Nucleoside Sultones: Synthons for the Preparation of Novel Nucleotide Analogues. 1. Synthesis and Ring-Opening Reactions[1]

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Received September 30, 1991 (Revised Manuscript Received January 28, 1992)

Treatment of either the 5′-*O*-tosyl or the 5′-*O*-mesyl derivative of 3′-*O*-mesylthymidine with lithium acetylide–ethylenediamine complex in DMSO affords the intramolecular 6,3-ester of 1,2,5,6-tetradeoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-*erythro*-hexofuranuronosulfonic acid (**2**). Similarly, the 5′-*O*-tosyl or 5′-*O*-mesyl derivative of 1-(2-deoxy-3-*O*-mesyl-β-D-*threo*-pentofuranosyl)thymine affords the intramolecular 6,3-ester of 1,2,5,6-tetradeoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-*threo*-hexofuranuronosulfonic acid (**5**). Sultone **5** reacts with a variety of nucleophiles to afford good yields of the corresponding 3′-substituted sulfonate salts (**6**, **7**, **9**, and **10**) and, in some cases, the unsaturated nucleoside **8**. Sultone **2** was generally much less susceptible to ring opening by nucleophiles. However, in the presence of base, nucleophilic substitution with azide ion did proceed via the intermediate anhydronucleoside, **11**, to afford **6**. Reaction of **2** with EtOH–NaOH afforded a 1:1 mixture of the epimeric 3′-hydroxy compounds **9** and **12**. The above sulfonate salts represent interesting new isosteres of nucleoside 5′-*O*-phosphates.

Introduction

Since the discovery and structure elucidation of the nucleoside antibiotics nucleocidin[3] and ascamycin,[4] which both bear a 5′-*O*-sulfamoyl moiety, interest in the synthesis and properties of related nucleosides has existed not only because of the known activity of these natural products but also because the $-SO_2-$ moiety would be an excellent choice as an uncharged, stable, and isosteric replacement for the $-PO_2^-$– group. A number of synthetic nucleosides have now been reported that contain a 5′-extended $-SO_2-$ moiety including sulfamoyl derivatives of 4′-fluorouridine,[4] sulfamoyl derivatives of ribavirin,[6] nonisosteric sulfonate analogues of adenosine monophosphate,[7] a nonhydrolyzable sulfonate analogue of adenosine phosphosulfate,[8] substituted sulfamoyl analogues of uridine 5′-diphosphate glucose, and 5′-*O*-[*N*-(alkyl)sulfamoyl]substituted uridines,[9] *N*-sulfonyl derivatives of 5′-amino-2′,5′-dideoxy-5-iodouridine,[10] 5′-*O*-methanesulfonyl and 5′-*N*-(benzenesulfonyl) derivatives of 2′-deoxy-5-ethyluridine, and 5′-amino-2′,5′-dideoxy-5-ethyluridine, respectively.[11]

Although numerous examples of 5′-*O*-sulfate esters of nucleosides exist,[12] there are few reports of the preparation of the structurally-related sulfonate analogues in which the 5′-oxygen atom has been replaced with a methylene group.[13] Such nucleoside analogues should be chemically and biologically more stable than the corresponding sulfates. The close homology between the $-SO_3H$ and $-PO_3H_2$ groups in terms of size, bond angles, bond lengths, and pK_a[14] suggests that nucleoside 6′-sulfonic acids might be interesting isosteres of 5′-monophosphorylated nucleosides. Furthermore, since the sulfonyl moiety is such an excellent choice as a phosphate isostere, the development of oligonucleotide analogues based on this unit is of great interest.[15]

Initially we considered a dual strategy for formation of the carbon(5′)–carbon(6′) bond of the nucleoside sulfonic acids: (1) reaction of a sulfonyl-stabilized α-phosphonate anion via the method reported by Carretero et al.[16] with a nucleoside 5′-aldehyde[17] and (2) reaction of a 3′-*O*-

(1) For a preliminary report on some aspects of this work see: Secrist, J. A., III; Crooks, P. A.; Maddry, J. A.; Reynolds, R. C.; Rathore, A. S.; Akhtar, M. S.; Montgomery, J. A. *Nucleic Acids Res.* **1991**, Symposium Series No. 24, 5–8.

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(14) (a) The pK_a of sulfonic acids ranges from 1.5 to 2.8 (King J. F. In *The Chemistry of Sulfonic acids, Esters and Their Derivatives*; Patai, S., Ed.; John Wiley and Sons: New York, 1991; Chapter 6, pp 251). (b) The first pK_a of phosphoric acids ranges from 1.5 to 2.15 (*Lange's Handbook of Chemistry*, 13th ed., Dean, J. A., Ed.; McGraw-Hill: New York, 1985; Section 5, pp 16–53.

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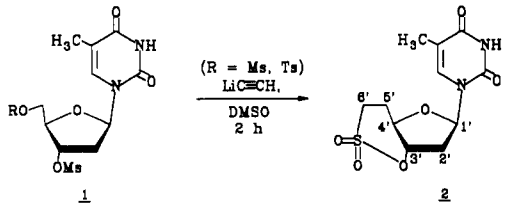
(16) Carretero, J. C.; Demillequand, M.; Ghosez, L. *Tetrahedron* **1987**, *43*, 5125–5134.

(17) During the course of this work the application of the method reported in ref 16 to nucleoside chemistry was published; see ref 13b.

