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Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

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Nucleosides. IX. Synthesis of Purine N³,5'-Cyclonucleosides and N³,5'-Cyclo-2',3'-seconucleosides via Mitsunobu Reaction as TIBO-like Derivatives

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Online publication date: 02 October 2004

To cite this Article Chen, Grace Shiahuy , Chen, Chien-Shu , Chien, Tun-Cheng , Yeh, Jun-Yen , Kuo, Chia-Chi , Talekar, Rahul Subhash and Chern, Ji-Wang(2004) 'Nucleosides. IX. Synthesis of Purine N³,5'-Cyclonucleosides and N³,5'-Cyclo-2',3'-seconucleosides via Mitsunobu Reaction as TIBO-like Derivatives ', *Nucleosides, Nucleotides and Nucleic Acids*, 23: 1, 347 – 359

To link to this Article: DOI: 10.1081/NCN-120027904

URL: <http://dx.doi.org/10.1081/NCN-120027904>

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**Nucleosides. IX.[#] Synthesis of Purine *N*³,5'-Cyclonucleosides
and *N*³,5'-Cyclo-2',3'-seconucleosides via Mitsunobu
Reaction as TIBO-like Derivatives[†]**

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ABSTRACT

The Mitsunobu reaction was applied to prepare, in one step, purine *N*³,5'-cyclonucleosides **10a–d**. A subsequent ring opening in the ribose moiety of the resultant *N*³,5'-nucleosides by sodium periodate led to the corresponding *N*³,5'-cyclo-2',3'-seconucleosides. These products consist of 5-, 6-, and 7-membered tricyclic system which is the basic skeleton of TIBO derivatives, known antiviral agents.

Key Words: TIBO; Mitsunobu reaction; *N*³,5'-cyclonucleoside; *N*³,5'-cyclo-2',3'-seconucleoside; Formycin B.

[#]Previous paper in this series: Ref. [1].

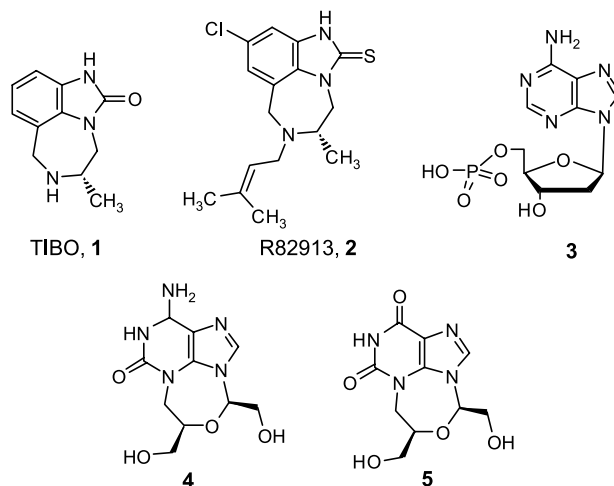
[†]In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

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INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) affects millions of people in the developed and developing countries, and its causative agent has been identified as the human immunodeficiency virus (HIV). Inhibitors of the HIV reverse transcriptase continue to be the most promising chemotherapeutic agents for AIDS. Even though 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxyinosine (ddI), 2',3'-dideoxycytidine (ddC), and 2',3'-didehydro-3'-deoxythymidine (d4T) are currently under clinical use, side effects and resistance to single agents have limited their use. Up to date, much effort has been devoted to search for new inhibitors more active and specific against HIV.^[2,3]

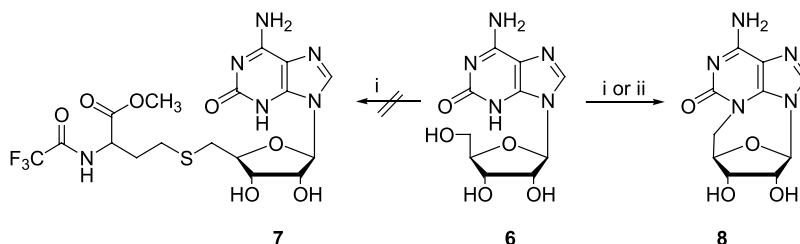
Pauwels and coworkers^[4,5] discovered a series of 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (**1**, TIBO) derivatives being highly effective and selective inhibitors of HIV-1 reverse transcriptase. One of the thioxo derivatives, R82913 (**2**), exhibits highly anti-HIV-1 activity,^[6] and its X-ray crystal structure revealed the overall similarity with deoxyadenosine 5'-monophosphate (**3**), where the base of **2** was superimposed with adenine of **3** perfectly.^[7] We reasoned that a cyclization between *N*³ and C-5' of purine nucleosides would lead to a seven-membered ring, and a subsequent ring opening of the ribose moiety of the resultant *N*³,5'-cyclonucleosides would lead to *N*³,5'-cyclo-2'-3'-seconucleosides such as **4** and **5**, consisting of a 5-, 6-, and 7-membered tricyclic TIBO-like skeleton.



