, CH_2Cl_2)].

Anal. Calcd for $C_{26}H_{28}O_5 \cdot 0.25H_2O$: C, 73.5; H, 6.76. Found: C, 73.6; H, 6.71.

A number of modifications for this hydrolysis were studied, but none were as satisfactory as the above procedure. Neutralization with solid NaOAc is crucial. If omitted, the product is considerably less pure and very difficult to crystallize. The rotation of the crystalline analytical sample after 18 months was $[\alpha]^{24}_D$ −32 (*c* 0.90, $CHCl_2$).

1-*O*-*p*-Nitrobenzoyl-2,3,4-tri-*O*-benzyl-D-arabinopyranoside (3).—To a cold (~0°) stirred solution of 3.34 g (18 mmol) of *p*-nitrobenzoyl chloride in 25 ml of dry pyridine was added a cold solution of 5.0 g (11.9 mmol) of **2** in 25 ml of pyridine. After stirring at 0° for 2 hr and room temperature overnight, the reaction mixture was recooled, treated with 5 ml of water and stirred for 15 min. It was partitioned between 100 ml of chloroform and 150 ml of water. The chloroform layer was washed with $NaHCO_3$ solution, water, dried, diluted with 50-ml portions of toluene and evaporated until free of pyridine, to leave 6.45 g (95%) of **3** as an amber oil that was suitable for use in the next step.

(29) M. Ikehara, M. Kaneko, K. Muneyama, and H. Tanaka, *Tetrahedron Lett.*, 3977 (1967).

(30) A. Hampton and A. W. Nichol, *J. Org. Chem.*, **32**, 1688 (1967).

(31) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Optical rotations were measured at ambient temperatures with a Perkin-Elmer Model 141 automatic polarimeter. Paper chromatograms were run by the descending techique in Whatman No. 1 paper with adenine as a reference. The spots were located relative to R_{Ad} 1.00. The solvent systems were (A) dimethylformamide–28% aqueous isopropyl alcohol (25:10:65), and (B) *n*-butyl alcohol–acetic acid–water (5:2:3). Tlc was run on silica gel HF (E. Merck AG Darmstadt) in methanol–ethyl acetate (ME) where the per cent of methanol is denoted by a number after ME; *e.g.*, ME-30 denotes the above solvent combination with 30% methanol. Likewise, EC-20 denotes ethyl acetate, 20%, in chloroform. All spots on chromatograms were detected by ultraviolet light. All solutions were dried with magnesium sulfate (anhydrous) and were concentrated *in vacuo* with a bath temperature of less than 50° unless otherwise noted. Skellysolve B is a petroleum fraction, essentially *n*-hexane, bp 62–70°.

(32) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **81**, 3967 (1959).

The oil from an earlier run was taken up in methanol and chilled to afford 47% of **3**: mp 82–83°; $[\alpha]^{23}D$ +50° (*c* 0.8, CH_2Cl_2); R_f 0.56 in EC–O. Another recrystallization from methanol afforded the analytically pure **3**: mp 103–104°; $[\alpha]^{23}D$ +52° (*c* 0.8, CH_2Cl_2); R_f 0.56 in EC–O.

Anal. Calcd for $C_{33}H_{31}NO_8$: C, 69.6; H, 5.49; N, 2.46. Found: C, 69.5; H, 5.54; N, 2.53.

After 18 months, the analytical sample had an unchanged melting point and $[\alpha]^{24}D$ +25 (*c* 0.90, CH_2Cl_2).

2,3,4-Tri-*O*-benzyl-D-arabinopyranosyl Chloride (4).—A solution of 7.4 g (13.0 mmol) of crude **3** in 120 ml of methylene chloride saturated at 0 to −5° with hydrogen chloride was kept at 0° for 7 days. The mixture was chilled in Dry Ice and filtered to remove precipitated *p*-nitrobenzoic acid (nearly quantitative). The filtrate was washed with 150 ml of saturated aqueous sodium bicarbonate, 100 ml of water, dried, and evaporated to afford 5.54 g (97%) of **4** as a light amber oil that is immediately used in the next step.

9-[2,3,4-Tri-*O*-benzyl-α- and -β-D-arabinopyranosyl]adenines (9a) and (9b).—A mixture of 5.30 g (7.35 mmol) of chloromercuri-6-benzamidopurine suspended on 36% Celite in 200 ml of xylene and 3.50 g (8.00 mmol) of crude **4** was heated at reflux for 2 hr and worked up by the usual procedure to afford 5.03 g (98.5%) of **8** as a yellow gum: R_f 0.05 (one anomer), 0.18 (other anomer), and some minor by-products with R_f 1.0. The crude **8** was heated for 30 min in 100 ml of methanol containing 1.00 g of sodium methoxide, cooled, and evaporated. The residue was treated with 25 ml of water and 10 ml of methanol and evaporated several times. The residue was dissolved in 200 ml of methylene chloride, washed with water, dried, and evaporated to afford 3.45 g (82% from **4**) of **9**, R_f 0.20 and 0.42 in EC-100. Most of this material was carried on to the next step.

