for $C_{19}H_{34}N_2O_2$, 322.262) ($M^+ - C_2H_4$), 264.229 (calcd for $C_{17}H_{30}NO$, 264.232), 194.152 (calcd for $C_{12}H_{20}NO$, 194.154); IR (CCl_4) 3250 (OH), 1620 cm^{-1} (double bond); ^{13}C NMR δ 165.7, 163.4, 160.6, 115.0.

Monoacetyl Isoxazole Derivative 11. Acetylation of **10** (100 mg) with acetic anhydride (0.8 mL) and pyridine (0.5 mL) at room temperature for 24 h gave an oily monoacetate, **11**: mass spectrum, m/e 420.333 (calcd for $C_{25}H_{44}N_2O_3$, 420.335); IR ($CHCl_3$) 1768 ($NCOCH_3$), 1620 cm^{-1} (double bond). Anal. Calcd for $C_{25}H_{44}N_2O_3$: C, 71.42; H, 10.48; N, 6.67; O, 11.43. Found: C, 71.50; H, 10.45; N, 6.63; O, 11.43.

Elasnin Ketal (12). A solution of **1** (400 mg) in benzene (7.2 mL) was refluxed with ethylene glycol (0.2 mL) and a trace amount of *p*-toluenesulfonic acid for 7 h. To the reaction mixture was added benzene (40 mL), and the mixture was washed with water and then 5% $NaHCO_3$ solution. The organic solvent layer was dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel, using the solvent system benzene–acetone (60:1 to 15:1), to give ketal **12** (270 mg) as a colorless oil: mass spectrum, m/e 394 ($M^+ - C_3H_6$), 380 ($M^+ - C_4H_8$), 365 ($M^+ - C_5H_{11}$), 293 ($M^+ - C_8H_{15}O_2$), 223 ($M^+ - C_{13}H_{25}O_2$); UV (EtOH) λ_{max} 284 nm (ϵ 4000); IR (CCl_4) 1700 (α-pyrone CO), 1660 (γ-pyrone CO), 1630 cm^{-1} (double bond). Anal. Calcd for $C_{25}H_{44}O_5$: C, 71.56; H, 10.09; O, 18.35. Found: C, 72.05; H, 10.13; O, 17.82.

Methylelasnin Ketal (13). A solution of the ketal **12** (100 mg) in ethyl ether was treated with CH_2N_2 to give the methyl ether **13**: mass spectrum, m/e 450 ($C_{27}H_{46}O_5$), 408 ($M^+ - C_3H_6$), 379 ($M^+ - C_5H_{11}$), 265 ($M^+ - C_8H_{15}O_2 - C_3H_6$), ($CH_3$-$(CH_2)_3\overline{COCH_2CH_2O}$); UV λ_{max} 254.5 nm (ϵ 7450); IR (CCl_4) 1560 (α-pyrone CO), 1620 and 1600 cm^{-1} (enolic double bond).

Acetylelasnin Ketal (14). Ketal **13** (35 mg) was acetylated with acetic anhydride and pyridine at room temperature. The crude acetate was purified on silica gel preparative TLC (benzene–acetone, 25:1) to afford **14** (24 mg) as a colorless oil: mass spectrum, m/e 478 ($C_{28}H_{46}O_6$), 407 ($M^+ - 71$), 335 ($M^+ - C_8H_{15}O_2$), 293 (335 - C_3H_6), 292 (335 - $COCH_3$), 213 ($C_{13}H_{25}O_2$); UV λ_{max} 305 nm (ϵ 7400); IR (CCl_4) 1775 (enolic acetyl CO), 1720 (α-pyrone CO), 1190 cm^{-1} (C-O-C).

Incorporation of [1,2-^{13}C]Acetate. An elasnin-producing strain, *Streptomyces noboritoensis* KM-2753, was inoculated into a medium containing 2% dextrin, 0.2% glucose, 1.5% soybean meal, 0.3% yeast extract, and 0.3% $CaCO_3$ at pH 7.0 and cultivated at 27 °C. A 48-h culture was transferred into a producing medium containing 2% glucose, 2% soybean meal, and 0.1% NaCl in a reciprocal flask, and the initial pH was adjusted to 7.0. After cultivation for 7 h at 27 °C, [1,2-^{13}C]CH_3COONa as the ^{13}C-labeled precursor was added at a concentration of 0.1% to the culture, and the fermentation was continued for an additional 48 h. The culture filtrate (500 mL) was extracted with EtOAc (200 mL) and the extract was concentrated to dryness, affording a brownish oil (180 mg). The crude oil was chromatographed over a silica gel thin-layer plate, using benzene–ethanol (10:1) as the developing solvent, to isolate pure ^{13}C-labeled elasnin (70 mg). The methyl ether was obtained by treatment of ^{13}C-labeled elasnin with CH_2N_2.

Registry No. 1, 68112-21-0; 2, 73891-54-0; 3, 73891-55-1; 4, 73907-88-7; 5, 73891-56-2; 6, 73891-57-3; 7, 73891-58-4; 8, 73891-59-5; 9, 1168-16-7; 10, 73891-60-8; 11, 73891-61-9; 12, 73891-62-0; 13, 73891-63-1; 14, 73907-89-8.

