Table IV. Conformational Populations under the C_5 Exclusion Alone

compd	weighting	gauche fractions for H_1-H_2	H_2-H_3	X-X
meso	equal	0.73	0.18	0.27
	2G only[a]	0.50	0	0
	0.3/G[b]	0.61	0.10	0.12
(±)	equal	0.64	0.73	0.91
	2G only	0.50	1	1
	0.3/G	0.56	0.85	0.95
	C_4X exclusion, 0.3/G[c]	0.23	0.77	1

[a] Only conformations with the lowest possible number (two) of gauche carbon segments counted. [b] Conformations given a weighting of 0.3/gauche carbon segment. [c] Assuming the C_4X exclusion also, with conformation II weighted 0.3 relative to conformation I.

conformation in the (±) case, and the NMR data indicate that this must be conformation I. Conformation I contains two gauche carbon segments while conformation II contains three: this might make the latter less stable by approximately 800 cal/mol, producing a mole fraction population of 0.2. Our vibrational spectra appear to weigh against the presence of this much II; however, our NMR $J_{1,2}$ values would fit such a population nicely.

A basic remaining question is as follows. While the C_5 and C_4X exclusions operating together adequately explain our observations, would those observations be equally well explained by the C_5 exclusion alone? To answer this question, it is necessary to examine the allowed conformations available to 2,5-dimethylhexane. There are five of these, two of symmetry C_2 and one each of symmetries C_{2h}, C_i, and C_1. (The C_2 and C_1 forms have, of course, two optical isomers each.) Upon introduction of the two halogens, there result seven conformations in the meso case and eight in the case of either optical isomer of the (±) compound. Table IV gives local conformation (gauche-anti) populations for mixtures of these conformations under three different assumptions: (1) that all conformations contribute equally (i.e., with symmetry-number weighting only), (2) that only conformations with the smallest possible number (i.e., two) of gauche five-carbon segments contribute, and (3) that each gauche five-carbon segment present leads to a Boltzmann weighting factor of 0.3 (equivalent to a destabilization by about 700 cal/mol). In both compounds, the predicted gauche populations are at variance with the NMR results. In the meso case, a $J_{1,2}$ value of 2.2 Hz does not fit an anti population of 27–50%. In the (±) case, a $J_{1,2}$ of 7.9 Hz is equally poorly explained by a gauche population of 50–64%. The small number of infrared and Raman lines observed also weighs against the presence of any large number of conformations.

We conclude that the C_4X exclusion may be used with confidence in predictions of thermodynamic and equilibrium properties of conformational mixtures of chlorine- and bromine-substituted hydrocarbons.

Acknowledgment. We acknowledge with gratitude the help of Dr. James Gano and Dr. Deane Horne with details of the syntheses and with the running and interpretation of the NMR spectra, Mr. Ronald Hohmann for running the Raman spectra, Dr. Duane Burow for discussions of the vibrational spectra, and Dr. Gano and Dr. Jean Jacob for valuable suggestions regarding the manuscript.

Registry No. *meso*-3,4-Dichloro-2,5-dimethylhexane, 76599-70-7; *meso*-3,4-dibromo-2,5-dimethylhexane, 40084-93-3; (±)-3,4-dichloro-2,5-dimethylhexane, 76599-71-8; (±)-3,4-dibromo-2,5-dimethylhexane, 40084-92-2; *cis*-2,5-dimethyl-3-hexene, 10557-44-5; *trans*-2,5-dimethyl-3-hexene, 692-70-6.

Facile Synthesis of 2-Deoxy-2-substituted-D-arabinofuranose Derivatives[1]

Tsann-Long Su, Robert S. Klein,* and Jack J. Fox

Laboratory of Organic Chemistry, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Received January 14, 1981

Several methyl 2-deoxy-2-substituted-D-arabinofuranosides (**4a–e** and **5b–e**) to be used as intermediates in the synthesis of 2′-substituted arabinonucleosides of biomedical interest were prepared by treatment of methyl 3,5-di-*O*-benzyl-2-*O*-(trifluoromethanesulfonyl)-α- and -β-D-ribofuranosides **2** and **3** with the lithium, sodium, or tetrabutylammonium salts of various nucleophiles (F^-, Cl^-, Br^-, I^-, N_3^-). While the α anomer **2** could be readily converted into the desired arabinofuranosides **4a–e** in good yields, the β anomer **3** afforded the corresponding 2-substituted products **5b–e** only in modest amounts together with furfuryl ether **7** as the major product. A possible interpretation for the difference in the course of these reactions is discussed.

