Table IV. Electrophoretic and Chromatographic Mobilities of Products and Standard Specimens (Electrophoresis in E_1 and TLC System S_6)

compd	electrophoretic mobility[a]	R_f
Cp	1.00	0.41
A	2.73	0.69
C-C-A (16a)	1.85	0.20
C-C-A(Z-Gly) (16d)	1.53	0.71
C-C-A-Gly (16g)	2.45	0.25
C-C-A(Z-Ala) (16c)	1.32	0.68
C-C-A-Ala (16f)	2.20	0.23
C-C-A(Z-Phe) (16b)	1.12	0.75
C-C-A-Phe (16e)	2.05	0.45

[a] Relative mobility toward cathode; mobility of Cp = 1.00.

desired intermediate products range between 35% and 50%.

(b) Removal of 2-Chlorophenyl Groups from Phosphorus with F^-. The protected derivative from the previous experiment (approximately 0.01 mmol) was dissolved in 0.05 M tetrabutylammonium fluoride in a mixture of tetrahydrofuran–pyridine–water (1.2 mL, 3 equiv, 8:1:1 v/v/v) and allowed to stand for 6 h at room temperature. After this time, TLC in systems S_5 and S_4 indicated essentially quantitative conversion of the starting triester to diester. The solution was evaporated in vacuo and the residue partitioned between methylene chloride and water. The organic layer was washed with water (3×) and back-extracted with ethyl acetate (2×), and the combined organic layers were dried with sodium sulfate and evaporated in vacuo. The residue was directly used in the next step without further purification.

(c) Removal of the Methoxytetrahydropyranyl and Methoxytrityl Groups in Acidic Medium. The residue from the previous step was dissolved in a mixture of 0.1 N HCl and dioxane (5 mL, 1:1 v/v), and the reaction mixture was allowed to stand at room temperature for 16 h. The workup of the reaction was as described above for the synthesis of C-C-A(Z-Gly) (**16d**). The yields of chromatographically and electrophoretically uniform compounds **16b** and **16f** were in the 15–20% range in three consecutive deblocking steps. For C-C-A(Z-Phe) (**16b**): UV (0.01 N HCl) λ_{max} 269 nm; $A(250/260) = 0.76$, $A(280/260) = 0.96$, $A(290/260) = 0.66$. For C-C-A(Z-Ala) (**16c**): UV (0.01 N HCl) λ_{max} 269 nm; $A(250/260) = 0.76$, $A(280/260) = 1.04$, $A(290/260) = 0.69$.

2′(3′)-*O*-Aminoacyl Derivatives of Cytidylyl(3′–5′)cytidylyl(3′–5′)adenosine (16e–g). The *N*-benzyloxycarbonyl derivatives **16b–d** (10–20 μmol) were hydrogenated as described previously,[5] with the exception that the reaction time was approximately 2–3 h (until TLC in system S_6 showed quantitative conversion to the slower moving aminoacyl derivative). The products were further purified (for the purpose of biochemical investigations) by preparative electrophoresis in system E_1. For the characterization of the final products, see Tables III and IV. The compounds **16e–g** were quantitatively hydrolyzed during paper chromatography in system S_9 to C-C-A and the corresponding amino acid.

Acknowledgment. The expert technical assistance of M. L. Wejrowski and G. Butke in the synthesis of nucleoside intermediates is gratefully acknowledged. We are further indebted to Dr. D. P. Lin, S. Grunfeld and W. Wittbold (Wayne State University) for their measurement of NMR spectra.

