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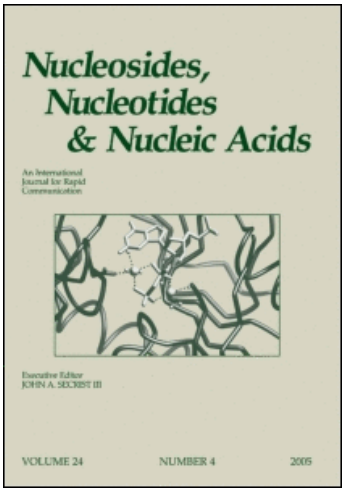

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Synthesis of a Novel Antiretroviral Thymidine Analog: 1-(2-Deoxy-β-D-ribofuranosyl)-4-acetylimidazolin-2-one (Imidine)

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SYNTHESIS OF A NOVEL ANTIRETROVIRAL THYMIDINE ANALOG: 1-(2-DEOXY-β-D-RIBOFURANOSYL)-4-ACETYLIMIDAZOLIN-2-ONE (IMIDINE)‡

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Abstract. The total synthesis of imidine (**8**), a novel isomer of thymidine is described. Depending on the coupling method used, either the anomeric mixture of the protected desired nucleoside, or the positional isomer **14** is obtained.

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As a new approach to anti-AIDS drug development, novel nucleoside analogs were designed in our laboratory to exploit the error-prone nature[1] of HIV reverse transcriptase. A prototype of these analogs, 1-(2-deoxy-β-D-ribofuranosyl)-4-acetylimidazolin-2-one (imidine, **8**), a structural isomer of thymidine in which the 4-carbonyl group is inserted between the ring and the CH_3 group, was synthesized[2-4] from 5-bromo-2′-deoxyuridine by the ring-contraction method.[5] Imidine showed promising biological activities,[3,4,6] including activity against HIV-1 and HIV-2 *in vitro*, and selective inhibition of HIV reverse transcriptase by the triphosphate form of the analog. Therefore, it was of interest to develop a method for the total synthesis of imidine, which would permit easier access to the analog and to a variety of its sugar-modified derivatives.

In this paper we describe the total synthesis of imidine (**8**), which involves preparation of the corresponding free base 4-acetylimidazolin-2-one (**2**), followed by coupling with the protected halo sugar **5** using the sodium salt method of Robins

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‡*This paper is dedicated to the memory of Roland K. Robins.*

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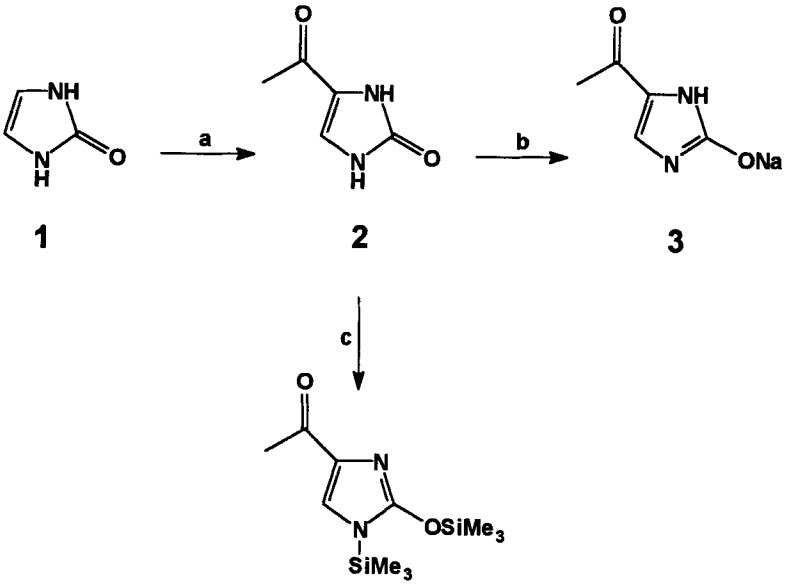

a) $CH_3COCl/PhNO_2/AlCl_3$/60-65 °C b) MeONa/MeOH
c) HMDS/$(NH_4)_2SO_4/ClCH_2CH_2Cl$/Reflux

SCHEME 1.