Previous studies in our laboratory on the synthesis of several (2′-halogeno-2′-deoxy-D-arabinosyl)pyrimidine nucleosides[2-4] have afforded substances of biological interest. Thus, 1-(2′-deoxy-2′-fluoro-β-D-arabinofuranosyl)cytosine[2,4] (2′-F-*ara*-C) exhibits pronounced inhibitory activity against the growth of L-1210 mouse leukemic cells in culture. 1-(2′-chloro-2′-deoxy-β-D-arabinofuranosyl)cytosine[3] was similarly active against several mouse leukemic cell lines in vitro. Finally, several 5-substituted (2′-deoxy-2′-fluoro-β-D-arabinofuranosyl)pyrimidines were shown to inhibit the replication of herpes simplex virus in vitro and in vivo.[5]

From these and other studies on pyrimidine nucleoside transformations, it is clear that direct introduction of a substituent in the 2′ "up" (arabino) configuration of a preformed pyrimidine nucleoside may be difficult, if not impossible, because of the ease with which the 2-carbonyl

(1) This investigation was supported by funds from the National Cancer Institute, National Institutes of Health, U.S. Public Health Service (Grants CA-08748 and CA-18601).

(2) J. A. Wright, D. P. Wilson, and J. J. Fox, *J. Med. Chem.*, **13**, 269 (1970).

(3) G. Ritzmann, R. S. Klein, D. H. Hollenberg, and J. J. Fox, *Carbohydr. Res.*, **39**, 227 (1975).

(4) U. Reichman, K. A. Watanabe, and J. J. Fox, *Carbohydr. Res.*, **42**, 233 (1975).

(5) K. A. Watanabe, U. Reichman, K. Hirota, C. Lopez, and J. J. Fox, *J. Med. Chem.*, **22**, 21 (1979); C. Lopez, K. A. Watanabe, and J. J. Fox, *Antimicrob. Agents Chemother.*, **17**, 803 (1980); J. J. Fox, 2nd Chemical Congress of the North American Continent, 180th National Meeting, of the American Chemical Society, San Francisco, Aug 1980; Abstract MEDI 2.

0022-3263/81/1946-1790$01.25/0 © 1981 American Chemical Society

group of the pyrimidine moiety participates in any nucleophilic displacement.[6] For this reason, condensation of a suitably blocked, preformed 2′-deoxy-2′-halogeno-arabinofuranoside with an appropriately derivatized pyrimidine base has remained the method of choice for the synthesis of all biologically active (2′-deoxy-2′-halogeno-β-D-arabinofuranosyl)cytosine derivatives we described above. In contrast, the possibility of direct introduction of a substituent at the C-2′ position of purine nucleosides has been recently exploited in studies of the nucleophilic substitution of the 2′-triflate group of purine nucleosides by various reagents under relatively mild conditions.[7,8] The method which was utilized to introduce substituents in the C-2-down[7] (ribo) and C-2-up[8] (arabino) configuration must owe its success to the lack of neighboring-group participation by the purine base and to the exceptional properties of the triflate function, an excellent leaving group with solvolysis reaction rates 10^5–10^7 times greater than those of the corresponding tosylates or halides.[9-12] As part of our continuing program on the synthesis of nucleosides of biomedical interest, we report herein the synthesis of several 2-deoxy-2-modified arabinofuranose derivatives by the facile displacement of the C-2-triflate function of suitably protected methyl ribofuranosides under mild conditions.