0022-3263/92/1957-2830$03.00/0

Scheme I



1

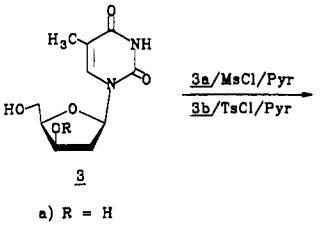
a) R = H
b) R = Ts
c) R = Ms

2

(methanesulfonyl)-5′-*O*-toluenesulfonyl nucleoside with base to give a 6′,3′-sultone product.[18] Classical methods of sulfonic acid preparation (e.g., the Strecker reaction) generally necessitate harsh conditions and would require a substrate with a preformed C5′–C6′ bond and were therefore rejected.[19] We selected the second approach because the necessary starting materials were readily available and stable. Generation of the 5′-aldehyde would require an oxidation step, and the resulting aldehyde could potentially epimerize at C4′ under basic conditions.[20] Furthermore, the sultone products would be stable, nonpolar compounds that should be easily isolated and purified; we were concerned about the stability and ease of isolation of the sulfonic acids or their simple aliphatic alkyl esters. Finally, the unique sultone products would essentially be thymidine analogues with the 3′-carbon already activated for displacement by nucleophiles, thus giving this approach a versatility not available with the other methods mentioned above.

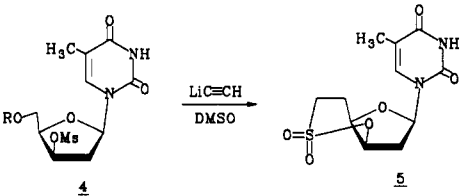
One documented report exists describing the synthesis of a carbohydrate-derived sultone from a mixed sulfonate precursor,[21] although formation of noncarbohydrate five- and six-membered sultones has been reported using *n*-BuLi and either 1,2- or 1,3-di-*O*-mesylalkanes.[22] These reports prompted us to consider generation of nucleoside 6′-sulfonic acids via appropriate bicyclic nucleoside-derived sultones. Such sultones might be prepared from 5′-*O*-mesyl or 5′-*O*-tosyl derivatives of nucleosides containing either a 3′-α or 3′-β-*O*-mesyl substituent via base-catalyzed intramolecular displacement of the 5′-moiety by the 3′-*O*-mesyl carbanion. In contrast to the formation of the carbohydrate sultones previously described,[21] however, such an application might not be straightforward, and the formation of nucleoside sultones via this procedure might be compromised by other competing base-catalyzed reactions. Such reactions include the generation of anhydronucleosides[23] as a consequence of proton removal from the nucleoside base, followed by subsequent displacement of either the 5′- or 3′-*O*-sulfonyl leaving group, and the formation of β-elimination products resulting from removal of the 4′-H and/or the 2′-H.[20] In addition, base-catalyzed

Scheme II



3

a) R = H
b) R = Ms



4

a) R = Ts
b) R = Ms

5

cleavage of the anomeric bond, resulting in elimination of the nucleoside base, was another possible complicating factor in this reaction.[24]

In order to determine the feasibility of preparing nucleoside sultones via this route, the synthesis of the thymidine sultones **2** and **5** from appropriate *O*-sulfonate precursors was initially examined, using the base lithium acetylide–ethylenediamine complex (LAC·EDA) in DMSO. The synthetic utility of the resulting sultones in nucleophilic displacement reactions that afforded the corresponding ring-opened sulfonate salts was also explored.

Results and Discussion

The synthesis of sultone **2** was achieved via two different routes from thymidine, as shown in Scheme I. 5′-O-Tosylation of 3′-*O*-mesylthymidine (**1a**)[25-27] followed by cyclization of the resulting mixed sulfonate, **1b**, with LAC·EDA in DMSO, gave **2** in 48% yield. Other products that formed in this cyclization reaction were thymine and the known elimination products 5-methyl-1-(5-methyl-2-furanyl)-2,4(1*H*,3*H*)-pyrimidinedione[24a] and (*R*)-1-(2,5-dihydro-5-methylene-2-furanyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione.[24] Sultone **2** could also be prepared from 3′,5′-di-*O*-mesylthymidine (**1c**)[25] by similar treatment. In this reaction, **2** was formed in 35% yield along with thymine, 5-methyl-1-(5-methyl-2-furanyl)-2,4-(1*H*,3*H*)-pyrimidinedione,[24a] (*R*)-1-(2,5-dihydro-5-methylene-2-furanyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione,[24] and the known 5′-*O*-mesyl-2,3′-anhydronucleoside of thymidine.[25] As expected from the results of Durst and Tin,[22] only the sultone product resulting from generation of the carbanion of the 3′-*O*-mesyl group followed by displacement of the 5′-*O*-mesyl moiety was observed and not the product resulting from attack of the carbanion at the 5′-*O*-mesyl on the secondary 3′-mesylate. In a system very comparable to ours, Durst and Tin reasoned that the two isomeric lithio derivatives equilibrated rapidly, thereby allowing the preferential production of the sultone isomer resulting from cyclization through the least hindered pathway. Our

(18) During the course of this work two groups reported reactions that are basically intermolecular versions of the chemistry reported herein: (a) Attack of dianions on 5′-deoxy-5′-iodothymidine to form novel thymidine analogues: Ray, P. S.; Jaxa-Chamiec, A. A. *Heterocycles* **1990**, *31*, 1777–1780. (b) Preparation of a uridine 6′-sulfonate via attack of an α-lithio sulfonate ester on a 5′-deoxy-5′-iodouridine, see ref 13a.

(19) For a recent review of the preparation of sulfonic acids see: Hoyle, J. In *The Chemistry of Sulfonic Acids, Esters and Their Derivatives*; Patai, S., Ed.; John Wiley and Sons: New York, 1991; Chapter 10, pp 352–399.