RESULTS AND DISCUSSION

S-Adenosyl-L-homocysteine derivatives have been reported to possess potent and selective activity against HSV, VV, and HSV.^[8] In the course of our studies on potential antiviral activity of *S*-adenosyl-L-homocysteine analogues, an attempt to synthesize *S*-isoguanosyl-*N*-trifluoroacetyl-L-homocysteine methyl ester (**7**) by a





Scheme 1. (i) *N,N*-bis(trifluoroacetyl)-L-homocystine dimethyl ester, PBU_3^n , pyridine, room temperature, 11%. (ii) PPh_3 , CCl_4 , pyridine, rt, 75%.

condensation of *N,N*-bis(trifluoroacetyl)-L-homocystine dimethyl ester^[9] with isoguanosine (**6**) in the presence of tri-*n*-butylphosphine in pyridine, did not lead to the formation of the expected product but rather a cyclized product, *N*³,5'-cycloisoguanosine (**8**) in 11% yield (Scheme 1). The formation of **8** could be reasoned due to the formation of the quaternary phosphonium intermediate. Even though the *N*-trifluoroacetyl-L-homocystine ion is a weak nucleophile, the lone pair of *N*³ in adenosine was delocalized in the aromatization of the purine ring, and therefore *S*-adenosyl-trifluoroacetyl-L-homocysteine was easily obtained.^[9] However, in the case of isoguanosine the *N*³ is a stronger nucleophile compared to *N*-trifluoroacetyl-L-homocystine ion, and the electrostatic interaction between the phosphorus cation and purine base favors a cyclization.^[10] The similar results were also illustrated by other groups.^[11,12] Mitsunobu et al. reported that guanosine in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (PPh_3) gave an *N*³,5'-cycloguanosine derivative while the reaction of DEAD/ PPh_3 with adenosine gave no cyclized product.^[13,14] To ascertain this postulation, we treated **6** with 4-methoxyphenyl disulfide as a nucleophile undergoing condensation; under the same reaction condition *N*-[5'-4-methoxyphenylthioisoguanosine-6-yl]-tri-*n*-butylphosphazene was isolated as the sole product,^[15] and no cyclonucleoside was detected. Both of the two protons at C-5' position of **8** were coupled to the proton at 4' position, and this is in accord with the reported bifurcation of the two protons by the plane of the purine ring. It is of interest to note that the two methylene protons exhibited distinguished chemical shifts in which 5'-Ha appeared upfield at 3.74 ppm while 5'-Hb was shifted considerably downfield to 4.56 ppm. However, Rosemeyer et al.^[16] reported that the two protons at 5' position having the same chemical shift of 3.87 ppm. In our case, the structural assignment of **8** is verified by COSY and HETCOR NMR, and the HETCOR spectrum is shown in Figure 1.

It has been known that under suitable condition, tosylation or halogenation of the 5'-OH could lead to cyclonucleosides.^[17,18] Although most of the conditions required the protection of 2' and 3'-OH groups, **6**^[16] and xanthosine (**9a**)^[19] were directly converted to the corresponding cyclonucleoside without the protection of hydroxyl groups. We also found that a treatment of **6** with PPh_3 and carbon tetrachloride in pyridine^[20] at room temperature could provide **8** directly in moderate yield of 75% (Scheme 1).

However, an attempt to prepare cyclonucleosides of **9a** and guanosine (**9c**) by the similar condition using $\text{PPh}_3/\text{CCl}_4$ for the preparation of **8** failed due to the chlorination