A 100-mg portion of crude **9** was separated by preparative tlc (EC-100 on silica gel) to afford 35 mg each of the anomers **9a** [R_f 0.20 in EC-100; $[\alpha]^{22}D$ −12 (*c* 1.5, CH_2Cl_2)] and **9b** [R_f 0.42 in EC-100; $[\alpha]^{22}D$ +32 (*c* 1.5, CH_2Cl_2)].

Anal. Calcd for $C_{31}H_{31}N_5O_4$: C, 69.3; H, 5.81; N, 13.02. Found for **9a**: C, 69.0; H, 5.96; N, 12.83. Found for **9b**: C, 68.9; H, 6.05; N, 13.12.

Subsequently, **9a** was recrystallized from toluene–ether to afford crystalline **9a**, mp 168–169.5°.

Crystalline **9a** was very soluble in liquid ammonia and treatment with sodium (see procedure below) readily afforded **10a**: R_f 0.24 in ME-30 (authentic **10a**, R_f 0.24; authentic **10b**, R_f 0.47, on some tlc plate).

1,2,3,4-Tetra-*O*-*p*-nitrobenzoyl-β-D-arabinose (12).—A mixture of 9.0 g (60 mmol) of D-arabinose in 300 ml of pyridine was maintained at −15 to −30° in an acetone–Dry Ice bath and vigorously stirred (with an overhead stirrer) during the addition of a solution of 55.6 g (0.30 mol) of *p*-nitrobenzoyl chloride in 500 ml of CH_2Cl_2 (about 30–40 min). A precipitate appeared during the addition. The addition funnel was washed down with 100 ml of CH_2Cl_2, then the stirred reaction was allowed to warm gradually from −30° to room temperature overnight. The slurry was concentrated to about 200 cc, then diluted with 2 l. of water and stirred 1 hr. The white solid was collected on a filter, washed with 3 l. of water, and ten times with 50-ml portions of ether. The solid was dried [20 hr at 60° (aspirator pressure)] to afford 44.0 g (99%) of **12**: mp 296–295°; R_f 0.18 R_f 0.18 in solvent EC–O. Recrystallization of similar material from an earlier run from CH_2Cl_2–petroleum ether, bp 65–110°, afforded the analytical sample of **12**: mp 297–298°; R_f 0.20 in solvent EC–O; $[\alpha]^{25}D$ −387 (*c* 0.85, CH_2Cl_2).

Anal. Calcd for $C_{33}H_{22}N_4O_{17}$: C, 53.2; H, 2.97; N, 7.51. Found: C, 53.2; H, 2.77; N, 7.58.

2,3,4-Tri-*O*-*p*-nitrobenzoyl-β-D-arabinopyranosyl Bromide (7).—To a stirred mixture of 3.14 g (4.21 mmol) of **12** in 80 ml of methylene chloride at room temperature was added 12.0 ml of 30% hydrogen bromide in glacial acetic acid. The mixture, protected from moisture, was stirred 3 hr at room temperature, diluted with 75 ml of toluene and evaporated to semidryness at 15–20 mm pressure (water aspirator). The residue was again slurried with 75 ml of toluene and evaporated. It was treated with 50 ml of methylene chloride and filtered to remove some insoluble *p*-nitrobenzoic acid. The solution was washed with 100 ml each of saturated aqueous sodium bicarbonate and water, dried, and evaporated to afford 3.07 g (over 100%) of crystalline (seeded during evaporation) crude **7**, R_f 0.39 with a trace at the origin in EC–O. A small portion was dried at 56° (1 mm) for several hours to afford the analytical sample of **7**: mp 150–151°; R_f 0.39 in EC–O.

Anal. Calcd for $C_{26}H_{18}BrN_3O_{13}$: C, 47.3; H, 2.75; N, 6.36. Found: C, 47.3; H, 2.87; N, 6.12.

For the next step, it was desirable not to obtain the crystalline **7** because it was not nearly as soluble in xylene as the crude **7**, evaporated without seeding.