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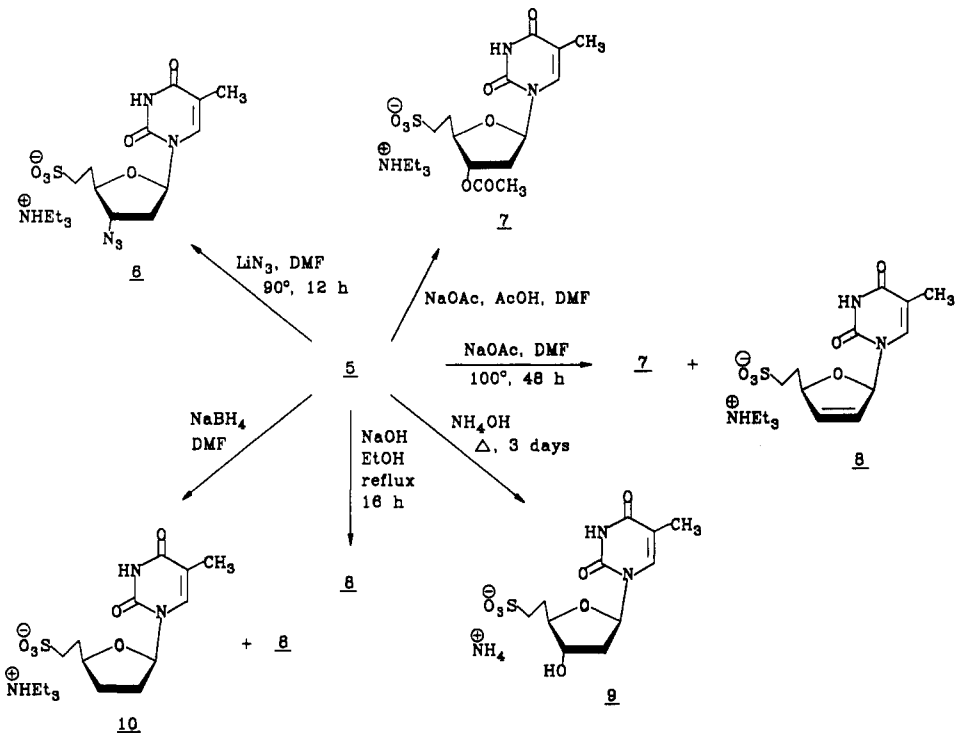
(26) Horwitz, J. P.; Urbanski, J. A.; Chua, J. *J. Org. Chem.* **1962**, *27*, 3300–3302.

(27) Fox, J. J.; Miller, N. C. *J. Org. Chem.* **1963**, *28*, 936–941.

Scheme III



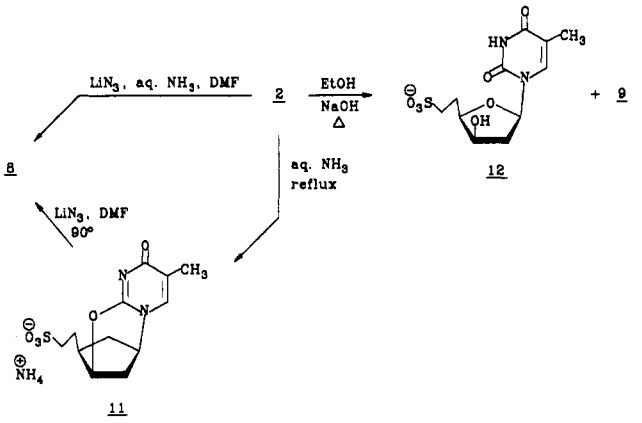
results similarly suggest that it is not always necessary to have sulfonates of different reactivities (i.e., mixed sulfonates such as mesyl–tosyl derivatives) so that one group can be deprotonated preferentially while the other would be the favored leaving group, as has been suggested.

Sultone **5** was prepared via the two reaction sequences shown in Scheme II. In the first route, 5′-O-tosylation of 1-(2-deoxy-3-*O*-mesyl-β-D-*threo*-pentofuranosyl)thymine (**3b**)[25-27] afforded **4a**, which then yielded sultone **5** in 66% yield on treatment with LAC·EDA in DMSO. The alternative route to **5** utilized the previously unreported 3′,5′-di-*O*-mesyl derivative of 1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (**4b**). Cyclization of **4b** under the usual conditions gave **5** in 40% yield. In the reaction of **4b** to form **5** a large portion of the starting material remained at termination, and the conversion to **5** in comparison with the 3′-*O*-mesyl-5′-*O*-tosyl precursor **4a** was much slower. The formation of significant quantities of polar impurities, however, precluded longer reaction times. In the formation of sultone **5** the mixed sulfonate starting material **4a** is clearly the precursor of choice, and again, as was observed in the 2′-deoxyribose series, none of the sultone product resulting from displacement of the 3′-*O*-mesyl group was found in the reaction mixture derived from **4b**.

Treatment of **5** with a variety of nucleophiles generally afforded good yields of the corresponding ring-opened sulfonate salt and, in some cases, the 2′,3′-unsaturated nucleoside **8** (Scheme III). Thus, reaction of **5** with LiN_3 in DMF at 90 °C afforded sulfonate **6** in 72% yield. Similarly, treatment of **5** with NaOAc in DMF afforded a good yield of a 5:3 mixture, respectively, of the 3′-*O*-acetyl sulfonate **7** and the unsaturated sulfonate **8**. We found that the elimination byproducts could be reduced by the reaction of **5** in a buffered solution of NaOAc/AcOH/DMF. Compound **7** was isolated from this modification in a crude form (43% yield) that was difficult to separate from nonnucleosidic material.

The heating of **5** with aqueous ammonia for 3 days at reflux afforded a good yield of the hydrolysis product **9**, whereas treatment of **5** with hot ethanolic NaOH gave only the elimination product **8** in excellent yield. Reduction of **5** with $NaBH_4$ in DMF afforded an inseparable 1:1 mixture of **8** and the 3′-deoxy sulfonate **10**.

Scheme IV



Sultone **2** was generally much less susceptible to nucleophilic substitution at the 3′-carbon than was sultone **5**, a property that is consistent with the known relative reactivities of the corresponding erythro and threo mesylates.[22,28] Reaction of **2** with LiN_3 in DMF in the presence of aqueous ammonia afforded a 65% yield of **6** with none of the threo azide being detected in the reaction mixture. This reaction likely proceeds via initial base-catalyzed formation of the 2,3′-anhydro sulfonate **11**, followed by azide attack at C-3′; this anhydro intermediate can be isolated as the only product by heating sultone **2** in aqueous NH_3. Again, this reactivity is highly consistent with the known reactivity of 3′-*O*-mesylthymidine, where displacement of the mesyl group by external nucleophiles is quite uncommon but formation and subsequent nucleophilic opening of the 2,3′-anhydro ring is extremely

(28) (a) Horwitz, J. P.; Chua, J.; Urbanski, J. A.; Noel, M. *J. Org. Chem.* **1963**, *28*, 942-944. (b) Horwitz, J. P.; Chua, J.; Noel, M. *J. Org. Chem.* **1964**, *29*, 2076-2078.

facile.[23,28] Subsequent reaction of 11 with LiN_3 in DMF afforded 6 in 72% yield. The anhydronucleoside 11 represents another potentially useful synthon for the preparation of stereochemically defined sulfonyl-based nucleoside analogues.

