Hz, C(10)H*H'*); UV-vis (CH_3CN) 251, 303, 536 nm.

***cis*-1-Hydroxy-2-(methylamino)-7-aminomitosene (11a)**: ^1H NMR (DMSO-d_6) δ 1.72 (s, C(6)CH_3), 2.35 (s, NCH_3), 3.50–3.55 (m, C(2)H), 3.61 (dd, J = 8.54, 11.65 Hz, C(3)H_β), 4.34 (dd, J = 6.61, 11.65 Hz, C(3)H_α), 4.91 (d, J = 4.60 Hz, C(1)H), 5.01 ($^1/_2$ ABq, J = 12.49 Hz, C(10)*H*H'), 5.06 ($^1/_2$ ABq, J = 12.49 Hz, C(10)H*H'*); ^{13}C NMR (DMSO-d_6) δ 8.30 (C(6)CH_3), 34.00 (NCH_3), 49.68 (C(3)), 56.62 (C(10)), 62.38 (C(2)), 65.59 (C(1)), 104.62 (C(6)), 112.61 (C(8a)), 120.48 (C(9)), 128.07 (C(9a)), 142.40 (C(7)), 146.95 (C(5a)), 156.69 (C(10)O*C*(O)NH_2), 176.47 (C(8)), 178.39 (C(5)); UV-vis (CH_3CN) 248, 312, 516 nm.

***trans*-1-Hydroxy-2-(methylamino)-7-aminomitosene (11b)**: ^1H NMR (CD_3OD) δ 1.79 (s, C(6)CH_3), 2.45 (s, NCH_3), 3.58–3.62 (m, C(2)H), 4.00 (dd, J = 3.20, 13.34 Hz, C(3)H_β), 4.47 (dd, J = 6.32, 13.34 Hz, C(3)H_α), 4.96 (d, J = 3.00 Hz, C(1)H), 5.16 ($^1/_2$ ABq, J = 12.97 Hz, C(10)*H*H'), 5.24 ($^1/_2$ ABq, J = 12.97 Hz, C(10)H*H'*); UV-vis (CH_3CN) 249, 312, 518 nm.

***cis*-1-Methoxy-2-(methylamino)-7-aminomitosene (12a).** Compound **12a** was separated by reversed-phase TLC (R_f = 0.29) using 50% aqueous CH_3CN as the eluant and then purified by passing through a SiO_2 gel column using $CHCl_3$/MeOH (4/1) as the eluant: ^1H NMR (CD_3OD) δ 1.80 (s, C(6)CH_3), 2.49 (s, NCH_3), 3.41 (s, OCH_3), 3.70–3.80 (m, C(2)H, C(3)H_β), 4.56 (dd, J = 4.99, 9.75 Hz, C(3)H_α), 4.76 (d, J = 4.50 Hz, C(1)H), 5.26 (s, C(10)H_2); ^{13}C NMR (DMSO-d_6) δ 8.45 (C(6)CH_3), 34.03 (NCH_3), 49.66 (C(3)), 56.02 (OCH_3), 57.35 (C(10)), 65.96 (C(2)), 71.41 (C(1)), 104.48 (C(6)), 114.55 (C(8a)), 119.98 (C(9)), 128.99 (C(9a)), 138.78 (C(7)), 147.25 (C(5a)), 156.49 (C(10)O*C*(O)NH_2), 176.41 (C(8)), 178.45 (C(5)); UV-vis (CH_3CN) 245, 310, 500 nm.

***trans*-1-Methoxy-2-(methylamino)-7-aminomitosene (12b).** Compound **12b** was separated by reversed-phase TLC (R_f = 0.21) using 50% aqueous CH_3CN as the eluant and then purified by passing through a SiO_2 column using $CHCl_3$/MeOH (4/1) as the eluant: ^1H NMR (CD_3OD) δ 1.80 (s, C(6)CH_3), 2.43 (s, NCH_3), 3.42 (s, OCH_3), 3.71–3.75 (m, C(2)H), 4.13 (d, J = 13.27 Hz, C(3)H_β), 4.34 (dd, J = 5.56, 13.27 Hz, C(3)H_α), 4.65 (s, C(1)H), 5.21 ($^1/_2$ ABq, J = 12.99 Hz, C(10)*H*H'), 5.27 ($^1/_2$ ABq, J = 12.99 Hz, C(10)H*H'*); ^{13}C NMR (DMSO-d_6) δ 8.38 (C(6)CH_3), 33.71 (NCH_3), 51.63 (C(3)), 55.71 (OCH_3), 56.92 (C(10)), 68.71 (C(2)), 78.22 (C(1)), 104.65 (C(6)), 114.08 (C(8a)), 121.01 (C(9)), 128.30 (C(9a)), 139.11 (C(7)), 147.18 (C(5a)), 156.45 (C(10)O*C*(O)NH_2), 176.43 (C(8)), 178.33 (C(5)); UV-vis (CH_3CN) 243, 303, 494 nm.

Solvolysis of 7-Aminoaziridinomitosenes 3 in Buffered MeOH Solutions. A Kinetic Study. 7-Aminoaziridinomitosene (**3a** or **3b**, 2 mg, final concentration 13 mM) was dissolved in DMSO-d_6 (0.5 mL) and deaerated with Ar (15 min). A 50-μL sample of the DMSO-d_6 stock solution was then added to a buffered MeOH solution (0.5 mL) maintained at 20 ± 1 °C. Bis·tris·HCl (0.05 M) + tris·HCl (0.05 M) was utilized in the "pH" 7.0 transformations, and bis·tris·HCl (0.03 M) + tris·HCl (0.07 M) was used in the "pH" 8.5 transformations. Each reaction was carried for at least 2 half-lives and monitored by HPLC. Verification of the product peaks (i.e., **4a**, **4b**, **12a**, **12b**) was conducted by coinjection (cospotting) of an authentic sample with the reaction mixture in the HPLC (TLC). Standard data plots yielded linear slopes from which pseudo-first-order rate constants (k_1, s^{-1}) were calculated. Duplicate kinetic runs were performed and the results averaged (Table II).

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Supplementary Material Available: Copies of the NMR spectra for compounds **3a,b**, **7**, **9a,b**, **10b**, **11a,b**, and **12a,b** (13 pages). Ordering information is given on any current masthead page.

1′,2′-Secothymidines. The Preparation of 2,3′-Anhydro Derivatives and the Formation of Two Unusual Dimeric Products

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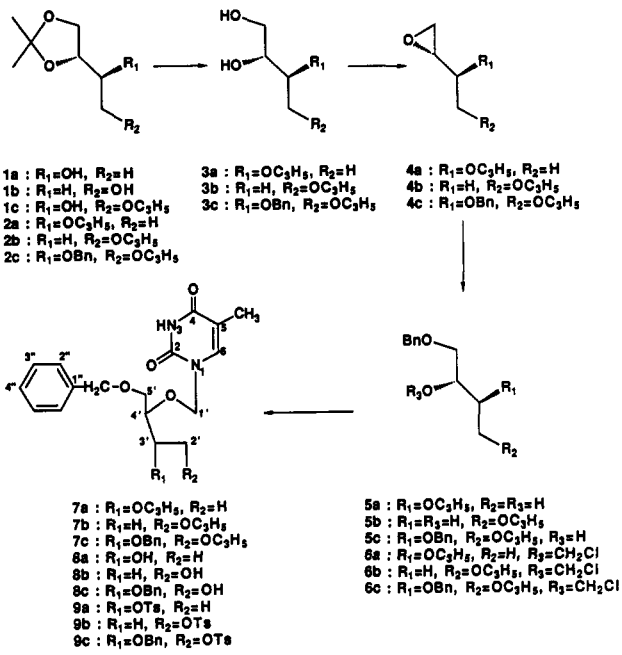
2,2′- and 2,3′-anhydropyrimidine nucleosides are rigid compounds that are restricted to the syn conformation. In certain cases, this enforced conformational rigidity has led to biologically active compounds. To capitalize on this rationale, attempts were made to prepare the corresponding anhydro analogues of 1′,2′-secothymidine. Starting with the functionalized butanetetrols and -triols (**1a–c** and **2a–c**), derived from D-isoascorbic acid, the 1′,2′-seco nucleoside tosylates **9a–c** were prepared. While attempts to form the 2,3′-anhydro derivatives (**10a** and **12**) were successful, no 2,2′-anhydro analogues could be obtained even under a variety of reaction conditions. Instead, unusual dimeric compounds were formed whose structures were confirmed by ^{13}C NMR and mass spectrometry. The dimerization reaction does not appear to have been previously reported.