Registry No. 1a (isomer 1), 80185-90-6; **1a** (isomer 2), 80185-91-7; **1b** (isomer 1), 80226-97-7; **1b** (isomer 2), 80226-98-8; **1b** 5′-(α,α-dimethoxybenzyl) ether, 80185-92-8; **2a** (2′-isomer), 6554-16-1; **2a** (3′-isomer), 6554-17-2; **2b** (2′-isomer), 80185-93-9; **2b** (3′-isomer), 80185-94-0; **2c** (2′-isomer), 80185-95-1; **2c** (3′-isomer), 80185-96-2; **3a**, 77451-35-5; **3b**, 80185-97-3; **3c** (2′-isomer), 80185-98-4; **3c** (3′-isomer), 72677-41-9; **4** triethylammonium salt, 80186-00-1; **5**, 3250-02-0; **6a**, 55697-22-8; **6b**, 33485-36-8; **7**, 80186-01-2; **8a**, 80186-02-3; **8b**, 80186-03-4; **8c**, 80186-04-5; **8d**, 80186-05-6; **8g**, 80186-06-7; **9a**, 80186-07-8; **9b**, 78272-39-6; **10a**, 3309-58-8; **10b** (isomer 1), 80226-99-9; **10b** (isomer 2), 80227-00-5; **11a** (isomer 1), 80186-08-9; **11a** (isomer 2), 80227-01-6; **11b** triethylammonium salt, 80206-09-3; **12**, 80206-10-6; **13a**, 78272-40-9; **13a** N^4,N^4,N^6-tridebenzoyl, 80186-09-0; **13a** N^4,N^4,N^6-tridebenzoyl, bis(de-2-chlorophenyl), 80186-10-3; **13b**, 80186-11-4; **13b** N^4,N^4,N^6-tridebenzoyl, 80206-11-7; **13b** N^4,N^4,N^6-tridebenzoyl, bis(de-2-chlorophenyl), 80186-12-5; **14**, 80186-13-6; **15**, 2536-99-4; **16a**, 2866-39-9; **16b** 2′-isomer, 80186-14-7; **16b** 3′-isomer, 78280-90-7; **16c** 2′-isomer, 80186-15-8; **16c** 3′-isomer, 80186-16-9; **16d** 2′-isomer, 80186-17-0; **16d** 3′-isomer, 78280-88-3; **16e** 2′-isomer, 80186-18-1; **16e** 3′-isomer, 78280-91-8; **16f** 2′-isomer, 80186-19-2; **16f** 3′-isomer, 80186-20-5; **16g** 2′-isomer, 80186-21-6; **16g** 3′-isomer, 78280-89-4; adenosine, 58-61-7; methyl orthobenzoate, 707-07-3; 4-methoxy-5,6-dihydro-2*H*-pyran, 17327-22-9; 2′,3′,-*O*-isopropylideneadenosine, 362-75-4; 3′,5′-di-*O*-acetyladenosine, 6554-24-1; 2′-*O*-(4-methoxytetrahydropyran-4-yl)adenosine, 28219-91-2; levulinic acid, 123-76-2; *N*-(benzyloxycarbonyl)-L-phenylalanine, 1161-13-3; *N*-(benzoyloxycarbonyl)-L-alanine, 1142-20-7; cytidine, 65-46-3.

Alkoxyl Migration in Displacement of a 5-Trifluoromethanesulfonyloxy Group from Ribofuranosides[1a]

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Methyl 2,3-*O*-isopropylidene-5-*O*-triflyl-β-D-ribofuranoside (**2**) reacts at room temperature with primary aralkanols such as benzyl alcohol and the steroid alcohols **3a,b** in dichloromethane and in the presence of sodium sulfate to give the corresponding aralkyl 2,3-*O*-isopropylidene-5-*O*-methyl-β-D-ribofuranosides **5a,b** and **11** in 40–45% yields. Migration of the methoxyl group from C-1 to C-5, via a tricyclic oxonium ion (**7a**), is suggested as the basis of formation of the new β-glycoside. Anchimeric assistance by a benzyloxy group in the displacement of the sulfonate is observed in the reaction of benzyl 2,3-*O*-isopropylidene-5-*O*-triflyl-β-D-ribofuranoside (**14**) with methanol, which affords methyl 5-*O*-benzyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (**15**) in 40% yield on treatment with Na_2SO_4 in CH_2Cl_2. The elements of anomeric control in these facile transformations remain to be elaborated.

Trifluoromethanesulfonate (triflate) esters are exceedingly useful substrates in nucleophilic substitution reactions because of their high level of reactivity and ready accessibility.[2] These considerations have attracted interest

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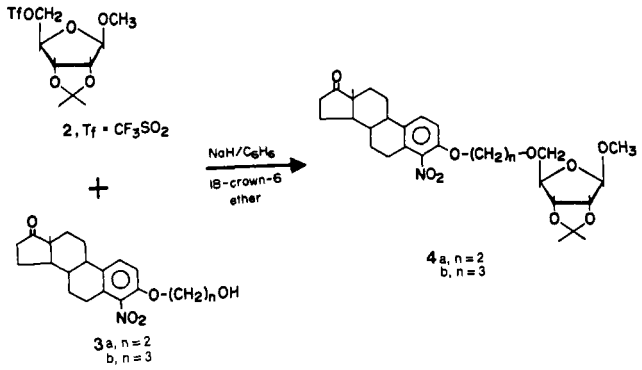
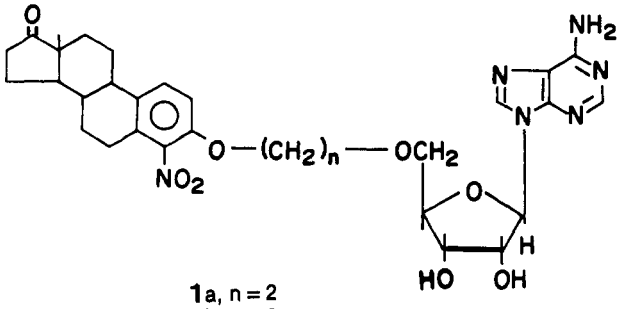
Scheme I



in carbohydrate chemistry (inter alia) where the advantages of this exceptionally good leaving group have provided the basis of (i) a convenient synthesis of deoxyhalogeno sugars,[3] (ii) highly stereoselective syntheses of β- or α-glycosides and disaccharides,[4,5] and (iii) the preparation of benzyl ether derivatives of appropriately protected carbohydrates.[6,7]

The alkylation (etherification) of sugar triflates has been the subject of study in our laboratory in connection with the design of a feasible synthetic approach to nucleosides, which are bridged at the 5′-*O*-position to steroidal hormones through ring-A oxygen (at 3) via carbon chains of varying length as exemplified by 1. The requisite nu-

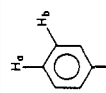


1a, n = 2
b, n = 3

cleoside precursors in one series, **4a,b** have now been obtained by the reaction of methyl 2,3-*O*-isopropylidene-5-*O*-triflyl-β-D-ribofuranoside (**2**) with the 4-nitroestrone 3-*O*-(ω-hydroxyalkyl) ethers **3a,b** in benzene and in the presence of sodium hydride[8] (Scheme I).

