Nucleosides. 116. 1-(β-D-Xylofuranosyl)-5-fluorocytosines with a Leaving Group on the 3′ Position. Potential Double-Barreled Masked Precursors of Anticancer Nucleosides[1]

K. A. Watanabe, U. Reichman, C. K. Chu, D. H. Hollenberg, and J. J. Fox*

Laboratory of Organic Chemistry, Sloan-Kettering Institute for Cancer Research, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Division of Graduate School of Medical Sciences, Cornell University, New York, New York 10021.
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Syntheses of five pairs of cytosine and 5-fluorocytosine xylofuranosyl nucleosides in which the 3′-hydroxyl group is replaced by Cl, Br, I, OMs, or OTs are described. Those xylosyl nucleosides with a good leaving group at the 3′ position exhibit good inhibitory activity against L5178Y and P815 mouse leukemic cells in vitro at rather low concentrations, and like that of *ara*-C this cytotoxicity is reversed by 2′-deoxycytidine but not by thymidine. Xylosylcytosines are not active against *ara*-C resistant lines of L5178Y and P815 cells; however, the corresponding *5-fluorocytosine* analogues exhibit significant cytotoxicity against these *ara*-C resistant leukemic cell lines, and this activity is reversed by thymidine but not by deoxycytidine. These data support the "double-barreled" masked precursor hypothesis in that xylosyl-5-fluorocytosines substituted at the 3′ position by a good leaving group exhibit activity akin to that of *ara*-C in the *ara*-C sensitive lines, while these nucleosides act as 5-fluoropyrimidines in the *ara*-C resistant lines.

1-(β-D-Arabinofuranosyl)cytosine (*ara*-C, see Scheme I) is probably the most important drug currently available for the treatment of human acute myeloblastic leukemia.[2] This drug, however, is rapidly converted by enzymatic deamination in vivo to the chemotherapeutically inactive uracil derivative (*ara*-U).[3] We have demonstrated[4] that 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine (AAC) is unstable in neutral, buffered solutions and under these mild conditions is converted into *ara*-C; we have also showed[5] that AAC produces increases in the life span of leukemic mice. Subsequently, it was found[6,7] that at high dose levels AAC is markedly effective against mouse leukemia L1210.

We have synthesized 1-(β-D-arabinofuranosyl)-5-fluorocytosine (*ara*-FC)[8] and its 5-fluorouracil analogue (*ara*-FU)[9] and have shown that the mode of action of *ara*-FC was akin to that of *ara*-C (presumably on the DNA polymerase level), whereas that of *ara*-FU was akin to that of 5-fluorouracil (presumably on the thymidylate synthetase level).[8-11] From these data and from a consideration of the chemical properties of 2,2′-anhydronucleosides,[4,5] we synthesized 2,2′-anhydro-*ara*-FC (AAFC)[12] with the hope that such a drug would act not only as a slow releaser of *ara*-FC but also (if the latter underwent enzymatic

Scheme I

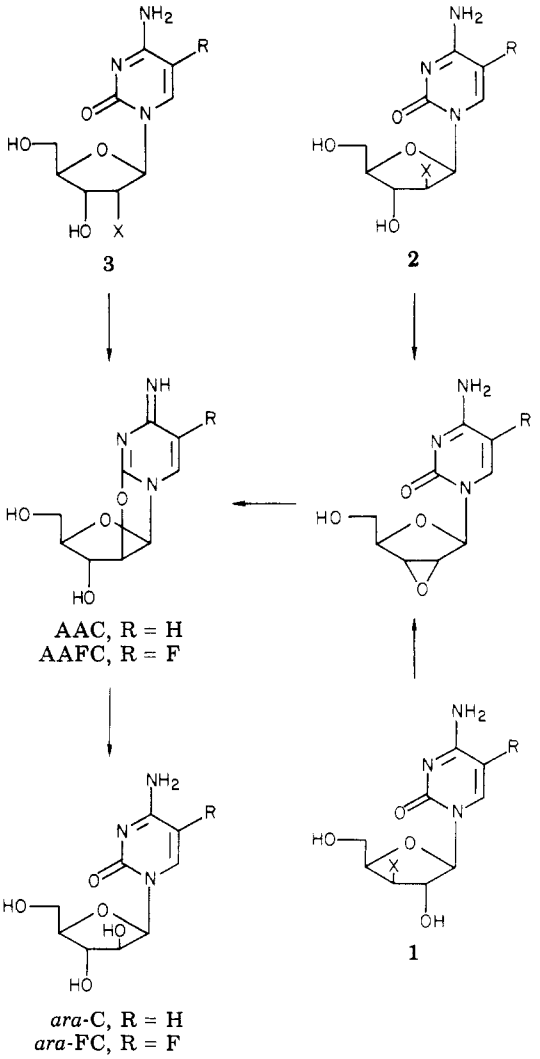

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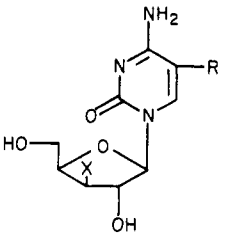
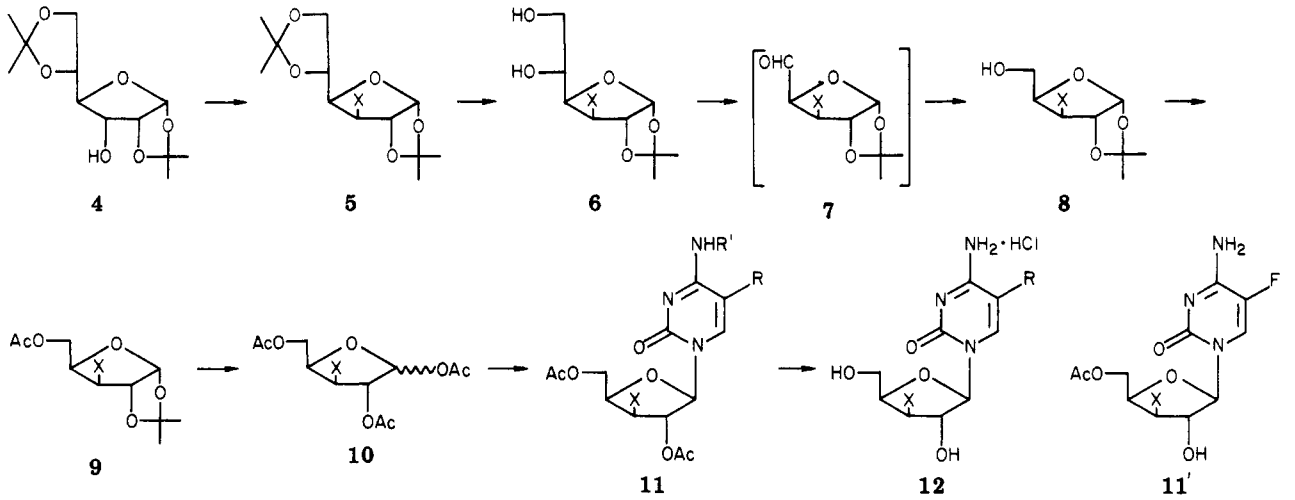
Table I