Nucleosides. 115. Reaction of 3′-*O*-Mesylthymidine. Formation of 1-(3-Azido-2,3-dideoxy-β-D-*threo*-pentofuranosyl)thymine and Its Conversion into 6,3′-Imino-1-(2,3-dideoxy-β-D-*threo*-pentofuranosyl)thymine[1]

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Treatment of 5′-*O*-trityl-3′-*O*-mesylthymidine (**3**) with NaN_3 in DMF at reflux gave 5′-*O*-trityl-3′-azido-3′-deoxythymidine (**5**) and 6,3′-imino-1-(5-*O*-trityl-3-deoxy-β-D-*threo*-pentofuranosyl)thymine (**8**). Compound **8** was formed from the 3′-azido-*threo*-pentofuranosylthymine derivative **6**. A mechanism is proposed for the formation of **8** from **6**. Also, the 6,5′-imino-bridged thymidine **18** was prepared. Conformational features of these imino-bridged nucleosides are discussed.

3′-Amino-3′-deoxythymidine (**1**, Scheme I), synthesized in our laboratory in 1964,[2] was recently found to exhibit interesting biological activity against murine Sarcoma 180[3,4] and L1210[4,5] cells. For further biological evaluations, large amounts of **1** were required. **1** was prepared[2] originally by treatment of 5′-*O*-trityl-3′-*O*-mesylthymidine (**3**) with phthalimide followed by deprotection. The reaction was shown to proceed via the anhydronucleoside intermediate (**2**).[2] Subsequently, the synthesis of **1** was reported by reaction of NaN_3 with either **2**[6] or 5′-*O*-trityl-3′-*O*-mesyl-2′-deoxy-β-D-*threo*-pentofuranosylthymine (**4**).[4,7]

In an attempt to find an easier route to **1**, compound **3** was treated with NaN_3 in DMF at reflux temperature for 24 h. Two nucleosidic products were isolated from the reaction mixture. One of the products was identical with the known[6] 3′-azido-3′-deoxy-5′-*O*-tritylthymidine (**5**) from which 3′-amino-3′-deoxythymidine (**1**) was prepared. The formation of the "down" azido derivative **5** from **3** ap-

(1) This investigation was supported by funds from the National Cancer Institute, NIH, U.S. Public Health Service Grants No. CA-08748 and 18601.

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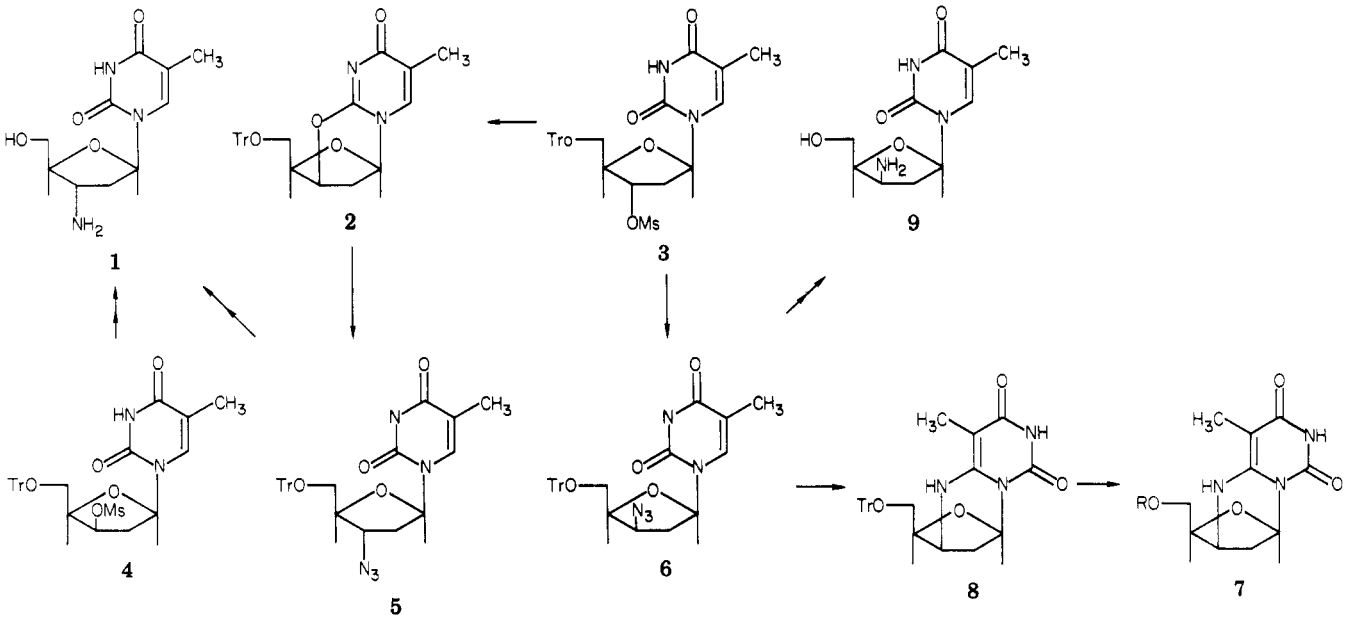
0022-3263/80/1945-3274$01.00/0