The D-Arabinopyranosyladenines (10a, 10b, and Z). Method A.—A solution of 26.0 g (theory 25.3 g; 38.3 mmol from 38.3 mmol of D-arabinose; **12** not isolated) of crude **7** in 500 ml of dry xylene (dried over Linde 3A Molecular Sieves)[33] was added to a vigorously stirred suspension of 28.5 g (38.5 mmol) of chloromercuri-6-benzamidopurine on 36% Celite in 1.0 l. of hot dry xylene. A fine precipitate began to form immediately. After vigorously stirring at reflux temperature for 5 hr, the xylene was evaporated at 60–70°. The residue was suspended in 1.0 l. of absolute methanol and refluxed. Sodium methoxide (8.0 g, 0.15 mol) was added in three equal portions during 2 hr, until the pH value was about 9. After a total of 3 hr of heating, during which the precipitate had dissolved, the reaction mixture was cooled slightly, acidified with 20 ml (0.35 mol) of acetic acid and filtered on a Celite pad. The filter was washed with 500 ml of methanol. This and the filtrate were combined. The solution was evaporated to dryness, and redissolved in 200 ml of water to give solution A. This was washed with two 200-ml portions of ether. The residue on the filter was further washed with 400 ml of 10% aqueous acetic acid. This was combined with solution A and evaporated to dryness. The residue was slurried in water and placed on a column of 560 g of Dowex 1 (OH). Progressive elution with water, 30% methanol, and 60% methanol afforded **10a** (in the 30% methanol fraction) and **10b** (in the 60% methanol fraction) in the yields given in Table III. Identical ratios of anomers and yields were obtained in a smaller run. A larger run gave 31.6 g (48%) of **10a**, 8.5 g (12.8%) of **10b** and 49 mg (0.07%) of **Z** (eluted just before **10b** in 60% methanol). Recrystallization from water of **10a** and **10b** prepared by method B afforded the analytical samples: **10a**, mp 167–168°, R_f 0.22 in ME-30; **10b**, mp 195–196°, R_f 0.44 in ME-30. Recrystallization from 60% aqueous methanol of **Z** prepared from the halo sugar **6** afforded the analytical sample of **Z**: long needles, mp 268–270° dec (violent shattering at 200–235° to form a dark tan powder); R_f 0.18 in ME-30. In solvent A,[21] R_{Ad} = 0.81, 1.10 and 0.86, and in B, R_{Ad} = 0.51, 0.75, and 0.47 for **10a**, **10b** and **Z**, respectively.

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.1; H, 5.30; N, 24.6. Found for **10a**: C, 42.1; H, 5.26; N, 24.8. Found for **Z**: C, 42.1; H, 5.30; N, 24.6.

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.9; H, 4.90; N, 26.2. Found for **10b**: C, 44.7; H, 5.21; N, 26.0.

The coupling of **7** with chloromercuri-6-benzamidopurine formed a precipitate of small nodules if stirring was vigorous. The precipitate was very difficult to handle if allowed to cake. It was insoluble in every solvent tried except hot methanolic sodium methoxide. The use of toluene instead of xylene for the coupling reaction was not as satisfactory. When the other halo sugars **5** and **6** were used in the coupling reaction, the usual work-up[32] was employed.

Method B.—To a solution of 6.2 g (11.5 mmol) of crude **9** in 100 ml of ethyl acetate was added 14.7 g of Celite grade 560,[13] a coarse grade. This slurry was evaporated at 30° overnight, then at 40–50° for 1–2 hr, and powdered with a spatula. The free-flowing powder was added to about 200 ml of liquid ammonia. The vigorously stirred mixture was cooled in a Dry Ice–acetone bath and to this 1.1 g (47.8 mmol) of sodium was added in small pieces over 10–15 min. As soon as a blue color developed permanently, the reaction was neutralized as rapidly as possible (30–60 sec) with 4.0 g (75 mmol) of ammonium chloride, thereby discharging the blue color. After the bath was removed and most of the ammonia had evaporated overnight, the mixture was evaporated at 25–30° using a water aspirator. The residue was extracted with 300 ml of methanol and filtered through Celite. The filtrate was evaporated to afford 9.0 g of solids. This was dissolved in 50 ml of hot methanol and diluted with 75 ml of 1,2-dimethoxyethane to precipitate most of the ammonium chloride. The filtrate was evaporated, the residue redissolved

(33) Drying the commercial xylene, bp 137–140°, with molecular sieves is preferred over drying by azeotropic distillation. The latter seemed to remove the low-boiling fraction and caused a harder and more intractable cake to form during the coupling reaction.

in hot water and chromatographed through a Dowex 1 (OH) column to afford yields of 18% **10a** and 18% **10b** and about 0.65% of a mixture of **Z** and its anomer. Crystallization of this mixture from methanol afforded a few crystals of **Z**, mp 265–270°.

