$$k_d = k_2 + k_3 \quad (6)$$

where [Ado] denotes the concentration of adenosine at moment t and $[UpA]_0$ is the initial concentration of the starting material (either 2',5'-UpA or 3',5'-UpA). The rate constants, k_2, k_3, and k_5, are defined in Scheme I. The values of k_5 were taken from literature.[26] Under alkaline conditions depurination is extremely slow compared to phosphoester hydrolysis. In other words, k_3 and k_5 are negligible compared to k_2, and eq 5 thus reduces to the first-order rate law.

First-order rate constants for hydrolysis, k_2, and depurination, k_3, of isomeric ApU at pH < 2 were calculated by eqs 6 and 7,

$$\frac{[AMP]}{[ApU]_0} = \frac{k_2}{k_4 - k_d}(e^{-k_d t} - e^{-k_4 t}) \quad (7)$$

where [AMP] stands for the total concentration of 2'- and 3'-AMP at moment t and $[ApU]_0$ is the initial concentration of the starting material. The rate constants, k_2, k_3, and k_4, are defined in Scheme I. The values for k_4 were taken from literature.[10] It should be noted that 2',3'-cAMP is not accumulated at pH < 2. At higher pH, dephosphorylation of 2'- and 3'-AMP is, in turn, fast enough to prevent their accumulation.[10] Under these conditions eq 8 was applied. Again the rate constants refer to Scheme I. Under

$$\frac{[Ado]}{[ApU]_0} = \frac{k_2}{k_5 - k_d}(e^{-k_d t} - e^{-k_5 t}) \quad (8)$$

alkaline conditions k_3 and k_5 are negligible compared to k_2, and a simple first-order rate law is obtained.

First-order rate constants for hydrolysis, k_2, and depurination, k_3, of isomeric ApAs at pH < 2 were calculated by eqs 6 and 9.

$$\frac{[Ado]}{[ApA]_0} = \frac{k_2}{k_5 - k_d}(e^{-k_d t} - e^{-k_5 t}) \quad (9)$$

Here [Ado] is the concentration of adenosine at moment t, and $[ApA]_0$ is the initial concentration of the starting material. Under these conditions the dephosphorylation of 2'- and 3'-AMP is so slow compared to phosphoester hydrolysis that the concentration of adenosine is not increased by this route in the course of a kinetic run. In alkaline solutions eq 9 is reduced to a first-order rate equation.

Table IV. Kinetically Determined pK_a values for 2'-OH of 3',5'-Dinucleoside Monophosphates and 3'-OH of Their 2',5'-Isomers and First-Order Rate Constants for Hydrolysis of the Ionized Species at 333.2 K.[a]

compd	pK_{a2}	$k_g/10^{-3}$ (s^{-1})
2',5'-UpU	12.84	12.8
3',5'-UpU	12.55	6.92
2',5'-UpA	12.97	18.8
3',5'-UpA	12.52	7.41
2',5'-ApU	12.73	5.13
3',5'-ApU	12.04	2.00
2',5'-ApA	12.70	7.38
3',5'-ApA	12.24	5.68

[a] See Scheme II.

(26) Lönnberg, H.; Lehikoinen, P. *Nucleic Acids Res.* **1982**, *10*, 4339.

Selenoxide Elimination for the Synthesis of Unsaturated-Sugar Uracil Nucleosides

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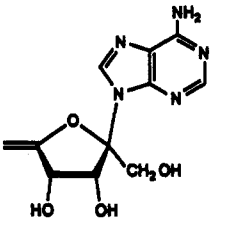
Received April 2, 1991

Introduction of a phenylseleno group to the sugar portion of uracil nucleosides and selenoxide elimination reactions of the resulting selenium-containing derivatives are described. A phenylselenide anion prepared by reducing $(PhSe)_2$ with $LiAlH_4$ was found to be highly reactive. By using this selenide as a nucleophile, ring openings of various types of cyclonucleosides and nucleosides having an anhydro structure in the sugar portion were accomplished. The products, which contain a phenylseleno group in the sugar portion, were oxidized with *m*-CPBA in CH_2Cl_2, and their susceptibility to the selenoxide elimination and regiochemistry of the reaction was investigated.

Selenium-containing organic molecules have been known to be versatile synthons in organic synthesis. Among various synthetic utilities of the organoseleniums,[1] selenoxide elimination would constitute one of the most frequently used synthetic operations leading to unsaturated organic molecules such as allylic alcohols.[2] It can be carried out under very mild reaction conditions, and its syn elimination pathway provides an additional merit for regio- and stereodefined synthetic planning of a target molecule.

Although the occurrence of nucleoside antibiotics bearing unsaturated sugars, such as angustmycin A (1),[3-5] has stimulated the synthesis of unsaturated-sugar nucleosides of various types,[6-8] the methods available until recently have been based on base-promoted elimination of the corresponding halogeno or sulfonyl derivatives.[9] An

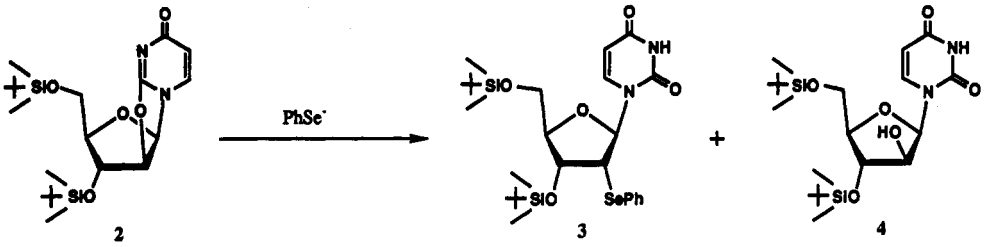


1

(1) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.
(2) For an example: Sharpless, K. B.; Rauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.
(3) Hoeksema, H.; Slomp, G.; van Tamelen, E. E. *Tetrahedron Lett.* **1964**, 1787.
(4) McCarthy, J. R., Jr.; Robins, R. K.; Robins, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 4993.
(5) Prisbe, E. J.; Smejkal, J.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1976**, *41*, 1836.
(6) For the synthesis of 4',5'-unsaturated nucleosides: (a) Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 5684. (b) Robins, M. J.; McCarthy, J. R., Jr.; Robins, R. K. *J. Heterocycl. Chem.* **1967**, *4*, 313. (c) Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 3573.
(7) For the synthesis of 2',3'-unsaturated nucleosides: (a) Horwitz, J. P.; Chua, J.; Klundt, I. L.; Da Rooge, M. A.; Noel, M. *J. Am. Chem. Soc.* **1964**, *86*, 1896. (b) Horwitz, J. P.; Chua, J.; Da Rooge, M. A.; Noel, M. *Tetrahedron Lett.* **1964**, 2725. (c) Horwitz, J. P.; Chua, J.; Da Rooge, M. A.; Klundt, I. L. *J. Org. Chem.* **1966**, *31*, 205. (d) Kowollik, G.; Gaertner, K.; Etzold, G.; Langen, P. *Carbohydr. Res.* **1970**, *12*, 301.
(8) For the synthesis of 1',2'-unsaturated nucleosides: (a) Robins, M. J.; Trip, E. M. *Tetrahedron Lett.* **1974**, 3369. (b) Ranganathan, R. *Ibid.* **1977**, 1291.

0022-3263/91/1956-5401$02.50/0

Scheme I



apparent disadvantage of this approach would be a limited choice of hydroxyl-protecting group that has to be compatible with the basic conditions. Furthermore, in case where the product is unstable, like 1′,2′-unsaturated nucleosides, some loss of the product would be inevitable.

Despite the widespread use of organoselenium chemistry in synthesis, interest regarding selenium in the nucleoside field seems to have been focused on preparing those containing selenium in the base moiety.[10,11] We recently reported that a phenylselenide anion prepared by reducing $(PhSe)_2$ with $LiAlH_4$[12,13] could effect a high-yield conversion of 3′,5′-bis-*O*-(TBDMS) (*tert*-butyldimethylsilyl) derivative of O^2,2′-cyclouridine **2** to 2′-deoxy-2′-(phenylseleno)uridine derivative **3** (Scheme I).[14] Its highly nucleophilic character was further demonstrated by reacting with several types of anhydronucleosides and also with simple oxetanes and oxolanes.[14,15]

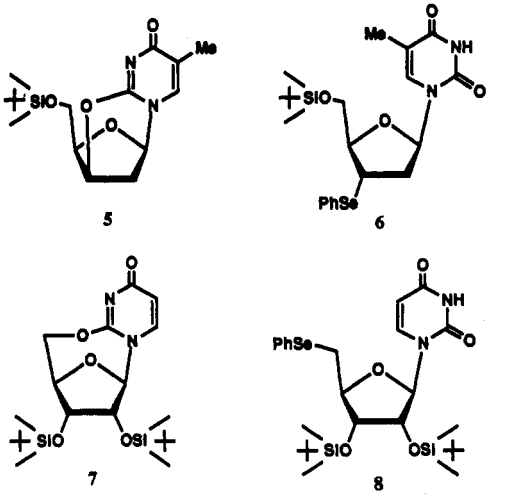
As a part of our continuing program of utilizing organoselenium chemistry for nucleoside synthesis,[16] we describe herein details of the introduction of a phenylseleno group into the sugar portion of uracil nucleosides.[14,15] We also show the results of selenoxide elimination leading to various types of unsaturated-sugar uracil nucleosides.[17]

Introduction of a Phenylseleno Group into the Sugar Portion. Because of the stench and toxicity of benzeneselenol, phenylselenide anion is usually prepared from diphenyl diselenide with a reducing agent. The anion generated from $(PhSe)_2$/Na has been used for the reaction with esters and lactones,[18] while that derived from $(PhSe)_2/NaBH_4$ is reported to be effective for oxirane ring cleavage.[19] A reactivity order of these phenylselenide anions has been proposed.[20]

Treatment of **2** with $(PhSe)_2$/Na in THF at room temperature for 7 h in the presence of 18-crown-6 gave one product that did not contain a phenylseleno group. From the ^1H NMR, mass, and CD spectra, this product was shown to be an arabinofuranosyluracil derivative **4** (43% yield).[21] When **2** was treated with $(PhSe)_2$ (0.8 mol equiv)/$NaBH_4$ (1.6 mol equiv) in THF–EtOH, no reaction took place at room temperature. However, by conducting the reaction at reflux for 7 h, the starting material was completely consumed to form two products. The major product (60% yield) was **4**, while the minor product was the desired 2′-deoxy-2′-(phenylseleno)uridine derivative **3** (38% yield).