Scheme I

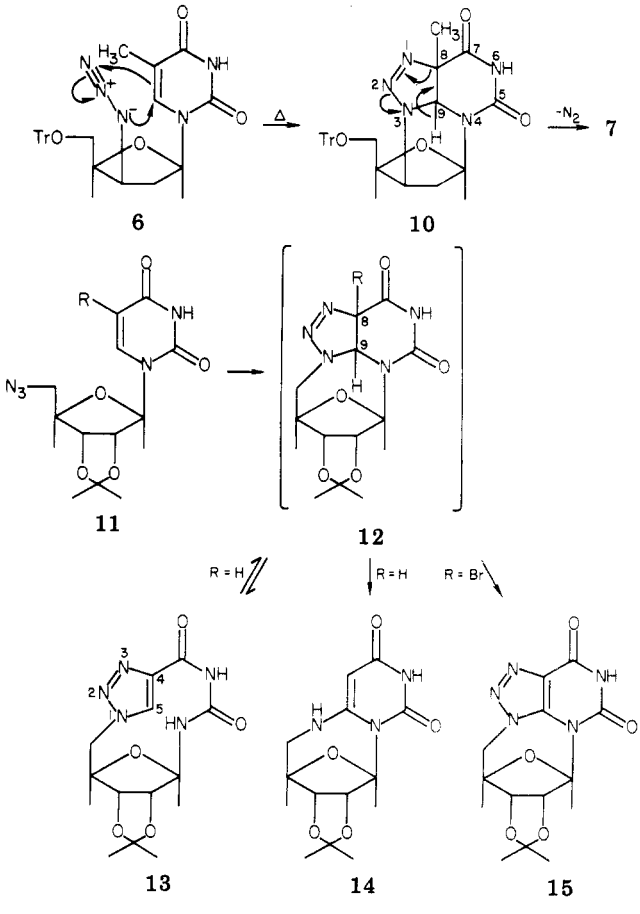


parently proceeded via the 2,3′-anhydronucleoside **2**. Intramolecular nucleophilic attack by the 2-C=O group at C-3′ of **3** with concomitant release of mesylate ion would give rise to the 2,3′-anhydro intermediate **2**. Cleavage of the 2,3′-anhydro linkage via nucleophilic attack by azide ion at C-3′ of **2** would result in the formation of **5**.

The second product, which is more polar than **5**, was assigned the 6,3′-imino-1-(3-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine structure (**8**) on the basis of the following data. The IR spectrum of **8** does not exhibit a band for an azide function. The maximum of UV absorption of this compound in MeOH occurred at 283 nm, indicating that a modification of the aglycon structure had occurred. After detritylation, a crystalline product **7** (R = H) with UV characteristics similar to **8** was obtained. The ^{1}H NMR spectrum of the detritylated product showed the absence of H-6, indicating substitution at C-6 of the thymine aglycon and the presence of three dissociable protons. The overall ^{1}H NMR spectral pattern is akin to that of 2,3′-imino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)-thymine.[8] These data, together with combustion analyses (empirical formula $C_{10}H_{13}N_3O_4$) and mass spectroscopic data (M^+, *m/e* 239), are consistent with the detritylated 6,3′-*N*-bridged structure **7** (R = H). Thus, the structure of the more polar product isolated from the reaction of **3** with NaN_3 is established as **8** and as **7** (R = H) for the detritylated product. Acetylation of **7** (R = H) gave the crystalline monoacetate **7** (R = Ac). As expected,[8] the 6,3′-imino bridge of **7** and **8** was stable to 1 N HCl and 1 N NaOH at room temperature overnight.

It follows that the "up" azide structure **6** is an intermediate in the formation of N-bridged structure **8** from **3**. Actually, we were able to isolate the "up" azido intermediate **6** as colorless crystals in 47% yield by brief treatment of **3** with NaN_3 in DMF at reflux temperature. Reaction at lower temperatures gave almost exclusively the 2,3′-anhydronucleoside **2** and the "down" azido derivative **5**. **6** was subsequently converted into the hitherto unknown 3′ "up" amino nucleoside **9**. The ^{1}H NMR spectrum of **9** showed a quartet for H-1′ at δ 6.00, indicating that the conformation of **9** in Me_2SO solution is deviated from the 3′-exo conformation of thymidine[9,10] and close to

Scheme II



the 3′-endo conformation of the α-anomer of thymidine.[9] The HCl salt of **9**, however, assumed the 2′-endo-3′-exo conformation, as evidenced by the ^{1}H NMR (H-1′ signal appeared as a triplet at δ 5.96).