A variety of other conditions were studied for this reaction, but were found unsatisfactory—reaction at reflux temperature of ammonia; use of diluents such as 1,2-dimethoxyethane or tetrahydrofuran to help dissolve the glassy **9** in the liquid ammonia; and use of alcohol to destroy the excess sodium. If the large amount of ammonium chloride is not removed before the products are placed on the column, the Dowex 1 (OH) is deactivated and separation of the anomers is poor.

Registry No.—**1**, 18039-25-3; **2**, 18039-26-4; **3**, 18039-21-9; **4** 18039-22-0; **7** 18039-23-1; **9a** 18039-24-2; **9b** 18031-17-9; **10a** 17434-52-5; **10b** 18031-19-1; **11a** 18031-20-4; **11b**, 18031-28-2; **12**, 18031-29-3; **Z**, 18031-42-0; **Y**, 18031-41-9.

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Improved Syntheses of 5-Thio-D-glucose[1]

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Two convenient and improved routes for the synthesis of 5-thio-D-glucose are described starting with 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose (II). II reacts with thiourea in methanol to give 3-*O*-benzyl-5,6-dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose (III) which, on nucleophilic ring opening with potassium acetate in acetic acid–acetic anhydride, gives 6-*O*-acetyl-5-*S*-acetyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (IV). Reduction of IV with sodium in liquid ammonia, followed by hydrolysis in 0.5 *M* sulfuric acid, gives 5-thio-D-glucopyranose (VI) in 32% over-all yield from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. On reaction with sodium in benzyl alcohol, followed by *p*-tolylsulfonylation, II gives 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-β-L-idofuranose (X). Nucleophilic displacement of the *p*-tolylsulfonyloxy group with thiolacetate anion in dry N,N-dimethylformamide (DMF) gives 5-*S*-acetyl-3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (XI). Reduction of XI with sodium in liquid ammonia, followed by hydrolysis in 0.05 *M* sulfuric acid, gives VI.

In recent years this laboratory and others have been interested in the syntheses of 4-thio and 5-thio sugars which can be cyclized readily into furanose and pyranose sugars in which sulfur replaces the oxygen as the heteroatom. Thus 4-thio-D- and L-ribose,[2,3] 5-thio-L-arabinose,[4] 5-thio-D-ribose,[5] 5-thio-D-xylose,[6] 5-thio-D-glucose,[7] and a few others have been synthesized. The nucleosides synthesized from these thio sugars may possess unusual physiological properties. However, the syntheses of most of these thio sugars in quantity for biological examination requires the development of approaches which will lead to higher yields.

We wish to report the synthesis of 5-thio-D-glucose by two different routes using 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose (II) which has now been prepared in very high yields by modifications of the published procedure.[8]

An earlier synthesis of 5-thio-D-glucose[7] from this laboratory utilized 5,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose which was prepared in 61% yield from 6-*O*-acetyl- (or benzoyl-) 1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose. However, the preparation of this latter 5-tosyl compound by a selective tosylation of 6-*O*-acetyl- (or benzoyl-) 1,2-*O*-isopropylidene-α-D-glucofuranose is in itself a poor preparation, giving a yield of 20% or less of the desired 5-tosyl compound, as the product is contaminated with the 3,5-ditosylate. Also, the free hydroxyl group on C-3 has made most of these compounds, both in the gluco- and idofuranose series, fairly water soluble, making their isolation difficult. If the hydroxyl group on C-3 is blocked with a group that is fairly stable to acid and alkali, such as a benzyl ether group, the water solubility of this class of compounds is lessened and problems of selective tosylation do not arise. Thus 6-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-(*p*-tolysulfonyl)-α-D-glucofuranose (I), prepared from 5,6-di-*O*-acetyl-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose in 92% yield, was selected as the starting material.

3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, prepared in 90% yield by a slight modification of the literature procedure,[8] is selectively hydrolyzed to remove the 5,6-isopropylidene group and is acetylated in the usual manner. The resulting crystalline 5,6-di-*O*-acetyl-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose is isolated in an over-all yield of 77% starting from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. The above 5,6-di-*O*-acetyl derivative is deacetylated using a catalytic amount of sodium methoxide in methanol and selectively benzoylated at −15° (rather than 0° as earlier recommended[8]). The 6-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose, isolated in almost quantitative yield, is tosylated in the manner described earlier.[8] The resulting 6-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose (I) is then isolated in 92% yield.

Compound I in dry chloroform is treated with methanolic sodium methoxide to obtain a 90% yield of 5,6-

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