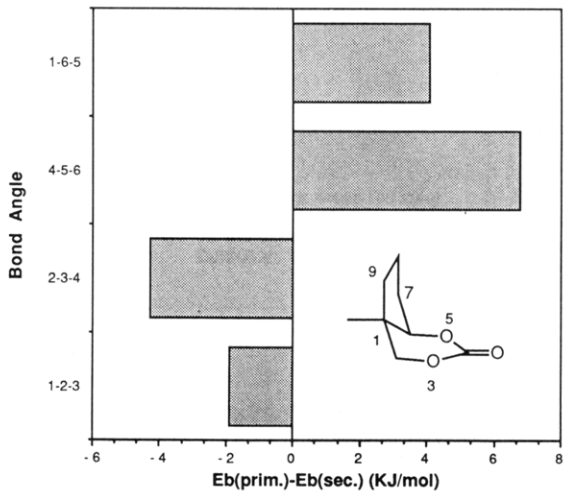

Figure 4. Difference in angle bending energy (>0.5 kJ/mol) for primary vs secondary C–O bond of cis carbonate **6b** at 1.7 Å.

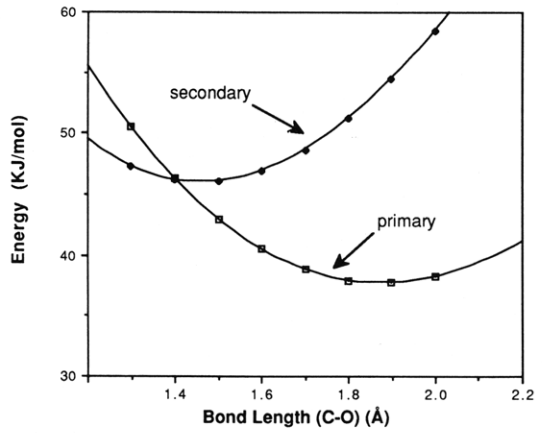

Figure 5. Energy vs bond length for trans carbonate **1a**.

length of 1.70 Å. The negative bars indicate favorable primary bond cleavage (inhibition of secondary cleavage) while the positive bars show favorable secondary bond cleavage. The relief of bond angle strain is principally in ∠2,3,4 and ∠5,6,7 with smaller, near equal contributions from ∠1,2,3, ∠6,7,8, ∠2,1,9, and ∠6,1,9. Only the increase in ∠4,5,6 and ∠1,6,5 inhibits primary fragmentation. Figure 4 illustrates the same principle applied to the cis cyclic carbonate **6b**. Bond angle strain is now relieved by reduction of ∠4,5,6 and ∠1,6,5 when the secondary bond is lengthened. These two effects outweigh the energy increase associated with the increase in ∠1,2,3 and ∠2,3,4.

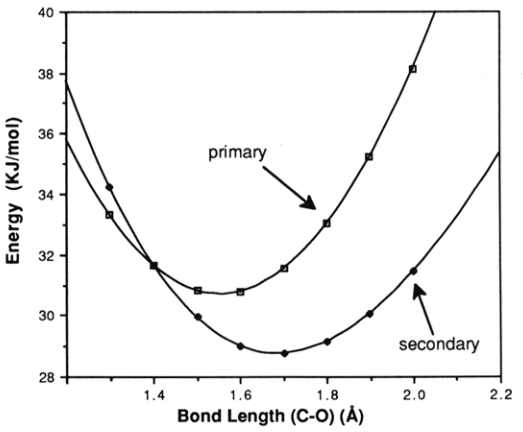

Figure 6. Energy vs bond length for cis stereoisomer of trans carbonate **1a**.

Figures 3 and 4 illustrate another interesting feature of the relief of bond angle strain. While the relief of bond angle strain of the cis isomer **6b** is highly localized in two complementary pairs of internal bond angles of the heterocyclic ring, the relief of bond angle strain in trans isomer **5b** is more global in nature. Not only are the internal angles of the heterocyclic ring that play a role in the cis isomer **6b** involved, but also external bond angles to both rings (∠2,1,9 and ∠5,6,7) and internal angles of the cyclopentane ring (∠6,1,9 and ∠6,7,8).