A plausible mechanism for the formation of **8** from **6** is shown in Scheme II. Nucleophilic attack by the root

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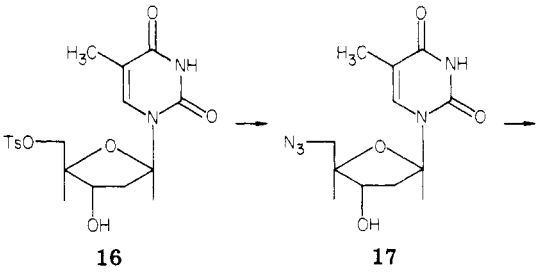
nitrogen of the azido group at C-6 of **6** followed by a series of electron shifts would produce the triazolino intermediate **10**. Abstraction of H-9 from **10** would be followed by elimination of N_2 to form **8**, as shown in Scheme II. Sasaki et al.[11] proposed a somewhat similar triazolinopyrimidine structure **12** in the thermal reaction of 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**11**, R = H, Scheme II). In their case the major product isolated was 1,5′-anhydro-N^{ω}-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-4-allophanoyl-1,2,3-triazole (**13**, 80% yield). 6,5′-Imino-1-(5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)uracil (**14**) was isolated in very low yield (5.3%). Dissociation of more acidic H-8 from **12** (R = H) would produce the allophanoyl derivative **13**, whereas loss of H-9 would cause elimination of N_2 from **12**, resulting in the formation of **14**. They also reported[12] the formation of 9,5′-cyclo-3-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaxanthine (**15**) in high yield from the 5-bromo analogue of **11** (see Scheme II, **11**, R = Br) by heating in DMF. They proposed the triazolinopyrimidine intermediate (**12**, R = Br) for this conversion. Obviously, elimination of HBr from the intermediate **12** (R = Br) led to the formation of **15**. In our case, however, intermediate **10** does not contain a leaving group at the bridgehead C-8 position; consequently, only H-9 could be lost to form the imino cyclonucleoside **8**.

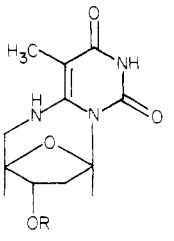
Kowollik and Langen[13] reported the isolation of 3′-(ethylthio)-3′-deoxy-β-D-xylofuranosyluracil (11%) from the reaction of 3′-*O*-mesyl-2′,5′-di-*O*-trityluridine with NaSEt in DMF at 140 °C. Beranek and Sorm[14] described the formation of 5′-*O*-acetyl-3′-iodo-β-D-xylosyl-6-azauracil in 50% yield as the intermediate in the synthesis of 3′-deoxy-6-azauridine by treatment of 5′-*O*-acetyl-3′-*O*-tosyl-6-azauridine with NaI in DMF at 150 °C. Generally, however, pyrimidine nucleosides bearing sulfonyloxy leaving groups at C-2′ or C-3′ in the "down" configuration undergo intramolecular nucleophilic attack by the 2-carbonyl of the aglycon preferentially.[15] The isolation of the "up" azido product **6** or the 6,3′-imino-bridged nucleoside **8** from the reaction of the "down" mesylate **3** with NaN_3 is of significance to pyrimidine nucleosides, for it indicates clearly that direct *intermolecular* nucleophilic displacement of the "down" 3′-mesyloxy function in such nucleosides can compete with the *intramolecular* (neighboring group) reaction. Also, conversion of the "up" azido derivative **6** into the 6,3′-N-bridged nucleoside **8** is of interest, for although pyrimidine nucleosides containing a 6,5′-imino linkage[12,16] are known, to our best knowledge no example of the corresponding 6,3′-imino system (viz., **8**) has been reported. The 6,3′-imino-bridged nucleosides **7** and **8** have the 2,4,8-triaza-12-oxatricyclo[3,2,1,$0^{2,7}$]dodecane ring system (Chart I). The anomeric proton signal of **7** (R = H) in the ^{1}H NMR spectrum appeared at δ 6.28 as a doublet, indicating H-1′ coupled only with H-2′ exo. Signals for H-2′ endo and H-2′ exo were found at δ 2.05 as a doublet ($J_{2',2''}$ = 11.3 Hz) and at δ 2.31 as a doublet of deformed triplets, respectively. These data indicate the 2′ exo envelop conformation for the sugar ring.

Treatment of 5′-*O*-tosylthymidine (**16**) (Scheme III) in DMF at reflux temperature afforded 6,5′-imino-5′-deoxythymidine (**18**). As expected, this reaction proceeded via the 5′-azido derivative **17**.