We reasoned that the observed difference in reactivity between $(PhSe)_2$/Na and $(PhSe)_2/NaBH_4$ could be a reflection of coordination with the ether oxygen or to the base moiety, which should accelerate nucleophilic attack of the selenide anion at the 2′-position. This suggests that a phenylselenide anion having a higher degree of Lewis acid character would work more efficiently in this system. This assumption led us to prepare another species of selenide anion with $LiAlH_4$ as reducing agent.

The selenide anion was prepared by adding $LiAlH_4$ (1.2 mol equiv) portionwise to a THF solution of $(PhSe)_2$ (1.6 mol equiv) at room temperature over 10 min, whereupon the initial yellow solution turned to a colorless suspension. As had been anticipated, the above-prepared selenide reacted readily with **2** (1 molar equiv) at room temperature in THF. After 18 h, **3** was obtained in almost quantitative yield. Under similar conditions, O^2,3′-cyclothymidine derivative **5** gave the 3′-phenylselenated product **6** in 55% yield. A similar conversion of O^2,5′-cyclouridine derivative **7** into **8** (89%) can be accomplished with $(PhSe)_2$ (0.8 mol equiv)/$NaBH_4$ (1.6 mol equiv) in THF–EtOH (at room temperature for 2 h).



(9) For other reports concerning formation of 2′,3′-unsaturated uracil nucleosides: (a) Ruyle, W. V.; Shen, T. Y.; Patchett, A. A. *J. Org. Chem.* **1965**, *30*, 4353. (b) Lin, T.-S.; Yang, J.-H.; Liu, M.-C.; Zhu, J.-L. *Tetrahedron Lett.* **1990**, *31*, 3829.

(10) Witczak, Z. J. In *The Chemistry of Organoselenium and Tellirium Compounds*; Patai, S., Ed; Intersciences: New York, 1987; Vol. 2, Chapter 18.

(11) Before our study cited in ref 14, there was only one report dealing with the introduction of a seleno group into the sugar portion of nucleoside and subsequent selenoxide elimination: Takaku, H.; Nomota, T.; Kimura, K. *Chem. Lett.* **1981**, 1221.

(12) The combination of $(PhSe)_2$ and $LiAlH_4$ has a precedent in preparing aryl difluoromethyl selenides: Suzuki, H.; Yoshinaga, M.; Takaoka, K.; Hiroi, Y. *Synthesis* **1985**, 497.

(13) $LiAlH_4$ treatment of $(MeSe)_2$ in the presence of trimethylchlorosilane has been reported and used for the preparation of selenoacetals: Jensen, K. A.; Nielsen, P. H. *Acta Chem. Scand.* **1966**, *20*, 597.

(14) Haraguchi, K.; Tanaka, H.; Hayakawa, H.; Miyasaka, T. *Chem. Lett.* **1988**, 931.

(15) Haraguchi, K.; Tanaka, H.; Miyasaka, T. *Synthesis* **1989**, 434.

(16) A radical-mediated stereoselective C–C bond formation at the 5′-position of uracil nucleosides has been accomplished by the use of organoselenium reagents: Haraguchi, K.; Tanaka, H.; Miyasaka, T. *Tetrahedron Lett.* **1990**, *31*, 227.

(17) Quite recently, two reports have been published concerning the preparation of 2′,3′-unsaturated nucleosides by selenoxide elimination: (a) Vial, J.-M.; Agback, P.; Chattopadhyaya, J. *Nucleosides Nucleotides* **1990**, *9*, 245. (b) Chu, C. K.; Babu, J. R.; Beach, J. W.; Ahn, S. K.; Huang, H.; Jeong, L. S.; Lee, S. J. *J. Org. Chem.* **1990**, *55*, 1418.

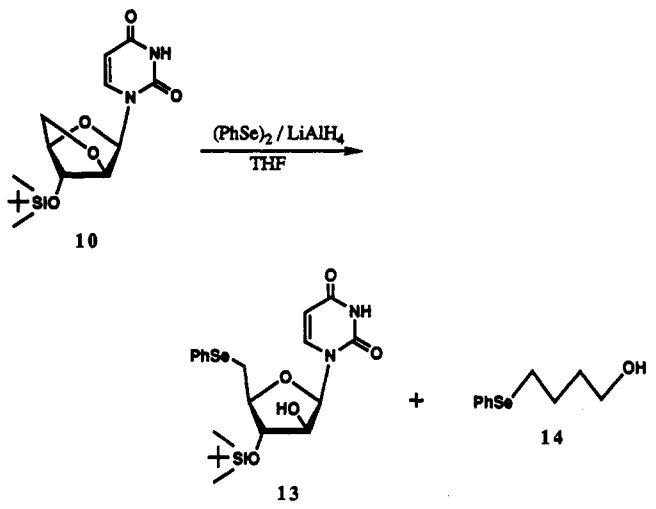
(18) (a) Liotta, D.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 4365. (b) Liotta, D.; Santiesteban, H. *Ibid.* **1977**, 4369.

(19) Dowd, P.; Kennedy, P. *Synth. Commun.* **1981**, *11*, 935.

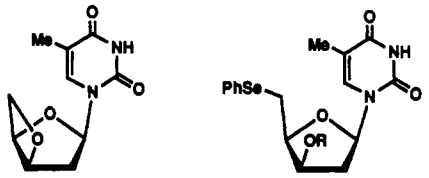
(20) Liotta, D. *Acc. Chem. Res.* **1984**, *17*, 28.

(21) A similar observation has been reported in the reaction of an O^2,3′-cyclothymidine derivative with sodium methanethiolate: Mansuri, M. M.; Wos, J. A.; Martin, J. C. *Nucleosides Nucleotides* **1989**, *8*, 1463.

Scheme II



To demonstrate the usefulness of $(PhSe)_2/LiAlH_4$, nucleosides having an anhydro structure in the sugar portion, such as **9** and **10**,[22,23] were selected as substrates. Compound **9** gave the corresponding 5′-phenylseleno derivative **11**[24] in 86% yield under the same conditions as mentioned above for **2**. Silylation of **11** led to **12**. The reaction of **10**, however, was found to be very sluggish and, even after 24 h, TLC of the reaction mixture indicated only a partial conversion into **13** with a small amount of a nonnucleosidic product (Scheme II). Compound **13** was isolated in 13% yield by silica gel column chromatography. The structure of the other product was determined to be δ-(phenylseleno)butanol (**14**) from its ^1H NMR spectrum (18% yield, calculated on the basis of the reagent used).

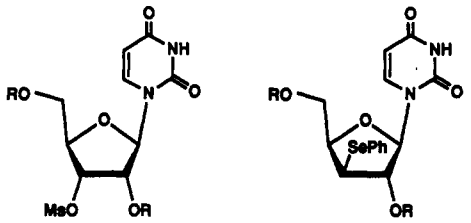


9

11 R= H
12 R= TBDMS

We therefore turned to the use of dioxane as a solvent, since the origin of **14** in the above reaction is apparently THF. When a dioxane solution of **10** was treated with $(PhSe)_2/LiAlH_4$ at refluxing temperature for 11 h, **13** was obtained in 44% yield without formation of products derived from the solvent.[14] The cleavage of an oxirane ring in **15**[25,26] can be accomplished at room temperature. Although it has been shown in many cases that 2′,3′-lyxo epoxides of pyrimidine nucleosides undergo highly preferential nucleophilic attack at the 3′-position,[25-28] no significant regioselectivity was observed in the reaction of **15** with $(PhSe)_2/LiAlH_4$ in dioxane (Scheme III). Almost equal amounts of **16** (46%) and **17** (45%),[29] fully characterized after converting to the respective 5′-*O*-(*tert*-butyldimethylsilyl) derivatives **18** and **19**, were formed.

Treatment of 3′-*O*-mesyl-2′,5′-di-*O*-trityluridine (**20**)[30] with $(PhSe)_2/LiAlH_4$ in dioxane at 70 °C for 6 h gave the "3′-up"-selenide, which was isolated in 80% yield as its 2′,5′-bis-*O*-(*tert*-butyldimethylsilyl) derivative **21** after detritylation and subsequent silylation. The isomeric "3′-down"-selenide was not formed in any detectable amount. Quite unexpectedly, when the 3′-mesylate of 2′,5′-di-*O*-pivaloyluridine (**22**)[31] was subjected to the reaction under similar conditions, only a trace amount of the "3′-up"-selenide **23** was detected and the starting material was recovered almost quantitatively.