Reaction of 2 with alcoholic NaOH resulted in the formation of an almost quantitative yield of an inseparable 1:1 mixture of the epimeric alcohols 9 and 12. The erythro epimer probably resulted from hydroxide attack either on the sulfur atom of 2 or the 3'-carbon of the intermediate 2,3'-anhydro nucleoside. In contrast to sultone 5, sultone 2 afforded none of elimination product 8 under these reaction conditions.

In summary, chemistry has been reported which supplies moderate to good yields of two novel sultones of thymidine, the intramolecular 6,3-esters of 1,2,5,6-tetradeoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-*erythro*-hexofuranuronosulfonic acid 2 and 1,2,5,6-tetradeoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-*threo*-hexofuranuronosulfonic acid 5.[29] In addition to the novelty of these structures, they are easily isolated and stable and can be directly utilized in a variety of ring-opening reactions to obtain novel, substituted nucleoside sulfonic acids. As such, these compounds have certain advantages over previous reports of nucleoside and carbohydrate sulfonates.[13] Current work in our laboratories is focusing on the utilization of sultones 2 and 5 in ring-opening reactions with a variety of nucleophiles to generate thymidine 5'-sulfonates with defined stereochemistry at C-3'. These compounds, as novel isosteres of 5'-monophosphorylated nucleosides, may have chemotherapeutic potential. For example, 6 is an analogue of 3'-azidothymidine (AZT) monophosphate. In addition, appropriate derivatives of 6 and 7 are presently being utilized in the synthesis of oligonucleotide analogues containing sulfonate ester and novel sulfonamide internucleoside linkages.[30] Finally, we have been able to apply this chemistry to other purine and pyrimidine nucleosides, and this work will be reported in due course.

Experimental Section

All evaporations were carried out in vacuo with a rotary evaporator or by short-path distillation into a dry ice/acetone-cooled receiver under high vacuum. Analytical samples were normally dried in vacuo over P_2O_5 at room temperature for 16 h. Analtech precoated (250-μm) silica gel GF plates were used for TLC analyses; the spots were detected by irradiation with a Mineralight. All analytical samples were homogeneous by TLC. Melting points were determined with a Kofler Heizbank apparatus and are uncorrected. Purifications by flash chromatography were carried out on Merck silica gel 60 (230–400 mesh) using the slurry method of column packing. NMR spectra were determined on a Nicolet-GE NT 300NB spectrometer operating at 300.635 MHz and using tetramethylsilane as an internal reference. Chemical shifts (δ) quoted in the case of multiplets were measured from the approximate center. Mass spectral data were obtained with a Varian MAT 311A mass spectrometer in the fast atom bombardment mode using a glycerol matrix.

3'-*O*-Mesylthymidine (1a). This intermediate was synthesized from 3'-*O*-mesyl-5'-*O*-tritylthymidine via the following procedure, which afforded a superior yield to those previously reported.[25-27] 3'-*O*-Mesyl-5'-*O*-tritylthymidine (1.20 g, 2.26 mmol) was added to a stirred solution of CH_2Cl_2–CF_3COOH acid (9:1 v/v, 10 mL), whereupon a yellow solution was obtained. The mixture was stirred for a further 5 min and then poured into hexane (150 mL). The resulting yellow oily residue was triturated well with hexane and the yellow supernatant decanted. A further aliquot of hexane (150 mL) was added to the residue and the process repeated. The viscous residue was then dissolved in absolute EtOH and the solvent evaporated to a low volume. On cooling, a white solid was deposited (0.58 g, 89%): mp 154–155 °C (lit.[25] 153–155 °C, lit.[26] 150–153 °C, lit.[27] 116 °C); ^{1}H-NMR (DMSO-d_6) δ 11.38 (bs, 1 H, exchangeable with D_2O, NH), 7.69 (s, 1 H, thymine 6 H), 6.20 (t, 1 H, 1'-proton), 5.25 (m superimposed on bs, 2 H, decreases to 1 H with D_2O, 3'-proton and 5'-OH), 4.12 (m, 1 H, 4'-proton), 3.64 (m, 2 H, 5'-protons), 3.29 (s, 3 H, OSO_2CH_3), 2.48–2.38 (m, 2 H, 2'-protons), 1.80 (s, 3 H, 5-CH_3); MS (pos-FAB) *m/z* 321 $(M + H)^+$.

3'-*O*-Mesyl-5'-*O*-tosylthymidine (1b). Method A. 3'-*O*-Mesylthymidine[25-27] (0.50 g, 1.6 mmol) was dissolved in dry pyridine (4 mL) containing TsCl (0.32 g, 1.7 mmol) and 4-(dimethylamino)pyridine (DMAP, 2 mg), and the mixture was left at ambient temperature for 12 h. The reaction mixture was poured into an ice–water mixture (40 mL) to give a brown gummy deposit, which crystallized on scratching. The resulting solid was filtered, washed well with H_2O, and dried to afford an off-white solid (0.75 g, 91%). A sample was recrystallized from CH_2Cl_2–hexane: mp 159 °C; ^{1}H-NMR (DMSO-d_6) δ 9.80 (bs, 1 H, exchangeable with D_2O, NH), 7.80 (d, 2 H, aromatic ortho portions of tosyl groups), 7.39 (d, 2 H, aromatic meta protons of tosyl group), 7.40 (s, 1 H, thymidine 6-proton), 6.35 (d of d, 1 H, 1'-proton), 5.25 (m, 1 H, 3'-proton), 4.52 (m, 1 H, 4'-proton), 4.40 (m, 2 H, 5'-protons), 3.12 (s, 3 H, $-OSO_2CH_3$), 2.61 (m, 1 H, 2'α-proton), 2.48 (s, 3 H, CH_3 of tosyl group), 2.40 (m, 1 H, 2'β-proton), 1.95 (s, 3 H, thymine 5-CH_3); MS (pos-FAB) *m/z* 475 $(M + H)^+$. Anal. Calcd for $C_{18}H_{22}N_2O_9S_2$: C, 45.56; H, 4.67; N, 5.90. Found: C, 45.64; H, 4.85; N, 5.79.