When the primary/secondary bond stretching computation was applied to the trans cyclic carbonate **1a**, the cleavage of the primary bond was favored (Figure 5). Because our synthetic objective requires fragmentation of a secondary C–O bond, the calculation on the cis cyclic carbonate stereoisomer of **1a** suggests that this goal can be realized (Figure 6). The computational method also confirmed the mode of fragmentation of thionocarbonates **7** and **8**.

This study illustrates the power of computational methods for the illucidation of a reaction mechanism that is not obvious based upon steric arguments derived from inspection of molecular models.

Acknowledgment. This work was supported by a grant from the National Cancer Institute, NIH (CA-39976). We thank Professors J. A. Berson, J. M. McBride, and K. B. Wiberg for their assistance, and Professor W. C. Still, Columbia University, for MacroModel. We are grateful to Gayle Schulte, Yale Chemical Instrumentation Center, for performing the X-ray determinations.

A Highly Stereoselective Glycosylation of 2-(Phenylselenenyl)-2,3-dideoxyribose Derivative with Thymine: Synthesis of 3′-Deoxy-2′,3′-didehydrothymidine and 3′-Deoxythymidine

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Received November 14, 1989

Summary: A highly stereoselective synthesis of 3′-deoxy-2′,3′-didehydrothymidine (D4T) and 3′-deoxythymidine (D2T) was achieved from the condensation of 2-(phenylselenenyl)-2,3-dideoxyribose derivative and silylated thymine in the presence of trimethylsilyl triflate.

Since the discovery of the anti-human immunodeficiency viral (HIV) activity of 3′-azido-3′-deoxythymidine (AZT, Retrovir) by Mitsuya et al.,[1] a number of nucleosides have been found to possess potent anti-HIV activity in vitro. At the time of this writing, 3′-azido-2',3′-dideoxyuridine (AZddU, AZDU or CS-87),[2,3] 2′,3′-dideoxycytidine

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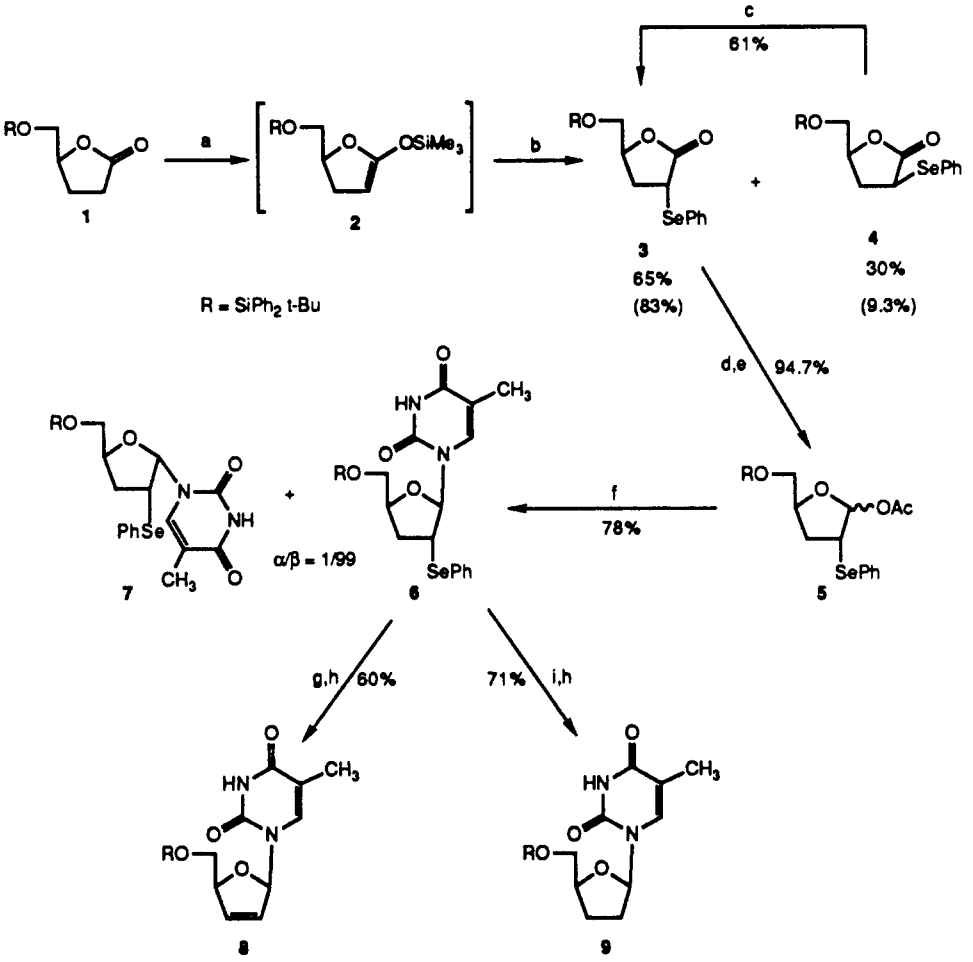
Scheme I[a]



