Synthesis and Antiviral Activity of 3′-Fluorocarbocyclic Oxetanocin A

Yoshiko SATO and Tokumi MARUYAMA*

Department of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, Japan.
Received July 28, 1994; accepted August 25, 1994

A new procedure for the synthesis of 3′-fluorocarbocyclic oxetanocin A (1b) was developed. Addition of iodine fluoride to *O*-cyclohexylidene-*cis*-2-hydroxymethyl-3-methylene-1-cyclobutanol (4) afforded *O*-cyclohexylidene-(1*S,2*S**,3*R**)-3-fluoro-3-iodomethyl-2-hydroxymethyl-1-cyclobutanol (5) and the undesired (1*S**,2*S**,3*S**)-isomer (6) in 6.2% and 38% yields, respectively. When fluorine was introduced into the carbocycle after condensation of 6-chloropurine, 6-chloro-9-[(1*R**,2*S**,3*R**)-3-fluoro-3-iodomethyl-2-(trityloxymethyl)cyclobutyl]purine (10) was obtained as a sole addition product, which was readily converted to 1b. This compound (1b) exhibited a broad spectrum of antiviral activity, especially against human cytomegalovirus.**

Keywords carbocyclic oxetanocin; methylenecyclobutane; addition reaction; fluorocyclobutane; antiviral activity; cytomegalovirus

Oxetanocin A, isolated from *B. megaterium* by Shimada *et al.*, was found to exhibit antiviral activity against human immunodeficiency virus (HIV) type 1 *in vitro*.[1] Synthesis of carbocyclic analogues of oxetanocin and evaluation of their antiviral activity have been reported by several groups, including ours.[2,3] In particular, carbocyclic oxetanocin G (C.OXT-G) showed excellent activity against herpes simplex virus (HSV) and it was suggested that C.OXT-G was phosphorylated by virus-encoded thymidine kinase prior to exert its antiviral effect.[2b] In contrast, the adenine congener **1a** (C.OXT-A) was a good inhibitor of cytomegalovirus (CMV) *in vitro* and *in vivo*.[2c] However, strong cytotoxicity to host cells prevented further development of **1a** as an anti-CMV agent. The cytotoxicity of C.OXT-A could be explained in terms of inhibition of cellular DNA polymerase after phosphorylation to its active form. By analogy with nucleocidin,[4] therefore, we planned to change the 3′-proton of C.OXT-A to fluorine. In this paper, a new synthetic route to 3′-fluorocarbocylic oxetanocin A is described (Fig. 1),[5] and the antiviral activity of the product against several viruses is presented.

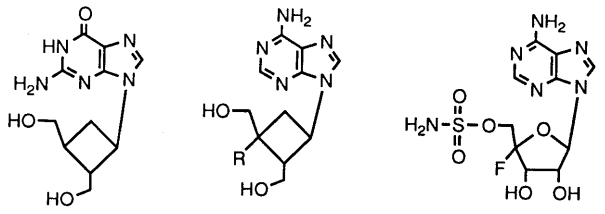

Fig. 1

Chemical Synthesis Jenkins *et al.*[4] synthesized nucleocidin by the addition of iodine fluoride ($AgF–I_2$) to 4′-methylenenucleoside, and methods to introduce methoxy and azido groups using a similar approach were subsequently reported by the same group.[4a,6] We adopted this approach for the synthesis of 3′-fluorocarbocyclic oxetanocin A (F-C.OXT-A), as follows: *O*-cyclohexylidene-*trans*-*cis*-2,3-bis(hydroxymethyl)-1-cyclobutanol[2c] (**2**) was converted to the iodide **3** by methyltriphenoxyphosphonium iodide and subsequent elimination by treatment with potassium *tert*-butoxide in *tert*-butanol in the presence of pyridine afforded the methylenecyclobutane **4** in good yield.[7] Addition of iodine fluoride to **4** gave two products. The major one was identified as *O*-cyclohexylidene-(1*S**,2*S**,3*S**)-3-fluoro-3-iodomethyl-2-hydroxymethyl-1-cyclobutanol (**6**), the configuration of which was determined by nuclear Overhauser exchange spectroscopy (NOESY) experiments on the corresponding 3′-*O*-benzoate **7** (Fig. 2). The stereoisomer **5** was obtained as a minor product in only 6.2% yield. The mechanism could be explained in terms of nucleophilic attack of fluoride ion on the intermediary 3′-carbocation from the less-hindered up-side. To prevent this undesired attack, a purine base was introduced prior to the addition reaction. The cyclohexylidine group in **4** was hydrolyzed in the presence of acid and the product was partially protected to afford the methylenecyclobutanol **8**. Condensation of **8** with 6-chloropurine was performed by use of