The discovery of acyclovir as an antiviral agent[1] has stimulated the search for other acyclic nucleosides with comparable or broader spectra of activity. Subsequently, 9-(dihydroxypropoxymethyl)guanine (DHPG) was synthesized,[2] shown to have antiherpetic activity, and has recently been approved for clinical use against human cytomegalovirus. In addition, two phosphonic acid acyclic nucleosides, 9-[(*S*)-3-hydroxy-2-(phosphonylmethoxy)propyl]adenine (*S*-HPMPA) and 9-[(phosphonylmethoxy)ethyl]adenine (PMEA) have also demonstrated antiherpetic[3] activity as well as anti-HIV activity.[4]

(1) Schaeffer, H. J.; Beauchamp, L.; De Miranda, P.; Elion, G.; Bauer, D. G.; Collins, P. *Nature (London)* **1978**, *272*, 583.
(2) Martin, J. C.; Dvorak, C. A.; Smee, D. F.; Matthews, T. R.; Verheyden, J. P. H. *J. Med. Chem.* **1983**, *26*, 759 and references cited therein.
(3) De Clercq, E.; Sakuma, T.; Baba, M.; Pauwels, R.; Balzarini, J.; Rosemberg, I. *Antiviral Res.* **1987**, *8*, 261.

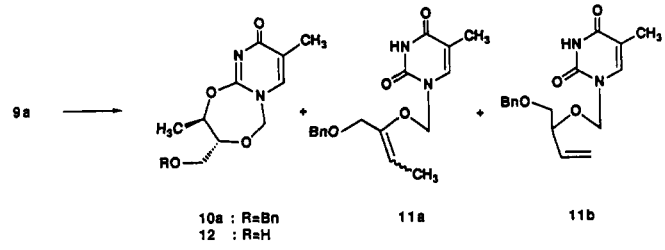
0022-3263/91/1956-4653$02.50/0

Scheme I



The potential for chemotherapeutic activity by these acyclic nucleosides has spurred the synthesis of a large number of analogues.[5,6] Among them are the 1′,2′-seco nucleosides, a class of compounds that retains the entire carbon framework and chirality of the sugar moiety of the nucleoside, and thus has two chiral centers. Recent reports from our laboratory[7-10] have described a chiral synthetic approach to this class of compounds starting with chirons derived from L-ascorbic and D-isoascorbic acids.[11] Unfortunately, antiviral evaluation of these compounds did not reveal any significant activity. It was rationalized that the flexibility of the acyclic moiety might have prevented their interaction with kinases to form the corresponding 1′,2′-seco nucleotides. Should this be the case, the free rotation of the acyclic moiety can be restricted without affecting the overall conformation of the molecule by anchoring the chain to the heterocyclic base in the form of an anhydro derivative. Such an approach finds precedence in nucleoside literature where a variety of anhydro nucleosides have been prepared[12] and some have been found to have antiviral activity.[13,14] In addition, molecular modeling studies showed that thymidine (in the syn conformation) and 2,2′-anhydro-1′,2′-secothymidine were almost superimposable.[15] This finding suggests that conformationally restricted acyclic nucleosides may resemble the natural compounds more closely and, hence, increase the likelihood of their phosphorylation.

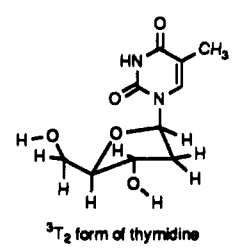
Scheme II

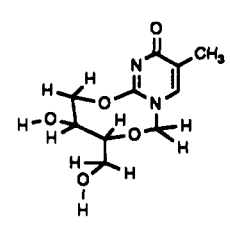


Thus, the syntheses of 2,3′- and 2,2′-anhydro-1′,2′-secothymidines were undertaken. Retrosynthetic analysis of the target molecule **12** led to (2*R*,3*S*)-1,2-*O*-isopropylidenebutane-1,2,3-triol (**1a**), which has been obtained from D-isoascorbic acid in high yields.[11] Alcohol **1a** provides the necessary functionality for further elaboration into tosylate **9a** and subsequently to the anhydrothymidine **12** (Schemes I and II). Allylation of **1a** followed by hydrolysis furnished diol **3a**, which was converted to epoxide **4a** via the Mitsunobu reaction[16] in 82% yield. Regiospecific ring opening of **4a** with sodium benzylate[17] afforded alcohol **5a** in 67% yield. Compound **5a** was chloromethylated and coupled[10] with the persilylated thymine in the presence of a catalytic amount of tetrabutylammonium iodide to furnish the protected 1′,2′-secothymidine **7a** in 88% yield. Selective removal[18] of the allyl group at the 3′-position provided alcohol **8a**, which was tosylated to give **9a** in 86% yield. The cyclization of compound **9a** was then attempted using a variety of reaction conditions (refluxing DMF or acetonitrile, NaH molar ratios ranging from 1:1 to 5:1 (NaH:**9a**), and reaction times ranging from 30 min to 24 h). TLC analysis (EtOAc) of the reaction mixtures consistently demonstrated the presence of two major products. One product was identified as the desired 2,3′-anhydrothymidine compound **10a**, which was isolated from the reaction mixture by recrystallization in yields ranging from 24 to 56%. The target

(4) Pauwels, R.; Balzarini, J.; Schols, D.; Baba, M.; Desmyter, J.; Rosemberg, I.; Holy, A.; De Clercq, E. *Antimicrob. Agents Chemother.* **1988**, *32*, 1025.
(5) For a recent review, see: Chu, C. K.; Cutler, S. J. *J. Heterocycl. Chem.* **1986**, *23*, 289.
(6) Schaeffer, H. J. In *Nucleosides, Nucleotides and Their Biological Applications*; Rideout, J. L., Henry, D. W., Beacham, L. M., Eds.; Academic Press; New York, 1983; p 1-17.
(7) Vemishetti, P.; Leiby, R. W.; Abushanab, E.; Panzica, R. P. *J. Heterocycl. Chem.* **1988**, *25*, 651.
(8) Abushanab, E.; Sarma, M. S. P. *J. Med. Chem.* **1989**, *32*, 76.
(9) Vemishetti, P.; Abushanab, E.; Leiby, R. W.; Panzica, R. P. *Nucleosides Nucleotides* **1989**, *8*, 201.
(10) Vemishetti, P.; Saibaba, R.; Panzica, R. P.; Abushanab, E. *J. Med. Chem.* **1990**, *33*, 681.
(11) Abushanab, E.; Vemishetti, P.; Leiby, R. W.; Sing, H. K.; Mikkilineni, A. B.; Wu, D. C.-J.; Saibaba, R.; Panzica, R. P. *J. Org. Chem.* **1988**, *53*, 2598.
(12) For a review, see: Fox, J. J. *Pure and Applied Chemistry*; Butterworth: London, 1969; Vol. 18, p 223.
(13) Ashwell, M.; Jones, A. S.; Kumar, A.; Sayers, J. R.; Walker, R. T.; Sakuma, T.; De Clercq, E. *Tetrahedron* **1987**, *43*, 4601.
(14) Lin, T.-S.; Shen, Z.-Y.; August, E. M.; Brankovan, V.; Yang, H.; Ghazzouli, I.; Prusoff, W. H. *J. Med. Chem.* **1989**, *32*, 1891.