[a] (a) Li-HMDS, −78 °C, $(CH_3)_3SiCl$, −78 °C → room temperature, THF; (b) −78 °C, PhSeBr; (c) DBU or diethylamine, THF; (d) DIBAL, toluene, −78 °C; (e) Ac_2O/Py, 0 °C; (f) silylated thymine, TMSOTf, $ClCH_2CH_2Cl$; (g) 10% H_2O_2, cat. Py; (h) n-Bu_4NF, THF; (i) n-Bu_3SnH, Et_3B, benzene, room temperature.

(D2C,[4] 2′,3′-dideoxyinosine (D2I),[5] and 3′-deoxy-2′,3′-didehydrothymidine (D4T)[6] are currently undergoing various stages of clinical trials in acquired immunodeficiency syndrome (AIDS) and AIDS-related complex patients.

Recently we have reported[7] the total synthesis of AZT and AZddU from D-mannitol as an alternative procedure for these compounds without using the preformed nucleosides, thymidine and 2′-deoxyuridine, respectively. Although the condensation of uracil and the appropriate carbohydrate gave 2:1 ratio of β:α for AZddU, the overall stereoselectivity of this type of condensation has been poor. The total synthesis of D2C from the condensation of 2,3-dideoxyribose derivative and cytosine gave similar poor stereoselectivity.[8] D4T was first synthesized by Horwitz et al.[9] from thymidine and a slightly modified procedure is being used for a large-scale preparation.[10] Total synthetic approach toward the synthesis of D4T using the 2,3-unsaturated ribose seems unlikely as this ribose derivative is highly unstable.[11] However, due to the high demand of thymidine as the starting material for AZT as well as probably for D4T in the future, an alternative synthesis for D4T without using thymidine as the starting material is highly desirable.

Our initial effort on obtaining a favorable selectivity for the formation of β-nucleoside in a condensation reaction by substituting the 2,3-dideoxyribose at 3-position with phenylsulfenyl group did not give the desired selectivity.[12] Hence, the possibility of using a 2,3-dideoxyribose with substitution at 2-position, which would direct the condensation towards the formation of β-isomer, was explored. Phenylselenenyl group was chosen because of the ease with which it can be removed as well as chemical stability during the synthesis. Hanessian and Murray[13] have used the selenenylation and de-selenenylation method to pre-