20 R= Tr
22 R= COCMe$_3$

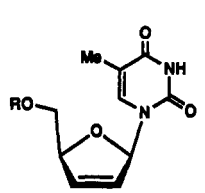
21 R= TBDMS
23 R= COCMe$_3$

Selenoxide Elimination. Uracil nucleosides containing a phenylseleno group prepared by the reactions mentioned above were subjected to selenoxide elimination by oxidizing with *m*-CPBA in CH_2Cl_2.[32]

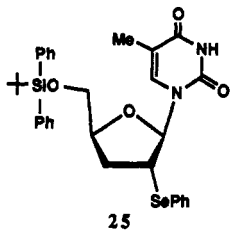
Compound **6** was treated with *m*-CPBA (1.3 equiv) at 0 °C for 1 h. The incipient selenoxide as well as 3′-deoxy-2′,3′-didehydrothymidine derivative **24** were detected during this reaction by TLC.[33] However, silica gel column chromatography of the reaction mixture gave only **24** in 94% yield. There are β- and β′-hydrogens, H-2′ and H-4′, available for the syn elimination of **6**. Although several factors are known to affect regiochemistry of selenoxide elimination,[34] in this particular case we believe the sole formation of **24** can be rationalized by taking two facts into consideration. One is that H-2′ is a methylene proton while H-4′ is a methine proton.[35] The other is that C-4′ bears an electronegative oxygen atom, O-1′.[36] Chu et al. recently reported that **25**, prepared by condensation of an appropriately protected sugar with silylated thymine, gave the 2′,3′-unsaturated product **26** upon oxidation.[17b] This regiochemical outcome may also fall into the same category as the case of **6**.

The *m*-CPBA treatment of **3**, **8**, **12**, and **21**, which uniformly have only one β-*syn*-hydrogen to the phenylseleno group, was next examined. When **3** was treated with

(22) Horwitz, J. P.; Chua, J.; Da Rooge, M. A.; Noel, M.; Klundt, I. L. *J. Org. Chem.* **1966**, *31*, 205.
(23) The corresponding free nucleoside, 2′,5′-anhydro-1-(β-D-arabinofuranosyl)uracil, was prepared according to the published method: Hirota, K.; Kitade, Y.; Tomishi, T.; Maki, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 108.
(24) A comparative study of the conversion of **9** to **11** has been reported by using several types of phenylselenide anion: see ref 15.
(25) Codington, J. F.; Fecher, R.; Fox, J. J. *J. Org. Chem.* **1962**, *27*, 163.
(26) Ashwell, M.; Jones, A. S.; Walker, R. T. *Nucleic Acids Res.* **1987**, *15*, 2157.
(27) (a) Mete, A.; Hobbs, J. B.; Scopes, D. I. C.; Newton, R. F. *Tetrahedron Lett.* **1985**, *26*, 97. (b) Perlman, M. E.; Watanabe, K. A. *Nucleosides Nucleotides* **1987**, *6*, 621. (c) Webb, T. R.; Mitsuya, H.; Broder, S. *J. Med. Chem.* **1988**, *31*, 1475. (d) Wu, J.-C.; Pathak, T.; Tong, W.; Vial, J.-M.; Remaud, G.; Chattopadhyaya, J. *Tetrahedron* **1988**, *44*, 6705. (e) Matsuda, A.; Satoh, M.; Nakashima, H.; Yamamoto, N.; Ueda, T. *Heterocycles* **1988**, *27*, 2545.
(28) After our study of $(PhSe)_2/LiAlH_4$ was published as a communication,[14] this reagent was used for the cleavage of a 5′-*O*-protected 2′,3′-epoxide of 1-(β-D-lyxofuranosyl)uracil: Wu, J.-C.; Chattopadhyaya, J. *Tetrahedron* **1989**, *45*, 4507.
(29) The reaction of **15** with $(PhSe)_2/NaBH_4$ can also be carried out at room temperature in THF–EtOH (59% of **16** plus 30% of **17**).
(30) Yung, N. C.; Fox, J. J. *J. Am. Chem. Soc.* **1961**, *83*, 3060.
(31) Kamaike, K.; Uemura, F.; Yamakage, S.; Nishino, S.; Ishido, T. *Nucleosides Nucleotides* **1987**, *6*, 669.
(32) Selenoxide eliminations of **13** and **23** were not examined due to a small quantity of the material.
(33) When the oxidation of **6** was carried out at −30 °C, only a mixture of the selenoxides could be detected by TLC.
(34) Paulmier, C. In *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press, Oxford; 1986; Chapter 5.
(35) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697–1705.
(36) Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1974**, *39*, 429–430.



24 R= TBDMS
26 R= TBDPS



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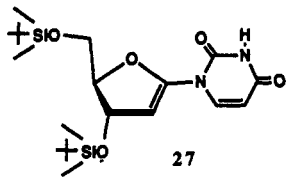
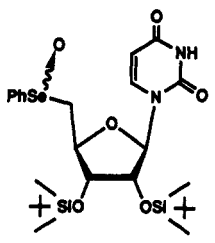


27

m-CPBA (1.5 equiv) at room temperature for 4 h, two polar products resulted. A mixture of these products could be isolated by short-column chromatography.[37] Heating of the mixture in THF at 50 °C for 7 h gave the elimination product **27** in 67% yield from **3**. Formation of uracil was also detected by TLC.[38] Addition of Et_3N increased the yield of **27** to 89% without concomitant formation of uracil. When **8** was oxidized in a similar manner, the corresponding selenoxide **28** was isolated in quantitative yield and fully characterized. To complete the elimination reaction of **28**, heating for 10 h at 70 °C (3.0 equiv of Et_3N in THF) was required. This gave a 4',5'-unsaturated product **29** in 91% yield. The selenoxide derived from **12**, on the other hand, produced **30** (85%) after only 2 h of heating under the same conditions. This may reflect that the steric environment of H-4' of **12** is less hindered. A silyl enol ether **31** was prepared in 71% yield simply by treating **21** with *m*-CPBA at room temperature.



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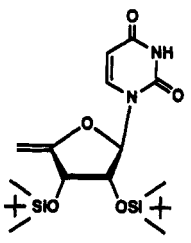

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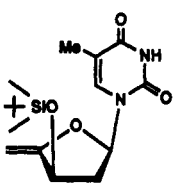

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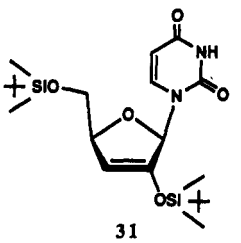


31

Finally, selenoxide elimination of compounds **18** and **19** was examined. These compounds have two *β-syn*-hydrogens to the phenylseleno group. Furthermore, both of their *β*- and *β'*-carbons bear an electronegative substituent.

Compound **18** was treated with *m*-CPBA, and the resulting mixture of selenoxides was heated at 60 °C for 2 h in THF containing Et_3N. After column chromatography, an allylic alcohol **32** and a 2'-keto nucleoside **33** were obtained in 36 and 21% yields, respectively. As **33** is the keto form of 2',3'-unsaturated product, this result shows that the occurrence of both elimination pathways is almost equally likely (Scheme IV). Quite interestingly, however, acetylation of the 2'-hydroxyl group of **18** altered the regioselectivity to a greater extent. Thus, when a mixture of selenoxides prepared from **34** was kept neat at 40 °C for 12 h, an allylic acetate **35** was the sole product (88%).

In the case of **19**, heating of the corresponding selenoxides at 60 °C for 2.5 h in THF containing Et_3N gave a nucleosidic product, that we assume to be **36**, and uracil (**37**, 83%) (Scheme V). Although the structure of **36** was not confirmed because of its instability, it may be assumed that the selenoxide elimination took place between the 2'- and 3'-positions to give **36**, which further eliminated uracil under basic conditions. On the basis of the aforementioned exclusive formation of **35** from **34**, we reasoned that 3'-*O*-acetylation of **19** would alter the regiochemistry of the elimination to some extent. Compound **38** was oxidized, and a mixture of its selenoxides was heated at 60 °C for 2 h in THF containing Et_3N. Column chromatography of the reaction mixture gave two products **39** and **40** in 30 and 22% yields, respectively. The formation of **40** could be explained by selenoxide elimination between the 1'- and 2'-positions to form a putative intermediate **41**, which would have a propensity to undergo aromatization.[39]

Experimental Section

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^1H NMR spectra were measured at 23 °C (internal standard, Me_4Si) with either a JEOL JNM-FX 100 or a JEOL-JNM GX-400 spectrometer. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer in electron impact mode. Ultraviolet (UV) spectra were recorded on a Shimadzu UV-240 spectrophotometer. THF was distilled from benzophenone ketyl. Dioxane was distilled from $LiAlH_4$. Column chromatography was carried out on silica gel (silica gel 60, Merck). TLC was performed on silica gel (precoated silica gel plate F_{254}, Merck).