(15) These data result from an in-depth study using the molecular modeling program MACROMODEL (MM-2). Two sugar conformations, for *syn*-thymidine, the $^3T_2$ and the $^2T_3$, were considered. Molecular mechanics calculations found these two forms to be of comparable energy. (The $^3T_2$ conformation (shown below) was more stable by 0.322 kcal/mol.) (The acyclic nucleoside analogue, 1′,2′-seco-2,2′-anhydrothymidine, had two local minimal energy forms the more stable of which is illustrated below. It was determined by root mean square deviation (rms) measurements that the $^3T_2$ form of thymidine overlapped with the more stable conformation of the seco analogue to give the best fit. The rms deviations for matched atoms ranged from 0.201 to 0.725 Å. Thus, despite large conformational changes that occur in going from *syn*-thymidine to 1′,2′-seco-2,2′-anhydrothymidine, formation of the anhydro linkage appears to be feasible and overlap with the natural compound is possible.


$^3T_2$ form of thymidine


more stable form of 1′,2′-seco-2,2′-anhydrothymidine

(16) Mitsunobu, O. *Synthesis* **1981**, 1.
(17) Mikkilineni, A. B.; Kumar, P.; Abushanab, E. *J. Org. Chem.* **1988**, *53*, 6005.
(18) Boss, R.; Scheffold, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 558.

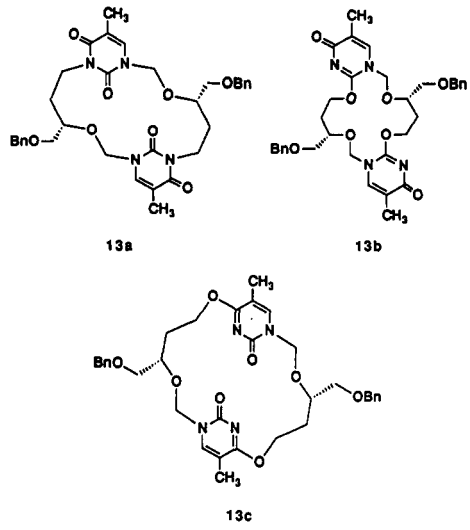


Figure 1.

nucleoside **12** was obtained by the transfer hydrogenolysis[19] of **10a** in 42% yield.

Subsequent ^{1}H NMR analysis of the other major reaction constituent proved it to actually be a mixture of elimination products. Attempts at purification of this mixture were of limited success. Spectral data on a partially purified sample[20] (ca. 90%) allowed us to assign **11a** as the structure of one of the components; however, we were unable to assign the geometry. Careful reexamination of the ^{1}H NMR data for the mixture[21] led us to assign structure **11b** for the other component present. Our structural designation of isomeric alkenes was confirmed by elemental analysis of the mixture.[22] In addition, we found that the ratio of the two isomers is solvent dependent, giving a 1:1 (**11a**:**11b**) mixture in DMF and a 3:1 (**11a**:**11b**) mixture in acetonitrile. It is worth mentioning that when **10a** was subjected to identical reaction conditions as for cyclonucleoside formation, i.e., NaH in DMF or acetonitrile at reflux, no alkenyl products were obtained. This evidence suggests that the elimination reaction leading to the formation of such products occurs prior to, not after, anhydronucleoside formation. It is of interest to note that when the cyclization of **9a** was attempted using 1,8-diazabicyclo[5.4.0]undec-7-ene[23] (DBU) in refluxing acetonitrile, **10a** was obtained in an 82% yield without the formation of any alkene side products.

Extension of this synthetic methodology to prepare the seco-2,2'-anhydrothymidine analogue **10b** required the formation of tosylate **9b**. The known alcohol **1b**,[24] derived from D-isoascorbic acid, was converted to **9b** following the same synthetic sequence outlined earlier. Intramolecular cyclization of the tosylate **9b** was attempted using NaH (2:1, NaH:**9b**) in dry DMF and yielded after column chromatography a homogeneous gum. ^{1}H NMR spectral analysis of the product suggested that cyclization did take place as evidenced by the lack of the tosyl and the N3 proton signals. However, the high-resolution mass spectrum (HRMS) of this product did not give the expected molecular ion peak MH^+ of the anhydro derivative **10b**. Instead, a MH^+ peak that was double the molecular weight of the desired product (MH^+ = 633.2838) was observed. These data suggest the formation of a dimeric compound via *inter*molecular cyclization rather than the expected monomeric product by an *intra*molecular reaction.

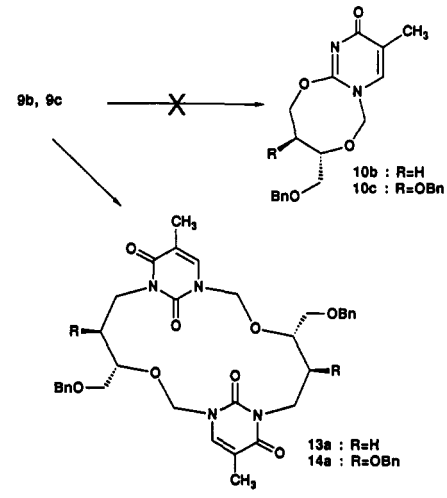
Deprotonation of N3 using sodium hydride generates the corresponding anion, which may be localized via resonance at either N3, O2, or O4. Hence, three possible dimeric structures[25] (Figure 1, **13a,b,c**) may be formulated for the reaction product. Dimer **13a** would result from the intermolecular nucleophilic attack of the N3 anion, one from each of the two nucleoside molecules involved in the dimerization, on the appropriate tosylate-bearing C2' position of the opposite nucleoside. Dimers **13b** and **13c** would be formed from a pair of nucleosides in a comparable fashion by either O2 or O4 attack at the C2' positions, respectively. From these three possible dimeric isomers, we assigned structure **13a** as the reaction product by comparing the ^{13}C chemical shifts of its C2 and C4 carbons to those obtained with model alkylated compounds[26-28] (Table I). In addition, comparison of the ^{13}C NMR data for **10a** and **12** to that given for known anhydropyrimidine nucleosides[26,27] confirmed our structural assignment for these compounds (Scheme III).

Table I. Selected ^{13}C Chemical Shifts for 10a, 12, 13a, and 14a and Related Model Compounds

compd	C2	C4
10	158.2_6	172.7_4
12	157.9_8	171.6_4
2,2'-anhydrothymidine[a]	159.2_9	172.3_3
2,5'-anhydro-2',3'-isopropylideneuridine[b]	157.5_0	171.1_0
13a	153.4_7	163.9_4
14a	151.1_2	163.7_1
1,3-dimethyluracil[b]	151.5_0	162.8_0
4-methoxythymidine[c]	158.7_0	173.1_0

[a] Cited from ref 26. [b] Cited from ref 27. [c] Cited from ref 28.