Scheme III

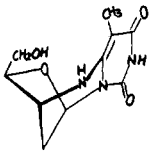


16 **17**

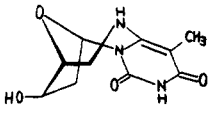


18

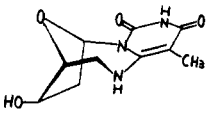
Chart I



7, R = H



18B
boat conformation



18A
chair conformation

In the ^{1}H NMR spectrum of **18** (Me_2SOd_6/D_2O), the signal for H-5′a appeared at δ 2.97 as an apparent doublet ($J_{4',5'a} < 1$, $J_{5'a,5'b}$ = 14.0 Hz), and the H-5′b signal appeared at δ 3.45 as a doublet of doublets ($J_{4',5'b}$ = 2.4, $J_{5'a,5'b}$ = 14.0 Hz), indicating that the dihedral angles defined by H-4′ and H-5′a and by H-4′ and H-5′b are in the range of 70–75° and 45–50°, respectively. These data are consistent with the chair conformation (A) assigned to structure **18** (see Chart I). The possibility of a boat conformation (B) for **18** is ruled out since examination of molecular models show that in this conformation (B) the dihedral angle between H-4′ and H-5′a is close to 0°, and consequently it follows that the coupling between these protons should be large and the signal for H-5′a should be a well-resolved quartet. This is not the case. It is noteworthy that based on ^{1}H NMR data Inoue and Ueda[16] had also proposed a chair conformation for the seven-membered ring of an analogous compound, namely, 6,5′-imino-5′-deoxy-2′,3′-*O*-isopropylideneuridine. It should be noted that the seven-membered ring of 6,5′-*O*,[17] 6,5′-*S*[16] and 6,5′-methylene[18] bridged pyrimidine ribonucleosides is in a chain conformation.

The furanose ring in **18** appears to exist in the 4′ endo conformation on the basis of the following data. Although the signals for H-1′ and H-3′ in the ^{1}H NMR spectrum are not first order due to virtual coupling[19] (the difference in chemical shifts of protons of C-2′ is less than the coupling constant between them), the width of the anomeric signal (~14 Hz) shows strong coupling between H-1′ and H-2′ exo (cis protons). The narrower width of the H-3′ signal (~10 Hz) indicates that the dihedral angle between H-3′ and H-2′ endo (cis protons) is larger than that between

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H-1′ and H-2′ exo. The apparent singlet for H-4′ indicates very little coupling between H-3′ and H-4′; that is, the dihedral angle between these protons is almost 90°. These data are consistent with a conformation for the furanoid ring in which C-4′ sits above the plane defined by C-1′, C-2′, and C-3′. An examination of Dreiding models for 18 supports this assignment. It should be noted that Inoue and Ueda[16] reported zero couplings between H-1′ and H-2′ and between H-3′ and H-4′ for their 6,5′-imino-5′-deoxy-2′,3′-O-isopropylideneuridine. On the basis of their data, the furanose portion of their molecule should be in an envelope conformation in which the ring oxygen is out of plane.

3′-Amino-3′-deoxythymidine (1) is active against P815 mouse leukemia cells, showing an ID_{50} of 0.08 μg/mL. The "up" amino isomer 9 is much less active than 1, as expected, with an ID_{50} of 3.0 μg/mL.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary apparatus and are corrected. ^1H NMR spectra were recorded on a JEOL PFT-100 with Me_4Si as the internal standard. Chemical shifts are reported in parts per million (δ), and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Values given for coupling constants are first order. UV spectra were measured on a UNICAM SP-800 spectrometer. IR spectra were recorded on a Perkin-Elmer Infracord with pressed KBr pellets. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and Spang Microanalytical Laboratory, Eagle Harbor, MI.

Reaction of 2′-Deoxy-3′-O-mesyl-5′-O-tritylthymidine (3) with NaN_3. A mixture of 3 (2.8 g, 5 mmol) and NaN_3 (1.0 g, 15.4 mmol) in dry DMF (50 mL) was heated at reflux for 24 h with stirring. The solvent was removed in vacuo and the residue partitioned between CH_2Cl_2 and H_2O. The organic layer was dried (Na_2SO_4), concentrated to a small volume, and chromatographed over a column of silica gel G60 (32 × 3.6 cm). The column was washed successively with 400 mL each of CH_2Cl_2, 5% AcOEt–CH_2Cl_2, 10% AcOEt–CH_2Cl_2, 20% AcOEt–CH_2Cl_2, and 40% AcOEt–CH_2Cl_2. 3′-Azido-2′,3′-dideoxy-5′-O-trityl-β-D-*erythro*-pentofuranosylthymine (5, 1.04 g, 41%) was obtained as a homogeneous liquid from the last two fractions: IR ν 2100 cm^{-1} (N_3); UV λ_{max} (MeOH) 260 nm; ^1H NMR ($CDCl_3$) δ 9.29 (br s, 1 H, NH), 8.02 (s, 1 H, H-6), 7.58–7.23 (m, 15 H, aromatic), 6.27 (t, 1 H, H-1′, $J_{1',2'} = J_{1',2''} = 6.4$ Hz), 4.33 (m, 1 H, H-3′), 4.00 (m, 1 H, H-4′), 3.57 (dd, 1 H, H-5′, $J_{4',5'} = 2.9$, $J_{5',5''} = 10.8$ Hz), 3.32 (dd, 1 H, H-5″, $J_{4',5''} = 2.7$, $J_{5',5''} = 10.8$ Hz), 2.45 (t, 2 H, H-2′, spacing 12.8 Hz), 1.52 (s, 3 H, 5-Me).

This compound was converted quantitatively into 3′-amino-3′-deoxythymidine (1) after detritylation (80% AcOH) and hydrogenation (10% Pd–C), mp 185–187 °C. (lit.[2] mp 187–187.5 °C).