3',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-O^2,2'-cyclouridine (2). O^2,2'-Cyclouridine (2.26 g, 10 mmol) was added to a solution of TBDMSCl (3.77 g, 25 mmol) and imidazole (2.38 g, 35 mmol) in DMF (30 mL). The mixture was stirred at room temperature for 3 h and then partitioned between EtOAc and H_2O. The organic layer separated was evaporated and chromatographed on a silica gel column (benzene:EtOAc = 5:1). This gave **2** (10.4 g, 92%), which was crystallized from EtOAc–hexane (mp 155.5–157 °C): UV (MeOH) λ_{max} 227 (ϵ 8100), 249 nm (ϵ 7700); ^1H NMR ($CDCl_3$) δ 0.14 and 0.17 (12 H, each as s, SiMe), 0.84 and 0.91 (18 H, each as s, SiBu-*t*), 3.36 and 3.57 (2 H, each as dd, J_{gem} = 10.9 Hz, $J_{4',5'}$ = 7.0, 4.6 Hz, CH_2-5'), 4.11 (1 H, m, H-4'), 4.61 (1 H, m, H-3'), 5.11 (1 H, dd, $J_{1',2'}$ = 5.8 Hz, $J_{2',3'}$ = 1.0 Hz, H-2'), 6.05 (1 H, d, $J_{5,6}$ = 7.5 Hz, H-5), 6.15 (1 H, d, H-1'), 7.32 (1 H, d, H-6); MS *m/z* 439 (M^+ – Me), 397 (M^+ – Bu-*t*). Anal. Calcd for $C_{21}H_{38}N_2O_5Si_2$: C, 55.47; H, 8.42; N, 6.16. Found: C, 55.56; H, 8.66; N, 6.00.

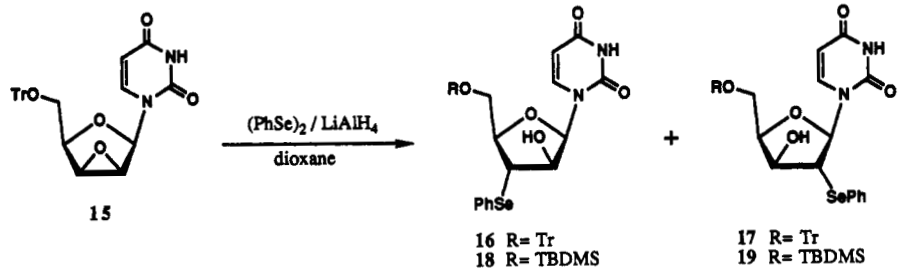
Reaction of 2 with $(PhSe)_2$/Na. To a THF (4 mL) solution of $(PhSe)_2$ (125 mg, 0.4 mmol) was added Na (18 mg, 0.8 m atom), and the solution was refluxed for 4 h under positive pressure of dry Ar. After the solution was cooled to room temperature, 18-crown-6 (6.6 mg, 0.03 mmol) and **2** (227 mg, 0.5 mmol) were added and the resulting mixture was stirred at room temperature for 7 h. The reaction mixture was treated with 10% AcOH in MeOH and partitioned between $CHCl_3$ and H_2O. The organic layer separated was chromatographed on a silica gel column (5% EtOH in $CHCl_3$). This gave **4** (111 mg) as a solid in 43% yield, which was analytically pure: UV (MeOH) λ_{max} 263 nm (ϵ 10000);

(37) A mixture of these products gave a complex ^1H NMR spectrum (in $CDCl_3$), and only two anomeric protons were assignable (δ 5.99, $J_{1',2'}$ = 4.4 Hz; δ 6.43, $J_{1',2'}$ = 8.8 Hz). Correct elemental analysis could not be obtained, due to partial conversion to **27**.

(38) Presumably, the resulting phenylselenenic acid caused the formation of uracil. Instability of an 1',2'-unsaturated uracil nucleoside under acidic conditions has been reported; see ref 8a.

(39) After this manuscript was submitted, a report dealing with the reaction between a thymidine derivative and $(PhSe)_2/LiAlH_4$ appeared: Cosford, N. D. P.; Schinazi, R. F. *J. Org. Chem.* **1991**, *56*, 2161.

Scheme III

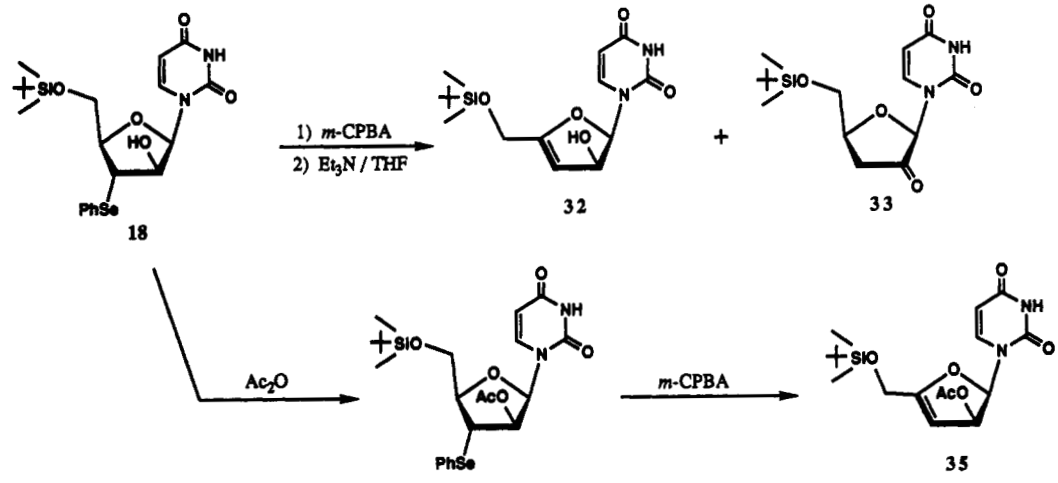


15

16 R= Tr
18 R= TBDMS

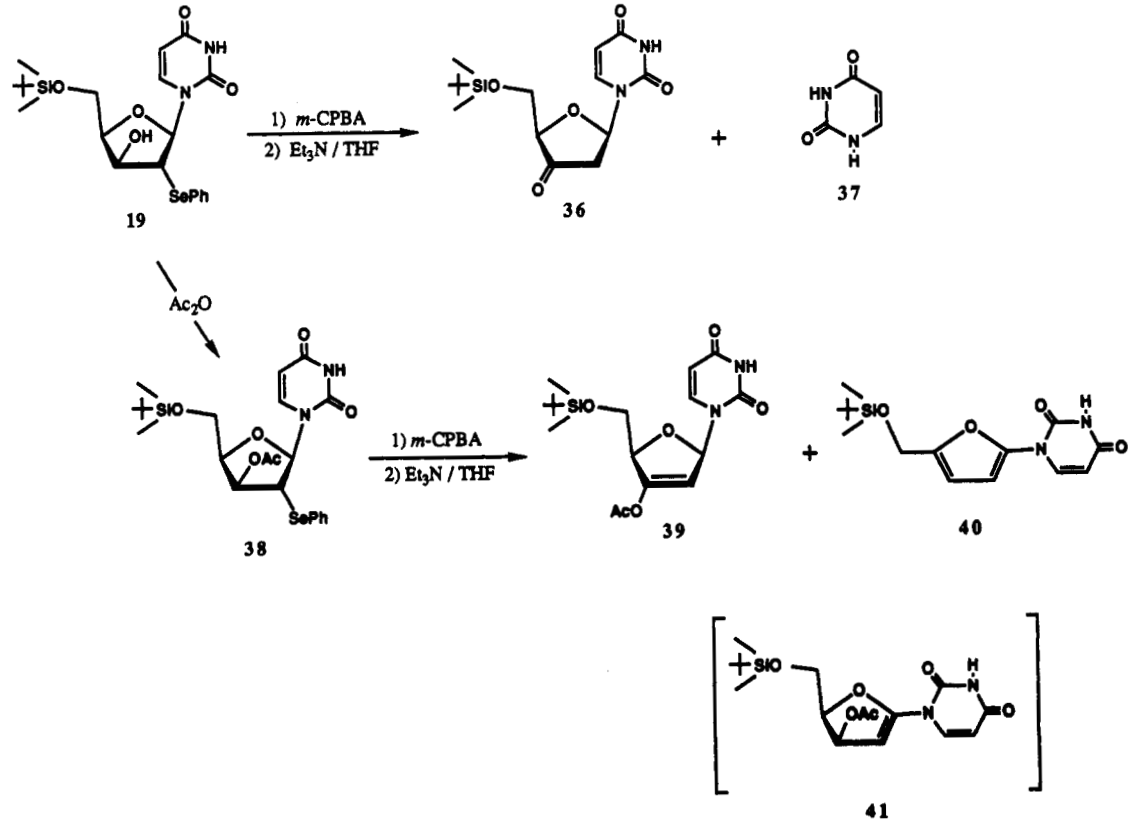
17 R= Tr
19 R= TBDMS

Scheme IV



18 32 33 34 35

Scheme V



19 36 37 38 39 40

41

^{1}H NMR ($CDCl_3$, after addition of D_2O) δ 0.10, 0.13, 0.15 (12 H, each as s, SiMe), 0.90 and 0.93 (18 H, each as s, SiBu-*t*), 3.69–4.71 (5 H, m, H-2′, H-3′, H-4′, and CH_2-5′), 5.63 (1 H, d, $J_{5,6}$ = 8.3 Hz, H-5), 6.10 (1 H, d, $J_{1',2'}$ = 3.4 Hz, H-1′), 7.72 (1 H, d, H-6); MS *m*/*z* 415 (M^+ – Bu-*t*). Anal. Calcd for $C_{21}H_{40}N_2O_6Si_2$: C, 53.38; H, 8.53; N, 5.93. Found: C, 53.59; H, 8.75; N, 5.77.