Scheme III



(19) Ogilvie, K. K.; Cheriyan, V. O.; Radatus, B. K.; Smith, K. O.; Galloway, K. S.; Kennell, W. L. *Can. J. Chem.* **1982**, *60*, 3005.

(20) Spectral data for compound **11a**: ^{1}H NMR ($CDCl_3$) δ 1.63 (d, 3, J = 7.0 Hz), 1.86 (s, 3), 4.08 (s, 2), 4.50 (s, 2), 5.00 (q, 1, J = 7.0 Hz), 5.38 (s, 2), 7.12 (s, 1), 7.31 (m, 5), 8.72 (br s, 1, D_2O exchangeable).

(21) Cancellation of the resonances applicable to **11a** (obtained on the partially purified sample[20]) gave the ^{1}H NMR for **11b** as follows: ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3), 3.49 (d, 2, J = 5.3 Hz), 4.20 (m, 1), 4.52 (s, 2), 5.09 (d, 1, J = 10.5 Hz), 5.28 (m, 2), 5.42 (m, 1), 5.75 (m, 1), 7.18 (s, 1), 7.30 (m, 5), 8.78 (br s, 1, D_2O exchangeable).

(22) Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.56; H, 6.33; N, 8.86. Found: C, 64.36; H, 6.53; N, 8.59.

(23) Hrebabecky, H.; Holy, A.; De Clercq, E. *Collect. Czech. Chem. Commun.* **1990**, *55*, 1801.

(24) Saibaba, R.; Sarma, M. S. P.; Abushanab, E. *Synth. Commun.* **1989**, *19*, 3077.

(25) We thank the original reviewer for suggesting the dimeric structures **13a** and **13c**.

(26) Vargeese, C.; Abushanab, E. Unpublished results.

(27) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH Publishers: New York, 1987; pp 404–8.

(28) Allore, B. D.; Queen, A.; Blonski, W. J.; Hruska, F. E. *Can. J. Chem.* **1983**, *61*, 2397.

It was speculated that this unusual cyclization could be prevented by the introduction of a bulky substituent at the 3′-position. Subsequently, the 3′-*O*-benzyl derivative **9c** was prepared following synthetic routes similar to those discussed earlier for the synthesis of **9a**. Thus, alcohol **1c**, obtained from (2*R*,3*S*)-3,4-epoxy-1,2-*O*-isopropylidenebutane-1,2-diol[11] on treatment with sodium allylate in *t*-BuOH, was benzylated and converted to tosylate **9c**. Here again, when this compound was subjected to cyclization conditions, a dimeric molecule **14a** was obtained in similar yields. Comparison of the ^{13}C NMR data for **14a** (Table I) to that obtained for dimer **13a** demonstrated that the substitution patterns were identical. Our attempts to favor an intramolecular reaction, including variations in the type of base used, solvent, reaction temperature, and dilution, failed to give the desired monomeric compounds.

The preferential *intra-* and *inter*molecular cyclization of **9a** on one hand, and **9b** and **9c** on the other, is attributable to the difference in the ring size of the desired product. This is not surprising since seven-membered rings are more readily formed than are eight-membered ones.[29] A literature search indicated that this type of heterocyclic dimer has not been previously reported. The closest analogy was found in the area of aza-crown ethers.[30] The utility of this methodology, which leads to the unusual dimeric products, as well as the compounds themselves, is currently under investigation.

Experimental Section

Melting points were determined on a Buchi 535 melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on either a Varian EM-390 and/or Bruker 300 MHz spectrometer. Chemical shifts are in parts per million with respect to TMS. High-resolution mass spectra were obtained on a Kratos MS-50 instrument. Optical rotations were measured on a Perkin-Elmer Model-141 digital readout polarimeter. Silica gel (Merck grade 60, 230–400 mesh, 60 Å) suitable for column chromatography was purchased from Aldrich. All solvent proportions are by volume unless otherwise stated. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

(2*R*,3*S*)-4-*O*-Allyl-1,2-*O*-isopropylidenebutane-1,2,3,4-tetrol (1c). (2*R*,3*S*)-3,4-Epoxy-1,2-*O*-isopropylidenebutane-1,2-diol[11] (14.4 g, 0.10 mol), allyl alcohol (34.8 g, 0.40 mol), and *tert*-butyl alcohol (275 mL) were added successively to a stirred solution of sodium hydroxide (8.1 g, 0.20 mol) in water (8.1 mL) at room temperature. The reaction mixture was stirred vigorously for 6 h at 90 °C. The excess allyl alcohol and remaining *tert*-butyl alcohol were removed under reduced pressure. The residue was then diluted with water (100 mL) and extracted with Et_2O (3 × 100 mL). The ether extract was washed with a saturated sodium chloride solution (2 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated to furnish **1c** (17.5 g, 86.6%). An analytical sample was obtained by short-path distillation: bp 100 °C (0.1 mmHg); $[\alpha]^{26}_D$ −2.34° (*c* 4.4, EtOH); ^1H NMR (CCl_4) δ 1.26 (s, 3), 1.33 (s, 3), 2.56 (m, 1, D_2O exchangeable), 3.22–3.70 (m, 3), 3.72–4.12 (m, 5), 5.00–5.34 (m, 2), 5.56–6.02 (m, 1). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.32; H, 8.76.

(2*R*,3*S*)-3-*O*-Allyl-1,2-*O*-isopropylidenebutane-1,2,3-triol (2a). Sodium hydride in mineral oil (60%, 5.6 g, 140 mmol) was washed free from the oil with hexanes, and then anhydrous dimethylformamide (DMF, 100 mL) was added. A solution of the alcohol **1a**[11] (17.0 g, 116 mmol) in dry DMF (50 mL) was slowly added with stirring. After 1.5 h, a solution of allyl bromide (12.1 mL, 16.9 g, 140 mmol) in dry DMF (50 mL) was added and the mixture was stirred for 12 h at room temperature before being poured into ice–water (400 mL) and extracted into Et_2O (4 × 100 mL). The combined ether extracts were backwashed with water (8 × 100 mL) to remove residual DMF and subsequently dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by distillation of the reaction product at reduced pressure (43 °C (0.25 mmHg)) gave **2a** (18.28 g, 84%) as a viscous liquid: $[\alpha]^{26}_D$ +33.4° (*c* 2.53, EtOAc); ^1H NMR ($CDCl_3$) δ 1.20 (d, 3, *J* = 6.0 Hz), 1.34 (s, 3), 1.40 (s, 3), 3.27–4.34 (m, 6), 5.00–5.37 (m, 2), 5.58–6.20 (m, 1). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.52; H, 9.68. Found: C, 64.70; H, 9.84.

(*S*)-4-*O*-Allyl-1,2-*O*-isopropylidenebutane-1,2,4-triol (2b). Compound **2b** was prepared in 88% yield from **1b**[24] utilizing the procedure described for the synthesis of **2a**: $[\alpha]^{25}_D$ −2.81° (*c* 0.57, EtOH); ^1H NMR ($CDCl_3$) δ 1.34 (s, 3), 1.40 (s, 3), 1.82 (br q, 2, *J* = 9 Hz), 3.36–3.64 (m, 3), 3.84–4.30 (m, 4), 5.00–5.34 (m, 2), 5.60–6.12 (m, 1). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.52; H, 9.68. Found: C, 64.36; H, 9.42.