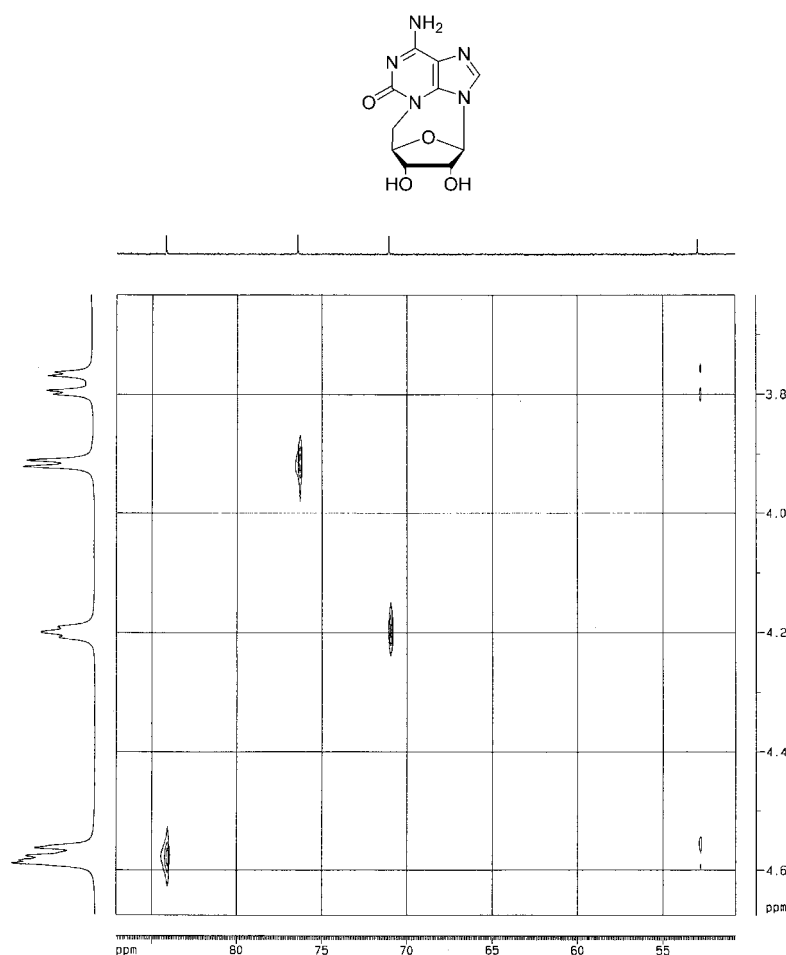
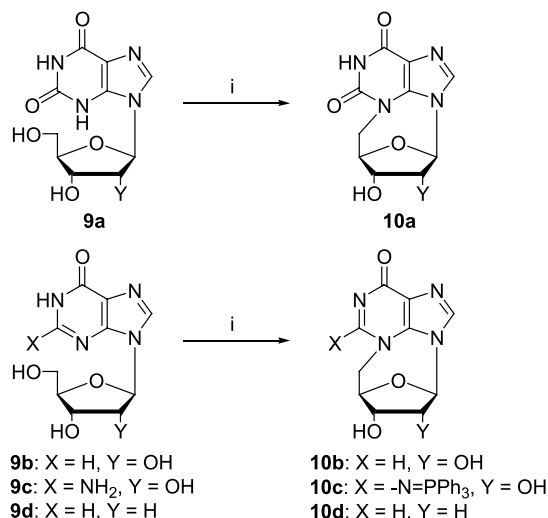


Figure 1. HETCOR spectrum of **8**.

at the 6 position. A perusal of literature showed that the 6 position of **9a** and inosine (**9b**) would be chlorinated with $\text{PPh}_3/\text{CCl}_4$.^[21–23] Consequently, an alternate route is needed for the intramolecular cyclization of these systems. Cycloguanosine^[24] and cyclo-2'-deoxyinosine derivative^[25] have been reported as side products in Mitsunobu reaction. As a result, **9a**, **9b**, **9c**, and 2'-deoxyinosine (**9d**) were subjected to undergo Mitsunobu reaction, and the expected cyclonucleosides **10a**, **10b**, and **10d** were obtained in moderate yield while **9c** gave the corresponding iminophosphorane derivative **10c** (Scheme 2). It was reported^[24] that *N*³,5'-cycloguanosine was obtained in 90% yield in 1:5 DMSO/THF while the corresponding iminophosphorane **10c** was formed in a more polar system (1:1 DMSO/THF). In our case, a sole product **10c** was obtained because of the polar solvent DMF.

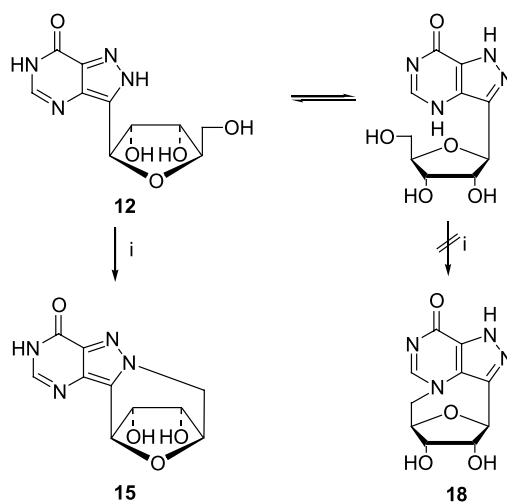
Formycin (**11**) and formycin B (**12**) are C-nucleosides that have been reported to possess antiviral activity.^[26,27] The structures of **11** and **12** consist of a purine aglycone





Scheme 2. (i) PPh_3 , DEAD, DMF, rt.

covalently bonded a D-ribose in a β -configuration. An X-ray study revealed the hydrate of **11** being an intermediate between classical anti and syn conformations with aglycosyl torsion angle of 109.8° in the solid state^[28] while an earlier X-ray study of **11** showed a syn conformation.^[29] On the contrary, Townsend et al.^[30] investigated the conformation of **11** in solution by magnetic circular dichroism (MCD) spectra and found that **11** was in the anti form with a negative B_{2u} Cotton effect at 293 nm. Žemlička^[31] also reported a similar result. Nevertheless, he noticed that **11** could be converted to both $N^2,5'$ - (**13**) and $N^4,5'$ -cycloformycins (**14**) under different conditions,



Scheme 3. (i) PPh_3 , DEAD, DMF, rt.