Reaction of 2 with $(PhSe)_2/NaBH_4$. $NaBH_4$ (30 mg, 0.8 mmol) was added portionwise to a dry EtOH (4 mL) solution of $(PhSe)_2$ (125 mg, 0.4 mmol) under positive pressure of dry Ar. The mixture was stirred at room temperature for 10 min. To this was added a THF (5 mL) solution of **2** (227 mg, 0.5 mmol), and the reaction mixture was refluxed for 7 h. Quenching with 10%

AcOH in MeOH followed by evaporation gave a residue, which was chromatographed on a silica gel column ($CHCl_3$). This gave **3** (115 mg, 38%) and **4** (143 mg, 60%). Compound **3** was crystallized from MeOH–H_2O (mp 143–145 °C): UV (MeOH) λ_{max} 263 nm (ϵ 9300); ^1H NMR ($CDCl_3$) δ 0.09 and 0.21 (12 H, each as s, SiMe), 0.92 and 0.97 (18 H, each as s, SiBu-*t*), 3.59 (1 H, dd, $J_{1',2'}$ = 9.3 Hz, $J_{2',3'}$ = 5.1 Hz, H-2'), 3.76–3.81 (2 H, m, CH_2-5'), 4.06 (1 H, m, H-4'), 4.49 (1 H, d, H-3'), 5.34 (1 H, dd, $J_{5,6}$ = 8.3 Hz, $J_{5,NH}$ = 2.4 Hz, H-5), 6.52 (1 H, d, H-1'), 7.14–7.54 (6 H, m, Ph and H-6), 7.95 (1 H, br, NH); MS *m/z* 555 (M^+ – Bu-*t*). Anal. Calcd for $C_{27}H_{44}N_2O_5SeSi_2$: C, 53.03; H, 7.25; N, 4.58. Found: C, 53.34; H, 7.44; N, 4.43.

Reaction of 2 with $(PhSe)_2$/$LiAlH_4$. $LiAlH_4$ (23 mg, 0.6 mmol) was added portionwise to a THF (3 mL) solution of $(PhSe)_2$ (250 mg, 0.8 mmol) under positive pressure of dry Ar. The mixture was stirred at room temperature for 10 min. To this was added a THF (3 mL) solution of **2** (227 mg, 0.5 mmol), and the reaction mixture was stirred for 18 h at room temperature. Quenching with 10% AcOH in MeOH followed by evaporation gave a residue, which was chromatographed on a silica gel column ($CHCl_3$). This gave 296 mg (97%) of **3**.

5'-*O*-(*tert*-Butyldimethylsilyl)-O^2,3'-cyclothymidine (5). This compound was prepared from O^2,3'-cyclothymidine (673 mg, 9.0 mmol) by the procedure described for the preparation of **2**. Column chromatography (6% EtOH in $CHCl_3$) gave 873 mg (86%) of **5** as an analytically pure solid: UV (MeOH) λ_{max} 250 nm (ϵ 8500); ^1H NMR ($CDCl_3$) δ 0.06 (6 H, s, SiMe), 0.88 (9 H, s, SiBu-*t*), 1.94 (3 H, d, $J_{5\text{-Me},6}$ = 1.0 Hz, 5-Me), 2.42 and 2.70 (2 H, each as m, CH_2-2'), 3.73–3.81 (2 H, m, CH_2-5'), 4.27 (1 H, m, H-4'), 5.20 (1 H, m, H-3'), 5.49 (1 H, d, $J_{1',2'a}$ = 3.4 Hz, H-1'), 6.96 (1 H, d, H-6); MS *m/z* 281 (M^+ – Bu-*t*). Anal. Calcd for $C_{16}H_{28}N_2O_4Si$: C, 56.79; H, 7.75; N, 8.28. Found: C, 56.73; H, 7.79; N, 8.29.

5'-*O*-(*tert*-Butyldimethylsilyl)-3'-deoxy-3'-(phenylseleno)thymidine (6). This compound was prepared from **5** (300 mg, 0.9 mmol) by the procedure described for the reaction of **2** with $(PhSe)_2$/$LiAlH_4$. The reaction was continued overnight at room temperature. Column chromatography (hexane:EtOAc = 2:1) gave 244 mg (55%) of **6** as a syrup: UV (MeOH) λ_{max} 268 nm (ϵ 11400); ^1H NMR ($CDCl_3$) δ 0.09 (6 H, s, SiMe), 0.92 (9 H, s, SiBu-*t*), 1.90 (3 H, s, 5-Me), 2.43 (2 H, m, H-2'), 3.74 (1 H, m, H-3'), 3.85–4.07 (3 H, m, H-4' and CH_2-5'), 6.06 (1 H, t, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.28–7.35 (3 H, m, Ph), 7.53–7.62 (3 H, m, Ph and H-6), 8.49 (1 H, br, NH); Ms *m/z* 439 (M^+ – Bu-*t*). Anal. Calcd for $C_{22}H_{32}N_2O_4SeSi$: C, 53.33; H, 6.51; N, 5.65. Found: C, 53.58; H, 6.66; N, 5.49.

2',3'-Bis-*O*-(*tert*-butyldimethylsilyl)-O^2,5'-cyclouridine (7). For the preparation and physical data of this compound, see ref 40.

2',3'-Bis-*O*-(*tert*-butyldimethylsilyl)-5'-deoxy-5'-(phenylseleno)uridine (8). This compound was prepared from **7** (114 mg, 0.25 mmol) by the procedure described for the reaction of **2** with $(PhSe)_2$/$NaBH_4$. The reaction was continued for 2 h at room temperature. Column chromatography (benzene:EtOAc = 10:1) gave 136 mg (89%) of **8** as a foam: UV λ_{max} 263 nm (ϵ 13800); ^1H NMR ($CDCl_3$, after addition of D_2O) δ 0.02 and 0.04 (12 H, each as s, SiMe), 0.86 and 0.88 (18 H, each as s, SiBu-*t*), 3.16 and 3.27 (2 H, each as dd, J_{gem} = 12.3 Hz, $J_{4',5'a}$ = 4.4 Hz, $J_{4',5'b}$ = 3.9 Hz, CH_2-5'), 3.88 (1 H, m, H-4'), 4.28–4.73 (2 H, m, H-2' and H-3'), 5.64 (1 H, d, $J_{5,6}$ = 8.3 Hz, H-5), 5.69 (1 H, d, $J_{1',2'}$ = 4.9 Hz, H-1'), 7.24–7.32 (4 H, m, Ph and H-6), 7.46–7.58 (2 H, m, Ph); MS *m/z* 597 (M^+ – Me), 555 (M^+ – Bu-*t*). Anal. Calcd for $C_{27}H_{44}N_2O_5SeSi_2$: C, 53.03; H, 7.25; N, 4.58. Found: C, 53.31; H, 7.36; N, 4.62.

1-[2,5-Anhydro-3-*O*-(*tert*-butyldimethylsilyl)-β-D-arabinofuranosyl]uracil (10), 1-[2,5-Dideoxy-5-(phenylseleno)-β-D-*threo*-pentofuranosyl]thymine (11), 1-[3-*O*-(*tert*-Butyldimethylsilyl)-5-deoxy-5-(phenylseleno)-β-D-arabinofuranosyl]uracil (13), and δ-(Phenylseleno)butanol (14). For the preparations and physical data of these compounds, see ref 15.

1-[3-*O*-(*tert*-Butyldimethylsilyl)-2,5-dideoxy-5-(phenylseleno)-β-D-*threo*-pentofuranosyl]thymine (12). A mixture of **11** (670 mg, 1.8 mmol), TBDMSCl (398 mg, 2.6 mmol), and imidazole (300 mg, 4.4 mmol) in DMF (20 mL) was heated at 50 °C overnight with stirring. The reaction mixture was worked up by the procedure described for the preparation of **2**. Silica gel column chromatography (benzene:EtOAc = 4:1) gave **12** (777 mg, 89%) as a foam: UV (MeOH) λ_{max} 268 nm (ϵ 12500); ^1H NMR ($CDCl_3$) δ 0.06 and 0.15 (6 H, each as s, SiMe), 0.89 (9 H, s, SiBu-*t*), 1.90 (3 H, s, 5-Me), 2.03 and 2.57 (2 H, each as m, CH_2-2'), 3.20 (2 H, m, CH_2-5'), 4.05 (1 H, m, H-4'), 4.42 (1 H, m, H-3'), 6.13 (1 H, dd, $J_{1',2'}$ = 2.0 and 7.8 Hz, H-1'), 7.26–7.35 (3 H, m, Ph), 7.48–7.58 (3 H, m, Ph and H-6), 8.40 (1 H, br, NH); MS *m/z* 496 (M^+), 439 (M^+ – Bu-*t*). Anal. Calcd for $C_{22}H_{32}N_2O_4SeSi$: C, 53.33; H, 6.51; N, 5.65. Found: C, 53.60; H, 6.85; N, 5.57.