Method B. 5'-*O*-Tosylthymidine[25] (0.5 g, 1.3 mmol) was dissolved in a mixture of dry CH_2Cl_2 (6 mL) and pyridine (0.35 mL), and MsCl (0.35 g, 3 mmol) was added dropwise at 0 °C. The reaction was left to stand at ambient temperature overnight and then poured into ice–water (50 mL) with vigorous mechanical stirring. The organic layer was separated, washed with 1% aqueous HCl solution (2 × 5 mL) and then dilute aqueous $NaHCO_3$ (1 × 5 mL), and dried over $MgSO_4$. Evaporation of solvent afforded a white solid, which was recrystallized from CH_2Cl_2–hexane to afford a product (0.52 g, 87% yield) with characteristics identical to that prepared by method A above.

1,2,5,6-Tetradeoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1-(2*H*)-pyrimidinyl)-β-D-*erythro*-hexofuranurono-6,3-sultone (2). Method A. A mixture of 3'-*O*-mesyl-5'-*O*-tosylthymidine (0.6 g, 1.3 mmol) and LAC-EDA (0.35 g, 3.8 mmol) was dissolved in dry DMSO (10 mL) and the solution stirred under a dry nitrogen atmosphere at ambient temperature for 2 h. The reaction mixture was cooled in an ice bath, and 0.5% aqueous AcOH solution (30 mL) was added with stirring. The solution was then extracted with ethyl acetate (3 × 50 mL), the organic layers were combined, washed with H_2O (2 × 50 mL), and dried over $MgSO_4$, and the EtOAc was removed in vacuo. Residual DMSO was removed at high vacuum by short-path distillation. The resulting residue was submitted to flash column chromatography using $CHCl_3$ as eluent. After an early band containing the two known unsaturated products 5-methyl-1-(5-methyl-2-furanyl)-2,4-(1*H*,3*H*)-pyrimidinedione[24a] and (*R*)-1-(2,5-dihydro-5-methylene-2-furanyl)-5-methyl-2,4-(1*H*,3*H*)-pyrimidinedione[24] was eluted from the column, a second homogeneous band was obtained, which upon removal of solvent afforded light-tan crystals of 3 (134 mg, 48% yield): mp 157 °C; ^{1}H-NMR (DMSO-d_6) δ 11.35 (bs, 1 H, exchangeable with D_2O, NH), 7.60 (s, 1 H, thymine 6-proton), 6.25 (d of d, 1 H, 1'-proton), 4.99 (m, 1 H, 3'-proton), 3.85–3.72 (m, 2 H, 4'- and one of the 6'-protons), 3.42 (m, 1 H,

(29) A number of conditons have been tried in an effort to optimize yields of the sultones. Most of these reactions were carried out using 4a as a model compound. The modifications using 4a include (base/solvent/temperature/yield): (a) LAC-EDA/1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)/20 °C/60%; (b) CaC≡CH/DMSO/20 °C/no reaction in 24 h; (c) CaH_2/DMSO/20 °C/no reaction in 24 h; (d) *n*-BuLi/THF–DMSO (9:1)/20 °C/product–starting material (10:90) by TLC, not isolated; (e) PhC≡CLi/THF–DMSO (9:1)/20 °C/product–starting material (90:10) by TLC, not isolated; (f) Me_3SiC≡CLi/THF–DMSO (9:1)/−75 °C to 20 °C (no reaction apparent by TLC until the reaction was warmed to ambient temperature/70%. In addition, one reaction was tried to modify the yield of sultone 5 using the starting material 1c, 3',5'-di-*O*-mesylthymidine: LAC-EDA/DMPU/RT (no reaction), Δ (complex mixture)/no product isolated.

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one of the 6'-protons), 2.62–2.30 (m, 2 H, 2'-proton), 2.20 (m, 2 H, 5'-proton), 1.82 (s, 3 H, thymidine 5-CH_3); MS (pos-FAB) m/z 303 $(M + H)^+$. Anal. Calcd for $C_{11}H_{14}N_2O_6S$: C, 43.74; H, 4.67; N, 9.27. Found: C, 43.37; H, 5.00; N, 9.14.

Method B. A mixture of 3',5'-di-*O*-mesylthymidine (**1c**)[31] (4.29 g, 0.011 mol) and LAC·EDA (2.28 g, 0.025 mol) was dissolved in dry DMSO (75 mL) and the mixture stirred at ambient temperature under dry nitrogen for 16 h. Processing of the reaction mixture, as described in method A above, afforded four fractions from flash column chromatography [corresponding to the known elimination products 5-methyl-1-(5-methyl-2-furanyl)-2,4-(1*H*,3*H*)-pyrimidinedione[24a] and (*R*)-1-(2,5-dihydro-5-methylene-2-furanyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione[24] (first band), sultone **2** (second band), the known 5'-*O*-mesyl-2,3'-anhydro derivative of thymidine[25] (third band), and thymine (fourth band)]. Sultone **2** was obtained in 35% yield via this procedure and had identical characteristics to the product obtained from method A above.