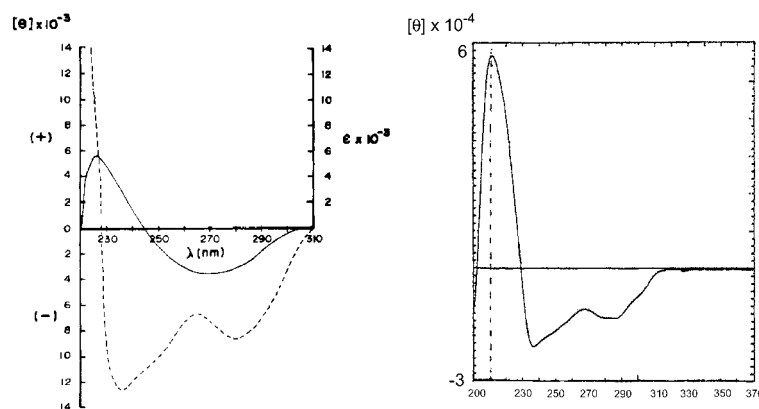
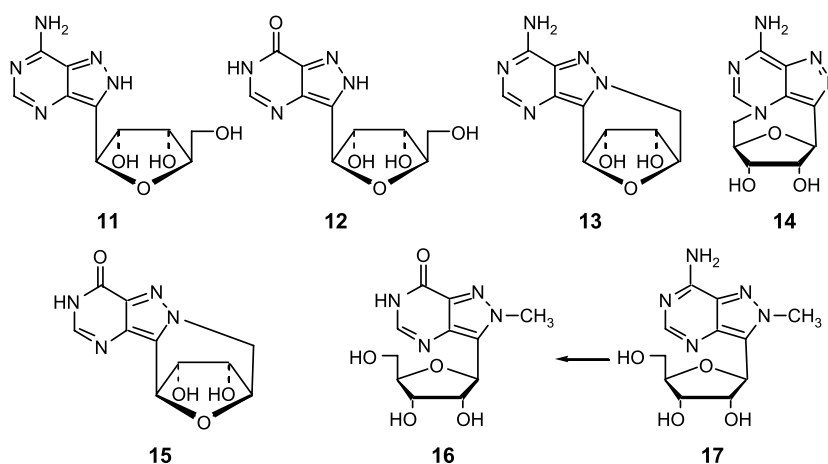
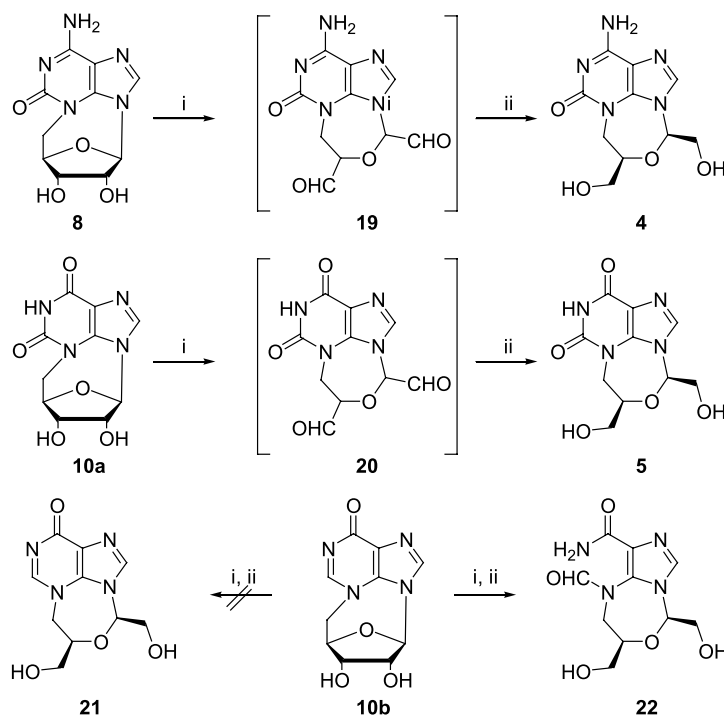


Figure 2. The CD spectra of (A) cycloformycin B (**12**, —) and $N^2,5'$ -cycloformycin B (**15**, - - -) reported by Žemlička^[31] and (B) $N^2,5'$ -cycloformycin B (**15**) obtained herein.