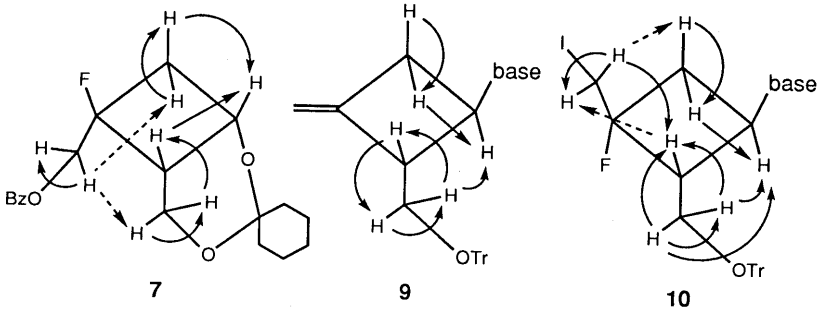

Fig. 2. NOESY Experiments on Compounds **7**, **9**, and **10**

© 1995 Pharmaceutical Society of Japan

NII-Electronic Library Service

the Mitsunobu reaction.[8] An unstable product obtained in 56% yield was concluded to be the cyclobutenyl derivative from its mass spectrum ($m/z=338$ (M^+)). The second product **9** showed a UV absorption spectrum resembling that of 6-chloropurine riboside,[9] and from this, in combination with the ^{1}H-NMR and MS data, the structure was identified as 6-chloro-9-(*trans*-3-methylene-2-trityloxymethylcyclobutyl)purine. An addition reaction similar to that described in the reaction of **4** was attempted, and the single addition product obtained after work-up of the reaction mixture was identified as 6-chloro-9-[(1*R**,2*S**,3*R**)-3-fluoro-3-iodomethyl-2-(trityloxymethyl)cyclobutyl]purine (**10**); the corresponding (*E*)-isomer was not detected on TLC. It is supposed that electrostatic interaction between N^3 of the purine base and the C3′ cation center would cause severe steric hindrance above the cyclobutane ring, allowing the nucleophilic attack only from below. Reaction of the 3′-iodide **10** with benzoate at 55 °C in *N*,*N*-dimethylformamide (DMF) afforded the 3′-benzoate **11** in 69% yield. Jenkins *et al.*[5] reported that nucleophilic displacement of adenine 4′-fluoro-5′-deoxy-5′-iodoriboside by benzoate was unsuccessful and conversion to the 5′-hydroxy compound was achieved by photolysis of the corresponding 5′-azido derivative. This differential reactivity of the iodide could be explained by the neighbouring polar substituents.[10] In the cyclobutane ring, an electron-withdrawing α-substituent is only fluorine. In the case of adenine 4′-fluoro-5′-deoxy-5′-iodoriboside, both ring oxygen (O4) and 4′-fluorine generate the permanent dipoles associated with the substituent-to-carbon bonds, and therefore the iodide becomes less reactive in an S_N2 reaction. Compound **11** was successively treated with liquid ammonia and 1 N HCl to afford the target compound **1b** in good yield. Since yields were not satisfactory in several steps, an alternative route was explored. Permanganate oxidation of the