Alkyl triflates react at ambient temperature with alcohols of low nucleophilicity in chlorinated solvents and in the presence of an (heterogeneous) acid scavenger such as

Table I. 100-MHz Proton Magnetic Resonance Spectra[a]

	shift, ppm							
compd	 H_1	H_2	H_3	H_4	H_5	OCH_3	CH_3CCH_3	others
4a	7.32, 6.87	4.95 (s)	4.66 (d)	4.57 (d)	4.29 (t)	3.44 (d)	3.32 (s)	1.47 (s), 1.32 (s)	4.06 (t, 2, $C_6H_5OCH_2CH_2$), 3.63 (t, 2, $C_6H_5OCH_2CH_2O$), 0.91 (s, 3, $C_{18}CH_3$), 1.60–2.35 (m, 15)
4b	7.32, 6.87	4.98 (s)	4.62 (d)	4.54 (d)	4.29 (t)	3.33 (d)	3.28 (s)	1.46 (s), 1.27 (s)	4.14 (t, 2, $C_6H_5OCH_2CH_2CH_2O$), 3.63 (t, 2, $C_6H_5OCH_2CH_2CH_2O$), 0.90 (s, 3, $C_{18}CH_3$), 1.94–2.77 (m, 17)
5a	7.34, 6.86	5.09 (s)	4.59 (d)	4.50 (d)	4.31 (t)	3.41 (d)	3.36 (s)	1.47 (s), 1.31 (s)	4.13 (t, 2, $C_6H_5OCH_2CH_2O$), 3.67 (t, 2, $C_6H_5OCH_2CH_2O$), 0.91 (s, 3, $C_{18}CH_3$), 1.59–2.78 (m, 15)
5b	7.28, 6.83	5.04 (s)	4.66 (d)	4.56 (d)	4.31 (t)	3.38 (d)	3.30 (s)	1.48 (s), 1.31 (s)	4.07 (t, 2, $C_6H_5OCH_2CH_2CH_2O$), 3.62 (t, 2, $C_6H_5OCH_2CH_2CH_2O$), 0.92 (s, 3, $C_{18}CH_3$), 1.94–2.77 (m, 17)

[a] Chemical shifts in parts per million from Me_4Si in $CDCl_3$.

(1) (a) This work was supported in part by a grant from the U. S. Public Health Service (CA-23079) and an institutional grant to the Michigan Cancer Foundation from the United Foundation of Greater Detroit. Iyer, V. K.; Horwitz, J. P. Presented in part to the Division of Carbohydrate Chemistry at the 182nd National Meeting of the American Chemical Society, Aug 23–28, 1981, New York; Abstract CARB 20. (b) To whom all requests for reprints should be addressed at the Michigan Cancer Foundation, 110 E. Warren Avenue, Detroit, MI 48201.

(2) For a review of this subject with pertinent references, see: Howells, R. D. *Chem. Rev.* **1977**, *77*, 69–92.

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(5) Schmidt, R. R.; Moering, V.; Reichrath, M. *Tetrahedron Lett.* **1980**, 3565–3568.

(6) Lemieux, R. U.; Kondo, T. *Carbohydr. Res.* **1974**, *35*, C4–C6.

(7) Berry, J. M.; Hall, L. D. *Carbohydr. Res.* **1976**, *47*, 307–310.

(8) Iyer, V. K.; Corombos, J. D.; Zemlicka, J.; Rozhin, J.; Brooks, S. C.; Horwitz, J. P. Presented in part to the Division of Medicinal Chemistry at the 182nd National Meeting of the American Chemical Society, New York, Aug 23–28, 1981; Abstract MEDI 74.