The column was washed further with AcOEt (800 mL) and 15% MeOH–CH_2Cl_2 (500 mL). 6,3′-Imino-1-(2,3-dideoxy-5-O-trityl-β-D-*threo*-pentofuranosyl)thymine (8) was obtained from the last fraction. After crystallization from AcOEt, 1.05 g (43%) of 8 was obtained: mp 229–231 °C; UV λ_{max} (MeOH) 283 nm; ^1H NMR (Me_2SO-d_6) δ 10.43 (br s, 1 H, 3-NH), 7.41–7.14 (m, 16 H, aromatic and bridgehead NH), 6.29 (d, 1 H, H-1′, $J_{1',2'} = 3.4$ Hz), 4.21 (m, 1 H, H-3′), 3.06 (d, 2 H, H-5′, H-5″, spacing 6.1 Hz), 2.29 (dt, 1 H, H-2′$_{exo}$, $J_{2',2''} = 10.1$ Hz), 2.04 (d, H-2′$_{endo}$, $J_{2',2''} = 10.1$ Hz), 1.48 (s, 3 H, 5-Me).

Anal. Calcd for $C_{29}H_{27}N_3O_4 \cdot 0.5H_2O$: C, 70.96; H, 5.75; N, 8.57. Found: C, 71.04; H, 6.03; N, 8.50.

6,3′-Imino-1-(2,3-dideoxy-β-D-*threo*-pentofuranosyl)thymine (7, R = H). A mixture of 8 (300 mg) in 80% AcOH (10 mL) was heated at reflux for 1 h. After the mixture cooled, the solvent was removed in vacuo, and the residue was triturated with H_2O and filtered from insoluble materials. The filtrate was evaporated, and the residue was crystallized from EtOH to give 7 (R = H, 113.5 mg, 77.6%): mp 258–260 °C dec; mass spectrum, *m/e* 239 (M^+); UV λ_{max} (H_2O) 283 nm (ε 24 700), λ_{max} (0.5 N HCl) 284 (ε 24 300), λ_{max} (0.5 N NaOH) 284 (ε 18 300); ^1H NMR (Me_2SO-d_6) δ 10.45 (s, 1 H, 3-NH), 7.23 (d, 1 H, bridgehead NH, spacing 4.9 Hz), 6.28 (d, 1 H, H-1′, $J_{1',2'exo} = 4.0$ Hz), 4.81 (t, 1 H, 5′-OH), 4.02–3.91 (m, 2 H, H-3′,4′), 3.52–3.67 (m, 2 H, H-5′, H-5″), 2.31 (br d, 1 H, H-2′$_{exo}$, $J_{2',2''} = 11.6$ Hz), 2.05 (d, 1 H, H-2′$_{endo}$), 1.63 (s, 3 H, 5-Me).

Anal. Calcd for $C_{10}H_{13}N_3O_4$: C, 50.20; H, 5.48; N, 17.57. Found: C, 50.26; H, 5.58; N, 17.47.

6,3′-Imino-1-(5-O-acetyl-2,3-dideoxy-β-D-*threo*-pentofuranosyl)thymine (7, R = Ac). 7 (R = H, 19 mg) was acetylated in pyridine (5 mL) with Ac_2O (0.2 mL) and crystallized from EtOH: mp 133–135 °C; ^1H NMR (Me_2SO-d_6) δ 10.50 (br s, 1 H, 3-NH), 7.32 (br d, 1 H, bridgehead NH, spacing 4.6 Hz), 6.30 (d, 1 H, H-1′, $J_{1',2'} = 4.0$ Hz), 4.32–3.80 (m, 4 H, H-3′, -4′, -5′, -5″), 2.00 (s, 3 H, OAc), 1.62 (s, 3 H, 5-Me). The analytical sample was slightly wet, as the presence of H_2O was detected by ^1H NMR.

Anal. Calcd for $C_{12}H_{15}N_3O_5 \cdot 0.25H_2O$: C, 50.43; H, 5.38; N, 14.70. Found: C, 50.65; H, 5.15; N, 14.51.

1-(3-Azido-2,3-dideoxy-5-O-trityl-β-D-*threo*-pentofuranosyl)thymine (6). A solution of 3 (5.6 g, 10 mmol) in dry DMF (25 mL) was added dropwise over a 5-min period to a mixture of NaN_3 (2.0 g, 31 mmol) in dry DMF (75 mL) which was heated at reflux. Heating was continued for 25 min after the addition was complete. The reaction mixture was cooled quickly in an ice bath, and the solvent was removed in vacuo below 50 °C. The residue was triturated with $CHCl_3$ and filtered from insoluble materials, and the filtrate was chromatographed over a column of silica gel G60 (30 × 5 cm), using $CHCl_3$ as the eluant. 5 was eluted first, followed by 6, which was crystallized from Et_2O to give colorless crystals (2.39 g, 47%): mp 128–130 °C (lit.[20] mp 127–129 °C, lit.[21] 105 °C dec); UV λ_{max} (MeOH) 268 nm; IR ν 2100 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.76 (br s, 1 H, NH), 7.54–7.26 (m, 16 H, aromatic and H-6), 6.15 (dd, 1 H, H-1′, $J_{1',2'} = 7.6$, $J_{1',2''} = 2.8$ Hz), 4.26–4.02 (m, 2 H, H-3′, H-4′), 3.63 (dd, 1 H, H-5′, $J_{4',5'} = 5.8$, $J_{5',5''} = 9.9$ Hz), 3.35 (dd, 1 H, H-5″, $J_{4',5''} = 5.6$, $J_{5',5''} = 9.9$ Hz), 2.76 (ddd, 1 H, H-2′, $J_{2',2''} = 15.0$, $J_{1',2'} = 7.6$, $J_{2',3'} = 6.7$ Hz), 2.13 (br dd, 1 H, H-2″, $J_{2',2''} = 15.0$, $J_{1',2''} = 2.8$ Hz), 1.84 (s, 3 H, 5-Me).