(2*R*,3*S*)-4-*O*-Allyl-3-*O*-benzyl-1,2-*O*-isopropylidenebutane-1,2,3,4-tetrol (2c). The alcohol **1c** was benzylated by a procedure similar to that described for the preparation of **2a** using benzyl bromide instead of allyl bromide. Workup, followed by silica gel column chromatography eluting with hexanes–ethyl acetate (95:5), gave pure **2c** in 95% yield: $[\alpha]^{26}_D$ +26.2° (*c* 4.04, EtOH); ^1H NMR (CCl_4) δ 1.25 (s, 3), 1.34 (s, 3), 3.30–3.60 (m, 3), 3.66–4.14 (m, 5), 4.58 (q_{AB}, 2, *J* = 12 Hz), 4.95–5.34 (m, 2), 4.96–6.04 (m, 1), 7.20 (s, 5). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.74; H, 8.11.

(2*R*,3*S*)-3-*O*-Allylbutane-1,2,3-triol (3a). Amberlite IR-120 resin (11 g), water (6 mL), and concentrated HCl (4 mL) were added to a solution of the compound **2a** (10.5 g, 56.4 mmol) in 95% ethanol (200 mL), and the mixture was stirred for 72 h at room temperature. After filtration of the resin, the filtrate was concentrated to give an oily material that was dissolved in Et_2O (100 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave **3a** (7.60 g, 92%) as a viscous liquid: $[\alpha]^{26}_D$ +32.7° (*c* 5.20, EtOH); ^1H NMR ($CDCl_3$) δ 1.12 (d, 3, *J* = 6 Hz), 3.20–4.06 (m, 8, 2 H D_2O exchangeable), 4.99–5.33 (m, 2), 5.59–6.08 (m, 1). Anal. Calcd for $C_7H_{14}O_3$: C, 57.53; H, 9.59. Found: C, 57.41; H, 9.66.

(*S*)-4-*O*-Allylbutane-1,2,4-triol (3b). The hydrolysis of **2b** was carried out as described for compound **3a**. After workup, the residue was chromatographed using hexanes–ethyl acetate (1:1) as eluent to give the diol **3b** (96%) as an oil: $[\alpha]^{25}_D$ −26.4° (*c* 4.54, EtOH); ^1H NMR ($CDCl_3$) δ 1.70 (q, 2, *J* = 9 Hz), 3.34–3.89 (m, 5), 3.95 (d, 2, *J* = 6 Hz), 4.16 (br s, 2, D_2O exchangeable), 5.03–5.38 (m, 2), 5.64–6.12 (m, 1). Anal. Calcd for $C_7H_{14}O_3$: C, 57.53; H, 9.59. Found: C, 57.06; H, 9.05.

(2*R*,3*S*)-4-*O*-Allyl-3-*O*-benzylbutane-1,2,3,4-tetrol (3c). Compound **2c** was used to prepare **3c** by the procedure described for the formation of **3a**: $[\alpha]^{26}_D$ +8.82° (*c* 3.5, EtOH); ^1H NMR ($CDCl_3$) δ 2.67 (br t, 1, *J* = 8 Hz, D_2O exchangeable), 3.16 (d, 1, *J* = 8 Hz, D_2O exchangeable), 3.45–3.88 (m, 6), 4.08 (d, 2, *J* = 7 Hz), 4.62 (q_{AB}, 2, *J* = 12 Hz), 5.05–5.39 (m, 2), 5.64–6.11 (m, 1), 7.30 (s, 5). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.62; H, 7.82.

(2*R*,3*S*)-3-(Allyloxy)-1,2-epoxybutane (4a). Triphenylphosphine (TPP, 17.0 g, 64 mmol) and the diol **3a** (9.3 g, 64 mmol) were dissolved in dry benzene (150 mL) in a single-necked 250-mL round-bottom flask. The solution was concentrated to ca. 25 mL and then cooled to room temperature. To this cooled solution was added diisopropyl azodicarboxylate (DIAD, 12.6 mL, 12.85 g, 64 mmol) dropwise, and the resulting viscous mixture was stirred at room temperature for 30 min. Residual benzene was removed under diminished pressure, and distillation of this reaction mixture at reduced pressure (43 °C (0.35 mmHg)) afforded **4a** (6.70 g, 82%) as an oil: $[\alpha]^{24}_D$ −3.70° (*c* 6.87, EtOAc); ^1H NMR ($CDCl_3$) δ 1.21 (d, 3, *J* = 6 Hz), 2.49–2.89 (m, 3), 3.13–3.43 (m, 1), 3.88–4.05 (m, 2), 4.93–5.33 (m, 2), 5.55–6.03 (m, 1). Anal. Calcd for $C_7H_{12}O_2$: C, 65.63; H, 9.38. Found: C, 65.76; H, 9.48.

(*S*)-4-(Allyloxy)-1,2-epoxybutane (4b). Diisopropyl azodicarboxylate (DIAD, 3.9 g, 19.3 mmol) was added dropwise to a stirred solution of **3b** (2.3 g, 15.8 mmol) and triphenylphosphine (5.0 g, 19.2 mmol) in dry benzene (23 mL). After the mixture was cooled to room temperature, benzene was removed under reduced pressure, and the remaining residue was distilled at 40 °C (0.4 mmHg) to give 1.52 g (76%) of the epoxide **4b**. An analytically pure sample was obtained by silica gel column chromatography

(29) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*; Plenum Press: New York, 1984; Part A, p 147.

(30) Krakowiak, K. E.; Bradshaw, J. S.; Zamecka-Krakowiak, D. J. *Chem. Rev.* **1989**, *89*, 929.

(31) Carbon and proton chemical shifts were assigned using COSY, HETCOR, and DEPT experiments.

using hexanes–ethyl acetate (9:1) as eluent: $[\alpha]^{25}_D$ –0.09° (*c* 3.88, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.60–1.96 (m, 2), 2.44 (dd, 1, *J* = 4.5 Hz, *J* = 3.0 Hz), 2.73 (t, 1, *J* = 4.5 Hz), 2.88–3.14 (m, 1), 3.56 (t, 2, *J* = 6 Hz), 3.95 (d, 2, *J* = 6 Hz), 5.02–5.44 (m, 2), 5.62–6.14 (m, 1). Anal. Calcd for $C_7H_{12}O_2$: C, 65.63; H, 9.38. Found: C, 65.61; H, 9.58.

(2*R*,3*S*)-4-(Allyloxy)-3-(benzyloxy)-1,2-epoxybutane (4c). To a cooled solution of the diol **3c** (6.0 g, 23.8 mmol) and triphenylphosphine (7.2 g, 27.5 mmol) in dry benzene (70 mL) was added dropwise diisopropyl azodicarboxylate (DIAD, 5.9 g, 28 mmol), and when the addition was complete the mixture was allowed to stir for 30 min. The remaining benzene was removed under diminished pressure, and the resulting solution was stirred at 140–145 °C (0.8 mmHg) for 15 min. After being cooled to room temperature, the reaction mixture was dissolved in Et_2O and the solids were precipitated by the addition of hexanes and then filtered. The filtrate was concentrated and chromatographed over silica gel (hexanes–ethyl acetate (95:5)) to provide the epoxide **4c** (4.4 g, 79%): $[\alpha]^{26}_D$ +4.71° (*c* 2.55, EtOH); ^{1}H NMR ($CDCl_3$) δ 2.41–2.78 (m, 2), 2.85–3.14 (m, 1), 3.20–3.64 (m, 3), 3.86–4.08 (d, 2, *J* = 7 Hz), 4.50 (s, 2), 4.88–5.35 (m, 2), 5.50–6.00 (m, 1), 7.20 (s, 5). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.91; H, 7.93.