compd	X	R	ID_{50}, μg/mL L5178Y	L5178Y/*ara*-C	P815	P815/*ara*-C
xylo-C	OH	H	20.0	79.0	10.0	40.0
3′-F-*xylo*-C	F	H	37.0	>100	21.0	>100
12a	Cl	H	2.0	>100	0.8	>100
12a	Cl	F	1.0	71	0.7	>30
12b	Br	H	0.03	>100	0.05	>100
12b	Br	F	0.06	2.6	0.2	5.0
12c	I	H	0.1	>100	0.3	>100
12c	I	F	0.08	10.0	0.1	8.0
21a	OMs	H	0.07	>100	0.03	22
21a	OMs	F	0.05	5.3	0.02	6.0
21b	OTs	H	0.08	>100	0.06	>30
21b	OTs	F	0.06	8.0	0.02	3.9

Scheme II[a]



[a] a, X = Cl; b, X = Br; c, X = I.

deamination in vivo) would produce *ara*-FU. Indeed, *ara*-FC showed excellent antileukemic activity against the *ara*-C sensitive lines of various mouse leukemias, and this activity was, like that of *ara*-C, reversed by deoxycytidine but not by cytidine or thymidine. In contrast to AAC, AAFC was found to be also active against *ara*-C resistant mouse leukemia in vitro, and this activity was reversed by thymidine but not by deoxycytidine. Thus, AAFC acts as a "double-barreled" masked precursor of both *ara*-FC and *ara*-FU, at least in vitro.

We also found[13] that 3′-bromo-3′-deoxy-*xylo*-C is active against various mouse leukemia cell lines, and this activity was, like that of *ara*-C, reversed by deoxycytidine but not by cytidine or thymidine. 1-(β-D-Xylofuranosyl)cytosine (*xylo*-C)[14] and 3′-deoxy-3′-fluoro-*xylo*-C[15] are not active.

Based on these findings and the data discussed above, an hypothesis was developed[16] that cytosine nucleosides bearing a good leaving group on the 3′ "up" (xylo) (**1**, Scheme I), 2′ "up" (arabino) (**2**), or 2′ "down" (ribo) (**3**) position may undergo intramolecular nucleophilic displacement reactions (in vivo), as shown in Scheme I, to liberate eventually *ara*-C nucleosides. As a test of this hypothesis, we synthesized several pairs of *xylo*-C and *xylo*-FC derivatives with a good leaving group on the 3′ position (Table I) and examined their activity against sensitive and resistant lines of mouse leukemia P815 and L5178 cells. The *xylo*-C analogues are expected to act as masked precursors of *ara*-C and the *xylo*-FC derivatives as double-barreled masked precursors of *ara*-FC and *ara*-FU.

Chemistry. 3′-Bromo-3′-deoxy-*xylo*-C was prepared by acidic deacetylation of the triacetate which was obtained from N^4-acetylcytidine[17] and acetyl bromide according to

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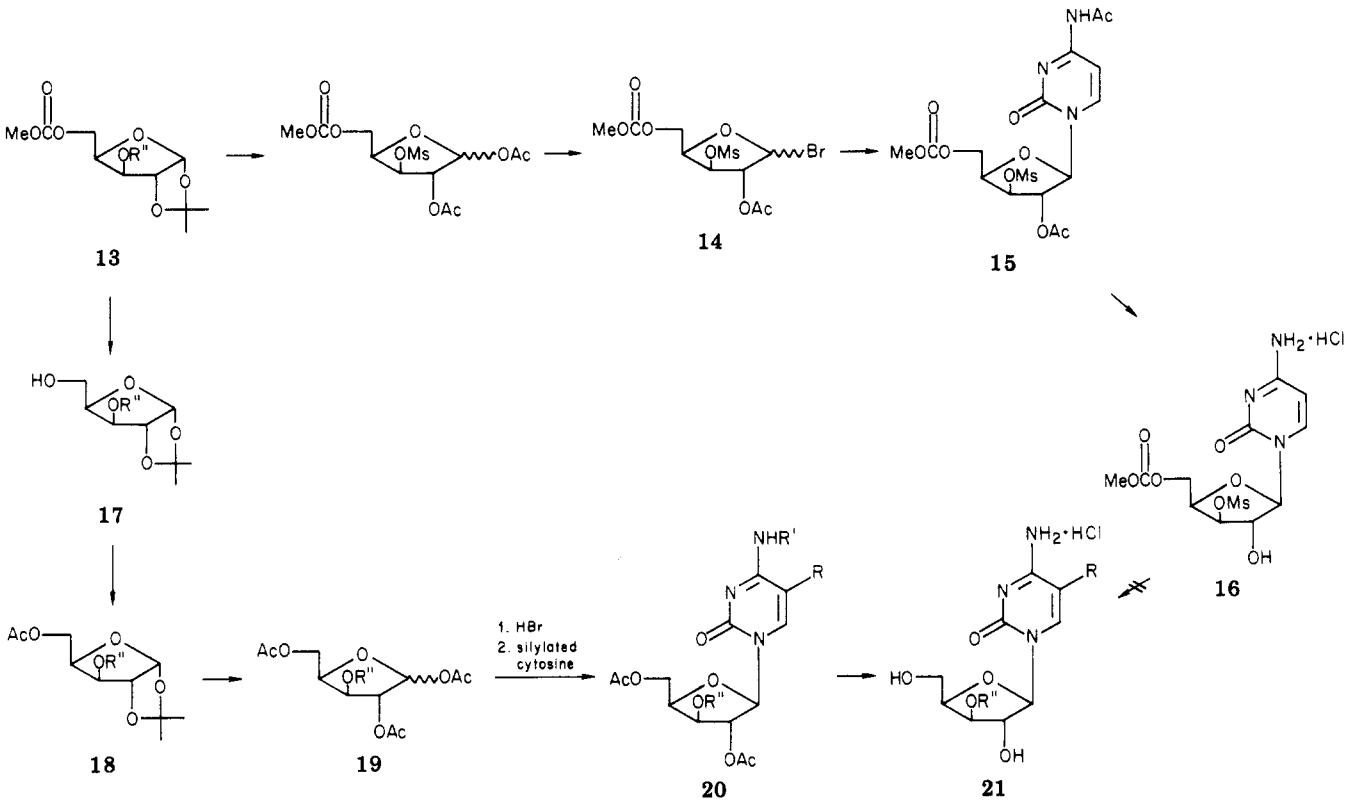
Scheme III[a]