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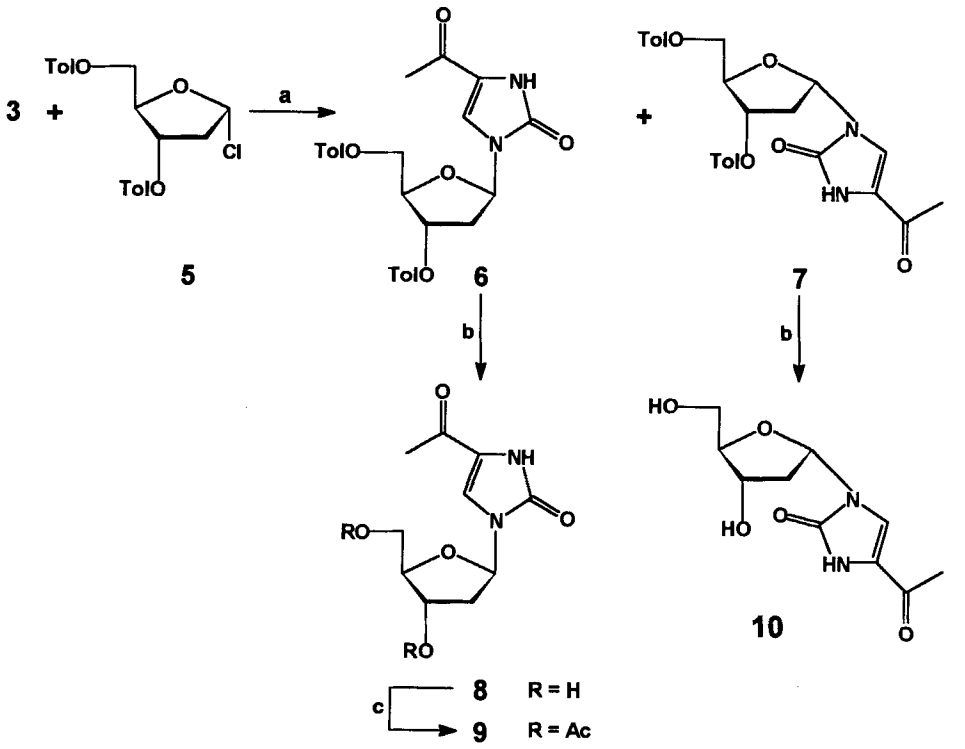
et al.[7,8] Coupling of silylated **2** with triacetylated sugar **11** lead to formation of the positional isomer **14**.

RESULTS AND DISCUSSION

The total synthesis of imidine (**8**) was started with the preparation of the heterocyclic base 4-acetylimidazolin-2-one (**2**). In the presence of $AlCl_3$,[9,10] imidazolin-2-one[9] (**1**) was reacted with acetyl chloride to give **2** in 93% yield. Two methods were chosen for conversion of the base to the nucleoside **8**: 1) the sodium salt method developed by Robins' group[7,8] and 2) the silyl modification of the Hilbert-Johnson procedure[11,12] most frequently employed in nucleoside synthesis.

In preliminary experiments, the coupling reaction between **2** and an appropriate chlorosugar was carried out under the



a) DME/RT b) MeONa/MeOH/RT c) Ac_2O/Pyridine

SCHEME 2.

usual conditions (*in situ* deprotonation by NaH in anhydrous solvent), but the coupling was not successful. Thus, **3**, the sodium salt[14] of **2**, was first prepared. It was stirred in anhydrous dimethoxyethane with chlorosugar[15] **5** for 2 days to give compound **6** and its α-anomer **7** in 42.8% combined yield, with an α:β ratio of about 1:1.7. Compounds **6** and **7** were each deprotected with 0.01 M sodium methoxide in MeOH to yield **8** and **10**, respectively, in high yield.