which were derived from the different rotameric forms anti and syn, respectively. $N^2,5'$ -Cycloformycin B (**15**), derived from anti form, could be obtained via an intramolecular cyclization of **12** treated with dimethylformamide dineopentyl acetal.^[31] Interestingly, 2-methylformycin B (**16**), with syn conformation, was obtained in an unusual fashion by Townsend et al.^[30] where the amino group of 2-methylformycin (**17**)^[32] was converted to a hydroxyl group under basic condition. We have explored the potentiality of **12** containing a *p*-(fluorosulfonyl)benzoyl moiety being a purine nucleoside phosphorylase (PNP) inhibitor.^[33] It is of interest to see whether $N^4,5'$ -cycloformycin B (**18**) could be obtained by a treatment of **12** under Mitsunobu conditions. When **12** was treated with PPh_3/DEAD in DMF, a sole product was isolated and identified as **15** in 81% yield by 1D and 2D (HETCOR and COSY) NMR and HRMS (Scheme 3). Further, the CD spectrum of the obtained **15**, shown in Figure 2, is almost identical with that in literature.^[31]





Scheme 4. (i) NaIO_4 , H_2O , 0°C to rt. (ii) (1) NaBH_4 , H_2O , rt; (2) 1 *N* HOAc.

The purine $N^3,5'$ -cyclonucleosides were obtained via Mitsunobu reaction effectively. It is of interest to prepare the corresponding $N^3,5'$ -cyclo-2',3'-seconucleosides which consist of a 5-, 6-, and 7-membered tricyclic system resembling to TIBO derivatives by the cleavage of the 2' and 3' carbon-carbon bonds of the ribopentofuranose from the prepared $N^3,5'$ -cyclonucleosides. Cyclonucleoside **8** could undergo oxidative cleavage by sodium periodate^[34] to provide dialdehyde **19** (Scheme 4). Nevertheless, **19** was not stable during purification, and therefore it was subjected to reduction by sodium borohydride directly without separation. In such a way, $N^3,5'$ -cyclo-2',3'-secoisoguanosine (**4**) was obtained in 96% yield. Accordingly, **10a** and **10b** were subjected to oxidation with sodium periodate, and the reaction mixture was subsequently treated with sodium borohydride. While **5** was obtained from **10a** as expected, a ring-opened derivative $N^3,5'$ -cyclo-1-(5'-deoxy-2',3'-seco- β -D-ribofuranosyl)-5-formamidoimidazole-4-carboxamide (**22**) was obtained in inosine system (Scheme 4). This similar hydrolytic ring-opening of purine system was also found in $N^3,5'$ -cyclo-2',3'-isopropylideneinosine.^[35]

CONCLUSION

The Mitsunobu reaction provides a convenient way to prepare the $N^3,5'$ -cyclonucleosides, and the subsequent oxidative cleavage and reduction lead to the



formation of a $N^3,5'$ -cyclo-2',3'-seconucleosides which resemble the tricyclic TIBO derivatives. The biological activity of these compounds is currently under active investigation and will be represented elsewhere.

EXPERIMENTAL

Melting Points Were Obtained on an Electrothermal Apparatus and Are Uncorrected. ^1H and ^{13}C nuclear magnetic resonance spectra were recorded on a Jeol JNM-EX400 or Bruker Model AM 300 spectrometer, and are reported in parts per million with $\text{DMSO}-d_6$ as internal standard on a δ scale. CD spectra were taken on JASCO J-720 spectropolarimeter. EI mass spectra were recorded on Jeol JMS-D100 mass spectrometer. Elemental analyses for C, H, and N were carried out either on a Heraeus Elemental Analyzer or a Perkin-Elmer 240 Elemental Analyzer, and were within $\pm 0.4\%$ of the theoretical values.

$N^3,5'$ -Cycloisoguanosine (8). Method A: To a solution of isoguanosine (0.6 g, 1.6 mmol) and N,N -bis(trifluoroacetyl)-L-homocystine dimethyl ester (3.2 g, 6.1 mmol) in anhydrous pyridine (20 mL) was added tri-*n*-butylphosphine (3.5 g, 17.3 mmol). After stirring at room temperature for 24 h, the mixture was evaporated, and the residue was chromatographed on silica gel to give **8** (60 mg, 11%) ($R_f = 0.33$; $\text{CHCl}_3/\text{MeOH}/\text{H}_2\text{O}$ 16:9:2) as a white solid; Method B: To a solution of triphenylphosphine (0.3 g, 1.14 mmol) in anhydrous pyridine (25 mL) was added isoguanosine (0.1 g, 0.4 mmol). The suspension mixture was stirred at room temperature for 10 min, and then carbon tetrachloride (0.2 g, 1.3 mmol) was added. The resulting mixture was stirred for additional 12 h. Then, the solution was evaporated. Ethanol (30 mL) was added to the residue, and a white precipitate of **8** (70 mg, 75%) was obtained; mp 247°C (dec.) [lit.^[16] 270°C]; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 3.74 (dd, 1H, $J = 14.6, 2.9$ Hz, 5'-Ha), 3.77 (d, 1H, $J = 5.4$ Hz, 2'-H), 3.91 (s, 1H, 3'-H), 4.56 (dd, 1H, $J = 5.1, 2.7$ Hz, 4'-H), 4.58 (dd, 1H, $J = 2.0$ Hz, 5'-Hb), 5.51 (s, 2H, 2',3'-OH), 6.14 (s, 1H, 1'-H), 7.41 (s, 2H, NH_2), 7.78 (s, 1H, 8'-H); ^{13}C -NMR (75 MHz, $\text{DMSO}-d_6$): δ 51.77, 70.35, 75.66, 83.85, 92.24, 112.83, 133.28, 141.13, 155.44, 158.33; MS (EI, 20 eV) m/z 265 (M^+); Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{N}_5\text{O}_4 \cdot \text{H}_2\text{O}$: C, 42.41; H, 4.63; N, 24.73. Found: C, 42.43; H, 4.42; N, 24.52.