(2*R*,3*S*)-3-*O*-Allyl-1-*O*-benzylbutane-1,2,3-triol (5a). Benzyl alcohol (29.1 mL, 30.4 g, 280 mmol), sodium hydroxide (3.8 g, 95 mmol) dissolved in water (3.8 mL), and *tert*-butyl alcohol (75 mL) were stirred at reflux for 30 min. After **4a** (6.0 g, 47 mmol) was added, the reaction mixture was stirred vigorously at reflux until **4a** was no longer detectable (TLC, hexanes–ethyl acetate (4:1), v/v). The solvents were removed under diminished pressure, and water (100 mL) was added to the reaction mixture. The aqueous solution was extracted with $CHCl_3$ (3 × 100 mL). The $CHCl_3$ layers were combined, backwashed with water (3 × 100 mL) and brine (100 mL), and then dried over anhydrous Na_2SO_4. Following concentration at reduced pressure (rotary evaporator), the benzyl alcohol was removed under high vacuum (68 °C (0.4 mmHg)) and continued distillation of this reaction mixture (135 °C (0.35 mmHg)) provided **5a** (7.4 g, 67%): $[\alpha]^{26}_D$ +19.6° (*c* 3.09, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.14 (d, 3, *J* = 6.5 Hz), 2.68 (br s, 1, D_2O exchangeable), 3.34–4.18 (m, 6), 4.50 (s, 2), 4.98–5.35 (m, 2), 5.60–6.07 (m, 1), 7.31 (s, 5). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.19; H, 8.48. Found: C, 71.34; H, 8.25.

(*S*)-4-*O*-Allyl-1-*O*-benzylbutane-1,2,4-triol (5b). Epoxide **4b** was opened with benzylate anion as in the synthesis of **5a**. The usual workup followed by distillation (110–115 °C (0.1 mmHg)) furnished **5b** (6.4 g, 91.4%): $[\alpha]^{25}_D$ –9.03° (*c* 2.47, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.70 (q, 2, *J* = 9 Hz), 3.00 (br s, 1, D_2O exchangeable), 3.32–3.68 (m, 4), 3.76–4.10 (m, 3), 4.48 (s, 2), 4.96–5.34 (m, 2), 5.58–6.06 (m, 1), 7.32 (s, 5). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.19; H, 8.48. Found: C, 71.00; H, 8.48.

(2*R*,3*S*)-4-*O*-Allyl-1,3-di-*O*-benzylbutane-1,2,3,4-tetrol (5c). Epoxide **4c** was converted to the alcohol **5c** by the procedure described for the formation of **5a**. The crude product was chromatographed over silica gel (hexanes–ethyl acetate (9:1)) to obtain 6.0 g (90%) of pure **5c**: $[\alpha]^{25}_D$ +12.1° (*c* 1.80, EtOH); ^{1}H NMR ($CDCl_3$) δ 2.64 (d, 1, *J* = 6 Hz, D_2O exchangeable), 3.54–4.12 (m, 8), 4.48 (s, 2), 4.60 (q, 2, *J* = 9 Hz), 5.00–5.38 (m, 2), 5.65–6.05 (m, 1), 7.30 (s, 10). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.77; H, 7.48.

(2*R*,3*S*)-3-(Allyloxy)-1-(benzyloxy)-2-(chloromethoxy)butane (6a). In a three-necked, flame-dried flask fitted with a gas-inlet and a drying tube were added, under N_2, paraformaldehyde (0.75 g, 8.3 mmol), **5a** (2.0 g, 8.5 mmol), and dry CH_2Cl_2 (40 mL). The mixture was cooled to 0 °C in an ice bath, the N_2 flow was discontinued, and dry HCl gas (concd H_2SO_4 tower) was bubbled into the solution for 6 h while the temperature was maintained at 0 °C. Calcium chloride (ca. 10 g) was added cautiously and the mixture stirred for 15 min. After filtration, the solution was concentrated under diminished pressure to give an oily material (2.5 g, quant), which contains ca. 90% of the chloromethyl ether **6a** as indicated by ^{1}H NMR analysis:[7] ^{1}H NMR ($CDCl_3$) δ 1.16 (d, 3, *J* = 6 Hz), 3.46–4.08 (m, 6), 4.46 (s, 2), 4.78–5.52 (m, 2), 5.56–6.05 (m, 3), 7.31 (s, 5).

(*S*)-4-(Allyloxy)-1-(benzyloxy)-2-(chloromethoxy)butane (6b). Chloromethylation of alcohol **5b** was carried out as for the synthesis of **6a** from **5a**. Product **6b** obtained after workup was used directly in the preparation of compound **7b**.

(2*R*,3*S*)-4-(Allyloxy)-1,3-bis(benzyloxy)-2-(chloromethoxy)butane (6c). Chloromethylation of alcohol **5c** was carried out as for the synthesis of **6a** from **5a**. Product **6c** obtained after workup was used directly in the preparation of compound **7c**.

1-[[3(*S*)-(Allyloxy)-1-(benzyloxy)-2(*R*)-butoxy]methyl]thymine (7a). Thymine (1.5 g, 11.9 mmol) and ammonium sulfate (ca. 50 mg) were added to hexamethyldisilazane (HMDS, 50 mL). The reaction mixture was stirred at reflux overnight with the exclusion of moisture. After the mixture was cooled to room temperature (clear solution), the excess HMDS was removed under reduced pressure and the residue dried under high vacuum. A solution of the chloromethyl ether **6a** (90% pure, 2.5 g, 8.5 mmol) in dry CH_2Cl_2 (40 mL) and tetrabutylammonium iodide (TBAI, ca. 100 mg) were added to the persilylated thymine, and the contents were stirred at reflux overnight. The reaction mixture was then diluted with water (10 mL) and methanol (20 mL), stirred for 15 min, and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (50 mL), washed successively with water (3 × 25 mL) and brine (25 mL), and then dried over anhydrous Na_2SO_4. The viscous material obtained after solvent removal at reduced pressure was chromatographed on a silica gel column eluting with hexanes–ethyl acetate (3:2) to give **7a** (2.60 g, 88%, yield based on pure chloromethyl ether) as a gum: $[\alpha]^{26}_D$ –0.54° (*c* 1.91, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.08 (d, 3, *J* = 6 Hz), 1.81 (s, 3), 3.38–3.98 (m, 6), 4.43 (s, 2), 4.96–5.28 (m, 4), 5.53–6.00 (m, 1), 7.06 (s, 1), 7.26 (s, 5), 9.02 (br s, 1, D_2O exchangeable). Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.17; H, 6.95; N, 7.49. Found: C, 63.97; H, 6.90; N, 7.45.

1-[[4-(Allyloxy)-1-(benzyloxy)-2(*S*)-butoxy]methyl]thymine (7b). The chloromethyl ether **6b** was reacted with persilylated thymine to give crude **7b** by following the procedure described for the formation of **7a**. Silica gel column chromatography using hexanes–ethyl acetate (4:1) afforded **7b** in 81% yield: $[\alpha]^{26}_D$ –34.8° (*c* 2.52, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.46–1.94 (m, 2), 1.84 (s, 3), 3.26–3.62 (m, 4), 3.70–4.07 (m, 3), 4.46 (s, 2), 4.92–5.36 (m, 4), 5.58–6.04 (m, 1), 7.10 (s, 1), 7.26 (s, 5), 9.98 (br s, 1, D_2O exchangeable). Anal. Calcd for $C_{20}H_{26}N_2O_5$: 64.17; H, 6.95; N, 7.49. Found: C, 63.92; H, 6.90; N, 7.44.