Scheme II

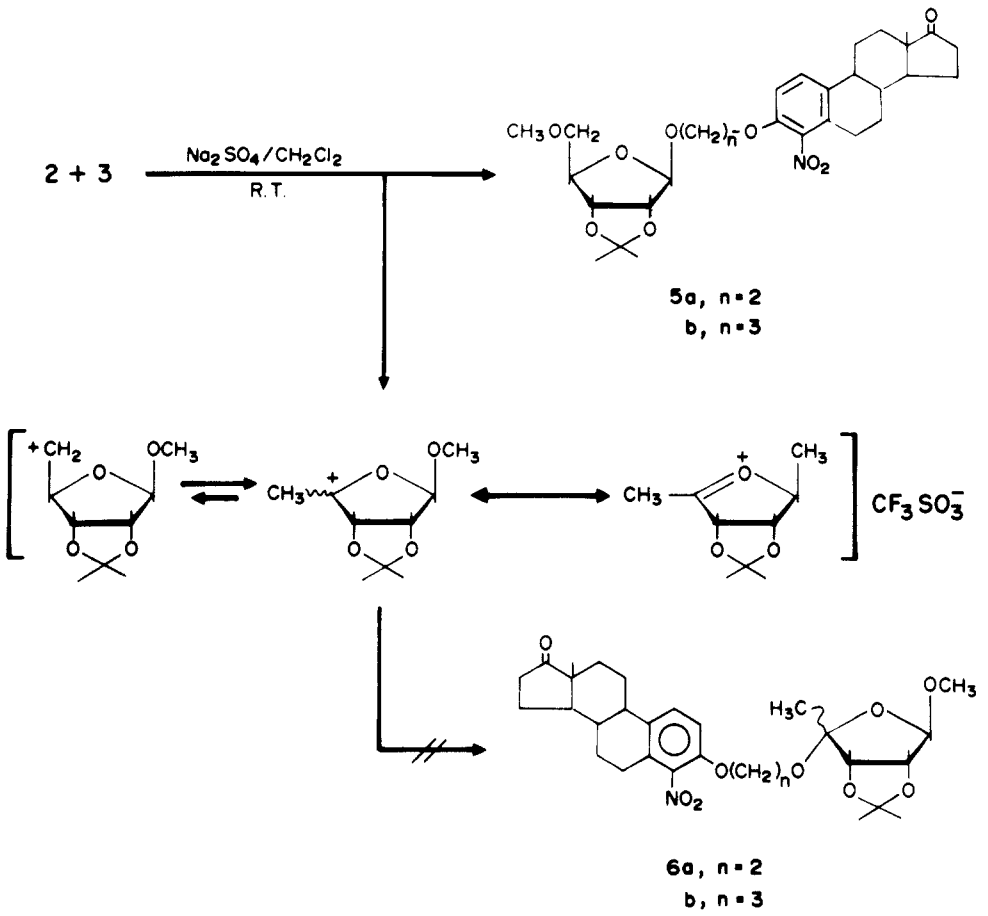


Table II. 100-MHz ^{13}C NMR Spectral Data[a]

compd	shift, ppm								
	C_1	C_2	C_3	C_4	C_5	CH_3O	O-C-O	*endo*-CH_3	*exo*-CH_3
4a	109.22	84.89	82.13	85.12	75.76	54.70	112.39	24.98	26.44
4b	109.37	85.00	82.07	85.19	75.79	54.83	112.33	25.00	26.46
5a	108.44	85.24	82.07	85.34	73.40	65.60	112.41	25.00	26.46
5b	108.25	84.90	82.17	85.29	73.50	66.14	112.44	25.00	26.51
11	107.29	85.18	82.14	85.36	73.66	59.03	112.44	24.92	26.44
13	109.93	85.77	81.49	88.28	63.94	55.40	112.09	24.75	26.38
15	109.34	85.18	82.20	73.25[b]	71.14[b]	54.76	112.38	25.04	26.50

[a] Chemical shifts in parts per million from Me_4Si in $CDCl_3$. [b] Assignment uncertain.

potassium carbonate and sodium sulfate to form ethers in acceptable yields.[9] Extension of this displacement reaction to the triflate group of **2** by the steroid-alcohol **3a** in Na_2SO_4/CH_2Cl_2 provided a mixture of three products after 72 h. The principal component (**5a**, Scheme II), which was isolated as a colorless foam (43% yield) following preparative TLC, afforded an ^1H NMR spectrum that showed slight but nonetheless significant differences in chemical shifts (see Table I) from those assigned to the anomeric and methyl glycoside protons, respectively, of **4a**. A disparity was also evident in carbon chemical shifts of the methyl glycoside substituents in the completely proton-decoupled ^{13}C NMR spectra (Table II) which, otherwise, showed essentially invariant shifts for the ribosyl and isopropylidene carbon atoms. Elemental analysis established that **4a** and **5a** were, indeed, isomeric.

The attempted removal of the isopropylidene group from **5a** with either 90% trifluoroacetic acid or 1% HCl in methanol at room temperature or 80% acetic acid at reflux led in each instance, instead, to the isolation of the precursor alcohol **3a**. The same phenomenon was observed in the attempted acid-catalyzed deblocking of the principal product (**5b**) of homologous alkylation of **2** with the 3′-hydroxypropyl ether **3b** (n = 3) carried out in Na_2SO_4–CH_2Cl_2. The homologue, isolated again as a foam in 45% yield, gave an elemental analysis compatible with **4b**; however, limited discrepancies, similar to those noted above in both the ^1H and ^{13}C NMR spectra of **5a**, were evident with **5b** (cf. Tables I and II). Indeed, the spectral, analytical, and chemical data derived with **5a,b** were indicative of corresponding positional isomers of **4**.