An anomeric mixture of methyl 3,5-di-*O*-benzyl-D-ribofuranoside **1** (obtained by the acid-catalyzed methanolysis of 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose[3]) was treated with 1.2 molar equiv of trifluoromethanesulfonic anhydride and dry pyridine in methylene chloride at −15 °C under nitrogen to afford a mixture of the corresponding anomeric triflates **2** and **3** in 97% overall yield (see Scheme I). Separation by chromatography on silica gel with toluene–ethyl acetate (98:2) afforded the β anomer **3** (77%, $[\alpha]^{23}_D$ +20.3°, in $CHCl_3$), which was eluted first, followed by the α anomer **2** (20% $[\alpha]^{23}_D$ +101°, in $CHCl_3$). Each of the anomers was identified by its ^1H NMR in $CDCl_3$; thus, the anomeric H-1 proton of **3** appeared as a singlet at δ 5.02 with the glycosidic OMe group at δ 3.32 while the anomeric H-1 proton in **2** showed as a doublet at δ 4.97 ($J_{1,2}$ = 4.3 Hz) and the OMe group at δ 3.49.

Preliminary studies on the displacement of the triflate group from **2** with various lithium halide salts in aprotic polar solvents under conditions similar to those previously reported[7,8] indicated that in dimethyl sulfoxide, substitution to give the deoxyhalogeno compounds occurred extremely slowly. Reaction in hexamethylphosphoramide (HMPA), on the other hand, led to extensive decomposition of the triflates. It was found, however, that addition of *small amounts* of HMPA[13] to Me_2SO allowed these reactions to proceed to completion at room temperature in relatively short times to give the corresponding 2-deoxy-2-substituted-α-arabinofuranosyl derivatives **4b–e** in generally good yields (see Table I) and without appreciable side reactions.

Reactions of the β anomer **3** with the same nucleophilic reagents in Me_2SO–HMPA, however, proceeded at much slower rates, and yields of the corresponding 2-substituted products **5b–e** were generally low. The major common byproduct of these reactions was the furan derivative **7** identified by its characteristic ^1H NMR. This compound presumably arises by a competing elimination of trifluoromethanesulfonic acid from **3** to give the 2,3-unsaturated intermediate **6** which readily loses methanol[14] as illustrated in Scheme I.

Triflates **2** and **3** were inert toward treatment with LiF[7] under a variety of conditions. However, treatment of the α anomer **2** with an excess of tetra-*n*-butylammonium fluoride (TBAF) in dry THF at −10 °C[7] readily afforded methyl 3,5-di-*O*-benzyl-2-deoxy-2-fluoroarabinoside **4a** in 62% yield. Similar treatment of β anomer **3** with TBAF, on the other hand, afforded exclusively furan derivative **7**.

The difference in reactivity between **2** and **3** can be readily explained by the large steric effect of the OMe group of the β anomer **3** which hinders nucleophilic attacks onto C-2. Direct substitution of the triflate of **3** by halide or azide anions thus competes unfavorably with the elimination pathway leading to the formation of furan **7** as the predominant product. In the case of the α anomer **2**, on the other hand, nucleophilic attack at C-2 is unhindered by the anomeric OMe group and proceeds relatively rapidly so that the competing elimination pathway is not observed. This interpretation finds support in several studies of the epoxide-ring opening of methyl 2,3-anhydro-D-ribofuranoside derivatives by various nucleophilic reagents,[15-20] a type of reaction closely related to our own studies. It was thus found that, while the corresponding α-glycosides react readily to afford the 2-deoxy-2-substituted-α-D-arabinofuranoside (generally as the major [15-19] and sometimes exclusive[20] product) together with the 3-deoxy-3-substituted-β-D-xylofuranoside, the corresponding β-glycosides give almost always the latter as the exclusive product, usually at slower rates.[15] It has been suggested in this respect that the decisive steric control exerted by the glycosidic β-OMe group might be due to the dipole interaction responsible for the "anomeric effect" in pyranoses, as such an interaction would force the methoxyl group into a pseudoaxial conformation, thus hindering the nucleophilic attack at C-2.[15] This plausible hypothesis would similarly explain the slower rates encountered in the nucleophilic displacement of triflate **3** and the preponderance of the product of elimination **7** discussed above.