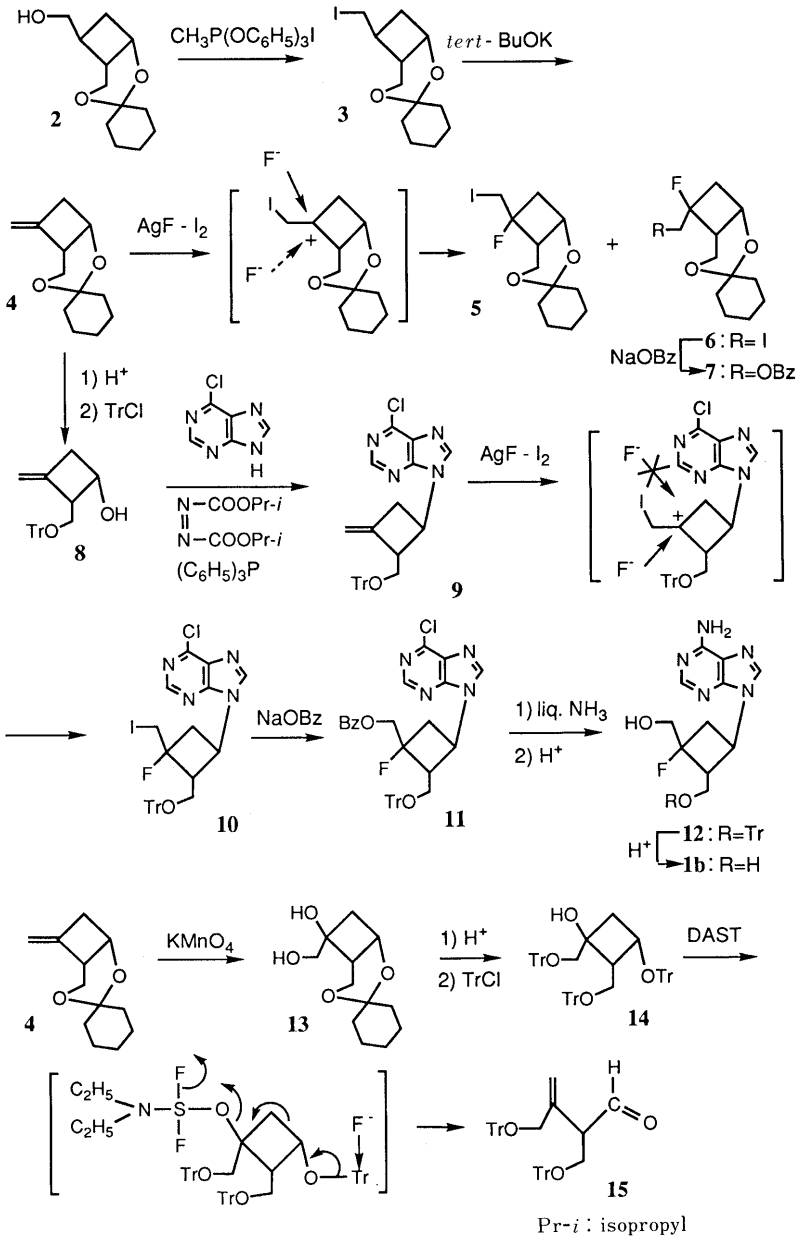

Chart 1

NII-Electronic Library Service

methylenecyclobutane **4** in alkaline solution[11] gave the cyclobutane-1,3-diol **13**, which, on treatment with acidic resin and protection with a trityl group, gave a tri-*O*-tritylated cyclobutane-1,3-diol **14**. Conversion of the 1-hydroxy group into the fluoride was attempted using diethylaminosulfur trifluoride (DAST).[12] The product was assigned the 2,3-bis(trityloxymethyl)-3-buten-1-one (**15**) structure on the basis of the following data. The ^{1}H-NMR spectrum of **15** revealed loss of one trityl group and appearance of a doublet at 9.53 attributable to an aldehyde proton. Mass spectroscopic data ($M^+ -$ trityl, m/z 371) also supported the structure. Although the mechanism is not clear at present, it seems that initial approach of DAST to the hydroxyl group of **14** results in the formation of an active intermediate, from which **15** is formed by the successive elimination reactions of the trityl group and diethylaminofluorosulfoxide, ring opening and double bond formation.

Antiviral Activity The antiviral effects of F-C.OXT-A (**1b**) were determined by a plaque reduction method (HSV-1, HSV-2 and HCMV),[13] an immunofluorescence method (HIV)[14] or a Southern blot method (hepatitis B virus, HBV).[15] ED_{50} values are defined as the concentration of drug required to achieve 50% inhibition compared to virus controls. F-C.OXT-A showed some activity against HSV-1 and HSV-2 with respective ED_{50} values of 2.72 and 1.33 μg/ml, which are seven times higher than those of acyclovir (Table I). It displayed potent activity against HCMV: at a concentration of 1.0 μg/ml, F-C.OXT-A completely inhibited HCMV replication, whereas ganciclovir[16] showed only partial inhibition (58%). Ganciclovir was almost inactive at 0.1 μg/ml while F-C.OXT-A still showed 34% inhibition. Bisacchi *et al.*[17] claimed that C.OXT-A was comparable in anti-CMV activity to ganciclovir *in vitro* and *in vivo*. The present data indicate that introduction of 3′-fluorine into C.OXT-A increases the antiviral activity against HCMV. F-C.OXT-A also exhibited some activity against HBV, but this activity was seen only at a concentration markedly higher than that at which Lamivudine[18] was active. Moderate activity was also observed against HIV-1 (HTLV-III$_B$). The effects on host cells such as Vero, human embryonic lung (HEL), human T-lymphocyte (MT-4) and 2.2.15 cell lines were also tested. F-C.OXT-A was not toxic below 10 μg/ml, but at the highest concentration tested (100 μg/ml), it was slightly toxic to proliferating intact cell monolayers, such as HEL or MT-4 cells. Although this toxicity is not strong compared with that of C.OXT-A (CC_{50} for HEL; 8 μg/ml, CC_{50} for MT-4; 12 μg/ml),[2c] it should be taken into account in assessing the potential utility of this compound as an anti-HCMV agent.