Reaction of 15 with $(PhSe)_2$/$LiAlH_4$ in Dioxane. $LiAlH_4$ (18.2 mg, 0.48 mmol) was added portionwise to a dioxane (5 mL) solution of $(PhSe)_2$ (200 mg, 0.64 mmol) under positive pressure of dry Ar. After being stirred for 2 h, a colorless suspension resulted. To this was added a dioxane (5 mL) solution of **15** (186 mg, 0.4 mmol), and the reaction mixture was stirred at room temperature for 1 h. Quenching with 10% AcOH in MeOH followed by evaporation gave a residue, which was chromatographed on a silica gel column (benzene:EtOAc = 2:1). This gave **16** (115 mg, 46%) and **17** (114 mg, 45%). Each product was treated with 80% aqueous AcOH (6 mL) at 100 °C for 10 min. After evaporation, the residue was dissolved in pyridine (4 mL) and treated with TBDMSCl (151 mg, 1.0 mmol) at room temperature overnight. Usual workup followed by column chromatography (hexane:EtOAc = 1:1) gave **18** (157 mg, 79%) and **19** (163 mg, 82%), respectively, as a foam.

Physical data of **18** are as follows: UV (MeOH) λ_{max} 265 nm (ϵ 12800); ^1H NMR ($CDCl_3$, after addition of D_2O) δ 0.06 and 0.09 (6H, each as s, SiMe), 0.89 (9 H, s, SiBu-*t*), 3.57 (1 H, m, H-3'), 3.95–4.12 (3 H, m, H-4' and CH_2-5'), 4.38 (1 H, dd, $J_{1',2'}$ = 5.4 Hz, $J_{2',3'}$ = 4.4 Hz, H-2'), 5.63 (1 H, d, $J_{5,6}$ = 8.3 Hz, H-5), 6.09 (1 H, d, H-1'), 7.28–7.34 (3 H, m, Ph), 7.58–7.75 (2 H, m, Ph), 7.98 (1 H, d, H-6); MS *m/z* 441 (M^+ – Bu-*t*). Anal. Calcd for $C_{21}H_{30}N_2O_5SeSi$: C, 50.71; H, 6.08; N, 5.63. Found: C, 50.54; H, 6.20; N, 5.57.

Physical data of **19** are as follows: UV (MeOH) λ_{max} 263 (ϵ 11200); ^1H NMR ($CDCl_3$, after addition of D_2O) δ 0.11 (6 H, s, SiMe), 0.91 (9 H, s, SiBu-*t*), 3.66 (1 H, dd, $J_{1',2'}$ = 4.7 Hz, $J_{2',3'}$ = 7.1 Hz, H-2'), 4.09–4.40 (3 H, m, H-4' and CH_2-5'), 4.37 (1 H, m, H-3'), 5.62 (1 H, d, $J_{5,6}$ = 8.3 Hz, H-5), 6.08 (1 H, d, H-1'), 7.26–7.34 (3 H, m, Ph), 7.56–7.66 (2 H, m, Ph), 7.74 (1 H, d, H-6); MS *m/z* 423 (M^+ – Bu-*t* – H_2O). Anal. Calcd for $C_{21}H_{30}N_2O_5SeSi$: C, 50.71; H, 6.08; N, 5.63. Found: C, 50.93; H, 6.16; N, 5.56.

1-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-(phenylseleno)-β-D-xylofuranosyl]uracil (21). The procedure described for the reaction of **15** with $(PhSe)_2$/$LiAlH_4$ in dioxane was also applied to **20** (2.42 g, 3.0 mmol). The reaction was continued for 6 h at 70 °C. After workup, column chromatography (benzene:EtOAc = 10:1) gave a product, which was not characterized. Detritylation of this product, with 80% aqueous AcOH (50 mL) at 100 °C for 30 min, followed by silylation, with TBDMSCl (2.26 g, 15 mmol) and imidazole (1.43 g, 21 mmol) in DMF (20 mL) at room temperature overnight, gave **21** (1.46 g, 80%) as a foam after column chromatography (benzene:EtOAc = 10:1): UV (MeOH) λ_{max} 266 nm (ϵ 14000); ^1H NMR ($CDCl_3$) δ 0.02 and 0.23 (12 H, each as s, SiMe), 0.86 and 1.02 (18 H each as s, SiBu-*t*), 3.76 (1 H, t, $J_{2',3'}$ = $J_{3',4'}$ = 7.3 Hz, H-3'), 4.05–4.07 (2 H, m, CH_2-5'), 4.37 (1 H, m, H-4'), 4.56 (1 H, m, H-2'), 5.75 (1 H, dd, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.0 Hz, H-5), 5.88 (1 H, d, $J_{1',2'}$ = 4.9 Hz, H-1'), 7.26–7.38 (3 H, m, Ph), 7.51–7.60 (2 H, m, Ph), 8.00 (1 H, d, H-6), 8.49 (1 H, br, NH); MS *m/z* 612 (M^+), 555 (M^+ – Bu-*t*). Anal. Calcd for $C_{27}H_{44}N_2O_5SeSi_2$: C, 53.03; H, 7.25; N, 4.58. Found: C, 52.91; H, 7.34; N, 4.40.

Selenoxide Elimination of 6 To Form 24. Compound **6** (204 mg, 0.41 mmol) in CH_2Cl_2 (5 mL) was treated with *m*-CPBA (92 mg, 0.53 mmol) at 0 °C for 1 h. The reaction mixture was neutralized by adding Et_3N and partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. The organic layer was chromatographed on a silica gel column (1% EtOH in $CHCl_3$). This gave **24** (131 mg, 94%) as a solid. Crystallization from MeOH gave an analytical sample (mp 173–175 °C): UV (MeOH) λ_{max} 266 nm (ϵ 9400); ^1H NMR ($CDCl_3$) δ 0.09 (6 H, s, SiMe), 0.91 (9 H, s, SiBu-*t*), 1.91 (3 H, d, $J_{5\text{-Me},6}$ = 1.0 Hz, 5-Me), 3.85 (2 H, d, $J_{4',5'}$

(40) Hayakawa, H.; Ashizawa, H.; Tanaka, H.; Miyasaka, T. *Chem. Pharm. Bull.* **1990**, *38*, 355.

= 3.9 Hz, CH_2-5'), 4.87 (1 H, m, H-4'), 5.85 (1 H, m, H-2'), 6.28 (1 H, m, H-3'), 6.97 (1 H, m, H-1'), 7.34 (1 H, d, H-6), 8.50 (1 H, br, NH); MS m/z 281 (M^+ - Bu-t). Anal. Calcd for $C_{16}H_{26}N_2O_4Si$: C, 56.79; H, 7.75; N, 8.28. Found: C, 57.04; H, 7.93; N, 8.13.

Selenoxide Elimination of 3 To Form 27. Compound **3** (306 mg, 0.5 mmol) in CH_2Cl_2 (7 mL) was treated with *m*-CPBA (113 mg, 0.65 mmol) at room temperature for 4 h, and the reaction mixture was worked up by the procedure described for the reaction of **6**. A mixture of two diastereomeric selenoxides obtained after column chromatography (2% EtOH in $CHCl_3$) was dissolved in THF (10 mL) containing Et_3N (230 μL, 1.7 mmol). The solution was heated at 50 °C for 7 h, evaporated, and chromatographed on a silica gel column (benzene:EtOAc = 5:1). This gave **27** (203 mg, 89%) as a solid, which was analytically pure (mp 129–130 °C): UV (MeOH) λ_{max} 275 nm (ε 18000); ^{1}H NMR ($CDCl_3$) δ 0.04, 0.06, and 0.08 (12 H, each as s, SiMe), 0.86 (18 H, s, SiBu-t), 3.63–3.73 (2 H, m, CH_2-5'), 4.32 (1 H, m, H-4'), 4.99 (1 H, t, $J_{2',3'}$ = $J_{3',4'}$ = 2.5 Hz, H-3'), 5.40 (1 H, d, H-2'), 5.73 (1 H, dd, $J_{5,6}$ = 8.4, $J_{5,NH}$ = 2.0 Hz, H-5), 7.72 (1 H, d, H-6), 11.60 (1 H, br, NH); MS m/z 439 (M^+ - Me), 397 (M^+ - Bu-t). Anal. Calcd for $C_{21}H_{38}N_2O_5Si_2$: C, 55.50; H, 8.43; N, 6.16. Found: C, 55.78; H, 8.32; N, 6.06.

Selenoxide Elimination of 8 To Form 29. Compound **8** (306 mg, 0.5 mmol) in CH_2Cl_2 (6 mL) was treated with *m*-CPBA (129 mg, 0.75 mmol) at room temperature for 4 h, and the reaction mixture was worked up by the procedure described for the reaction of **6**. Column chromatography (4% EtOH in $CHCl_3$) gave **28** (313 mg, 100%) as a foam.

Physical data of **28** are as follows: UV (MeOH) λ_{max} 259 nm (ε 10000); ^{1}H NMR ($CDCl_3$) δ 0.02, 0.03, 0.07, and 0.10 (12 H, each as s, SiMe), 0.83, 0.86, 0.90, and 0.93 (18 H, each as s, SiBu-t), 2.87–3.12 and 3.34–3.58 (2 H, m, CH_2-5'), 3.95–4.06 (m, H-4' and H-3'a), 4.48–4.70 (m, H-3'b and H-2'a), 4.90–5.00 (m, H-2'b), 5.33 and 5.65 (1 H, each as d, $J_{1',2'}$ = 5.4, 4.9 Hz, H-1'), 5.74 and 5.85 (1 H, each as d, $J_{5,6}$ = 8.3 Hz, H-5), 7.17 (d, H-6a), 7.53–7.59 (m, Ph and H-6b), 7.77–7.87 (2 H, m, Ph); MS m/z 612 (M^+ - O), 555 (M^+ - O - Bu-t). Anal. Calcd for $C_{27}H_{44}N_2O_6SeSi_2$: C, 51.68; H, 7.07; N, 4.46. Found: C, 51.41; H, 7.19; N, 4.47.