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pare 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-2,3-didehydroribonolactone from **1**, which can be readily prepared from various sources.[14-18] Since our several attempts to selenenylate the lithium enolate of **1** did not give a respectable total yield as well as favorable α:β ratio of the selenenylated product, trimethylsilyl enol ether **2** was prepared in situ by using lithium bis(trimethylsilyl)amide (Li-HMDS) as a base, followed by the addition of chlorotrimethylsilane.[19] The silyl enol ether was reacted with phenylselenium bromide at −78 °C.[20] In order to obtain the desired C2-α-isomer **3** as the major product, a bulky *tert*-butyldiphenylsilyl group was used as the protecting group for 5-OH (Scheme I). From the reaction, C2-α isomer **3** (65%) was obtained along with C2-β isomer **4** (30%). The separation of the desired α-isomer **3**[21] from **4**[22] was readily achieved by a silica gel column using a gradient mixture of ethyl acetate in hexane (0–6%) as the eluent. Subsequently, it was found that the isolated β-isomer **4** could be equilibrated to an extent of 61% to the α-isomer **3** by treatment with bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or diethylamine. Thus, α-isomer was obtained in overall yield of 83%. The desired lactone **3** was reduced to the lactol with DIBAL at −78 °C, followed by acetylation using acetic anhydride/pyridine at 0 °C to give the desired carbohydrate derivative **5**[23] in good yield (77% in three steps from **1**). The condensation of **5** and silylated thymine in the presence of trimethylsilyl triflate gave **6** and **7** in the ratio of 99 to 1 in 78% yield. Although TLC and HPLC (normal phase, 10 μm, 1% methanol in chloroform) showed the product[24] to be a single isomer, the desilylated condensation product showed ≈1% of the other isomer **7**.[25] The high stereoselectivity observed in glycosylation reaction may be attributed to the neighboring group participation of phenylselenenyl group to the cation generated at the anomeric position during the reaction, analogous to the Vorbrüggen's method[26,27] of glycosylation of 2-acetyl ribose derivative. The phenylselenenyl group could be removed either oxidatively to give the 2′,3′-dideoxy-2′,3′-didehydronucleoside or reductively to give the 2′,3′-dideoxynucleoside. The oxidative removal of phenylselenenyl group was achieved by reacting the condensed product with 10% hydrogen peroxide in dichloromethane. Although there are two α-hydrogens (1′ and 3′) available for syn-elimination of selenoxide,[28] the elimination proceeded smoothly in the desired direction to give 5′-(*O*-*tert*-butyldiphenylsilyl)-3′-deoxy-2′,3′-didehydrothymidine in 76% yield, which on desilylation with tetra-*n*-butylammonium fluoride gave 3′-deoxy-2′,3′-didehydrothymidine (D4T) **8**[29] (78%; overall yield from **3** was 36.4%). No α-anomer of D4T was observed after the oxidation and desilylation of **6**, as determined by HPLC. The α-isomer was probably eliminated during the work up process. Similarly, phenylselenenyl group in **6** was removed reductively with tri-*n*-butyltin hydride in the presence of triethylborane[30] in benzene at room temperature to give 5′-*O*-*tert*-butyldiphenylsilyl)-3′-deoxythymidine, which was desilylated to give 3′-deoxythymidine (D2T) **9**[31] (overall yield from **3** was 43.6%). In this case also no α-anomer could be detected.

In summary, a highly stereoselective total synthesis of D4T and D2T has been achieved from the condensation of 2-(phenylselenenyl)-2,3-dideoxyribose derivative with thymine. Significance of these results is that this novel approach may be utilized for the synthesis of other 2′,3′-dideoxy and 2′,3′-dideoxy-2′,3′-didehydronucleosides of biological interest including 2′,3′-dideoxyinosine (D2I) and 2′,3′-dideoxycytidine (D2C) without using expensive preformed nucleosides as the starting materials. Extension of this strategy to other 2′,3′-dideoxy- and 2′,3′-dideoxy-2′,3′-didehydronucleosides of biological interest are in progress.

Acknowledgment. This research was supported by the Public Health Service Research Grant (AI 26055 and AI 25899) from the National Institute of Allergy and Infectious Diseases.