[a] a, R'' = Ms; b, R'' = Ts.

the procedure of Marumoto and Honjo.[18] Other 3'-halogeno nucleosides were synthesized by condensation of silylated N^4-acetylcytosine or 5-fluorocytosine with an appropriate 3-halogenoxylofuranose prepared from 3-deoxy-3-halogeno-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**5**) (see Scheme II). The 3-chloro gluco derivative (**5**, X = Cl) was obtained from 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**) according to the procedure of Haylock et al.[19] by treatment with triphenylphosphine in carbon tetrachloride. Treatment of **4** with carbon tetrabromide and triphenylphosphine in pyridine afforded the 3-bromo analogue (**5**, X = Br). The 3-iodo gluco derivative[20] (**5**, X = I) was prepared from **4** by treatment with a mixture of triphenylphosphine, methyl iodide, and diethyl azodicarboxylate in benzene. This reagent combination was originally used by Loibner and Zbiral[21] for the synthesis of iodinated steroids.

After selective removal of the 5,6-*O*-isopropylidene group from **5** in a mixture of 0.8% sulfuric acid in methanol, the resulting monoisopropylidene derivative **6** was oxidized with potassium metaperiodate to the aldehyde **7**. Reduction of the aldehyde group of **7** with sodium borohydride proceeded smoothly, and 3-deoxy-3-halogeno-1,2-*O*-isopropylidene-α-D-xylose (**8**) was obtained in good yield. Acetylation of **8** to **9**, followed by acetolysis of the isopropylidene group, afforded the triacetate (**10**) as an α/β mixture in high yield. This method of preparation of **10** is amenable to large-scale syntheses and is much more practical than the procedures which had been reported for the preparation of 3-bromo[22] or 3-chloro[23] derivatives of xylofuranose. When **10** (α/β mixture) was condensed with the corresponding silylated *N*-acetylcytosine in the presence of stannic chloride in dichloromethane,[24] the corresponding protected nucleoside **11** (R = H; R' = Ac) was obtained. After deacetylation of **11** with MeOH–HCl, the desired nucleosides **12** were isolated as the crystalline HCl salts. When **10** was condensed with the silylated 5-fluorocytosine, however, two major products were always produced. These major products were separated on a silica gel column, and the less polar product was identified as the diacetate (**11**, R = F; R' = H) and the more polar product as the monoacetate (**11'**, R = F; R' = H) by ^{1}H NMR spectroscopy. Both products (**11** and **11'**) afforded the identical nucleoside **12** upon deacetylation.

For the synthesis of the 3'-*O*-mesyl and 3'-*O*-tosyl nucleosides, we first condensed 2-*O*-acetyl-3-*O*-mesyl-5-*O*-(methoxycarbonyl)-D-xylofuranosyl bromide (**14**, Scheme III) with bis(trimethylsilyl)-N^4-acetylcytosine. The reaction went smoothly and the protected nucleoside **15** was obtained in crystalline form in good yield. Deacetylation of **15** under acidic conditions could be effected, and compound **16** was obtained in crystalline form. The 5'-*O*-(methoxycarbonyl) group of **16** was found to be too stable to be removed under acidic conditions. Saponification of **16** under various alkaline conditions either afforded *ara*-C or intractable mixtures. It was found, however, that 1,2-*O*-isopropylidene-5-*O*-(methoxycarbonyl)-3-*O*-sulfonyl-α-D-xylofuranoses (**13**) could be converted into the 5-unsubstituted derivative **17** in good yield by brief treatment with sodium methoxide in methanol. After acetylation of **17**, the product **18** was acetolyzed to the triacetate **19**,

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Table II. New Compounds[a]