Compound **28** (251 mg, 0.4 mmol) was dissolved in THF (10 mL) containing Et_3N (167 μL, 1.2 mmol). The solution was heated at 70 °C for 10 h, evaporated, and chromatographed on a silica gel column (benzene:EtOAc = 10:1). This gave **29** (165 mg, 91%) as a solid, which was analytically pure (mp 155–156 °C): UV (MeOH) λ_{max} 261 nm (ε 9500); ^{1}H NMR ($CDCl_3$) δ 0.04, 0.06, and 0.12 (12 H, each as s, SiMe), 0.88 and 0.93 (18 H, each as s, SiBu-t), 4.15–4.37 (3 H, m, CH_2-5' and H-3'), 4.54 (1 H, m, H-2'), 5.79 (1 H, dd, $J_{5,6}$ = 8.3, $J_{5,NH}$ = 2.0 Hz, H-5), 6.07 (1 H, d, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.24 (1 H, d, H-6), 8.68 (1 H, br, NH); MS m/z 454 (M^+), 439 (M^+ - Me), 397 (M^+ - Bu-t). Anal. Calcd for $C_{21}H_{38}N_2O_5Si_2$: C, 55.50; H, 8.43; N, 6.16. Found: C, 55.75; H, 8.60; N, 6.01.

Selenoxide Elimination of 12 To Form 30. Compound **12** (714 mg, 1.44 mmol) in CH_2Cl_2 (16 mL) was treated with *m*-CPBA (323 mg, 1.87 mmol) at room temperature for 5 h, and the reaction mixture was worked up by the procedure described for the reaction of **6**. A mixture of selenoxides obtained after column chromatography (5% EtOH in $CHCl_3$) was dissolved in THF (15 mL) containing Et_3N (0.6 mL, 4.32 mmol). The solution was heated at 70 °C for 2 h, evaporated, and chromatographed on a silica gel column (benzene:EtOAc = 5:1). This gave **30** (412 mg, 85%) as a syrup: UV (MeOH) λ_{max} 266 nm (ε 8100); ^{1}H NMR ($CDCl_3$) δ 0.12 and 0.14 (6 H, each as s, SiMe), 0.89 (9 H, s, SiBu-t), 1.92 (3 H, d, $J_{5\text{-Me},6}$ = 1.5 Hz, 5-Me), 2.10 and 2.65 (2 H, each as m, CH_2-2'), 4.29 and 4.78 (2 H, each as d, J_{gem} = 2.5 Hz, CH_2-5'), 4.68 (1 H, dd, $J_{2',3'}$ = 3.4, 6.4 Hz, H-3'), 6.44 (1 H, dd, $J_{1',2'}$ = 3.4, 6.8 Hz, H-1'), 7.43 (1 H, d, H-6), 8.58 (1 H, br, NH); MS m/z 338 (M^+), 281 (M^+ - Bu-t). Anal. Calcd for $C_{16}H_{26}N_2O_4Si \cdot 1/4H_2O$: C, 56.04; H, 7.79; N, 8.17. Found: C, 55.95; H, 7.69; N, 8.15.

Selenoxide Elimination of 21 To Form 31. Compound **21** (586 mg, 0.96 mmol) in CH_2Cl_2 (7 mL) was treated with *m*-CPBA (215 mg, 1.25 mmol) at room temperature for 13.5 h. An additional *m*-CPBA (50 mg, 0.29 mmol) was added, and the reaction mixture was stirred for further 8 h. Neutralization with Et_3N followed by column chromatography (benzene:EtOAc = 20:1) gave **31** as a solid (310 mg, 71%), which was analytically pure (mp 118 °C): UV (MeOH) 260 nm (ε 9800); ^{1}H NMR ($CDCl_3$) δ 0.07, 0.16, and 0.21 (12 H, each as s, SiMe), 0.86 and 0.91 (18 H, each as s, SiBu-t), 3.69 and 3.87 (2 H, each as dd, $J_{4',5'}$ = 2.4, 2.9, J_{gem} = 11.5 Hz, CH_2-5'), 4.83 (1 H, m, H-4'), 4.97 (1 H, m, H-3'), 5.66 (1 H, dd, $J_{5,6}$ = 7.8 Hz, $J_{5,NH}$ = 2.4 Hz, H-5), 6.67 (1 H, dd, J = 1.0, 2.9 Hz, H-1'), 7.37 (1 H, d, H-6), 7.92 (1 H, br, NH); MS m/z 397 (M^+ - Bu-t). Anal. Calcd for $C_{21}H_{38}N_2O_5Si_2$: C, 55.50; H, 8.43; N, 6.16. Found: C, 55.70; H, 8.55; N, 6.22.

Selenoxide Elimination of 18 To Form 32 and 33. Compound **18** (95 mg, 0.19 mmol) in CH_2Cl_2 (3 mL) was treated with *m*-CPBA (39 mg, 0.23 mmol) at room temperature for 1 h, and the reaction mixture was worked up by the procedure described for the reaction of **6**. A mixture of selenoxides obtained after column chromatography (8% EtOH in $CHCl_3$) was dissolved in THF (3 mL) containing Et_3N (80 μL, 0.6 mmol). The solution was heated at 60 °C for 2 h, evaporated, and applied on a silica gel column. Compound **33** (14 mg, 21%) was obtained as a syrup by eluting with 0.5% EtOH in $CHCl_3$. Compound **32** (23 mg, 36%) was obtained as a solid (mp 144–146 °C) by eluting with 1% EtOH in $CHCl_3$.

Physical data of **32** are as follows: UV (MeOH) λ_{max} 261 nm (ε 9200); ^{1}H NMR ($CDCl_3$) δ 0.10 (6 H, s, SiMe), 0.92 (9 H, s, SiBu-t), 4.25 (2 H, m, CH_2-5'), 4.54 (1 H, br, 3'-OH), 5.21 (1 H, m, H-2'), 5.25 (1 H, br, H-3'), 5.58 (1 H, d, $J_{5,6}$ = 8.1 Hz, H-5), 6.49 (1 H, d, $J_{1',2'}$ = 5.9 Hz, H-1'), 7.40 (1 H, d, H-6), 10.78 (1 H, br, NH); MS m/z 283 (M^+ - Bu-t), 265 (M^+ - Bu-t - H_2O). Anal. Calcd for $C_{15}H_{24}N_2O_5Si$: C, 52.94; H, 7.11; N, 8.23. Found: C, 52.94; H, 7.16; N, 8.17.

Physical data of **33** are as follows: UV (MeOH) λ_{max} 260 nm (ε 9600); ^{1}H NMR ($CDCl_3$) δ 0.08 (6 H, s, SiMe), 0.90 (9 H, s, SiBu-t), 2.62 and 2.88 (2 H, each as dd, $J_{3',4'}$ = 7.3, 7.8 Hz, J_{gem} = 18.8 Hz, CH_2-3'), 3.81 and 3.95 (2 H, each as dd, $J_{4',5'}$ = 3.4, 3.9 Hz, J_{gem} = 11.0 Hz, CH_2-5'), 4.50 (1 H, m, H-4'), 5.48 (1 H, s, H-1'), 5.71 (1 H, dd, $J_{5,6}$ = 7.8 Hz, $J_{5,NH}$ = 2.0 Hz, H-5), 7.25 (1 H, d, H-6), 8.73 (1 H, br, NH); MS m/z 283 (M^+ - Bu-t). Anal. Calcd for $C_{15}H_{24}N_2O_5Si$: C, 52.94; H, 7.11; N, 8.23. Found: C, 53.29; H, 7.33; N, 7.91.

1-[2-*O*-Acetyl-5-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-(phenylseleno)-β-D-arabinofuranosyl]uracil (34). Compound **18** (72 mg, 0.14 mmol) in pyridine (2 mL) was treated with Ac_2O (40 μL, 0.42 mmol) at room temperature for 2.5 h. Evaporation followed by column chromatography (hexane:EtOAc = 2:1) of the reaction mixture gave **34** (75 mg, 99%) as a foam: UV (MeOH) λ_{max} 263 nm (ε 12000); ^{1}H NMR ($CDCl_3$) δ 0.10 (6 H, s, SiMe), 0.93 (9 H, s, SiBu-t), 2.04 (3 H, s, Ac), 3.65 (1 H, m, H-3'), 3.81–4.00 (3 H, m, H-4' and CH_2-5'), 5.60 (1 H, m, H-2'), 5.66 (1 H, d, $J_{5,6}$ = 8.3 Hz, H-5), 6.07 (1 H, d, $J_{1',2'}$ = 5.9 Hz, H-1'), 7.30–7.40 (3 H, m, Ph), 7.55–7.64 (2 H, m, Ph), 8.01 (1 H, d, H-6), 8.52 (1 H, br, NH); MS m/z 483 (M^+ - Bu-t). Anal. Calcd for $C_{23}H_{32}N_2O_6SeSi$: C, 51.21; H, 5.98; N, 5.19. Found: C, 51.13; H, 5.95; N, 4.93.