In this connection, it has been reported that pentyl triflate and 2,2-dinitropropanol react in refluxing 1,2-dichloroethane with Na_2SO_4 as an acid scavenger to give a mixture of 1-, 2-, and 3-pentyl ethers.[9] Apparently the alkylation, in the presence of Na_2SO_4, has the characteristics of a carbonium ion reaction,[9] despite a relatively nonpolar solvent. These considerations raised the possibility that the etherifications of **2** had occurred at C-4 to generate methyl 4-(arylalkoxy)-5-deoxyribofuranosides **6a,b**. The formation of the latter can be achieved, in

(9) Beard, C. D.; Baum, K.; Grakauskes, V. *J. Org. Chem.* **1973**, *38*, 3673–3677.

Table III. 100-MHz Proton Magnetic Resonance Spectral Data[a]

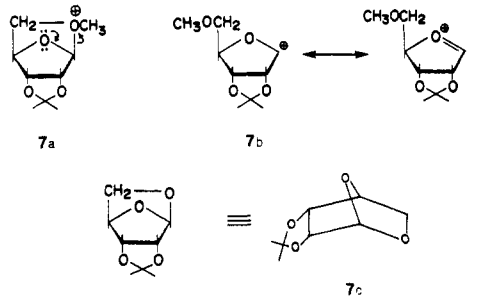
compd	shift, ppm								
	C_6H_5	H_1	H_2	H_3	H_4	H_5	OCH_3	CH_3CCH_3	others
11	7.30 (s)	5.15 (s)	4.76 (d)	4.49 (d)	4.36 (t)	3.42 (d)	3.34 (s)	1.46 (s), 1.29 (s)	4.66 (s, 2, $C_6H_5CH_2O$)
12	7.33 (s)	5.18 (s)	4.84 (d)	4.65 (d)	4.51 (t)	3.67 (m)		1.48 (s), 1.31 (s)	4.63 (s, 2, $C_6H_5CH_2O$), 3.15 (m, 1, OH)
13		5.00 (s)	4.85 (d)	4.71 (d)	4.41 (t)	3.67 (m)	3.44 (s)	1.48 (s), 1.32 (s)	
15	7.31 (s)	4.95 (s)	4.68 (d)	4.56 (d)	4.40 (t)	3.43 (d)	3.27 (s)	1.47 (s), 1.30 (s)	4.53 (s, 2, $C_6H_5CH_2O$)

[a] Chemical shifts in parts per million from Me_4Si in $CDCl_3$.

principle, through the generation of a methylcarbonium–methyloxonium ion pair (cf. Scheme II) which, conceptually, parallels the synthetic strategies for the introduction of a methoxyl substituent into nucleosides from 4′,5′-*exo*-methylene precursors.[10-14]

However, ^1H and ^{13}C NMR spectra failed to disclose the requisite (additional) methyl substituent in either **6a** or **6b**. Of equal significance is the fact that the product (**5b**) derived from **3b** showed a ^1H NMR signal at 4.33 ppm as a sharp triplet, which is consistent with an H-4′ resonance coupled to H-5′ and H-5″. Moreover, the triplet collapsed to a singlet on irradiation of an upfield (2 H) multiplet centered at 3.20 ppm, which confirms the presence of intact C-5 protons and, thereby, precludes structures **6a** or **6b**.

Structural assignments that derive from an alternative mechanistic hypothesis, which considers the carbocationic characteristics ascribed to the alkylation[9] and, more importantly, which is consistent with the chemical and spectral evidence, involves neighboring methoxyl participation in the displacement of the triflyl group from **2**. Migration of the methoxyl group from C-1 to C-5, via the tricyclic oxonium ion **7a** and synchronous or subsequent

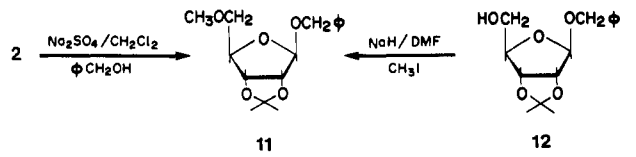


7a **7b** **7c**

stereoselective formation of a new β-glycoside bond with **3**, led to structures **5a** and **5b**, respectively, which were tentatively assigned to the principal products of neutral alkylation.

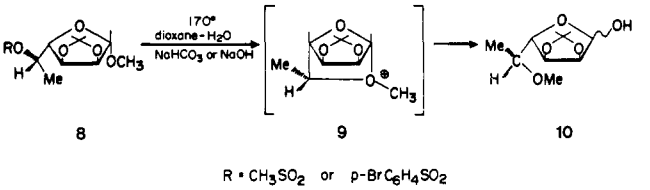
An analogous tricyclic ion (**9**), which, likewise, proceeds from methoxyl participation in the displacement of a sulfonyloxy group, was proposed[15] to explain the formation of 6-deoxy-2,3-*O*-isopropylidene-5-*O*-methyl-D-talofuranose (**10**) in the solvolysis of methyl 5-*O*-[(*p*-bromophenyl)-sulfonyl]-6-deoxy-2,3-*O*-isopropylidene-β-L-allofuranoside

Scheme III



11 **12**

(8) in dioxane–water (9:1) when heated to 170 °C in the presence of sodium bicarbonate or sodium hydroxide.