1-(2-Deoxy-3-*O*-mesyl-β-D-*threo*-pentofuranosyl)thymine (3b). This compound was synthesized from 1-(2-deoxy-3-*O*-mesyl-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine[28b] via the modification previously described for the preparation of 3'-*O*-mesylthymidine (**1b**), in 62% yield: mp 160–161 °C (lit.[28b] 161–162 °C); ^{1}H-NMR (DMSO-d_6) δ 11.34 (bs, 1 H, exchangeable with D_2O, NH), 7.42 (s, 1 H, thymine 6-proton), 6.13 (m, 1 H, 1'-proton), 5.25 (m, 1 H, 3'-proton), 4.10–4.00 (m, 1 H, 4'-proton), 3.74–3.64 (m, 2 H, 5'-protons), 3.24 (s, 3 H, OSO_2CH_3), 2.90–2.70 (m, 1 H, 2'α-proton), 2.30–2.20 (m, 1 H, 2'β-proton), 1.76 (s, 3 H, thymine 5-CH_3); MS (pos-FAB) m/z 321 $(M + H)^+$.

1-(2-Deoxy-3-*O*-mesyl-5-*O*-tosyl-β-D-*threo*-pentofuranosyl)thymine (4a). Compound **3b** (0.5 g, 1.6 mmol) was dissolved in dry pyridine (4 mL) containing TsCl (0.32 g, 1.7 mmol) and DMAP (2 mg) and the mixture stirred at ambient temperature for 6 h and then stored overnight at 4 °C. The reaction mixture was then left to stand at ambient temperature for 3 h and poured into ice–water (40 mL) to afford a gummy residue that slowly crystallized on vigorous mechanical stirring. The resulting mixture was filtered, and the preicpitate was washed well with H_2O and dried, affording off-white crystals of **4a** (0.72 g, 97% yield): mp 161–162 °C; ^{1}H-NMR (DMSO-d_6) δ 11.37 (bs, 1 H, exchangeable with D_2O, NH) 7.82 (m, 2 H, ortho protons of tosyl group), 7.47 (m, 2 H, meta protons of tosyl group), 7.30 (s, 1 H, thymine 6-proton), 6.14 (d of d, 1 H, 1'-proton), 5.34 (m, 1 H, 3'-proton), 4.48–4.20 (m, 2 H, 5'-protons), 4.30 (m, 1 H, 4'-proton), 3.25 (s, 3 H, $-OSO_2CH_3$), 2.82 (m, 1 H, 2'a-proton), 2.41 (s, 3 H, tosyl CH_3), 2.27 (m, 1 H, 2'β-proton), 1.78 (s, 3 H, thymine 5-CH_3); MS (pos-FAB) m/z 475 $(M + H)^+$. Anal. Calcd for $C_{18}H_{22}N_2O_9S$: C, 45.56; H, 4.67; N, 5.90. Found: C, 45.85; H, 4.86; N, 6.06.

1-(2-Deoxy-3,5-di-*O*-mesyl-β-D-*threo*-pentofuranosyl)thymine (4b). A mixture of 1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (184 mg, 0.8 mmol) and MsCl (0.13 mL, 1.14 mmol) in dry pyridine (1.0 mL) was cooled to −10 °C and left to stand overnight at 4 °C. Water (0.1 mL) was then added and the mixture stirred in an ice bath for 1 h. Pyridine was removed under high vacuum, and the resulting oil was triturated with EtOAc and chilled in the freezer, but failed to crystallize. The EtOAc solution was loaded onto preparative silica TLC plates, which were developed in $CHCl_3$–MeOH (7:1), and the major UV-active band separated and isolated. The resulting product, **4b**, was crystallized from absolute EtOH (100%) as white crystals, 250 mg, 80% yield: mp 80–82 °C; ^{1}H-NMR (DMSO-d_6), δ 11.48 (bs, 1 H, exchangeable with D_2O, NH), 7.46 (s, 1 H, thymine 6-proton), 6.20 (m, 1 H, 1'-proton), 5.40 (m, 1 H, 3'-proton), 4.62–4.30 (m, 3 H, 4'- and 5'-protons), 3.32 (s, 3 H, $-OSO_2CH_3$), 3.25 (s, 3 H, $-OSO_2CH_3$), 2.96–2.80 (m, 1 H, 2'α-proton), 2.32 (m, 1 H, 2'β-proton), 1.70 (s, 3 H, thymine 5-CH_3); MS (pos-FAB) m/z 399 $(M + H)^+$. Anal. Calcd for $C_{12}H_{18}N_2S_2O_9$: C, 36.18; H, 4.55; N, 7.03. Found: C, 36.29; H, 4.92; N, 6.87.

1,2,5,6-Tetradeoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-2-(4*H*)-pyrimidinyl)-β-D-*threo*-hexofuranurono-6,3-sultone (5). Method A. A mixture of compound **4a** (0.5 g, 1.1 mmol) and LAC·EDA (0.224 g, 2.4 mmol) was dissolved in dry DMSO (7.0 mL) and the solution stirred under a dry nitrogen atmosphere at ambient temperature for 2 h. The reaction mixture was then poured into 1% aqueous AcOH solution (50 mL) and the mixture extracted with EtOAc (2 × 200 mL). The organic layers were combined, washed with water (2 × 100 mL), and dried over $MgSO_4$. Residual DMSO was removed under high vacuum by short-path distillation and the residue crystallized from MeOH to afford light tan crystals of **5** (0.21 g, 66% yield): mp 200 °C dec; ^{1}H-NMR (DMSO-d_6) δ 11.49 (bs, 1 Hs, exchangeable with D_2O, NH), 7.39 (s, 1 H, thymine 6-proton), 6.21 (m, 1 H, 1'-proton), 5.19 (m, 1 H, 3'-proton) 4.01 (m, 1 H, 4'-proton) 3.55–3.23 (m, 2 H, 6'-proton), 2.88 (m, 1 H, 2'α-proton), 2.50 (m, 2 H, 5'-proton), 2.20 (1 H, 2'β-proton), 1.79 (s, 3 H, thymine 5-CH_3); MS (pos-FAB) m/z 303 $(M + H)^+$. Anal. Calcd for $C_{11}H_{14}O_6N_2S$: C, 43.74; H, 4.67; N, 9.27. Found: C, 43.72; H, 4.86; N, 9.23.