compd	R	R'	mp, °C	crystn solvent	formula
5b			syrup		$C_{12}H_{19}BrO_5$
5c			syrup		$C_{12}H_{19}IO_5$
6a			syrup		$C_9H_{15}ClO_5$
6b			syrup		$C_9H_{15}BrO_5$
6c			syrup		$C_9H_{15}IO_5$
8a			syrup		$C_8H_{13}ClO_4$
8b			syrup		$C_8H_{13}BrO_4$
8c			syrup		$C_8H_{13}IO_4$
9a			syrup		$C_{10}H_{15}ClO_5$
9b			syrup		$C_{10}H_{15}BrO_5$
9c			syrup		$C_{10}H_{15}IO_5$
10a			syrup		$C_{11}H_{15}ClO_7$
10b			syrup		$C_{11}H_{15}BrO_7$
10c			syrup		$C_{11}H_{15}IO_7$
11a	H	Ac	188-190	EtOH	$C_{15}H_{18}ClN_3O_7$[b]
11a	F	H	powder	Me_2CO	$C_{13}H_{15}ClFN_3O_6$
11c	H	Ac	175-176	MeOH	$C_{15}H_{18}IN_3O_7 \cdot MeOH$[c]
11c	F	H	105-108[d]	Me_2CO	$C_{13}H_{15}FIN_3O_6$
11'a	F	H	193-195 dec	Me_2CO	$C_{11}H_{13}ClFN_3O_5$[b,e]
11'b	F	H	175-176 dec	Et_2O	$C_{11}H_{13}BrFN_3O_5$
12a	H		176-179 dec	Me_2CO	$C_9H_{12}ClN_3O_4 \cdot HCl$
12a	F		180-183 dec	Me_2CO	$C_9H_{11}ClFN_3O_4 \cdot HCl$
12b	H		178-180 dec	EtOH	$C_9H_{12}BrN_3O_4 \cdot HCl$
12b	F		175-176 dec	Me_2CO	$C_9H_{11}BrFN_3O_4 \cdot HCl$
12c	H		176-177 dec	Me_2CO	$C_9H_{12}IN_3O_4 \cdot HCl$[b]
12c	F		152-160 dec	Me_2CO	$C_9H_{11}FIN_3O_4 \cdot HCl$[b]
15			197-199 dec	$CHCl_3$-MeOH	$C_{16}H_{21}N_3O_{11}S$
16			187-189 dec	MeOH-EtOH	$C_{12}H_{17}N_3O_9S \cdot HCl$
17a			79-80	C_6H_6-petr ether	$C_9H_{16}O_7S$
17b			85-87	C_6H_6-n-C_7H_{16}	$C_{15}H_{20}O_7S$
18a			82-84	i-PrOH	$C_{11}H_{18}O_8S$
18b			82-85	i-PrOH	$C_{17}H_{22}O_8S$
19a			114-115[f]	MeOH	$C_{12}H_{18}O_{10}S$
19b			foam		$C_{18}H_{22}O_{10}S$
20a	H		110-115[g]	MeOH	$C_{16}H_{21}N_3O_{10}S$
20a	F		powder	EtOH	$C_{14}H_{18}FN_3O_9S \cdot EtOH$[h]
20b	H		182-184 dec	EtOH	$C_{22}H_{25}N_3O_{10}S$
20b	F		129-130	EtOH	$C_{22}H_{24}FN_3O_{10}S$
21a	H		204-205 dec	i-PrOH-H_2O	$C_{10}H_{15}N_3O_7S \cdot HCl$
21a	F		powder	i-PrOH	$C_{10}H_{14}FN_3O_7S \cdot HCl$[b]
21b	H		192-196 dec	EtOH	$C_{16}H_{19}N_3O_7S \cdot HCl$
21b	F		173-178 dec	EtOH	$C_{16}H_{18}FN_3O_7S \cdot HCl$

[a] Except otherwise noted, compounds were analyzed for all the elements except oxygen, and analytical results were within ±0.4% of the theoretical values. [b] Cl not analyzed. [c] C: calcd, 37.59; found, 38.11. [d] Slowly softening at 105-108 and decomposed at 155-160 °C. [e] F not analyzed. [f] β-Anomer. [g] Slowly softening at 110-115 and decomposed at 166-170 °C. [h] C: calcd, 40.94; found, 39.72.

which was subsequently converted into the bromo sugar and condensed with the appropriate pyrimidines by the silyl procedure to afford the corresponding protected nucleosides **20**. Deacetylation of **20** was carried out in MeOH–HCl, and the desired nucleosides **21** were isolated as the crystalline HCl salts.

Biology. All of these new 3'-substituted xylonucleosides (except 3'-chloro analogues) are cytotoxic against the sensitive lines of leukemic cells at rather low concentrations (Table I), and the cytotoxicity is reversed, like *ara*-C, by 2'-deoxycytidine. Xylofuranosylcytosine (*xylo*-C) itself is not cytotoxic to these cell lines. The cytotoxicity exhibited by 3'-substituted *xylo*-C's is consistent with the hypothesis (Scheme I) that these nucleosides are converted to some extent to *ara*-C. The fact that the 3'-chloro analogues are much less cytotoxic and the 3'-fluoro analogues are hardly cytotoxic at all may be a reflection of the poor "leaving" capacity of the chloro and the fluoro substituents relative to the other halogeno or pseudohalogeno groups. It should also be noted that generally the 3'-iodo nucleosides are slightly less toxic than the corresponding bromo analogues. Semiquantative kinetic studies showed that both **12c** (R = H) and **12b** (R = H) are converted into *ara*-C via AAC in a bicarbonate buffer at room temperature, but the rate of conversion of **12c** is indeed smaller than that of **12b**. Studies with space-filling molecular models showed that the conformation of the sugar ring of 3'-iodo-*xylo*-C (**12c**) is much less flexible than that of 3'-bromo-*xylo*-C (**12b**) due to the larger size of iodine. The $J_{2',3'}$ value for **12c** (2.5 Hz; see Table III) is larger than that for **12b** (1.2 Hz), indicating that the 2' and 3' carbons of the former **12c** are more eclipsed than those of the latter **12b**. Consequently, nucleophilic attack by the 2'-hydroxyl group to form the "down" oxide (see Scheme I) should be more difficult for **12c** than for **12b**. Thus, **12c** could be converted into *ara*-C more slowly than **12b**, although iodide is a better leaving group than bromide.

The significant cytotoxicity shown by the 5-fluoro-*xylo*-C's containing good leaving groups at C-3' against the *ara*-C resistant cell lines (Table I) is reversed by thymidine but not by deoxycytidine. The 5-unsubstituted analogues do not exhibit such cytotoxicity. These data are consistent with the double-barreled masked precursor hypothesis in that 5-fluoro-3'-substituted-*xylo*-C's exhibit activities akin to *ara*-C in the *ara*-C sensitive lines, while these nucleosides act as 5-fluoropyrimidines in the *ara*-C resistant lines.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were per-