8 **9** **10**

R = CH_3SO_2 or *p*-$BrC_6H_4SO_2$

The ready occurrence of methoxyl migration in **2**, under relatively mild conditions, was further indicated in the reaction of **2** with benzyl alcohol. The major product, obtained in 40% yield following preparative TLC, gave ^1H NMR spectral and optical rotatory data which were identical with those of an authentic sample of benzyl 5-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (**11**, Scheme III)[16] which, in turn, was obtained by 5-*O*-methylation of **12**.

It was assumed that the reaction mixtures leading to **11** and, as well, **5a,b** included the corresponding α-glycosides. Unfortunately, attempts at further chromatographic resolution of residues, from which the β-glycosides were isolated, failed to yield the α anomers. However, there was obtained from a single reaction mixture which produced **5b** a small amount (~5% yield) of material whose ^1H NMR spectrum was superimposable with that of **4b**. Insufficient compound precluded a more rigorous characterization.

The results of the present study lend credence to the suggestion that the alkylations of triflate esters of primary alcohols in chlorinated alkanes and in the presence of Na_2SO_4 involve carbocation intermediates.[9] Clearly, the tricyclic oxonium ion (**7a**), which bears a close structural relationship to 1,5-anhydro-2,3-*O*-isopropylidene-β-D-ribofuranoside (**7c**)[17,18] is a reasonable precursor of the β-glycosides (**5a,b**) as well as the yet undetected α-glycosides. Though C-1 in **7a** is the more electrophilic site, attack at C-5 is evidently possible (vide supra). There is, however, no a priori reason to assume that the products of methoxyl migration derive solely from **7a**. In fact, the resonance-stabilized carbocation **7b** is certainly an equally plausible precursor of the (glycoside) products of methoxyl

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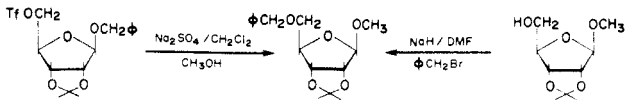
(18) Such structures may also be viewed as the corresponding 1,4-anhydropyranose (see ref 17). In any case, the parent structure of this group of structures is the bicyclic acetal 2,7-dioxabicyclo[2.2.1]heptane (**7c**).

Scheme IV



14 15 13

migration, though the elements of anomeric control by this pathway are unclear.

In the reactions discussed above involving MeO-1 participation, the methoxyl group remain in the molecule. However, among examples of anchimeric assistance by benzyloxy groups reported in the displacement of sulfuryloxy groups, the intermediate oxonium ion breaks down by benzyl oxygen fission (ion pair collapse) to give cyclic products together with products derived from benzyl sulfonic ester.[19] By contrast, benzyl 2,3-*O*-isopropylidene-5-*O*-triflyl-β-D-ribofuranoside (**14**), prepared by triflation of the precursory sugar **12**[16] in the usual manner, reacted with stoichiometric amounts of methanol in Na_2SO_4–CH_2Cl_2 to give methyl 5-*O*-benzyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (**15**) in 40% yield (Scheme IV). The identity of the latter was confirmed by comparison of its ^1H NMR spectrum with that of the product (**15**) obtained from the reaction of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**13**) and benzyl bromide in NaH–DMF (Table III).

These facile rearrangements involving migration of an anomeric alkoxy group in the internal displacement of a 5-triflyl substituent resemble, in certain aspects, the deamination of methyl 5-amino-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-allofuranoside with sodium nitrite in 90% acetic acid.[20] In the latter case, the products of rearrangement are also presumed to involve a tricyclic oxonium ion related to **7a** which, in turn, was suggested by analogy with the solvolysis of **8**.

Apart from the commonality of the intermediate species, the reactions of **2** with a nucleophile in Na_2SO_4–CH_2Cl_2 appear to be distinguished from the related solvolysis transformations by differences in the stereochemistry of the migration origin. However, the apparent distinction requires further elaboration.

Experimental Section

Thin-layer chromatography (TLC) was carried out with precoated silica gel F-254 aluminum foil in the following solvents: S_1, 90% dichloromethane, 10% methanol; S_2, 60% toluene, 40% ethyl acetate. For preparative TLC, 2-mm-thick, 20 × 20 cm precoated, silica gel GF plates (Analtech) were employed. ^1H and ^{13}C NMR spectra were measured with a JEOL FX-100 Fourier transform spectrometer in $CDCl_3$ with $(CH_3)_4Si$ as an internal reference. The data are summarized in Tables I–III. Electron-impact mass spectra were determined with a JEOL JMS-01SG2 spectrometer.

Dichloromethane and pyridine were distilled from phosphorus pentoxide and lithium aluminum hydride, respectively, and stored over 4A molecular sieves.