$N^3,5'$ -Cycloxanthosine (10a). To a solution of xanthosine (5.0 g, 14.7 mmol) in anhydrous N,N -dimethylformamide (10 mL) were added triphenylphosphine (11.5 g, 44.0 mmol) and diethyl diazodicarboxylate (7.0 mL, 45.0 mmol). The mixture was stirred under nitrogen at room temperature for 12 h. After removing the solvent in vacuo, ether was added to the residue, and a white precipitate was formed. The solid was separated by filtration, and the crude product was recrystallized from methanol and water to give **10a** (4.0 g, 86%) ($R_f = 0.28$; $\text{CHCl}_3/\text{MeOH}/\text{H}_2\text{O}$ 18:10:1) as needles; mp $222-224^\circ\text{C}$ (dec.) [lit.^[36] $310-314^\circ\text{C}$]; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 3.71 (dd, 1H, $J = 15.0, 3.1$ Hz, 5'-Ha), 3.87 (t, 1H, $J = 5.1$ Hz, 3'-H), 4.20 (dt, 1H, $J = 7.7, 3.5$ Hz, 2'-H), 4.55 (br s, 1H, 4'-H), 4.57 (dd, 1H, $J = 10.6, 2.5$ Hz, 5'-Hb), 5.45 (d, 1H, $J = 6.6$ Hz, 2'-OH), 5.52 (d, 1H, $J = 5.1$ Hz, 3'-OH), 6.25 (s, 1H, 1'-H), 7.81 (s, 1H, 8-H), 11.21 (s, 1H, 1-NH); ^{13}C -NMR (75 MHz, $\text{DMSO}-d_6$): δ 51.62, 70.44, 76.17, 85.05,

92.85, 118.17, 134.75, 140.97, 151.34, 157.74; MS (EI, 20 eV) m/z 266 (M^+); Anal. Calcd for $C_{10}H_{10}N_4O_5$: C, 45.12; H, 3.79; N, 21.05. Found: C, 45.12; H, 3.82; N, 20.89.

$N^3,5'$ -Cycloinosine (10b). To a solution of inosine (2.0 g, 7.36 mmol) in anhydrous N,N -dimethylformamide (10 mL) were added triphenylphosphine (5.9 g, 22.5 mmol) and diethyl diazodicarboxylate (3.5 mL, 22.5 mmol). After stirring under nitrogen at room temperature for 8 h, N,N -dimethylformamide was evaporated in vacuo, and ether was added to afford **10b** (1.5 g, 80%) (R_f = 0.11; $CHCl_3$ /MeOH/ H_2O 18:10:1) as a white solid; mp 265–266°C (dec); 1H NMR (300 MHz, DMSO- d_6): δ 3.89 (t, 1H, J = 5.1 Hz, 3'-H), 4.21 (dd, 1H, J = 10.0, 6.4 Hz, 2'-H); 4.36 (dd, 1H, J = 13.9, 2.3 Hz, 5'-Ha), 4.59 (br d, 1H, J = 3.6 Hz, 4'-H); 4.70 (br d, 1H, J = 13.7 Hz, 5'-Hb), 5.44 (d, 1H, J = 7.0 Hz, 2'-OH), 5.64 (d, 1H, J = 5.1 Hz, 3'-OH), 6.26 (s, 1H, 1'-H), 8.02 (s, 1H, 8-H), 8.23 (s, 1H, 2-H); ^{13}C -NMR (75 MHz, DMSO- d_6): δ 56.72, 70.48, 76.23, 83.95, 93.06, 124.16, 135.58, 138.76, 148.70, 164.11; MS (EI, 20 eV) m/z 250.1 (M^+).

$N^3,5'$ -Cyclo- N^2 -triphenylphosphoranylidenguanosine (10c). Guanosine (5.0 g, 17.6 mmol) was added to N,N -dimethylformamide (10 mL) and then followed by triphenylphosphine (18.5 g, 70.6 mmol) and diethyl diazodicarboxylate (11.0 mL, 70.6 mmol). After stirred under nitrogen at room temperature for 12 h, the mixture was evaporated, and the residue was chromatographed on silica gel to give **10c** (6.0 g, 65%) (R_f = 0.48; EtOH/MeOH 2:1) as a white solid; mp 225–226°C (dec) [lit.^[24] 180°C]; 1H NMR (300 MHz, DMSO- d_6): δ 3.85 (t, 1H, J = 5.0 Hz, 3'-H), 4.10 (d, 1H, J = 12.8 Hz, 5'-Ha), 4.22 (m, 1H, 2'-H), 4.64 (br s, 1H, 4'-H), 5.32 (d, 1H, J = 13.7 Hz, 5'-Hb), 5.52 (d, 1H, J = 3.5 Hz, 3'-OH), 5.55 (d, 1H, J = 4.5 Hz, 2'-OH), 6.15 (s, 1H, 1'-H), 7.54–7.68 (m, 10H), 7.83–7.90 (m, 6H).