Table III. ^{1}H NMR Parameters for 3-Deoxy-3-halogenofuranose Intermediates and 1-(3-Deoxy-3-halogeno-β-D-xylofuranosyl)cytosine[a]

compd	chemical shifts, δ							coupling, Hz				solvent
	H-1	H-2	H-3	H-4	H-5	H-6	Me	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	
5b	5.95 (d)	4.87 (d)	4.78 (d)			4.0–4.3	1.32, 1.36, 1.43, 1.51	3.3	0	2.7		$CDCl_3$
5c	5.97 (d)	5.06 (d)	4.46 (d)	3.28 (q)		4.0–4.3	1.32, 1.36, 1.42, 1.51	3.4	0	2.8	7.9	$CDCl_3$
6a	5.95 (d)	4.75 (d)	4.50 (d)	4.29 (q)		3.9–4.1	1.32, 1.51	3.3	0	1.7	8.6	Me_2SO-d_6
6b	5.93 (d)	4.90 (d)	4.51 (d)	3.91 (q)		3.3–3.5	1.27, 1.42	3.7	0	2.8	8.3	Me_2SO-d_6
6c	5.99 (d)	5.07 (d)	4.56 (d)	3.35 (q)		3.5–3.9	1.31, 1.52	3.4	0	2.7	7.9	$CDCl_3$
8a	5.97 (d)	4.72 (d)	4.38 (d)	4.54 (q)	3.95 (d)		1.32, 1.51	3.4	0	2.5	5.5	$CDCl_3$
8b	5.94 (d)	4.88 (d)	4.55 (d)	4.08 (m)	3.56 (d)[c]		1.27, 1.43	3.7	0	2.8	8.5	Me_2SO-d_6
8c	6.02 (d)	5.04 (d)	4.36 (d)	3.5–4.0			1.32, 1.53	3.3	0	2.7		$CDCl_3$
9a	6.00 (d)	4.73 (d)		4.2–4.7			1.32, 1.51, 2.09	3.7	0	2.0		$CDCl_3$
9b	5.99 (d)	4.92 (d)	4.68 (d)	4.31 (m)	4.14 (t)[d]		1.27, 1.42, 2.05	3.4	0	2.7	7.5	Me_2SO-d_6
9c	6.03 (d)	5.04 (d)	4.35 (d)	3.79 (m)	4.19 (d)		1.32, 1.52, 2.10	3.4	0	3.1	5.1	$CDCl_3$
10a (α)[b]	6.48 (d)	5.42 (t)		4.2–4.8			2.12, 2.15	4.6	4.7			$CDCl_3$
10a (β)[b]	6.15 (s)	5.38 (d)						0	0.5			$CDCl_3$
10b (α)[b]	6.34 (d)	5.40 (t)		4.2–4.8			2.06, 2.09, 2.10	4.6	4.8			Me_2SO-d_6
10b (β)[b]	6.02 (s)	5.30 (d)						0	0.6			Me_2SO-d_6
10c (α)[b]	6.41 (d)	5.47 (t)		4.2–4.8			2.09, 2.11, 2.12, 2.13	4.2	4.3			$CDCl_3$
10c (β)[b]	6.12 (s)	5.49 (d)						0	2.4			$CDCl_3$

compd	chemical shifts, δ								coupling, Hz				solvent
	H-1′	H-2′	H-3′	H-4′	H-5′	Me	H-5	H-6	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	
11a (R = H)	6.00 (s)	5.37 (s)		4.3–4.7		2.14, 2.17	7.49 (d)	9.07 (d)[e]	0	0	1.8		$CDCl_3$
11a (R = F)	5.96 (t)	5.33 (t)		4.3–4.6		2.10, 2.17		7.73 (q)[f]	1.2	1.2	2.4		$CDCl_3$
11b (R = F)	5.93 (t)	5.45 (t)		4.3–4.6		2.14, 2.16		7.78 (d)[f]	1.2	1.2			$CDCl_3$
11c (R = H)	5.94 (d)	5.60 (d)		4.2–4.6		2.14, 2.18	7.51 (d)	8.18 (d)[e]	1.2	0			$CDCl_3$
11c (R = F)	5.89 (t)	5.56 (d)		4.2–4.6		2.14, 2.15		7.83 (d)[f]	1.2	1.2	4.3		$CDCl_3$
11′a	5.61 (t)			4.2–4.6		2.07		7.82	1.8				Me_2SO-d_6
11′b	5.59			4.2–4.5		2.08		7.88	1.5				Me_2SO-d_6
12a (R = H)	5.77 (s)	4.71 (d)	4.53 (q)	4.79 (q)			6.28 (d)	8.21 (d)[e]	0	1.0	3.7	6.0	D_2O
12a (R = F)	5.74 (t)	4.62 (t)	4.47 (q)	4.71 (q)	4.05 (d)			8.28 (d)[f]	1.3	1.2	3.6	6.0	D_2O
12b (R = H)	5.75 (d)	4.76 (t)	4.49 (q)	4.67 (q)	4.00 (d)		6.22 (d)	8.18 (d)[e]	1.3	1.2		5.8	D_2O
12b (R = F)	5.72 (t)		4.4–4.8		4.03 (m)			8.34 (d)[f]	1.3				D_2O
12c (R = H)	5.73 (d)		4.62 (q)	4.44 (q)	3.92 (m)		6.23 (d)	8.23 (d)[e]	1.8	2.5	4.3		D_2O
12c (R = F)	5.70 (t)		4.43 (q)	4.13 (m)	3.92 (m)			8.37 (d)[f]	1.2	2.5	4.4		D_2O

[a] Signals (in parentheses) are expressed as s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Values given for coupling constants are first order. [b] Compounds **10a**, **10b**, and **10c** are anomeric mixtures. [c] $J_{4,5'} = 2.7$ Hz. [d] $J_{4,5'} = 3.5$ Hz. [e] $J_{5,6} = 8.0$ Hz. [f] $J_{6,5\text{-F}} = 6.7$ Hz; $J_{1',5\text{-F}} = 1.3$ Hz.