4-Nitroestrone 3-*O*-(2-Hydroxyethyl) Ether (3a). To a stirred mixture of 4-nitroestrone[21] (0.315 g, 1 mmol) and anhydrous K_2CO_3 (0.140 g, 1 mmol) in 50 mL of dry acetone was added, under reflux, bromoethanol (0.25 g, 1 mmol) with the system protected from moisture. After 19 h of reflux, the reaction mixture was allowed to cool and was then filtered through Celite, and the solvent was removed under reduced pressure. The residue was partitioned between benzene and water (100 mL/20 mL). The organic phase was washed (2 × 20 mL) with 1 N NaOH and then with water and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure yielded a chromatographically homogeneous solid which crystallized from benzene–petroleum ether (60–90 °C) in the form of yellow needles: yield 0.23 g (64%); mp 255–258 °C dec; mass spectrum, *m/e* 359 (M^+), 342 (M^+ – OH).

Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.58; H, 6.98; N, 3.65.

4-Nitroestrone 3-*O*-(3-Hydroxypropyl) Ether (3b). Compound **3b** was prepared by the interaction of 3-bromopropanol and 4-nitroestrone as described for **3a**. The product crystallized as yellow needles: 59% yield; mp 210–213 °C; mass spectrum, *m/e* 373 (M^+), 356 (M^+ – OH). Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.31; H, 7.42; N, 3.51.

β-[(17-Oxo-4-nitroestra-1,3,5(10)-trien-3-yl)oxy]ethyl 2,3-*O*-Isopropylidene-5-*O*-methyl-β-D-ribofuranoside (5a). To a solution of **2** at −5 °C prepared in situ[3] from 0.2 g (1.0 mmol) of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside, 0.36 g (1.26 mmol) of triflic anhydride, and 100 μL of anhydrous pyridine in 10 mL of dichloromethane were added 2.8 g (20 mmol) of anhydrous sodium sulfate and 0.32 g (0.89 mmol) of **3a**. The reaction mixture was stirred for 72 h at room temperature, and the filtered solution was evaporated to dryness at reduced pressure. The residue, on TLC (S_2), showed a major product and two minor constituents, in addition to **5a**. The principal component was isolated as a colorless foam (160 mg, 42% yield) following preparative TLC with solvent system S_2.

Anal. Calcd for $C_{29}H_{39}NO_9$: C, 64.38; H, 7.39; N, 2.50. Found: C, 64.38; H, 7.31; N, 2.41.

γ-[(17-Oxo-4-nitroestra-1,3,5(10)-trien-3-yl)oxy]propyl 2,3-*O*-Isopropylidene-5-*O*-methyl-β-D-ribofuranoside (5b). Compound **5b** was prepared as described above by reaction of **2**, generated from 0.2 g (1.0 mmol) of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside, with 0.32 g (0.86 mmol) of **3b** for 72 h in 10 mL of dichloromethane containing 2.8 g (20 mmol) of sodium sulfate. The product was isolated as a foam, 0.18 g (46% yield).

Anal. Calcd for $C_{30}H_{41}NO_9$: C, 63.83; H, 7.20; N, 2.57. Found: C, 63.61; H, 7.18; N, 2.36.

Benzyl 2,3-*O*-Isopropylidene-5-*O*-methyl-β-D-ribofuranoside (11). To a stirred solution of **2** at −5 °C, prepared in situ[3] from 0.2 g (1.0 mmol) of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside, 0.36 g (1.26 mmol) of triflic anhydride, and 100 μL of anhydrous pyridine in 10 mL of dichloromethane were added 2.8 g (20 mmol) of anhydrous sodium sulfate and benzyl alcohol (130 μL, 1.25 mmol). The reaction was stirred for 72 h at room temperature. The filtered solution was evaporated to dryness at reduced pressure and the oily residue revealed a single major spot on TLC (S_2). The residue, on preparative TLC with the same solvent system, afforded a crystalline solid (0.16 g, 42% yield): mp 36–37 °C; $[\alpha]^{23}_D$ −94.5° (*c* 1.0, pyridine) [lit.[16] mp 34 °C; $[\alpha]^{27}_D$ −100.6° (*c* 1.0, pyridine)].

The preparation of an authentic sample of **11** was as follows. To a solution of **12** (0.28 g, 1 mmol) in 5 mL of dry dimethylformamide was added 96 mg (4 mmol) of a 50% mineral oil emulsion of NaH and the reaction mixture was stirred for 15 min at room temperature. Excess (0.6 mL, 10 mmol) methyl iodide was then introduced with careful exclusion of moisture and the mixture was stirred at ambient temperature for 18 h, at the end of which time TLC (S_2) indicated the completion of the reaction. The mixture was poured into ice–water and the clear solution was extracted (3 × 30 mL) with chloroform. The extract was washed with water and dried (Na_2SO_4), and the filtered solution was evaporated to dryness under reduced pressure. The product (0.27 g, 90% yield) crystallized in the form of colorless needles from aqueous ethanol: mp 35–36 °C; $[\alpha]^{23}_D$ −94.5° (*c* 1, pyridine).

Methyl 2,3-*O*-Isopropylidene-5-*O*-benzyl-β-D-ribofuranoside (15). To a stirred solution of 0.37 g (1.37 mmol) of triflic anhydride in 4 mL of dichloromethane containing 0.11 mL of pyridine, cooled to −5 °C, was added a solution of 0.28 g (1 mmol) of benzyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**12**).