Selenoxide Elimination of 34 To Form 35. Compound **34** (400 mg, 0.74 mmol) in CH_2Cl_2 (15 mL) was treated with *m*-CPBA (153 mg, 0.89 mmol) at room temperature for 1 h, and the reaction mixture was worked up by the procedure described for the reaction of **6**. A mixture of selenoxides obtained after column chromatography (4% EtOH in $CHCl_3$) was kept standing at 40 °C (neat) for 12 h. The resulting mixture was dissolved in benzene (20 mL) and neutralized by adding Et_3N. Evaporation followed by column chromatography (hexane:EtOAc = 2:1) gave **35** (248 mg, 88%) as a syrup: UV (MeOH) λ_{max} 259 nm (ε 10500); ^{1}H NMR ($CDCl_3$) δ 0.11 (6 H, s, SiMe), 0.92 (9 H, s, SiBu-t), 2.00 (3 H, s, Ac), 4.27 (2 H, m, CH_2-5'), 5.24 (1 H, d, $J_{2',3'}$ = 1.3 Hz, H-3'), 5.73 (1 H, dd, $J_{5,6}$ = 8.1 Hz, $J_{5,NH}$ = 2.2 Hz, H-5), 5.84 (1 H, dd, $J_{1',2'}$ = 7.2 Hz, H-2'), 6.71 (1 H, d, H-1'), 7.26 (1 H, d, H-6), 8.67 (1 H, br, NH); MS m/z 283 (M^+ - Bu-t - Ac + H), 265 (M^+ - Bu-t - AcOH). Anal. Calcd for $C_{17}H_{26}N_2O_6Si$: C, 53.40; H, 6.85; N, 7.33. Found: C, 53.57; H, 7.13; N, 7.00.

Selenoxide Elimination of 19 To Form 36 and 37. Compound **19** (99.5 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) was treated with *m*-CPBA (42 mg, 0.24 mmol) at room temperature for 3 h, and the reaction mixture was worked up by the procedure described for the reaction of **6**. A mixture of selenoxides obtained after column chromatography (2% EtOH in $CHCl_3$) was dissolved in THF (3 mL) containing Et_3N (84 μL, 0.6 mmol). The solution was heated at 60 °C for 2.5 h, evaporated, and chromatographed on a silica gel column (2% EtOH in $CHCl_3$) to give **36** (11.2 mg,

17%) and uracil (37, 18.5 mg, 83%). Compound 36 decomposed when dissolved in $CDCl_3$ to give uracil and an unidentified product.

1-[3-*O*-Acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-(phenylseleno)-β-D-xylofuranosyl]uracil (38). This compound was prepared in 98% yield as a foam from 19 (477 mg) by the procedure described for the preparation of 34: UV (MeOH) λ_{max} 261 nm (ε 11 400); ^1H NMR ($CDCl_3$) δ 0.09 (6 H, s, SiMe), 0.91 (9 H, s, SiBu-*t*), 2.04 (3 H, s, Ac), 3.67-4.00 (3 H, m, H-2′ and CH_2-5′), 4.31 (1 H, m, H-4′), 5.34 (1 H, t, $J_{2',3'} = J_{3',4'} = 5.9$ Hz, H-3′), 5.64 (1 H, dd, $J_{5,6} = 8.3$ Hz, $J_{5,NH} = 1.5$ Hz, H-5), 6.15 (1 H, d, $J_{1',2'} = 5.4$ Hz, H-1′), 7.28-7.35 (3 H, m, Ph), 7.62-7.69 (2 H, m, Ph), 7.74 (1 H, d, H-6), 8.68 (1 H, br, NH); MS *m/z* 483 (M^+ - Bu-*t*), 423 (M^+ - Bu-*t* - AcOH). Anal. Calcd for $C_{23}H_{32}N_2O_6SeSi$: C, 51.21; H, 5.98; N, 5.19. Found: C, 51.03; H, 5.99; N, 5.09.

Selenoxide Elimination of 38 To Form 39 and 40. Compound 38 (102 mg, 0.19 mmol) in CH_2Cl_2 (3 mL) was treated with *m*-CPBA (39 mg, 0.23 mmol) at room temperature for 2 h and worked up by the procedure described for the reaction of 6. A mixture of selenoxides obtained after column chromatography (2% EtOH in $CHCl_3$) was dissolved in THF (5 mL) containing Et_3N (78 μL, 0.57 mmol). The solution was heated at 60 °C for 2 h, evaporated, and chromatographed on a silica gel column (hexane:EtOAc = 2:1). This gave 39 (22 mg, 30%, mp 144-146 °C) and 40 (14 mg, 22%, mp 173-174 °C) as solids, which were analytically pure.

Physical data of 39 are as follows: UV (MeOH) λ_{max} 260 nm (ε 10 400); ^1H NMR ($CDCl_3$) δ 0.08 (6 H, s, SiMe), 0.89 (9 H, s, SiBu-*t*), 2.23 (3 H, s, Ac), 3.87 and 3.93 (2 H, each as dd, $J_{4',5'} = 2.2$ and 1.5 Hz, $J_{gem} = 11.9$ Hz, CH_2-5′), 4.69 (1 H, m, H-4′), 5.67 (1 H, dd, $J_{5,NH} = 1.8$ Hz, $J_{5,6} = 8.1$ Hz, H-5), 5.86 (1 H, m, H-2′), 7.05 (1 H, m, H-1′), 8.01 (1 H, d, H-6), 9.05 (1 H, br, NH); MS *m/z* 325 (M^+ - Bu-*t*). Anal. Calcd for $C_{17}H_{26}N_2O_6Si$: C, 53.40; H, 6.85; N, 7.33. Found: C, 53.40; H, 7.01; N, 7.06.

Physical data of 40 are as follows: UV (MeOH) λ_{max} 224 nm (ε 10 000), 250 nm (ε 9300); ^1H NMR ($CDCl_3$) δ 0.10 (6 H, s, SiMe), 0.91 (9 H, s, SiBu-*t*), 4.62 (2 H, s, CH_2-5′), 5.84 (1 H, dd, $J_{5,6} = 8.3$, $J_{5,NH} = 1.5$ Hz, H-5), 6.32 and 6.43 (2 H, each as d, $J_{2',3'} = 3.4$ Hz, H-2′ and H-3′), 7.51 (1 H, d, H-6), 8.73 (1 H, br, NH); MS *m/z* 265 (M^+ - Bu-*t*). Anal. Calcd for $C_{15}H_{22}N_2O_4Si$: C, 55.89; H, 6.88; N, 8.69. Found: C, 55.64; H, 6.97; N, 8.66.

Acknowledgment. Generous financial support (to H.T.) from the Naito Foundation is gratefully acknowledged.

Syntheses and ^1H NMR Conformational Analyses of Diastereomeric 4,4′-(4,5-Dihydroxy-1,2-cyclohexanediyl)bis(2,6-piperazinedione)s and a Synthetically Related Tricyclic Octahydro-2,2-dimethyl-6-oxo-1,3-dioxolo[4,5-*g*]quinoxaline-5,8-diacetic Acid Ester

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Received February 27, 1991

Efficient syntheses for five of the six possible diastereoisomeric 4,4′-(4,5-dihydroxy-1,2-cyclohexanediyl)bis-(2,6-dioxopiperazine)s (5-9) and a synthetically related tricyclic 1,3-dioxolo[4,5-*g*]quinoxaline ring system 45 from their respective (4,5-dihydroxy-1,2-cyclohexanediyl)bis(carbamate)s 11-16 via isopropylidene-protected intermediates are described. Solution conformations of all targets and several synthetic intermediates in DMSO-d_6 were determined using ^1H NMR and NOE methods, and the structure for polyheterocycle 45, obtained during attempted preparation of the sixth possible dioxopiperazine diastereomer 10, was determined with the additional aid of 2D COSY, 2D HETCOR, and ^1H-^{13}C correlation of long-range coupling (COLOC). Taken together, these studies provide evidence for the differences in reaction conditions required for bis(dioxopiperazine) synthesis, a relatively comprehensive analysis of dioxopiperazine and hydroxyl substituent effects on cyclohexane DMSO-d_6 solution conformations, and a preliminary analysis of aqueous solubility differences.

Introduction

The regioisomeric dioxopiperazines 1-3 are found in numerous natural and unnatural organic compounds, and these substances possess a multitude of important biological properties.[1] Unlike compounds found in the 2,3- and 2,5-dioxo series 1 and 2, 2,6-dioxo regioisomers 3 mainly have biological significance as bis(2,6-dioxopiperazine)s (4a), and such analogues have unusually poor and/or unpredictable solubility properties.[1] Nonetheless, dioxopiperazines of this class exhibit synergistic antitumor effects in combination with clinically efficacious antineoplastic drugs, ameliorate the toxicity of cancer chemotherapeutic agents such as the anthracycline antibiotics, and have geometry-dependent anti- and prometastatic activities which are of both theoretical and clinical significance.[1-3]

Optically pure enantiomers[1,4] and bis(morpholinomethyl) Mannich derivatives[1,5,6] (4b) have had limited success when used to improve solubility properties of bis(dioxopiperazine)s, but to our knowledge there has been no systematic structure-property relationship analysis of

(1) For a comprehensive review of dioxopiperazines, see: Witiak, D. T.; Wei, Y. *Progress in Drug Research*; Jucker, E., Ed.; Birkhäuser Verlag: Basel, 1991; Vol. 35, pp 249-363.

(2) See pages 302-341 in ref 1.

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