When 2-deoxy-3,5-di-*O*-*p*-nitrobenzoyl-D-ribosyl chloride[16] was used instead of **5**, the yield of the desired nucleoside was poor, and separation of the two anomers was very difficult.

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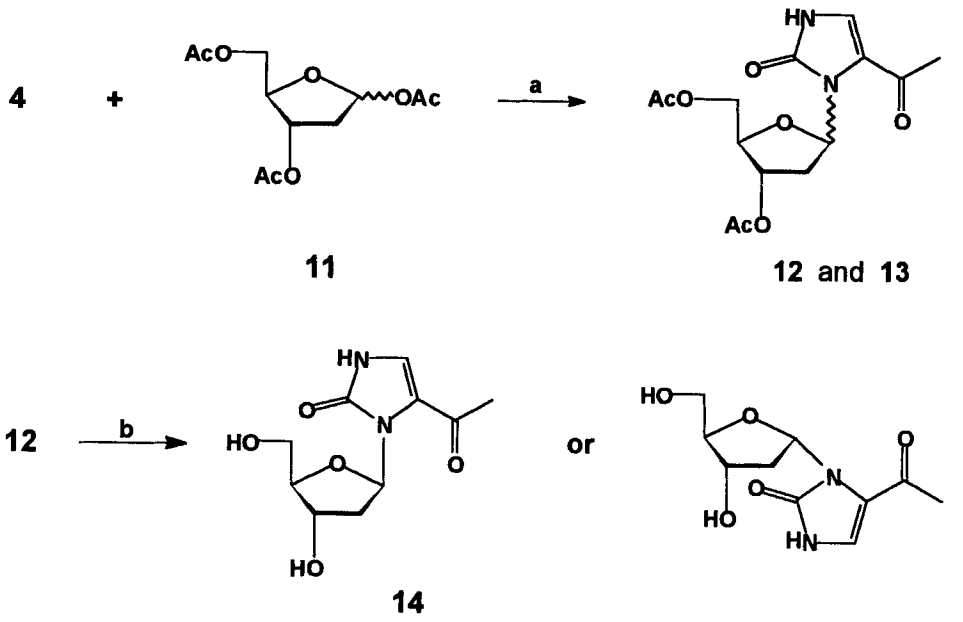

a)TMSOTf/$ClCH_2CH_2Cl$/-40 to -30 °C b) NH_4OH/NH_3/MeOH/RT

SCHEME 3.

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The ^{1}H-NMR spectrum, optical rotation and elemental composition of compound **8** and imidine[4] were found to be identical. In addition, the melting point of the mixture of compound **8** and imidine did not show depression. These results established the identity of **8** with imidine.

The elemental analysis showed that compound **10** has identical composition with **8**. The pK_a-values of **10** and **8** are also identical. However, the ^{1}H-NMR spectrum and the specific rotation value of **10** were found to be different from those of **8** (see Experimental Section). Although the chemical shifts of the 1′ protons of **8** and **10** coincide, the corresponding 1′,2′ coupling constants are significantly different. These results are consistent with **10** being the α anomer of imidine.

In our second approach to the synthesis of **8**, we used the silyl compound **4** to react with triacetyl-2-deoxy-D-ribose[12]

(**11**) in the presence of trimethylsilyl triflate at -40 to -30 °C in dichloroethane. However, this reaction did not yield the desired product (**9**),[4] the diacetylated form of imidine (**8**). Instead, **12** was obtained in 49% yield and a much smaller amount of **13**. Deblocking of compound **12** in NH_3/MeOH at room temperature did not take place. The conversion required the addition of concentrated ammonium hydroxide to afford **14**.