It is apparent that utilization of methyl 3,5-di-*O*-benzyl-2-*O*-(trifluoromethanesulfonyl)-α-D-ribofuranoside **2** as outlined in these studies provides a general method of choice for the synthesis of various 2-deoxy-2-substi-

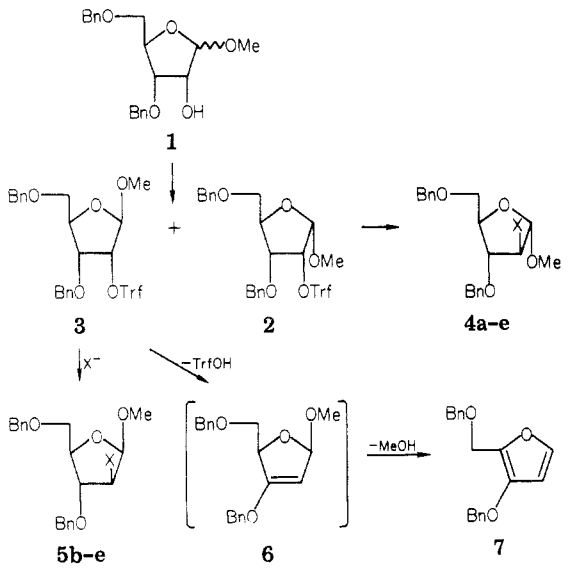
(6) J. J. Fox, *Pure Appl. Chem.*, 18, 223 (1969); K. A. Watanabe and J. J. Fox, *Chem. Pharm. Bull.*, 17, 211 (1969).
(7) R. Ranganathan, *Tetrahedron Lett.*, 1291 (1977).
(8) R. Ranganathan and D. Larwood, *Tetrahedron Lett.*, 4341 (1978).
(9) P. J. Stang and M. G. Mangum, *J. Am. Chem. Soc.*, 97, 6478 (1975), and references therein.
(10) T. E. Dueber, P. J. Stang, W. D. Pfeifer, R. H. Summerville, M. A. Imhoff, P. V. Ragué Schleyer, K. Hummel, S. Bocher, C. E. Harding, and M. Hanack, *Angew. Chem., Int. Ed. Engl.*, 9, 521 (1970).
(11) R. L. Hansen, *J. Org. Chem.*, 30, 4322 (1965).
(12) A. Streitwieser, Jr., C. L. Wilkins, and E. Kielman, *J. Am. Chem. Soc.*, 90, 1598 (1968).
(13) (a) It is noteworthy in this respect that HMPA and LiBr form an insoluble complex in ether,[13a] a property which was exploited in improving the yield and rate of Wittig reactions involving methyltriphenylphosphonium bromide and *n*-butyllithium. Addition of HMPA to Me_2SO has also been reported to facilitate direct displacement of *p*-toluenesulfonic acid esters LiCl.[13b] The intermediacy of a six-membered transition state in which HMPA is associated with the LiCl and the departing sulfonyloxy group has been proposed to explain this phenomenon.[13b,c] G. Magnusson, *Tetrahedron Lett.*, 2713 (1977). (b) M. E. Alonso, *J. Org. Chem.*, 41, 1410 (1976). (c) J. J. Normant and H. Deshayes, *Bull. Soc. Chim. Fr.*, 2455 (1967); H. Normant, *ibid.*, 801 (1968).
(14) Formation of a similar furan derivative from the decomposition of furanoid glycals via 2,3-unsaturated intermediates is discussed in K. Bischofberger and R. H. Hall, *Carbohydr. Res.*, 52, 223 (1976).
(15) E. J. Reist and S. H. Holton, *Carbohydr. Res.*, 9, 71 (1969).
(16) J. A. Wright, N. F. Taylor, and J. J. Fox, *J. Org. Chem.*, 34, 2632 (1969).
(17) T. van Es, *Carbohydr. Res.*, 21, 156 (1972).
(18) J. A. Montgomery, M. C. Thorpe, S. D. Clayton, and H. J. Thomas, *Carbohydr. Res.*, 32, 404 (1974).
(19) J. A. Montgomery, S. D. Clayton, and H. J. Thomas, *J. Org. Chem.*, 40, 1923 (1975).
(20) A. Yamashita and A. Rosowsky, *J. Org. Chem.*, 41, 3422 (1976).