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After 0.5 h, TLC (S_2) indicated quantitative conversion to **14**. Anhydrous sodium sulfate (1.49 g, 10.5 mmol) and dry methanol (50 μL, 1.25 mmol) were added directly, and the mixture was stirred at room temperature for 72 h. The filtered solution was evaporated to dryness at reduced pressure and the oily residue revealed a single major spot on TLC (S_2). The residue, on preparative TLC with the same solvent system, afforded a syrupy oil which was distilled under high vacuum at 150 °C (4×10^{-3} mm) [lit.[22] 120–140 °C (5×10^{-3} mm)]. NMR data shown in Table III are in accord with literature assignments.[23]

The preparation of an authentic sample of **15** was as follows. To a solution of **13** (0.20 g, 1 mmol) in 5 mL of dry dimethylformamide was added 96 mg (4 mmol) of a 50% mineral oil emulsion of NaH and the reaction mixture was stirred for 15 min at room temperature. Freshly distilled benzyl bromide (243 μL, 2 mmol) was then introduced with careful exclusion of moisture. The mixture was stirred at ambient temperature for 18 h, at the end of which time TLC (S_2) indicated the completion of the reaction. The mixture was poured into ice–water and the clear solution was extracted (3 × 30 mL) with chloroform. The extract was washed with water and dried (Na_2SO_4), and the filtered solution was evaporated to dryness under reduced pressure. The product (0.25 g, 85%) was obtained as a colorless syrup. The compound was further purified by preparative TLC (S_2) and the ^1H NMR spectrum of the product was identical with that (**15**) derived via the rearrangement reaction.

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Registry No. **2**, 70209-11-9; **3a**, 80082-66-2; **3b**, 80082-67-3; **4a**, 80082-68-4; **4b**, 80082-69-5; **5a**, 80082-70-8; **5b**, 80082-71-9; **11**, 64018-52-6; **12**, 23276-32-6; **13**, 4099-85-8; **14**, 70209-12-0; **15**, 33019-63-5; 4-nitroestrone, 5976-74-9; bromoethanol, 540-51-2; 3-bromopropanol, 627-18-9.

Thapsigargin and Thapsigargicin, Two Histamine Liberating Sesquiterpene Lactones from *Thapsia garganica*. X-ray Analysis of the 7,11-Epoxide of Thapsigargin

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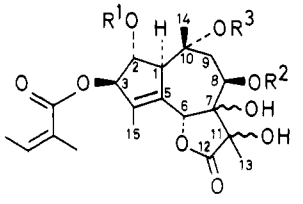
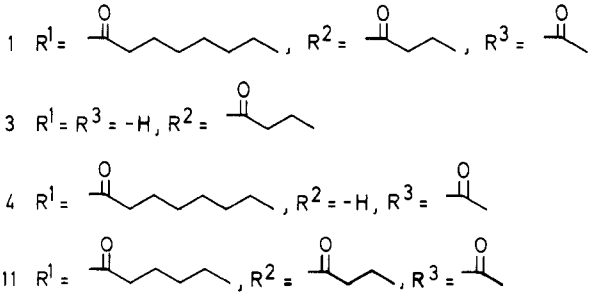
The hydrolysis of thapsigargin (**1**), a very potent histamine-liberating hexaoxygenated 6,7-guaianolide isolated from *Thapsia garganica* L., has been investigated. The procedure developed for selective cleavage of the ester groups in **1** and in the 7,11-epoxide (**2**) have been utilized in the structure elucidation of the closely related thapsigargicin (**11**) isolated from the same plant. X-ray analysis of the epoxide (**2**) has been performed.

The plant *Thapsia garganica* L.[1] (Apiaceae = Umbelliferae), especially the root, contains potent skin irritants.[2,3] Because of this property, described by Hippokrates about 400 B.C., drugs prepared from the plant have been recorded in several pharmacopoieas, most recently the 1937 edition of the French pharmacopoiea. The drugs are still used as ingredients of rheumatic pain releasing ointments in Arabian folk medicine.[2] Two very potent skin irritants, named thapsigargin (yield 0.1% of fresh material) and thapsigargicin (yield 0.02%), have been isolated from an ethanolic extract of the root. The constitution of thapsigargin (**1**) has been reported in a preliminary communication.[4] The stereochemistry of thapsigargin could not be deduced unequivocally from the NMR data, and therefore an X-ray crystallographic investigation was undertaken. The noncrystalline state of the natural product forced this analysis to be performed on the 7,11-epoxide **2**, prepared by treatment of **1** with thionyl chloride. Crystal data are listed in the Experimental Section. Figure 1 is a stereoscopic drawing of the molecule, showing the conformation and the relative configuration of the com-





(1) The morphology, the great population on the Cyrenaica peninsula, and the use of *T. garganica* in folk medicine have lead to the assumption that the plant was the source of the famous antique drug Silphion. This subject, however, is still open for discussion.[2]
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