Method B. A mixture of compound **4b** (0.1 g, 0.26 mmol) and LAC·EDA (0.120 g, 1.3 mmol) was dissolved in dry DMSO (2.5 mL) and the solution stirred under a dry nitrogen atmosphere at ambient temperature for 2 h. Processing of the reaction as previously described afforded compound **5** in 40% yield, identical in all respects to the product from method A above.

3-Azido-1,2,3,5,6-pentadeoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-*erythro*-hexofuranurono-sulfonic Acid (6). A mixture of **5** (120 mg, 0.4 mmol) and LiN_3 (100 mg, 2 mmol) in dry DMF (2 mL) was stirred at 90 °C under nitrogen for 12 h. The solvent was then removed by short-path distillation, the residue dissolved in CH_3CN, and the solution eluted through a silica gel column using CH_3CN as eluent. The first eluting band contained starting material. After changing the eluting solvent to CH_3CN/1 M NH_4OH (8:1), a second band consisting of the desired product was eluted. After removal of solvent by lyophilization, the resulting solid was recrystallized from EtOH to afford the ammonium salt of **6** as a white hygroscopic powder that was contaminated with inorganic salts. The above product was dissolved in 0.1 M triethylammonium acetate (TEAA) buffer, pH 6.5 (1.0 mL), and applied to an XAD-4 column (1 × 20 cm). The column was eluted first with buffer (40 mL), then distilled H_2O (40 mL), and finally CH_3CN (20 mL). The CH_3CN eluate containing UV-positive material was pooled and evaporated under reduced pressure to give a hygroscopic solid, which after drying under high vacuum for 3 days afforded the triethylammonium salt of **6** (99 mg, 72% yield): ^{1}H-NMR (D_2O) 7.39 (s, 1 H, thymine 6-proton), 6.09 (m, 1 H, 1'-proton), 4.16 (m, 1 H, 3'-proton), 3.95 (m, 1 H, 4'-proton), 3.11 [q, 6 H, $(CH_3CH_2)_3{}^+NH$], 2.95 (m, 2 H, $CH_2SO_3^-$), 2.42 (m, 2 H, 2'-proton), 2.20–1.94 (m, 2 H, 5'-proton), 1.80 (s, 3 H, thymine 5-CH_3), 1.18 [t, 9 H, $(CH_3CH_2)_3NH]^+$; MS (pos-FAB) m/z 102 $[(Et)_3NH]^+$, 346 $(M + H)^+$, 446 $[M + (Et)_3\,N^+H]^+$, MS (neg-FAB) m/z 344 $(M - H)^-$. Anal. Calcd for $C_{17}H_{30}N_6O_6S{\cdot}2.5H_2O$: C, 41.55; H, 7.13; N, 17.11. Found: C, 41.91; H, 7.20; N, 17.50.

Formation of 6 from Sultone 2. A solution of sultone **2** (30 mg, 0.1 mmol) in a mixture of DMF (0.5 mL) and concentrated NH_4OH (0.25 mL), 0.880 sp gr) containing LiN_3 (10 mg, 0.2 mmol) was stirred at 90 °C for 14 h with intermittent addition of NH_4OH (3 × 1 mL). The reaction mixture was then worked up following the procedure described for compound **9** to afford an off-white, hygroscopic solid, which after XAD chromatography gave 65% of a product with identical characteristics to compound **6** formed from the reaction of lithium azide with sultone **5**.

3-*O*-Acetyl-1,2,3,5,6-pentadeoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-*erythro*-hexofuranuro-nosulfonic Acid (7). A mixture of sultone **5** (100 mg, 0.33 mmol) and NaOAc (100 mg, 1.2 mmol) in DMF (2 mL) was stirred at 100 °C for 48 h and the solvent removed by short-path distillation at high vacuum. The resulting white solid was dissolved in distilled H_2O (2.0 mL), the solution extracted with EtOAc (3 × 2.0 mL), and the aqueous layer separated and chromatographed on an XAD-4 column, as previously described for the preparation of **6**. The product from the CH_3CN fraction was dried over P_2O_5 at 0.05 mmHg for 3 days to give 150 mg of a white hygroscopic solid, which by ^{1}H-NMR analysis was shown to be a 5:3 mixture, respectively, of **7** and **8**. The mixture was separated by dissolving in H_2O (100 μL) and eluting through a high-performance PRP-1 chromatographic column (Hamilton) with a linear gradient of 0.1 M TEAA, pH 6.9, CH_3CN (9:1) (solvent A), and 0.1 M TEAA, pH 6.9, CH_3CN (1:9) (solvent B) [0–55% of solvent B over 20 min].

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Compound 7 eluted at t_R 7.12 min, and 8 eluted at t_R 9.02 min. Removal of solvent by lyophilization afforded pure 7 and 8 as highly hygroscopoic white powders: ^{1}H-NMR (D_2O) of 7, δ 7.41 (s, 1 H, thymine 6-proton), 6.20 (m, 1 H, 1′-proton), 5.10 (m, 1 H, 3′-proton), 4.14 (m, 1 H, 4′-proton), 3.10 [q, 6 H, $(CH_3CH_2)_3^+NH$], 2.98–2.82 (m, 2 H, $-CH_2SO_3^-$), 2.39 (m, 2 H, 2′-proton), 2.12–1.88 (m, 2 H, 5′-proton), 2.04 (s, 3 H, $OCOCH_3$), 1.82 (s, 3 H, thymine 5-CH_3), 1.18 [t, 9 H, $(CH_3CH_2)_3^+NH$]; MS (pos-FAB) m/z 102 $[(Et)_3NH]^+$, MS (neg-FAB) m/z 361 $(M - H)^-$. Anal. Calcd for $C_{19}H_{33}N_3O_8S\cdot4.3H_2O$: C, 42.19, H, 7.70; N, 7.69. Found: C, 42.21; H, 7.65; N, 8.01. 8: ^{1}H-NMR (D_2O) δ 7.30 (s, 1 H, thymine 6-proton), 6.80 (m, 1 H, 1′-proton), 6.44 (m, 1 H, 2′-proton), 5.82 (m, 1 H, 3′-proton), 4.93 (m, 1 H, 4′-proton), 3.10 [q, 6 H, $(CH_3CH_2)_3^+NH$], 2.98–2.82 (m, 2 H, $-CH_2SO_3^-$), 2.12–1.88 (m, 2 H, 5′-proton), 1.80 (s, 3 H, thymine 5-CH_3), 1.18 [t, 9 H, $CH_3CH_2)_3^+NH$]; MS (pos-FAB) m/z 102-$[(Et)_3NH]^+$, MS (neg-FAB) 301 m/z $(M - H)^-$. Anal. Calcd for $C_{17}H_{29}N_3O_6S\cdot1.5H_2O$: C, 47.44; H, 7.44; N, 9.77. Found: C, 47.62; H, 7.80; N, 10.11.