Anal. Calcd for $C_{29}H_{27}N_5O_4$: C, 68.35; H, 5.34; N, 13.76. Found: C, 68.35; H, 5.33; N, 13.52.

6 (61 mg) was converted into 8 in 52% yield (30 mg) by heating with NaN_3 (5 mg) in DMF (3 mL) at reflux temperature for 2.5 h. The product was isolated by preparative TLC (20 × 20 cm) and crystallized from AcOEt, mp 128–130 °C.

1-(3-Azido-2,3-dideoxy-β-D-*threo*-pentofuranosyl)thymine. A solution of 6 (1.0 g, 1.96 mmol) in a mixture of EtOH (10 mL) and 50% aqueous HCO_2H (30 mL) was stirred for 2 h at room temperature. After evaporation of the solvent in vacuo, the residue was triturated with H_2O and filtered from the insoluble materials. The filtrate was evaporated to dryness in vacuo to give a homogeneous glass (400 mg): IR ν 2100 cm^{-1} (N_3); ^1H NMR (Me_2SO-d_6) δ 11.34 (br s, 1 H, NH), 7.50 (s, 1 H, H-6), 6.04 (dd, 1 H, H-1′, $J_{1',2'} = 7.8$, $J_{1',2''} = 3.8$ Hz), 4.47 (m, 1 H, H-4′), 4.00 (dd, 1 H, H-3′), 3.70 (t, 2 H, H-5′, H-5″), 2.68 (ddd, 1 H, H-2′, $J_{1',2'} = 7.8$, $J_{2',3'} = 7.6$, $J_{2',2''} = 15.0$ Hz), 2.05 (br dd, 1 H, H-2″, $J_{2',2''} = 15.0$, $J_{1',2''} = 3.8$, $J_{2'',3'} \simeq 1.0$ Hz), 1.80 (s, 3 H, 5-Me). This compound was not purified further but used directly in the next step.

1-(3-Amino-2,3-dideoxy-β-D-*threo*-pentofuranosyl)thymine (9). A mixture of the above glass (400 mg) and Ph_3P (1.18 g) in dry pyridine (20 mL) was stirred overnight at room temperature and then evaporated to dryness. The residue was suspended in EtOH (10 mL) and 1 N NH_4OH (20 mL), and the mixture was stirred overnight. After evaporation of the solvent, the residue was partitioned between H_2O and $CHCl_3$. The aqueous layer was applied to a column of Dowex 50 (H^+, 5 × 2.5 cm) which was washed with H_2O and then eluted with 1 N NH_4OH. The fractions which contained 9 were evaporated to a powder: ^1H NMR (Me_2SO-d_6) δ 8.15 (s, 1 H, H-6), 5.99 (dd, 1 H, H-1′, $J_{1',2'} = 7.0$, $J_{1',2''} = 4.9$ Hz), 1.78 (s, 3 H, 5-Me).

The powder was dissolved in 3% HCl/MeOH (5.0 mL) and the solvent was removed in vacuo to give the HCl salt of 9. The salt was dissolved in a small amount of MeOH and precipitated by addition of AcOEt. The precipitate was collected and dried

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over P_2O_5 in vacuo at room temperature to give 369 mg of powder (67.7% calculated from **6**). This compound does not have a clear melting point but slowly colorized above 150 °C: ^{1}H NMR (Me_2SO-d_6) δ 11.40 (br s, 1 H, NH), 8.44 (br s, 3 H, $NH_3^+Cl^-$), 7.94 (s, 1 H, H-6), 5.97 (t, 1 H, H-1', $J_{1',2'} = J_{1',2''} = 7.2$ Hz), 4.00 (m, 2 H, H-3',4'), 3.80 (m, 2 H, H-5',5''), 3.60 (br s, 1 H, 5'-OH), 2.66 (m, 1 H, H-2'), 2.00 (m, 1 H, H-2''), 1.81 (s, 3 H, 5-Me).

Anal. Calcd for $C_{10}H_{16}N_3O_4Cl\cdot0.5H_2O$: C, 41.89; H, 5.97; N, 14.66; Cl, 12.36. Found: C, 42.02; H, 5.67; N, 14.65; Cl, 12.07.