^{1}H-NMR studies revealed significant differences between the chemical shifts of the 1′- and 2′-protons of **14** and those of **8** and **10** (see Experimental Section). In addition, **14** melted 32-39 °C higher than **8**. We also observed that the mobility of **14** on TLC was significantly slower than that of **8** and **10** in different systems. Since **14**, **8** and **10** have identical elemental composition, **14** must be a positional isomer of imidine (see Scheme 3). This conclusion is further supported by the lower pK_a-value of **14** than that found for **8** and **10** (10.0 vs. 10.9, respectively), since the NH-group in **14** must be more acidic due to its conjugation with the α,β-unsaturated carbonyl system.

In conclusion, a method for the total synthesis of imidine, in 22.6 % overall yield (based on the chloroshugar) from the readily prepared and inexpensive **2**, was developed. This synthesis compares very favorably with the pyrimidine nucleoside transformation sequence[2-4] (15.7 % overall yield from the expensive BrdUrd). The total synthesis is also shorter and is more suitable for scale-up.

During the course of these synthetic studies we found that different coupling procedures can lead to exclusive formation of anomeric pairs of positional isomers. Further structural studies of the various isomers are in progress.

EXPERIMENTAL SECTION

^{1}H-NMR spectra were recorded at 300 MHz on a Varian Gemini spectrometer. TLC was performed on ANALTECH GHLF plates and spots were visualized under UV light. pK_a-values were determined by spectrophotometric titration at 315 nm using a

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Varian Cary 118C instrument. Elemental analyses were carried out by Atlantic Microlab, Norcross, Georgia. Melting points were determined on a MEL-TEMP apparatus and are uncorrected.

4-Acetylimidazolin-2-one (2)

To the mixture of **1**, prepared as described,[9] (0.84 g, 10 mmol) and acetyl chloride (0.725 mL, 10.2 mmol) in nitrobenzene, $AlCl_3$ was added portionwise at 0-5 °C with vigorous stirring. The reaction mixture was heated at 60-65 °C for 4-5 hours until HCl gas evolution stopped. The dark brown viscous syrup obtained was then poured on a mixture of ice (20 g), H_2O (10 mL) and Na_2CO_3 (0.15 g). The reaction mixture was allowed to stand at room temperature overnight. The solid collected by filtration was washed thoroughly with H_2O, ether, ethanol and dried in air to yield 1.17 g of **2** (93%). A sample for elemental analysis was recrystallized from DMF/H_2O (1:1). Mp 316-322 °C. ^{1}H-NMR (DMSO-d_6) δ 2.18 (s, 3H, 4-$COCH_3$), 7.61 (s, 1H, 5-H), 10.47 (s, 1H, NH), 10.76 (s, 1H, NH). Anal. calcd for $C_5H_6N_2O_2 \cdot 0.85\ H_2O$. C, 42.46; H, 5.49; N, 19.81. Found: C, 42.40; H, 5.49; N, 19.70.

4-Acetylimidazolin-2-one, Sodium Salt (3)

To a suspension of **2** (2.82 g, 20 mmol) in dry MeOH (150 mL) a solution of freshly prepared MeONa (600 mg of sodium, 26 mmol, in 50 mL of dry MeOH) was added in one portion at room temperature. The reaction mixture became a clear yellow solution from which the crude solid product precipitated. After 1 h stirring, the reaction mixture was filtered, the solid was washed with MeOH and a mixture of MeOH/ether, dried over P_2O_5 to yield 2.76 g of **3** as a light yellow powder which was used without further purification. ^{1}H-NMR (DMSO-d_6) δ 1.99 (s, 3H, 4-$COCH_3$), 7.38 (s, 1H, 5-H), 9.13 (s, 1H, NH).