1-[[4-(Allyloxy)-1,3(*S*)-bis(benzyloxy)-2(*R*)-butoxy]methyl]thymine (7c). Compound **7c** was prepared from **6c** following the procedure described for the formation of **7a**. The crude product, after column chromatography (hexanes–ethyl acetate, 9:1) gave pure **7c** (99%): $[\alpha]^{26}_D$ –0.09° (*c* 1.13, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 3), 3.48–4.15 (m, 8), 4.46 (s, 2), 4.58 (d, 2, *J* = 3 Hz), 4.98–5.38 (m, 4), 5.60–6.06 (m, 1), 7.02 (s, 1), 7.26 (s, 10), 9.68 (s, 1, D_2O exchangeable). Anal. Calcd for $C_{27}H_{32}N_2O_6$: C, 67.48; H, 6.71; N, 5.83. Found: C, 67.65; H, 6.84; N, 5.77.

1-[[1-(Benzyloxy)-3(*S*)-hydroxy-2(*R*)-butoxy]methyl]thymine (8a). A solution of compound **7a** (4.3 g, 11.5 mmol) in methanol (125 mL) and water (25 mL) was treated with 10% palladium on carbon (Pd/C, 0.90 g) and *p*-toluenesulfonic acid (0.61 g). The resulting suspension was stirred at reflux for 8 h. After being cooled to room temperature, the mixture was filtered through Celite and the solvents were removed at reduced pressure. The residue was dissolved in Et_2O (100 mL) and washed successively with 5% $NaHCO_3$ (3 × 100 mL), water (100 mL), and brine (100 mL). After the organic layer was dried with anhydrous Na_2SO_4, the solvents were removed at diminished pressure. Recrystallization from EtOAc gave 0.99 g of pure **8a** (26%) as a waxy solid. Silica gel column chromatography of the mother liquor using hexanes–ethyl acetate (1:3) gave an additional 2.6 g of **8a** (67%, total yield of **8a**, 93%): $[\alpha]^{26}_D$ –8.60° (*c* 2.61, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.13 (d, 3, *J* = 6 Hz), 1.83 (s, 3), 2.62 (br d, 1, D_2O exchangeable), 3.50–4.18 (m, 4), 4.47 (s, 2), 5.21 (s, 2), 7.06 (s, 1), 7.28 (s, 5), 9.12 (br s, 1, D_2O exchangeable). Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.08; H, 6.59; N, 8.38. Found: C, 61.04; H, 6.63; N, 8.26.

1-[[1-(Benzyloxy)-4-hydroxy-2(*S*)-butoxy]methyl]thymine (8b). Compound **8b** was prepared following the procedure described for the formation of **8a**. The usual workup followed by silica gel column chromatography eluting with hexanes–ethyl acetate (1:1) gave **8b** (95% yield): $[\alpha]^{26}_D$ –16.5° (*c* 1.89, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.52–1.90 (m, 2), 1.80 (s, 3), 3.24 (br s, 1, D_2O exchangeable), 3.38–3.74 (m, 4), 3.87–4.19 (m, 1), 4.47 (s, 2), 5.18 (q_{AB}, 2, *J* = 12 Hz), 7.06 (s, 1), 7.26 (s, 5), 9.92 (br s, 1, D_2O

exchangeable). Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.08; H, 6.59; N, 8.38. Found: C, 60.87; H, 6.43; N, 8.18.

1-[[1,3(*S*)-Bis(benzyloxy)-4-hydroxy-2(*R*)-butoxy]methyl]thymine (8c). Compound **8c** was prepared from **7c** in 42% yield using the procedure described for the formation of **8b**: $[\alpha]^{26}_D$ +3.42° (*c* 1.61, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3), 2.72 (br s, 1, D_2O exchangeable), 3.42–4.18 (m, 6), 4.44 (s, 2), 4.52 (s, 2), 5.16 (s, 2), 7.02 (s, 1), 7.26 (s, 10), 9.62 (br s, 1, D_2O exchangeable). Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.35; H, 6.54; N, 6.34.

1-[[1-(Benzyloxy)-3(*S*)-[(*p*-toluenesulfonyl)oxy]-2(*R*)-butoxy]methyl]thymine (9a). To a solution of compound **8a** (0.33 g, 0.99 mmol) in dry CH_2Cl_2 (5 mL) were added successively dry pyridine (0.55 mL) and *p*-toluenesulfonyl chloride (0.28 g, 1.48 mmol). After the solution was stirred at room temperature for 22 h, water (5 mL) and $CHCl_3$ (15 mL) were added to the reaction mixture. After separation of the layers, the organic phase was successively washed with 1.0 N HCl (3 × 10 mL), 5% aqueous NaOH (3 × 10 mL), water (3 × 10 mL), and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed at diminished pressure. Silica gel column chromatography, eluting with hexanes–ethyl acetate (1:1) gave **9a** (0.42 g, 86%) as a gum: $[\alpha]^{26}_D$ −21.0° (*c* 1.87, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.21 (d, 3, J = 5 Hz), 1.84 (s, 3), 2.31 (s, 3), 3.35–4.01 (m, 3), 4.38 (s, 2), 4.57–4.81 (m, 1), 5.11 (br s, 2), 7.03 (s, 1), 7.14–7.78 (m, 9), 9.50 (br s, 1, D_2O exchangeable). Anal. Calcd for $C_{24}H_{28}N_2O_7S$: C, 59.01; H, 5.74; N, 5.74; S, 6.56. Found: C, 59.13; H, 5.91; N, 5.54; S, 6.70.

1-[[1-(Benzyloxy)-4-[(*p*-toluenesulfonyl)oxy]-2(*S*)-butoxy]methyl]thymine (9b). A solution containing the alcohol **8b** (2.09 g, 6.3 mmol), *p*-toluenesulfonyl chloride (1.3 g, 7 mmol), and pyridine (2.5 mL) in dry CH_2Cl_2 (20 mL) was stirred at room temperature for 12 h. The usual workup and purification as described for the preparation of **9a** afforded **9b** (2.2 g, 75%): $[\alpha]^{26}_D$ −16.7° (*c* 1.66, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.62–2.10 (m, 5), 2.40 (s, 3), 3.36–3.62 (m, 2), 3.64–4.25 (m, 3), 4.44 (s, 2), 5.10 (s, 2), 7.02 (s, 1), 7.16–7.48 (m, 7), 7.64 (d, J = 6 Hz, 2), 8.88 (br s, 1, D_2O exchangeable). Anal. Calcd for $C_{24}H_{28}N_2O_7S$: C, 59.01; H, 5.74; N, 5.74; S, 6.56. Found: C, 59.08; H, 5.87; N, 5.60; S, 6.42.

1-[[1,3(*S*)-Bis(benzyloxy)-4-(*p*-toluenesulfonyl)-2(*R*)-butoxy]methyl]thymine (9c). A mixture of the alcohol **8c** (1.54 g, 3.5 mmol), *p*-toluenesulfonyl chloride (0.78 g, 4.2 mmol), and pyridine (1.5 mL) in dry CH_2Cl_2 (15 mL) was stirred for 36 h at room temperature. Following the usual workup, the crude product was purified by column chromatography eluting with hexanes–ethyl acetate (1:1) to give **9c** (1.5 g, 72%): $[\alpha]^{25}_D$ −6.27° (*c* 2.28, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 3), 2.36 (s, 3), 3.45–4.32 (m, 6), 4.40 (s, 4), 5.15 (s, 2), 6.90–7.36 (m, 13), 7.70 (d, 2, J = 6 Hz), 9.38 (br s, 1, D_2O exchangeable). Anal. Calcd for $C_{31}H_{34}N_2O_8S$: C, 62.61; H, 5.76; N, 4.71; S, 5.39. Found: C, 62.40; H, 5.82; N, 4.71; S, 5.51.