Table IV. ^{1}H NMR Parameters for 3-Sulfonyl-D-xylofuranose Intermediates and 1-(3-*O*-Sulfonyl-β-D-xylofuranosyl)cytosines[a]

	chemical shifts, δ						coupling, Hz					
compd	H-1	H-2	H-3	H-4	H-5	Me	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	solvent
17a	5.95 (d)	4.75 (d)	4.99 (d)	4.22 (m)	3.56 (m)	1.27, 1.42, 3.27	3.8	0	2.8	6.9	5.4	Me_2SO-d_6
17b	5.92 (d)	4.62 (d)	4.89 (d)	4.36 (m)	3.71 (m)	1.25, 1.48, 2.42	3.5	0	2.7	6.0	5.8	Me_2SO-d_6
18a	5.99 (d)	4.81 (d)	5.07 (d)	4.48 (m)	4.32 (m)	1.33, 1.52, 2.10, 3.10	3.7	0	2.7	6.0	5.8	$CDCl_3$
18b	5.94 (d)	4.72 (d)	4.85 (d)	4.39 (m)	4.10 (m)	1.30, 1.49, 1.97, 2.47	3.6	0	3.0	9.2	3.0	$CDCl_3$
19a (α)	6.42 (d)	5.2–5.5		4.0–4.8		2.12(3), 3.12	3.6					$CDCl_3$
19a (β)	6.20 (s)	5.31 (d)	5.19 (q)	4.80 (m)	4.38 (t)	2.12, 2.14, 2.17, 3.21	0	1.2	5.0			$CDCl_3$
19b (α)[b]	6.36 (d)	4.7–5.4		~4.6	~4.3	1.94, 2.05, 2.06	3.9					$CDCl_3$
19b (β)[b]	6.06 (s)	4.7–5.4		~4.6	~4.3	2.17, 2.47	0					$CDCl_3$

	chemical shifts, δ							coupling, Hz				
compd	H-1′	H-2′	H-3′	H-4′	H-5′	Me	H-6	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	solvent
15	5.92 (s)	5.35 (s)	5.33 (s)	4.4–4.7		2.11, 2.13, 3.29, 3.75	8.08 (d)					Me_2SO-d_6
16	5.70 (s)		5.04 (d)	4.4–4.6		3.31, 3.74	7.93 (d)	0				Me_2SO-d_6
20a (R = H)	6.06 (s)	5.43 (s)	5.07 (d)	4.58 (m)	4.58 (m)	2.14, 2.20, 2.23, 3.27	8.00 (d)	0	0			$CDCl_3$
20a (R = F)	6.00 (s)	5.26 (s)	5.04 (m)	4.5–4.6		2.18, 2.18, 3.20	7.69 (d)[c]	0	0			$CDCl_3$
20b (R = H)	5.96 (s)	5.12 (s)	5.12 (s)	4.4–4.6		2.10(2), 2.29, 2.40	7.88 (d)					$CDCl_3$
20b (R = F)	5.89 (t)	5.08 (t)	5.01 (t)	4.3–4.6		2.11(2), 2.44	7.55[d]	1.4	1.2	1.5		$CDCl_3$
21a (R = H)	5.67 (s)	4.39 (d)	4.98 (q)	4.48 (q)	3.79 (d)	3.27	7.92 (d)	0	0.5	1.1	5.4	Me_2SO-d_6
21a (R = F)	5.68 (t)	4.35 (t)	4.97 (q)	4.37 (q)	3.78 (q)	3.27	8.01 (d)[e]	1.3	1.3	2.5	5.2	Me_2SO-d_6
21b (R = H)	5.54 (s)	4.18 (s)	4.90 (d)	4.44 (g)	3.66 (m)	2.45	7.86 (d)	0	0	5.2	9.1	Me_2SO-d_6
21b (R = F)	5.57 (s)	4.25 (d)	4.91 (q)	4.39 (q)	3.66 (d)	2.44	8.09 (d)[f]	0	2.1	5.0	8.8	Me_2SO-d_6

[a] Signals (in parentheses) are expressed as s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Values given for coupling constants are first order. [b] Compound **19b** is a mixture of anomers. [c] $J_{6,5\text{-F}} = 6.4$ Hz. [d] $J_{1',5\text{-F}} = 1.5$; $J_{6,5\text{-F}} = 6.4$ Hz. [e] $J_{1',5\text{-F}} = 1.3$; $J_{6,5\text{-F}} = 7.0$ Hz. [f] $J_{6,5\text{-F}} = 7.1$ Hz.

formed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Eagle Harbor, Mich. ^{1}H NMR spectra were recorded on a JEOL PFT-100 spectrometer using Me_4Si as the internal standard for organic solvents and $Me_3Si(CH_2)_3SO_3Na$ for D_2O.

3-Bromo-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5b). To a solution of compound **4**[25] (26.0 g, 0.01 mol) and CBr_4 (43.5 g, 0.13 mol) in dry pyridine (500 mL) was added Ph_3P (52.5 g, 0.2 mol). The mixture was refluxed for 2 h and then evaporated in vacuo. The residue was triturated with a 5:1 mixture of petroleum ether (bp 30–60 °C) and C_6H_6 (500 mL), and insoluble Ph_3PO was removed by filtration. The filtrate was evaporated in vacuo, and the residue was placed on a column of silica gel G60 and eluted with a mixture of C_6H_6–Et_2O (9:1) to give 18 g (56%) of the product as a pale yellow syrup.

3-Deoxy-3-iodo-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5c). CH_3I (75 mL) was added dropwise to a solution of **4** (24 g, 0.092 mol), Ph_3P (120 g, 0.46 mol), and $(NCO_2Et)_2$ (80 g, 0.56 mol) in C_6H_6 (500 mL), and the mixture was heated under reflux for 15 h. The solvent was removed by evaporation in vacuo, and the residue was triturated with Et_2O (1 L). Insoluble Ph_3PO was removed by filtration, and the filtrate was chromatographed on a silica gel G60 column using petroleum ether (bp 30–60 °C) and EtOAc (7:3) as the eluent. Compound **5c** (31 g, 90%) was obtained as a pale yellow syrup.

3-Deoxy-3-halogeno-1,2-*O*-isopropylidene-α-D-glucofuranose (6). Compound **5b** (24 g, 0.074 mol) was dissolved in MeOH (300 mL) and 0.8% H_2SO_4 (100 mL). The mixture was stirred at room temperature for 24 h and then neutralized with $BaCO_3$. The mixture was boiled for 10 min and filtered, and the filtrate was evaporated in vacuo. The residue was purified by chromatography on a silica gel G60 column using C_6H_6–EtOH (9:1) as the eluent to give 20 g (95%) of **6b** as a pale yellow syrup.