1-(2-Deoxy-3,5-di-*O*-toluoyl-β-D-ribofuranosyl)-4-acetylimidazolin-2-one (6) and 1-(2-deoxy-3,5-di-*O*-toluoyl-α-D-ribofuranosyl)-4-acetylimidazolin-2-one (7)

Compound **3** (653.6 mg, 4 mmol) was stirred with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-ribosyl chloride **6** (388.8 mg, 1 mmol) in 15 mL of anhydrous dimethoxyethane at room temperature for

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40 h. After the solvent was removed under reduced pressure, the residue was chromatographed on a silica gel column with two different eluting systems: A) ethyl-acetate/hexanes = 1:2; B) CH_2Cl_2/MeOH = 150:1. The chromatographic separation was incomplete yielding 106 mg of pure β-anomer **6**, 39 mg of a mixture of **6** + **7**, and 60 mg of pure α-anomer **7**. Total yield: 42.8%; the α:β ratio was around 1:1.7.

β-anomer **6**: ^{1}H-NMR ($CDCl_3$) δ 1.97 (s, 3H, 4-$COCH_3$), 2.37-2.52 (m, 7H, 2′-H and *p*-CH_3), 2.72 (m, 1H, 2′-H), 4.58 (m, 2H, 5′-H), 4.80 (m, 1H, 4′-H), 5.68 (m, 1H, 3′-H), 6.23 (dd, *J* = 8.63 and 5.40 Hz, 1H, 1′-H), 7.09 (s, 1H, 5-H), 7.30 (m, aromatic H), 7.96 (m, aromatic H), 8.04 (s, 1H, NH). Anal. calcd for $C_{26}H_{26}N_2O_7 \cdot 0.12\ CH_2Cl_2$: C, 64.20; H, 5.41; N, 5.73. Found: C, 64.14; H, 5.59; N, 5.67.

α-anomer **7**: ^{1}H-NMR ($CDCl_3$) δ 2.15 (s, 3H, 4-$COCH_3$), 2.41, 2.43 (2s, 6H, *p*-CH_3), 2.60 (m, 1H, 2′-H), 2.95 (m, 1H, 2′-H), 4.55 (m, 2H, 5′-H), 4.85 (m, 1H, 4′-H), 5.62 (m, 1H, 3′-H), 6.24 (dd, *J* = 7.33 and 1.65 Hz, 1H, 1′-H), 7.27 (m, aromatic H), 7.89 (m, aromatic H), 8.19 (s, 1H, NH). Anal. calcd for $C_{26}H_{26}N_2O_7$: C, 65.26; H, 5.48; N, 5.85. Found: C, 65.14; H, 5.68; N, 5.61.

1-(2-Deoxy-β-D-ribofuranosyl)-4-acetylimidazolin-2-one (8)

A solution of compound **6** (66 mg, 0.14 mmol) in 0.01 M NaOMe in methanol (30 mL) was stirred at ambient temperature overnight. Solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column using a mixture of CH_2Cl_2/MeOH (25:1) to give 28 mg (83.8%) of **8**. A sample for elemental analysis was recrystallized from MeOH. Mp 180-183 °C. $[\alpha]_D$ -29.9° (c 0.375, 21 °C, MeOH). TLC ($CHCl_3$/MeOH, 4:1) R_f 0.67. ^{1}H-NMR (DMSO-d_6) δ 2.09 (m, 1H, 2′-H), 2.24 (s, 3H, 4-$COCH_3$), 2.29 (m, 1H, 2′-H), 3.51 (m, 2H, 5′-H), 3.73 (m, 1H, 3′-H), 4.27 (m 1H, 4′-H), 4.92 (t, 1H, 5′-OH), 5.22 (d, 1H, 3′-OH), 5.85 (dd, *J* = 7.69 and 6.05 Hz, 1H, 1′-H), 7.84 (s, 1H, 5-H), 10.78 (s, 1H, NH). Anal. calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.67; H, 5.84; N, 11.49.