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(21) Compound **3**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.02 (s, 9 H, t-Bu), 2.23–2.34 (m, 1 H, 4-H_a), 2.64–2.75 (m, 1 H, 4-H_b), 3.60 (dd, 1 H, $J_{6Ha,6Hb}$ = 11.6, $J_{5,6}$ = 3.2 Hz, 6-H_a) 3.83 (dd, 1 H, 6-H_b, $J_{6Ha,6Hb}$ = 11.5 Hz, $J_{5,6}$ = 3.2 Hz) 4.09 (dd, 1 H, J = 9.15, 4.4 Hz, 3-H), 4.31–4.39 (m, 1 H, 5-H), 7.2–7.7 (m, 15 H, Ar-H); IR (film) 1765 cm^{-1}. Anal. Calcd for $C_{27}H_{30}O_3SeSi$: C, 63.64; H, 5.93. Found: C, 63.73; H, 5.95.
(22) Compound **4**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.04 (s, 9 H, t-Bu), 2.17–2.29 (m, 1 H, 4-H_a), 2.58–2.70 (m, 1 H, 4-H_b), 3.65 (m, 2 H, 6-H), 4.03 (t, 1 H, J = 9.5 Hz, 3-H), 4.45–4.57 (m, 1 H, 5-H), 7.2–7.5 (m, 9 H, Ar-H), 7.6–7.7 (m, 6 H, Ar-H); IR (film) 1770 cm^{-1}. Anal. Calcd for $C_{27}H_{30}O_3SeSi$: C, 63.64; H, 5.93. Found: C, 63.45; H, 5.96.
(23) Compound **5** (α and β anomers): Since **5** was fairly pure and unstable it was used in condensation reaction without further purification. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 0.97 and 1.05 (s, 9 H, t-Bu), 1.85 and 2.10 (s, 3 H, $OCOCH_3$), 1.9–2.7 (m, 2 H, 3-H), 3.5–4.0 (m, 3 H, 2,5-H), 4.40 (m, 1 H, 4-H), 6.28 (s, 1-H), 6.46 (d, 1-H), 7.2-7.8 (m, 15 H, Ar-H).
(24) Condensed product (**6**): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.11 (s, 9 H, t-Bu), 1.45 (s, 3 H, 5-CH_3), 1.95–2.70 (m, 2 H, 3′-H), 3.60–4.30 (m, 4 H, 2′,4′,5′-H), 6.16 (d, 1 H, $J_{1'2'}$ = 8.1 Hz, 1′-H), 7.15–7.70 (m, 16 H, Ar-H and 6-H), 8.31 (br s, 1 H, NH, D_2O exchangeable); UV (MeOH) λ_{max} 266.0 nm (ϵ 9054), λ_{min} 240.5 (ϵ 4619). Anal. Calcd for $C_{32}H_{36}N_2O_4SeSi$: C, 62.02; H, 5.86; N, 4.52. Found: C, 61.94; H, 5.89; N, 4.49. This assignment was confirmed by oxidation of **6** to **8**.
(25) Compound **7** (desilylated): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.72 (d, 3 H, 5-CH_3, J = 1 Hz), 1.8–2.2 (m, 2 H, 3′-H), 3.4–3.8 (m, 2 H, 5′-H), 3.9 (m, 1 H, 2′-H), 4.3–4.6 (m, 1 H, 4′-H), 6.21 (d, 1 H, J = 5.5 Hz, 1′-H), 7.27–7.7 (m, 6 H, Ar-H, 6-H). Silylated **7** could not be separated from **6** by chromatography due to the low concentration (1%) as well as same R_f value (TLC) and retention time (HPLC). The coupling constant of desilylated **6** is $J_{1,2}$ = 7.3 Hz.
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(29) Compound **8**: mp 174 °C; UV (H_2O) λ_{max} 266.0 (ϵ 10149); $[\alpha]_D$ −39.4° (*c* 0.701, H_2O) [lit.[9] mp 165–166 °C; UV (H_2O) λ_{max} 266.0 (ϵ 9910); $[\alpha]_D$ −42° (*c* 0.69, H_2O)].
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(31) Compound **9**: mp 150–152 °C; UV(MeOH): λ_{max} 268.0 nm (ϵ 9985); $[\alpha]_D$ +18.3° (*c* 0.999, MeOH) [lit.[9] mp 149–150 °C].