Table I[c]

compd	X	reagent	time, h	state	yield, %	selected ^{1}H NMR data ($CDCl_3$) δ(H-1)	$\delta(OCH_3)$	$J_{1,2}$, Hz
4a	F	$(n\text{-Bu})_4NF$	3.5	syrup	62	5.09 (dd)	3.40	<1.0[b]
4b	Cl	LiCl	20	syrup	67	5.01 (br s)	3.36	<1.0
5b	Cl	LiCl	48	syrup	14[a]	4.88 (d)	3.37	3.7
4c	Br	LiBr	3	syrup	89	5.15 (br s)	3.40	<1.0
5c	Br	LiBr	48	syrup	19[a]	4.87 (d)	3.37	3.0
4d	I	NaI	20	syrup	84	5.27 (d)	3.40	1.5
5d	I	NaI	48	solid (mp 64–65 °C)	19[a]	4.75 (d)	3.35	3.7
4e	N_3	LiN_3	0.7	syrup	90	4.90 (br s)	3.41	<1.0
5e	N_3	LiN_3	20	syrup	54	4.58 (d)	3.35	4.6

[a] Obtained as the minor product. The major product was identified as 7. [b] $J_{1,F}$ = 12 Hz. [c] Satisfactory analytical values (C, H, N or C, H, X) were obtained for all compounds in the table.

Scheme I[a]



[a] X^-: a, F^-; b, Cl^-; c, Br^-; d, I^-; e, N_3^-. Trf = Trifluoromethanesulfonyl; Bn = benzyl.

tuted-arabinofuranosides. The only serious limitation to this approach has been the large and hence unfavorable ratio of anomers 3/2 which is determined by the composition of the anomeric mixture 1 (containing mostly the β anomer) prepared by the acid-catalyzed methanolysis of 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose.[3] An ongoing study aimed at the stereoselective synthesis of the more useful α-glycoside 1 by a different procedure will be the subject of a future paper.

Experimental Section

General Procedures. Melting points were determined on a Thomas–Hoover Unimelt apparatus (capillary method) and are uncorrected. NMR spectra were obtained on a JEOL PFT-100 spectrometer. Optical rotations were measured on a P&I digital photoelectric polarimeter, Model A. Microanalyses were performed by Spang Microanalytical Laboratory. Column chromatography was performed on E. Merck silica gel 60 (70–230-mesh AsTM).

Methyl 3,5-Di-*O*-benzyl-2-*O*-(trifluoromethanesulfonyl)-D-ribofuranosides 2 and 3. Methyl 3,5-di-*O*-benzyl-D-ribofuranoside 1[3] (10.0 g, 29 mmol) was dissolved in a mixture of dry pyridine (15 mL) and methylene chloride (400 mL) and cooled to −15 °C under nitrogen. Trifluoromethanesulfonic anhydride (6 mL, 35 mmol) in 20 mL of CH_2Cl_2 was then added slowly, and the reaction was allowed to proceed for 2 h. The solution was washed with saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, and evaporated to dryness in vacuo. The residue containing triflates 2 and 3 was chromatographed on a silica gel column with toluene–ethyl acetate (98:2) as the eluent.

The β anomer 3 was eluted first (10.5 g, 77%) and obtained as a clear syrup: $[\alpha]^{23}_D$ +20.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30 (10 H, arom H), 4.49 (2 H, q, CH_2), 4.46 (2 H, q, CH_2), 5.10 (1 H, d, $J_{2,3}$ = 3.1 Hz, H-2), 5.02 (1 H, s, H-1), 4.21–4.28 (2 H, m, H-3 and H-4), 3.54 (2 H, m, H-5, H-5′), 3.32 (3 H, s, OCH_3).