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1-(2-Deoxy-α-D-ribofuranosyl)-4-acetylimidazolin-2-one (10)

A solution of compound **7** (130 mg, 0.272 mmol) in 0.01 M NaOMe in MeOH (6 mL) was stirred at room temperature overnight. The solvent was removed under diminished pressure, and the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 25:1) to give 53 mg of **10** (80%). A sample for elemental analysis was recrystallized from MeOH. Mp 182-185 °C. $[\alpha]_D$ +102° (c 0.5, 21 °C, MeOH). TLC ($CHCl_3$/MeOH, 4:1) R_f 0.68). ^{1}H-NMR (DMSO-d_6) δ 2.06 (m, 1H, 2′-H), 2.23 (s, 3H, 4-$COCH_3$), 2.60 (m, 1H, 2′-H), 3.49 (m, 2H, 5′-H), 4.03 (m, 1H, 3′-H), 4.23 (m, 1H, 4′-H), 4.80 (br, 1H, 5′-OH), 5.47 (m, 1H, 3′-OH), 5.85 (dd, J = 7.45 and 3.21 Hz, 1H, 1′-H), 7.92 (s, 1H, 5-H), 10.76 (s, 1H, NH). Anal. calcd for $C_{10}H_{14}N_2O_5 \cdot 0.27$ H_2O: C, 48.60; H, 5.93; N, 11.34. Found: C, 48.59; H, 5.82; N, 11.48.

1-(2-Deoxy-3,5-di-*O*-acetyl-(β or α)-D-ribofuranosyl)-5-acetyl-imidazolin-2-one (12)

The mixture of **2** (282 mg, 2 mmol) and $(NH_4)_2SO_4$ (20 mg) in 6 mL of hexamethyldisilazane (HMDS) and 4 mL of anhydrous dichloroethane was refluxed for 3-4 h. The reaction mixture was concentrated and coevaporated with toluene to yield **4** as a light brown syrupy residue which was dissolved in anhydrous dichloroethane and used directly for the coupling reaction.

To the solution of **4** and acetylated sugar **11** (260 mg, 1 mmol) in 7 mL anhydrous dichloroethane, trimethylsilyl triflate (0.27 mL, 1.4 mmol) in anhydrous dichloroethane (2 mL) was added dropwise at -40 to -30 °C under argon. The reaction mixture was allowed to warm to room temperature (0.5 h) and then was poured into a mixture of $CHCl_3$, ice and 1 mL of saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the water layer was extracted three times with $CHCl_3$. The combined chloroform solution was washed twice with H_2O, dried over Na_2SO_4, and concentrated *in vacuo* to give 246 mg of yellow syrup. After chromatography on silica gel (CH_2Cl_2/MeOH, 50:1), 166 mg of **12** (49%) was obtained as a foam. ^{1}H-NMR ($CDCl_3$) δ 2.03 (s, 3H, $OCOCH_3$), 2.06 (m, 1H, 2′-

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H), 2.19 (s, 3H, $OCOCH_3$), 2.35 (s, 3H, 5-$COCH_3$), 3.35 (m, 1H, 2′-H), 3.95 (m, 1H, 5′-H), 5.13 (m, 1H, 4′-H), 5.58 (m, 1H, 3′-H), 6.46 (m, 1H, 1′-H), 7.25 (s, 1H, 4-H), 10.88 (s, 1H, NH). Anal. calcd for $C_{14}H_{18}N_2O_7 \cdot 0.16\ CH_2Cl_2$: C, 50.04; H, 5.43; N,8.24. Found: C, 50.10; H, 5.60; N, 8.35.

1-(2-Deoxy-3,5-diacetyl-(α or β)-D-ribofuranosyl)-5-acetylimidazolin-2-one (13, anomer of 12)

Compound **2** (100 mg, 0.7 mmol) and **11** (100 mg, 0.38 mmol) were reacted as described above for the synthesis of **12**. The residue was purified repeatedly with preparative TLC ($CHCl_3$/MeOH, 30:1) to yield 11 mg (8.9%) of **13** (contaminated with **12**). ^{1}H-NMR ($CDCl_3$) δ 2.07, 2.1 (2s, 6H, $OCOCH_3$), 2.20-2.30 (m, 1H, 2′-H), 2.34 (s, 3H, $COCH_3$), 3.29-3.36 (m, 1H, 2′-H), 4.24-4.46 (m, 3H, 4′,5′-H), 5.43 (m, 1H, 3′-H), 6.93 (t, 1H, 1′-H), 7.29 (s, 1H, 4-H), 10.49 (s, 1H, NH).