Compounds **6a** and **6c** were also obtained from the corresponding diisopropylidene derivatives (**5a** and **5c**) in a similar manner (see Table II).

3-Deoxy-3-halogeno-1,2-*O*-isopropylidene-α-D-xylofuranose (8). To a solution of **6b** (20 g, 0.07 mol) was added dropwise a solution of $NaIO_4$ (17 g, 0.08 mol), and the mixture was stirred at room temperature. After 15 h, the mixture was filtered and the filtrate evaporated to dryness in vacuo. The residue was triturated several times with Me_2CO to remove inorganic materials. Upon evaporation of the Me_2CO, compound **7b** (18 g, 100%) was obtained as a pale yellow syrup.

Without further purification this syrup was dissolved in EtOH (400 mL), and $NaBH_4$ (4 g, 0.11 mol) was added portionwise to the stirred solution. After 15 h, the solution was neutralized with Dowex 50 (H^+), filtered from the resin, and evaporated to dryness in vacuo to give 14 g (79%) of compound **8b** which was sufficiently pure (^{1}H NMR) to be used directly in the next step.

In a similar manner, the chloro (**8a**) and the iodo (**8c**) analogues were also prepared in good yields.

5-*O*-Acetyl-3-deoxy-3-halogeno-1,2-*O*-isopropylidene-α-D-xylofuranose (9). Compound **8b** (14 g, 0.06 mol) was dissolved in pyridine (130 mL) and Ac_2O (15 mL) was added. After 15 h at room temperature, the mixture was diluted with EtOH (200 mL), and the solvent was removed in vacuo. The residue was partitioned between H_2O and CH_2Cl_2 (300 mL each), and the organic layer was washed with H_2O (3 × 300 mL), dried (Na_2SO_4), and evaporated to dryness in vacuo to give **9b** (16 g, quantitative) as a pale yellow syrup.

The chloro and iodo analogues (**9a** and **9c**) were prepared in a similar manner from **8a** and **8c**, respectively.

1,2,5-Tri-*O*-acetyl-3-deoxy-3-halogeno-D-xylofuranose (10). To a solution of **9b** (16 g, 0.054 mol) in a mixture of AcOH (190 mL) and Ac_2O (20 mL) was added dropwise concentrated H_2SO_4 (20 mL) while cooling with ice. The mixture was stirred for 3 days, then poured onto iced H_2O (1 L), and extracted with $CHCl_3$ (3 × 700 mL), and the combined $CHCl_3$ extracts were washed with saturated $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated to dryness to give **10b** (13 g, 70%) as a pale yellow syrup.

Acetolysis of **9a** and **9c** in a similar manner afforded the

(25) Baker, D. C.; Horton, D.; Tindall, C. G. *Carbohydr. Res.* **1972**, *24*, 192.

corresponding triacetates **10a** and **10c**.

1-(2,5-Di-*O*-acetyl-3-chloro-3-deoxy-β-D-xylofuranosyl)cytosine (11a, R = H). To a stirred solution of **10a** (6.5 g, 0.02 mol) and crude bis(trimethylsilyl)-N^4-acetylcytosine (prepared from 3.8 g, 0.027 mol, of N^4-acetylcytosine) in CH_2ClCH_2Cl (55 mL) was added 6 mL of $SnCl_4$, and the mixture was stirred at room temperature for 24 h. The mixture was poured onto saturated $NaHCO_3$ (400 mL) and filtered through a Celite pad which was thoroughly washed with CH_2Cl_2 (600 mL). The organic layer was washed with H_2O (200 mL), dried (Na_2SO_4), and then evaporated in vacuo to 5.5 g of a syrup which solidified while standing overnight at room temperature. The solid was triturated with Et_2O and filtered. TLC (silica gel GF_{254}, $CHCl_3$–MeOH, 10:1) showed that the solid contained a small amount of faster running impurities which were removed by chromatography on a silica gel G60 column using $CHCl_3$–MeOH (30:1) as the eluent. The major product **11a** (R = H) (1.5 g) was obtained after recrystallization from EtOH.

Protected nucleosides **11b** (R = F), **11a** (R = F), and **11c** (R = H and R = F) were also obtained in a similar manner by condensation of the corresponding 3-halogenoxylofuranose triacetate (**10**) and the trimethylsilyl derivatives prepared from N^4-acetylcytosine and 5-fluorocytosine.

1-(3-Chloro-3-deoxy-β-D-xylofuranosyl)cytosine Hydrochloride (12a, R = H). Compound **11a** (R = H) (1.4 g) was dissolved in saturated HCl–MeOH (25 mL). After 24 h at room temperature, the solvent was removed in vacuo, and the residue was coevaporated several times with Et_2O until solidification occurred. The solid was triturated with Me_2CO and filtered to give 1.0 g of **12a**.

Similarly, treatment of **11a** (R = F), **11b** (R = F), and **11c** (R = H and R = F) with HCl–MeOH afforded the corresponding free nucleoside HCl salts **12a** (R = F), **12b** (R = F), and **12c** (R = H and R = F) (see Table II).

1-[2-*O*-Acetyl-3-*O*-mesyl-5-*O*-(methoxycarbonyl)-β-D-xylofuranosyl]-N^4-acetylcytosine (15). A solution of 1,2-di-*O*-acetyl-3-*O*-mesyl-5-*O*-(methoxycarbonyl)-D-xylofuranose[26] (**14**; 54 g, 0.146 mol) in CH_2Cl_2 (250 mL) was cooled in an ice bath and HBr bubbled through to saturation. The mixture was stirred at room temperature for 1 h and then evaporated in vacuo. The residue was azetropically dried with C_6H_6 (2 × 150 mL) and then dissolved in MeCN (175 mL).

To the above solution was added crude bis(trimethylsilyl)-N^4-acetylcytosine (prepared from 28 g, 0.18 mol, of N^4-acetylcytosine) dissolved in MeCN (70 mL), and the mixture was stirred for 2 days at room temperature. The solvent was removed in vacuo, the residue was triturated with MeOH (2 × 600 mL) and filtered, and the combined filtrates were evaporated in vacuo. The residue was dissolved in $CHCl_3$ (1 L), washed with H_2O (3 × 300 mL), dried (Na_2SO_4), and evaporated to a syrup, which was crystallized from *i*-PrOH. Recrystallization from $CHCl_3$–MeOH gave 14.1 g of analytically pure **15**.