$N^3,5'$ -Cyclo-2'-deoxyinosine (10d). To a solution of 2'-deoxyinosine (2.5 g, 10.0 mmol) in anhydrous N,N -dimethylformamide (10 mL) were added triphenylphosphine (3.9 g, 15.0 mmol) and diethyl diazodicarboxylate (2.5 mL, 16.1 mmol). After stirring under nitrogen at room temperature for 4 h, N,N -dimethylformamide was evaporated in vacuo, and ether was added to afford **10d** (1.6 g, 67%) (R_f = 0.52; $CHCl_3$ /MeOH/ H_2O 5:4:1); mp 233°C (dec); 1H NMR (300 MHz, DMSO- d_6): δ 2.22 (dd, 2H, J = 14.0, 3.3 Hz, 2'-H), 4.29 (dd, 1H, J = 14.0, 2.3 Hz, 5'-Ha); 4.42 (br d, 1H, J = 6.0 Hz, 3'-H), 4.63 (br d, 1H, J = 2.3 Hz, 4'-H); 4.67 (dd, 1H, J = 15.1, 2.1 Hz, 5'-Hb), 5.55 (d, 1H, J = 4.5 Hz, 3'-OH), 6.59 (t, 1H, J = 3.1 Hz, 1'-H), 7.93 (s, 1H, 8-H), 8.24 (s, 1H, 2-H); ^{13}C -NMR (75 MHz, DMSO- d_6): δ 45.07, 56.69, 70.06, 85.82, 88.75, 124.43, 135.21, 138.90, 148.67, 164.13; MS (EI, 20 eV) m/z 234 (M^+).

$N^3,5'$ -Cycloformycin B (15). To a solution of formycin B (0.4 g, 1.5 mmol) in anhydrous N,N -dimethylformamide (4 mL) were added triphenylphosphine (1.2 g, 4.5 mmol) and diethyl diazodicarboxylate (0.7 mL, 4.5 mmol). The mixture was stirred under nitrogen at room temperature for 6 h, and then evaporated. The residue was treated with ether to form precipitate, and the white solid was recrystallized from a mixture of methanol and water to furnish **15** (0.3 g, 81%) (R_f = 0.66; $CHCl_3$ /MeOH/ H_2O 5:4:1); mp 362.0–362.5°C (dec) [lit.^[31] >320°C]; 1H NMR (400 MHz,

DMSO- d_6): δ 4.08 (t, 1H, J = 5.7 Hz, 2'-H), 4.29 (t, 1H, J = 6.2 Hz, 3'-H), 4.34 (d, 1H, J = 13.6 Hz, 5'-Ha), 4.46 (dd, 1H, J = 13.7, 4.6 Hz, 5'-Hb), 4.55 (d, 1H, J = 4.3 Hz, 4'-H), 5.13 (d, 1H, J = 6.5 Hz, 3'-OH), 5.26 (s, 1H, 1'-H), 5.47 (d, 1H, J = 5.5 Hz, 2'-OH), 7.77 (s, 1H, 5-H), 11.86 (s, 1H, 6-NH); ^{13}C -NMR (100 MHz, DMSO- d_6): δ 52.5, 74.4, 75.9, 77.1, 80.5, 132.5, 132.6, 135.8, 143.3, 156.3; MS (EI, 70 eV) m/z 250.6 (M^+); HRMS (EI) Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_4\text{O}_4$: 250.0702. Found: 250.0700.