1-(2-Deoxy-(β or α)-D-ribofuranosyl)-5-acetylimidazolin-2-one (14)

Compound **12** (160 mg, 0.473 mmol) was dissolved in 12 mL of MeOH saturated with NH_3. To this solution, 3.5 mL of concentrated ammonium hydroxide was added. The reaction mixture was stirred at room temperature overnight, then concentrated under reduced pressure. The residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH, 15:1) to afford 36 mg of **14** (31%), as white crystals. A sample was recrystallized from MeOH for elemental analysis. Mp 215-219 °C. $[\alpha]_D$ -15° (c 0.5, 21 °C, MeOH). TLC ($CHCl_3$/MeOH, 4:1) R_f 0.53. ^{1}H-NMR (DMSO-d_6) δ 1.66 (m, 1H, 2′-H), 2.24 (s, 3H, 5-$COCH_3$), 3.11 (m, 1H, 2′-H), 3.46 (m, 3H, 3′-H, 5′-H), 3.97 (m, 1H, 4′-H), 4.65 (m, 2H, 3′-OH, 5′-OH), 6.14 (d, 1H, 1′-H), 7.81 (m, 1H, 4-H), 11.50 (s, 1H, NH). Anal. calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.66; H, 5.84; N, 11.56.

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REFERENCES

1. Bebenek, K.; Abbotts, J.; Roberts, J. D.; Wilson, S. H.; Kunkel, T. A. *J. Biol. Chem.* **1989**, *264*, 16948.
2. Kalman, T. I.; Jiang, X.-J. Presentation at the *Tenth International Roundtable: Nucleosides, Nucleotides and Their Biological Applications,* Park City, Utah, Sept. 16-20, 1992.
3. Kalman, T. I.; Jiang, X.-J. *Proc. Am. Assoc. Cancer Res.* **1993**, *34*, 280.
4. Kalman, T. I.; Jiang, X.-J.; et al., *in preparation.*
5. Otter, B. A.; Falco, E. A.; Fox, J. J. *J. Org. Chem.* **1969**, *34*, 2636.
6. Kalman, T. I.; Jiang, X.-J. *FASEB J.* **1993**, *7*, A1290.
7. Kazimierczuk, Z.; Cottam, H. B.; Revankar, G. R.; Robins, R. K. *J. Am. Chem. Soc.* **1984**, *106*, 6379.
8. Revankar, G. R.; Robins, R. K. *Nucleosides Nucleotides* **1989**, *8*, 709.
9. Duschinsky, R.; Dolan, L. A. *J. Am. Chem. Soc.* **1946**, *68*, 2350.
10. Duschinsky, R.; Dolan, L. A. *J. Am. Chem. Soc.* **1945**, *68*, 2079.
11. Sztaricskai, F.; Dinya, Z.; Batta, G.; Gergely, L.; Szabo, B. *Nucleosides Nucleotides* **1992**, *11*, 11.
12. Okabe, M.; Sun, R.-C.; Tam, S. Y.-K.; Todaro, L. J.; Coffer, D. L. *J. Org. Chem.* **1988**, *53*, 4780.
13. Robins, M. J.; Robins, R. K. *J. Am. Chem. Soc.* **1965**, *87*, 4934.
14. Kawakami, H.; Matsushita, H.; Naoi, Y.; Itoh, K.; Yoshikoshi, H. *Chemistry Lett.* **1989**, 235.
15. Hoffer, M. *Chem. Ber.* **1960**, *93*, 2777.
16. Ness, R. K.; MacDonald, D. L.; Fletcher, H. G. Jr. *J. Org. Chem.* **1961**, *26*, 2895.

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