Anal. Calcd for $C_{21}H_{23}O_7F_3S$: C, 52.93; H, 4.86; F, 11.94; S, 6.72. Found: C, 53.15; H, 4.96; F, 11.85; S, 6.92.

The α anomer 2 which eluted next (2.71 g, 20%) was obtained as a clear syrup: $[\alpha]^{23}_D$ +101° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.29 (10 H, arom H), 5.08 (1 H, dd, $J_{2,3}$ = 3.9 Hz, $J_{1,2}$ = 4.3 Hz, H-2), 4.97 (1 H, d, $J_{1,2}$ = 4.3 Hz, H-1), 4.60 (2 H, q, CH_2), 4.44 (2 H, q, CH_2), 4.06–4.19 (2 H, m, H-3 and H-4), 3.34–3.60 (2 H, m, H-5, H-5′), 3.49 (3 H, s, OCH_3).

Anal. Calcd for $C_{21}H_{23}O_7F_3S$: C, 52.93; H, 4.86; F, 11.94; S, 6.72. Found: C, 53.21; H, 4.87; F, 11.99; S, 6.45.

Preparation of Methyl 2-Deoxy-2-substituted-D-arabinofuranosides 4b–e and 5b–e. Triflate 2 (or 3, 1 mmol) was dissolved in a mixture of dry Me_2SO (1 mL) and dry HMPA (179 mg, 1 mmol). To this solution was added 1.1 mmol of the salt (LiCl, LiBr, NaI, or LiN_3). After vigorous stirring (see Table I for reaction time), the mixture was poured into 20 mL of an ice–water mixture, and the products were extracted with petroleum ether (30–60 °C) several times (6 × 20 mL). The combined extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness in vacuo. The products were isolated by chromatography on a column of silica gel with toluene–ethyl acetate (95:5) as the eluent and characterized as shown in Table I.

Methyl 3,5-Di-*O*-benzyl-2-fluoro-2-deoxy-α-D-arabinofuranoside (4a). To a solution of triflate 2 (464 mg, 1 mmol) in dry THF (20 mL) at −10 °C was added tetra-*n*-butylammonium fluoride (TBAF; 1.3 g, 5 mmol). The mixture was stirred in an ice bath for 3.5 h and evaporated to dryness in vacuo. Chromatography of the residue on a silica gel column (toluene–ethyl acetate, 9/1) afforded compound 4a (216 mg, 62%) isolated as a clear, analytically pure syrup (see Table I).

Reaction of 3 with TBAF. TBAF (1.3 g, 5 mmol) was added to a solution of triflate 3 (464 mg, 1 mmol) in dry THF (20 mL) at −10 °C. After being stirred in an ice bath for 5 h, the mixture was evaporated to dryness. 3-Hydroxyfurfuryl di-*O*-benzyl ether 7 was isolated by chromatography with toluene as the eluent and obtained as a colorless oil (223 mg, 76%) which decomposed rapidly upon being allowed to stand: ^{1}H NMR ($CDCl_3$) δ 7.31–7.35 (10 H, m, arom H), 7.22 (1 H, d, $J_{4,5}$ = 2.13 Hz, H-5), 6.27 (1 H, d, $J_{4,5}$ = 2.13 Hz, H-4), 5.00, 4.49, and 4.47 (3 s, 2 H each, 2 $CH_2C_6H_5$ and C-2 CH_2).

Acknowledgment. The authors thank Drs. B. Otter, S. Tam, and K. Watanabe for their useful suggestions and Mr. M. Olsen for recording the NMR spectra.

Registry No. 1, 55775-39-8; 2, 76832-95-6; 3, 76832-96-7; 4a, 76832-97-8; 4b, 55740-54-0; 4c, 76832-98-9; 4d, 76832-99-0; 4e, 76833-00-6; 5b, 76833-01-7; 5c, 76833-02-8; 5d, 76833-03-9; 5e, 76833-04-0; 7, 76833-05-1; LiCl, 7447-41-8; LiBr, 7550-35-8; NaI, 7681-82-5; LiN_3, 19597-69-4; TBAF, 429-41-4.