(2*R*,3*R*)-3-[(Benzyloxy)methyl]-2,8-dimethyl-2,3-dihydro-5*H*,9*H*-pyrimido[2,1-*b*]-1,5,3-dioxazepin-9-one (10a). Method A. To a stirred suspension of previously washed (3 × 2 mL hexanes) NaH (60% dispersion in mineral oil, 18.9 mg, 0.472 mmol) in dry DMF (5 mL) was added dropwise, a solution of **9a** (200 mg, 0.410 mmol) in dry DMF (5 mL). The reaction mixture was stirred at room temperature for 30 min and then at reflux for 45 min. At the end of this period, the solvents were removed at reduced pressure. Water (25 mL) was added, this aqueous layer was extracted with $CHCl_3$ (3 × 20 mL), and the chloroform layers were combined and backwashed with water (3 × 25 mL) and brine (25 mL). The organic layer was dried over anhydrous Na_2SO_4, and subsequent evaporation of the solvent at reduced pressure gave 1.13 g of a viscous mixture. The addition of ethyl acetate to this material caused the precipitation of pure **10a** as a white solid (73.3 mg, 56%): mp 182–185 °C; $[\alpha]^{26}_D$ +11.2° (*c* 2.15, $CHCl_3$); ^{1}H (300-MHz) NMR ($CDCl_3$) δ 1.38 (d, 3, J = 6.5 Hz), 1.97 (d, 3, J = 1.1 Hz), 3.63 (m, 2), 3.75 (m, 1), 4.32 (m, 1), 4.52 (q_{AB}, 2, J = 12.1 Hz), 5.27 (q_{AB}, 2, J = 11.3 Hz), 7.21 (d, 1, J = 1.1 Hz), 7.32 (m, 5); ^{13}C (300-MHz) NMR[31] ($CDCl_3$) δ 13.4_5 (C2′), 17.7_3 (C5*C*H3), 69.2_2 (C5′), 73.7_9 ($C_6H_5CH_2O$), 82.3_2 (C1′), 82.4_0 (C3′), 85.4_0 (C4′), 119.7_9 (C5), 127.8_8 (C2″), 128.0_8 (C4″), 128.5_4 (C3″), 137.2_0 (C1″), 137.3_1 (C6), 158.2_6 (C2), 172.7_4 (C4); HRMS(FAB) for $C_{17}H_{20}N_2O_4$ m/z calcd 317.1505, found 317.1501 (MH^+). Anal. Calcd: C, 64.56; H, 6.33; N, 8.86. Found: C, 64.48; H, 6.32; N, 8.79.

Method B. A solution of **9a** (225 mg, 0.5 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.1 mL, 0.65 mmol) in acetonitrile (5 mL) was heated under reflux for 24 h. Reaction workup, as described under Method A, followed by recrystallization from acetonitrile afforded **10a** (130 mg, 82.3%) as a white solid. Physical and spectral data for the product was identical with that obtained for compound **10a** as prepared under Method A.

(2*R*,3*R*)-2,8-Dimethyl-3-(hydroxymethyl)-2,3-dihydro-5*H*,9*H*-pyrimido[2,1-*b*]-1,5,3-dioxazepin-9-one (2,3′-Anhydro-1′,2′-secothymidine 12). Compound **10a** (0.15 g, 0.475 mmol) was dissolved in absolute ethanol (6 mL) to which 10% Pd/C (0.17 g) and cyclohexene (3 mL) were added. The reaction mixture was stirred at refluxing conditions and monitored by TLC (ethyl acetate–methanol (3:1)). The reaction was complete in 40 min as evidenced by the complete disappearance of starting material. The mixture was cooled to room temperature and filtered through Celite, and the solvents were removed at reduced pressure. The remaining residue was recrystallized from absolute EtOH to give **11** (0.046 g, 42%) as a white solid: mp 185–187 °C; $[\alpha]^{23}_D$ +4.55° (*c* 0.96, MeOH); ^{1}H (300-MHz) NMR (DMSO-d_6) δ 1.38 (d, 3, J = 6.4 Hz), 1.80 (d, 3, J = 1.0 Hz), 3.57 (m, 2), 3.68 (m, 1), 4.15 (m, 1), 4.88 (t, 1, J = 5.4 Hz, D_2O exchangeable), 5.34 (q_{AB}, 2, J = 11.4 Hz), 7.79 (d, 1, 1.1 Hz); ^{13}C (300-MHz) NMR (DMSO-d_6) δ 12.9_7 (C2′), 17.5_7 (C5*C*H3), 60.8_1 (C5′), 81.1_2 (C1′), 82.2_4 (C3′), 85.5_3 (C4′), 117.4_5 (C5), 138.5_4 (C6), 157.9_8 (C2), 171.6_4 (C4); UV λ_{max} (pH 1) 263 (ϵ 8927) λ_{max}(water) 248 (ϵ 11526) λ_{max}(pH 11) 248 (ϵ 10780) nm. Anal. Calcd for $C_{10}H_{14}N_2O_4 \cdot H_2O$: C, 49.18; H, 6.56; N, 11.48. Found: C, 49.48; H, 6.78; N, 11.58.

(4*S*,14*S*)-4,14-Bis[(benzyloxy)methyl]-9,19-dimethyl-3,13-dioxa-1,7,11,17-tetraazatricyclo[15.3.1.1^{7,11}]docosa-9,19-diene-8,18,21,22-tetrone (13a). To a stirred suspension of NaH (60% dispersion in mineral oil, 48 mg, 2 mmol) previously washed with petroleum ether (3 × 3 mL) in dry DMF (25 mL) was added a solution of the tosylate **9b** (480 mg, 0.98 mmol) in dry DMF (5 mL). The reaction mixture was stirred at room temperature for 1 h, heated at 60 °C for 15 h, cooled, concentrated in vacuo, and carefully quenched with water (10 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried, concentrated, and chromatographed on silica gel using hexanes–ethyl acetate (2:1) as eluent to afford the dimer **13a** (200 mg, 63%): $[\alpha]^{26}_D$ −23.9° (*c* 1.59, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.84 (m, 10), 3.06–4.20 (m, 10), 4.32 (s, 4), 4.75–5.26 (m, 4), 7.15 (br s, 12); HRMS(FAB) for $C_{34}H_{40}N_4O_8$ m/z calcd 633.2924, found 633.2838 (MH^+).

(4*S*,5*R*,14*S*,15*R*)-4,14-Bis[(benzyloxy)methyl]-5,15-bis(benzyloxy)-9,19-dimethyl-3,13-dioxa-1,7,11,17-tetraazatricyclo[15.3.1.1^{7,11}]docosa-9,19-diene-8,18,21,22-tetrone (14a). A solution of the tosylate **9c** (450 mg, 0.75 mmol) in dry DMF (50 mL) was added to a suspension of NaH (60% dispersion in mineral oil, 60 mg, 1.5 mmol) previously washed with hexanes (3 × 5 mL), in dry DMF (25 mL), and the reaction mixture was stirred for 3 days at 60–70 °C. After the usual workup, the crude product was purified by silica gel column chromatography using hexanes–ethyl acetate (4:1) as eluent to give 80 mg of the starting material, **9c** (17.8%), and 180 mg of the dimer **14a** (56%): $[\alpha]^{25}_D$ +14.8° (*c* 0.54, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.76 (s, 6), 3.54–4.22 (m, 12), 4.40 (s, 4), 4.62 (q_{AB}, 4, J = 12 Hz), 4.82 (m, 4), 6.94 (s, 2), 7.20 (split s, 20); HRMS(FAB) for $C_{48}H_{52}N_4O_{10}$ m/z calcd 845.3762, found 845.3744 (MH^+).

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