6,5'-Imino-5-deoxythymidine (18, R = H). A mixture of 5'-azido-5'-deoxythymidine[22] (100 mg) and LiN_3 (10 mg) in DMF (8 mL) was heated at reflux for 6 h, and then the solvent was removed in vacuo. **18** (R = H) was isolated by using preparative TLC (20 × 20 cm, CH_2Cl_2–EtOH 4:1) and crystallized from EtOH (64 mg, 71.5%): mp 226–227 °C dec; UV λ_{max} (H_2O) 291 nm (ϵ 18 400), λ_{max} (0.5 N HCl) 291 (ϵ 18 200), λ_{max} (0.5 N NaOH) 288 (ϵ 13 800); ^{1}H NMR (Me_2SO-d_6) δ 10.77 (br s, 1 H, NH), 6.80 (m, 1 H, H-1'), 6.08 (br d, bridgehead NH, spacing 6.4 Hz), 5.08 (d, 1 H, 3'-OH), 4.22 (m, 1 H, H-3'), 4.13 (s, 1 H, H-4'), 3.45 (m, 1 H, H-5' (this signal changed into a dd upon addition of D_2O), $J_{5',5''} = 13.9$, $J_{4',5'} = 2.4$ Hz), 2.97 (d, 1 H, H-5'', $J_{5',5''} = 13.9$ Hz), 2.50 (m, 2 H, H-2', H-2''), 1.71 (s, 3 H, 5-Me).

Anal. Calcd for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.48; N, 17.56. Found: C, 50.03; H, 5.40; N, 17.36.

Treatment of 5'-*O*-tosylthymidine[23] (**16**) under similar conditions also afforded **18** (R = H).

6,5'-Imino-3'-*O*-acetyl-5'-deoxythymidine (18, R = Ac). **18** (R = H, 135 mg) was acetylated with Ac_2O (0.5 mL) in pyridine (5 mL) and crystallized from EtOH to give 55.5 mg (35%) of the acetate **18** (R = Ac): mp 273–275 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 10.84 (br s, 1 H, NH), 6.84 (m, 1 H, H-1'), 6.17 (br d, bridgehead NH, spacing 6.4 Hz), 5.15 (m, 1 H, H-3'), 4.36 (br s, 1 H, H-4'), 3.45–3.33 (m, 1 H, H-5', upon addition of D_2O, this signal became a dd, $J_{5',5''} = 13.4$, $J_{4',5'} = 2.5$ Hz), 3.03 (d, 1 H, H-5'', $J_{5',5''} = 13.4$ Hz), 2.35 (t, 2 H, H-2', H-2''), 2.04 (s, 3 H, OAc), 1.72 (s, 3 H, 5-Me).

Anal. Calcd for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.27; H, 5.33; N, 14.81.

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Total Synthesis of *dl*-3-Oxodiplophyllin and *dl*-Yomogin[1]

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The eudesman-8,12-olides *dl*-3-oxodiplophyllin (**1a**) and *dl*-yomogin (**1b**) have been totally synthesized. The enedione **2** was converted into the enedione ester **5** by formation of the enamine of the saturated ketone function, alkylation with ethyl bromoacetate, and hydrolysis. Reduction of **5** with K Selectride gave the 7β,8β-dihydro γ-lactone **3** steroselectively. Protection of the unsaturated carbonyl group in **3** by ketalization gave a mixture of double bond isomers. The γ-lactone functions of this mixture were converted into the corresponding α-methylene lactones by using the procedure of Grieco and Hiroi. Deketalization of this mixture gave *dl*-**1a**. Conversion of the ring A enone system of **1a** into the corresponding cross-conjugated dienone by oxidation with DDQ gave *dl*-**1b**.

A number of naturally occurring eudesman-8,12-olides having important biological properties[2] contain a 7β,8β cis-fused α-methylene lactone grouping. Total syntheses of *dl*-alantolactone,[3] *dl*-isoalantolactone,[4a,b] and *dl*-isotekelin,[4c] which are members of this class of compounds, have been reported. Herein we wish to report the total synthesis of *dl*-3-oxodiplophyllin (**1a**), which was isolated recently from the European liverwort *Chiloscyphus polyanthus* by Asakawa and co-workers,[5] and *dl*-yomogin (**1b**), which was isolated several years ago from *Artemisia princeps* Pamp by Geissman[6,7] (Chart I). A relay synthesis of yomogin from α-santonin has been published recently.[8]

The starting material for the syntheses of **1a** and **1b** was the known enedione **2**.[9] This compound was prepared by annelation of 2-methyl-4-(ethylenedioxy)cyclohexanone with ethyl vinyl ketone according to the procedure of Ross and Levine[10] followed by transketalization of the resulting octalone derivative with a catalytic amount of *p*-toluenesulfonic acid (PTSA) in acetone. The yield in the last step was significantly improved if the acid catalyst was neutralized before, rather than after,[9] the workup step. The conversion of the enedione **2** into the enone lactone **3** having a cis-fused 7β,8β-butanolide grouping was accomplished by the same general method as was used by Marshall, Cohen, and Hochstetler[3] for the synthesis of the corresponding 2-deoxy derivative. The saturated carbonyl group was selectively reacted with 1 equiv of pyrrolidine in benzene with the removal of water by azeotropic dis-

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