***N*³,5'-Cyclo-2',3'-secoisoguanosine (4).** To a suspension of **8** (1.9 g, 7.16 mmol) in water (50 mL) was added sodium periodate (0.19 g, 0.89 mmol). After stirring at room temperature for 1 h, a solution of sodium borohydride (1.0 g, 26.4 mmol) in water (50 mL) was added. The mixture was reacted for an additional 1 h, and it was neutralized to pH = 7 by 1 *N* hydrochloric acid. The white precipitate was filtered, dried, and recrystallized from ethanol/water 1:1 to afford **4** (1.83 g, 96%) as needles; mp 260°C (dec); ^1H NMR (300 MHz, DMSO- d_6): δ 3.42–3.50 (m, 1H, 3'-Ha), 3.54–3.60 (m, 1H, 3'-Hb), 3.65 (dd, J = 14.8, 8.4 Hz, 1H, 5'-Ha), 3.97 (t, J = 4.6 Hz, 2H, 2'-H), 4.14 (dd, J = 12.5, 6.1 Hz, 1H, 4'-H), 4.54 (dd, J = 14.6, 1.2 Hz, 1H, 5'-Hb), 5.01 (t, J = 5.7 Hz, 1H, 3'-OH), 5.38 (t, J = 5.8 Hz, 1H, 2'-OH), 5.4 (t, J = 3.5 Hz, 1H, 1'-H), 7.30 (s, 1H, NH2), 7.78 (s, 1H, 8-H); ^{13}C -NMR (75 MHz, DMSO- d_6): δ 48.51, 61.65, 62.07, 80.00, 88.61, 112.32, 133.37, 142.34, 155.21, 158.23; MS (EI) m/z 267 (M^+); Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_5\text{O}_4 \cdot \text{H}_2\text{O}$: C, 42.11; H, 5.30; N, 24.55. Found: C, 42.31; H, 5.09; N, 24.55.

***N*³,5'-Cyclo-2',3'-secoxanthosine (5).** To a suspension of **10a** (0.2 g, 0.75 mmol) in water was added sodium periodate (0.19 g, 0.89 mmol). After stirring at room temperature for 1 h, a solution of sodium borohydride (0.1 g, 2.64 mmol) in water (5 mL) was added, and the reaction was carried out for another 2 h. The solution was neutralized to pH = 7 by 1 *N* aqueous acetic acid, and the resulting mixture was subjected to charcoal chromatography for purification (first by water and followed by 3% ammonium hydroxide in aqueous methanol (1:1). Recrystallization from aqueous methanol furnished **5** (0.11 g, 55%) as white needles; mp 208.8–209.3°C (dec); ^1H NMR (300 MHz, DMSO- d_6): δ 3.36–3.46 (m, 1H, 3'-Ha), 3.50–3.60 (m, 1H, 3'-Hb), 3.97 (m, 2H, 2'-H₂), 4.03 (d, 1H, J = 5.9 Hz, 5'-Ha), 4.19 (m, 1H, 4'-H), 4.50 (dd, 1H, J = 14.7, 2.5 Hz, 5'-Hb), 5.01 (t, 1H, J = 5.6 Hz, 3'-H), 5.46 (t, 1H, J = 5.7 Hz, 2'-OH), 5.79 (t, 1H, J = 3.9 Hz, 1'-H), 7.78 (s, 1H, 8-H), 11.14 (s, 1H, 1-NH); ^{13}C -NMR (75 MHz, DMSO- d_6): δ 46.3, 61.5, 61.9, 79.9, 87.3, 117.1, 134.9, 142.3, 151.1, 157.7; MS (EI, 70 eV) m/z 268.4 (M^+); HRMS (EI) Calcd for $\text{C}_{10}\text{H}_{12}\text{N}_5\text{O}_4$: 268.0807. Found: 268.0800.

***N*³,5'-Cyclo-1-(5'-deoxy-2',3'-seco- β -D-ribofuranosyl)-5-formamido-imidazole-4-carboxamide (22).** To a suspension of **10b** (0.25 g, 1.0 mmol) in water was added sodium periodate (0.25 g, 1.2 mmol). After stirring at room temperature for 1 h, sodium borohydride (0.08 g, 2.1 mmol) was added. A white precipitate was formed to furnish **22** (0.15 g, 53%); mp 235.0–236.8°C (dec); ^1H NMR (300 MHz, DMSO- d_6): δ 2.57 (dd, 1H, J = 14.1, 10.4 Hz, 5'-Ha), 3.36–3.54 (m, 2H, 3'-H₂), 3.73 (m, 1H, 4'-H), 3.96–4.05 (m, 2H, 2'-Ha), 4.66 (br d, 1H, J = 13.2 Hz, 5'-Hb), 4.94 (t, 1H, J = 5.8 Hz, 2'-Hb), 5.30 (t, 1H, J = 5.2 Hz, 1'-H), 5.46 (t, 1H, J = 5.6 Hz, 3'-OH), 7.24 (br s, 1H, 4-CONHa), 7.44 (br s, 1H, 4-CONHb), 7.79 (s, 1H, 2-H), 8.24 (s, 1H, *N*-CHO); ^{13}C -NMR (75 MHz, DMSO- d_6): δ 45.21, 60.77, 61.94, 82.68, 86.51, 125.94, 132.33,



133.76, 163.00, 163.89; MS (FAB) m/z 271.0 (M^+); Anal. Calcd for $C_{10}H_{14}N_4O_5 \cdot 1/4H_2O$: C, 43.72; H, 5.32; N, 20.39. Found: C, 43.64; H, 5.23; N, 20.51.

ACKNOWLEDGMENT

This work was supported by a research grant (No. NSC92-2320-B-002-080) from National Science Council of the Republic of China in Taiwan.

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Received August 8, 2003

Accepted October 21, 2003



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