1-[3-*O*-Mesyl-5-*O*-(methoxycarbonyl)-β-D-xylofuranosyl]cytosine Hydrochloride (16). A mixture of **15** (1.0 g) in 1% HCl–MeOH (25 mL) was stirred for 6 days at room temperature. The solvent was removed in vacuo, and the residue was crystallized from *i*-PrOH to afford 693 mg of the deacetylated product.

1,2-*O*-Isopropylidene-3-*O*-mesyl-α-D-xylofuranose (17a). To a solution of 1,2-*O*-isopropylidene-3-*O*-mesyl-5-*O*-(methoxycarbonyl)-α-D-xylofuranose[26] (**13**, R′ = Ms; 102 g, 0.31 mol) in MeOH (300 mL) was added small chips of Na metal (ca. 100 mg) with stirring. After 24 h, the mixture was neutralized with Amberlite IRC-50 (H^+). The resin was removed by filtration, and the filtrate was evaporated in vacuo. The residue was crystallized from C_6H_6–*n*-C_7H_{16} to give 80.2 g (96%) of **17a**.

In a similar manner, **17b** was obtained from 1,2-*O*-isopropylidene-5-*O*-(methoxycarbonyl)-3-*O*-tosyl-α-D-xylofuranose[26] in good yield.

5-*O*-Acetyl-1,2-*O*-isopropylidene-3-*O*-mesyl-α-D-xylofuranose (18a). Compound **17a** (77.5 g, 0.24 mol) was dissolved in pyridine (300 mL) and cooled in an ice bath, and Ac_2O (50 mL) was added. The mixture was stirred overnight at room temperature and then evaporated in vacuo. The residue was coevaporated several times with MeOH and then crystallized from *i*-PrOH to afford 86.6 g (92%) of **18a**.

Similarly, compound **18b** was obtained from **17b**.

1,2,5-Tri-*O*-acetyl-3-*O*-mesyl-β-D-xylofuranose (19a). A solution of **17a** (86 g, 0.26 mol) and Ac_2O (40 mL) in HOAc (300 mL) was cooled in an ice bath, and H_2SO_4 (13 mL) was added dropwise to the solution. The mixture was stirred for 24 h at room temperature and then partitioned between iced H_2O (450 mL) and EtOAc (900 mL). The organic layer was washed with H_2O (3 × 300 mL), saturated $NaHCO_3$ (150 mL), and H_2O (300 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was crystallized from MeOH to afford the β anomer of **19a** (49.9 g, 51%). Upon evaporation of the mother liquor of crystallization, 44.8 g of an anomeric mixture of **19a** was obtained as a syrup.

Similar treatment of **18b** afforded an anomeric mixture of **19b** as a syrup.

1-(2,5-Di-*O*-acetyl-3-*O*-mesyl-β-D-xylofuranosyl)-N^4-acetylcytosine (20a, R = H; R″ = Ac). Compound **19a** (30.0 g, 0.08 mol) was dissolved in CH_2Cl_2 (200 mL) and cooled in an ice bath. HBr was bubbled through the solution for 30 min, and the mixture was kept at room temperature for 1 h. Excess HBr and the solvent were evaporated in vacuo, and the traces of HBr were removed by azeotropical distillation with toluene (2 × 50 mL). The residue was dissolved in dry MeCN (100 mL).

To the above solution was added a solution of bis(trimethylsilyl)-N^4-acetylcytosine (prepared from 20.7 g, 0.14 mol, of N^4-acetylcytosine) in MeCN (50 mL). The mixture was stirred for 2 days at room temperature and then evaporated in vacuo to a syrup. The residue was dissolved in $CHCl_3$ (500 mL), and then MeOH (50 mL) was added slowly and stirred. After stirring for 30 min, the mixture was filtered through a Celite pad. The filtrate was washed with H_2O (2 × 200 mL) and saturated $NaHCO_3$ (200 mL), dried (Na_2SO_4), and evaporated to dryness in vacuo. The residue was crystallized from MeOH (400 mL) to afford 12.5 g (31%) of **20a** (R = H, R″ = Ac).

In a similar manner **20a** (R = F, R″ = H), **20b** (R = H, R″ = Ac), and **20b** (R = F, R″ = H) were prepared by condensation of the corresponding 3-sulfonylxylosyl bromides and silylated pyrimidines (see Table II).

1-(3-*O*-Mesyl-β-D-xylofuranosyl)cytosine Hydrochloride (21a, R = H). To a suspension of **20a** (R = H, R″ = Ac; 6.0 g, 0.014 mol) in MeOH (100 mL) was added 25 mL of MeOH saturated with HCl. The mixture was stirred overnight, and then the clear solution was evaporated in vacuo. The residue was crystallized from EtOH to afford 4.5 g (91%) of **21a** (R = H).

Similarly, unprotected nucleosides **21a** (R = F), **21b** (R = H), and **21b** (R = F) were obtained as their HCl salts by treatment of the corresponding protected nucleosides (**20**) with HCl–MeOH (see Table II).

Conversion of 12 into *ara*-C. Semiquantitative Kinetic Studies. Compound **12a** (6.25 mg), **12b** (6.8 mg), or **12c** (7.6 mg) (0.02 mM each) and $NaHCO_3$ (15 mg) were dissolved in D_2O (0.5 mL). The reaction was followed by ^1H NMR spectroscopy. No reaction was observed for **12a** during the course of 7 days. Compounds **12b** and **12c** were slowly converted into a mixture of AAC and *ara*-C [H-6 of AAC appeared as a doublet at δ 8.12 ($J_{5,6}$ = 7.3 Hz) and H-6 of *ara*-C appeared at δ 7.79 ($J_{5,6}$ = 7.6 Hz)]. After 7 days, 68% of **12b** was converted into a 1:2 mixture of AAC and *ara*-C, whereas 51% of **12c** was converted into a 2:3 mixture of AAC and *ara*-C.

(26) Anderson, C. D.; Goodman, L.; Baker, B. R. *J. Am. Chem. Soc.* **1958**, *80*, 5247.