Addition of 10% AcOH to the DMF solution afforded impure 7 in 43% yield after XAD-4 chromatography.

Compound 7 could also be prepared via 3-*O*-acetylation of 9 with $AcOAc/NEt_3$/DMAP in acetonitrile in 67% yield.

2,3-Dehydro-1,2,3,5,6-pentadeoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-*erythro*-hexofuranuronosulfonic Acid (8). Sultone 5 (100 mg, 0.33 mmol) was dissolved in a mixture of hot absolute EtOH (100%) (1.0 mL) and 1 N aqueous NaOH solution (2 mL, 6 equiv). The mixture was heated under reflux for 18 h, cooled, and extracted with EtOAc (3 × 3 mL) and the aqueous layer lyophilized to afford the impure sodium salt of 8 as a white hydroscopic solid. The above product was converted to its triethylammonium salt via XAD-4 chromatography, as described for the preparation of 6, to afford 87% of a product identical to compound 8 isolated from the reaction of NaOAc with sultone 5 (see above).

1,2,5,6-Tetradeoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1-(2*H*)-pyrimidinyl)-β-D-*erythro*-hexofuranuronosulfonic Acid (9). Sultone 5 (100 mg, 0.33 mmol) was dissolved in concentrated NH_4OH (2 mL, 0.880 sp gr) and the solution heated under reflux for 3 days with intermittent addition of NH_4OH (2 mL) every 12 h. The reaction mixture was extracted with EtOAc (3 × 10 mL) and the aqueous layer lyophilized to afford 9 as a white, highly hygroscopic solid (90 mg, 81% yield): ^{1}H-NMR (D_2O) δ 7.38 (s, 1 H, thymine 6-proton), 6.18 (m, 1 H, 1′-proton), 4.28 (m, 1 H, 3′-proton), 3.93 (m, 1 H, 4′-proton), 2.95 (m, 2 H, $-CH_2SO_3^-$), 2.29 (m, 2 H, 2′-proton), 2.00 (m, 2 H, 5′-proton), 1.82 (s, 3 H, thymine 5-CH_3); MS (neg-FAB) m/z 319 $(M - H)^-$. Anal. Calcd for $C_{17}H_{31}N_3O_7S\cdot2H_2O$: C, 44.64; H, 7.66; N, 9.19. Found: C, 44.68; H, 7.81; N, 9.51.

2,3-Anhydro-1,2,5,6-tetradeoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-*erythro*-hexofuranuronosulfonic Acid (11). Sultone 2 (0.5 g, 1.65 mmol) was dissolved in NH_4OH solution (5 mL, 0.880 sp gr) and the mixture heated under reflux for 30 h with intermittent addition of NH_4OH (2 mL) every 8 h. The reaction mixture was extracted with EtOAc (3 × 10 mL) and the aqueous layer lyophilized to afford the ammonium salt of 11 as a pale brown solid (0.42 g, 79% yield), which was used directly with the preparation of 6: ^{1}H-NMR (D_2O) δ 7.48 (s, 1 H, thymine 6-proton), 5.81 (m, 1 H, 1′-proton), 5.31 (m, 1 H, 3′-proton), 4.45 (m, 1 H, 4′-proton), 2.95 (m, 2 H, $-CH_2SO_3^-$), 2.61 (m, 2 H, 2′-proton), 1.98 (m, 2 H, 5′-proton), 1.82 (s, 3 H, thymine 5-CH_3); MS (neg-FAB) m/z 301 $(M - H)^-$.

Acknowledgment. This work was supported by the National Institutes of Health, Grant Nos U01 AI26054 and U01 AI26061.

Nucleophilic Addition of 2-Indolylacyl Anion Equivalents to *N*-Alkylpyridinium Salts

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Received November 5, 1991

The reactions of the anions derived from dithioacetals 1–3 and α-amino nitriles 4 toward pyridinium salts 5 are studied. Depending on the nucleophile used, 2-(dihydropyridylmethyl)indoles 6 and 7, which can be cyclized to tetracyclic methanoazocinindole systems 10 and 11, respectively, or 2-substituted 3-(dihydropyridyl)indoles 8 and 9 are formed.

The nucleophilic addition of ester enolates to *N*-alkylpyridinium salts has proved to be a useful and straightforward method in alkaloid synthesis.[1] Following this methodology, from 1-, 2-, and 3-indoleacetic ester anions, and subsequent cyclization of the resulting 1,4-dihydropyridines, we have recently reported a general method for the synthesis of tetracyclic substructures of *C*-mavacurine, *Strychnos*, and akuammiline-type alkaloids, respectively,[2] from which the synthesis of the indole alkaloids vinoxine[2,3] and tubifolidine[4,5] was accomplished.

In contrast, although the synthetic usefulness of acyl anion equivalents is well-known,[6] there are no studies about their reactivity as nucleophiles toward pyridinium salts.[7,8] In this context, we planned to explore the scope and synthetic usefulness of the addition of 2-indolylacyl anion equivalents to pyridinium salts.[9]

A priori, depending on factors such as the softness or hardness of the nucleophile and the reversibility of the

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