TABLE I. Antiviral Activity of F-OXT-A in Host Cells

Virus	Compd.	Concentration (μg/ml)	Inhibition (%)	EC_{50} (μg/ml)[a]
HSV-1(KOS) in Vero cell	Acyclovir	1.0	96.8	0.41
		0.3	32.9	
		0.1	6.6	
	F-C.OXT-A	10.0	100.0	2.72
		1.0	11.3	
		0.1	5.3	
HSV-2(186) in Vero cell	Acyclovir	1.0	100.0	0.18
		0.3	81.9	
		0.1	13.2	
	F-C.OXT-A	100.0	100.0	1.33
		10.0	100.0	
		1.0	43.2	
		0.1	−15.0	
HCMV (AD169) in HEL cell	Ganciclovir	10.0	100.0	0.71
		1.0	58.4	
		0.1	3.0	
	F-C.OXT-A	100.0[b]	100.0	0.18
		10.0	100.0	
		1.0	100.0	
		0.1	34.0	
		0.01	−5.1	
HIV (HTLV-III$_B$) in MT-4 cell	Didanosine	1.0	70.0	0.46
		0.1	<10.0	
	F-C.OXT-A	100.0[b]	100.0	3.73
		10.0	80.0	
		1.0	<10.0	
		0.1	<10.0	
HBV in 2.2.15 cell	Lamivudine	100.0	95.4	0.0089
		10.0	95.3	
		1.0	94.9	
		0.1	90.1	
		0.001	13.9	
	F-C.OXT-A	100.0[b]	92.9	0.41
		10.0	91.6	
		1.0	67.8	
		0.1	21.4	
		0.01	9.4	

a) The 50% effective concentration, or concentration required to reduce virus-induced cytopathogenicity by half. *b*) A weak cytotoxicity was observed.

Experimental

Melting points (mp) were determined using a Yanagimoto micro-melting point apparatus (hot stage type) and are uncorrected. UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. Low-resolution mass spectra were obtained on a JEOL JMS-AX500 mass spectrometer in the direct-inlet mode. ^{1}H-NMR spectra were recorded on a Varian UNITY 200 (200 MHz) or UNITY 600 (600 MHz) in $CDCl_3$ (or dimethyl sulfoxide (DMSO)-d_6) with tetramethylsilane as an internal standard. Merck Art 5554 plates precoated with Silica gel 60 containing fluorescent indicator F_{254} were used for thin-layer chromatography and Silica gel 60 (Merck 7734, 60—200 mesh) was employed for column chromatography.

***O*-Cyclohexylidene-*cis*-2-hydroxymethyl-*trans*-3-iodomethyl-1-cyclobutanol (3)** Methyltriphenoxyphosphonium iodide (8.4 g, 18.6 mmol) was added to a solution of *O*-cyclohexylidene-*trans*-*cis*-2,3-bis(hydroxymethyl)-1-cyclobutanol (**2**, 2.55 g, 12 mmol)[2c] in DMF (50 ml) and the mixture was stirred for 30 min at room temperature. After addition of water (5 ml), the solution was evaporated and the residue was dissolved in benzene (300 ml). The organic layer was washed successively with water (200 ml), 5% $Na_2S_2O_3$ (250 ml), cooled 1 N NaOH solution (20 ml) and water (200 ml) and dried over $MgSO_4$. The solution was concentrated to a small volume and chromatographed over a column of Silica gel G (4.0 × 15 cm) with benzene (1.2 l) to give a caramel (2.77 g, 78%). ^{1}H-NMR ($CDCl_3$) δ: 4.31 (1H, t, J=5.0 Hz, H1), 3.93 (1H, dd, J=12.4, 5.2 Hz, one of 2-CH_2O) and 3.77 (1H, d, J=12.4 Hz, one of 2-CH_2O), 3.25 (2H, d, J=6.7 Hz, 3-CH_2I), 3.04 (1H, m, H2), 1.3—2.2 (*ca.* 13H, H3, H4, C_6H_{10}).

***O*-Cyclohexylidene-*cis*-2-hydroxymethyl-3-methylene-1-cyclobutanol (4)** *tert*-Butanol (120 ml) containing potassium *tert*-butoxide (10 g, 89.2 mmol) was added to a solution of **3** (3.16 g, 9.81 mmol) in pyridine (120 ml) and the solution was stirred for 6 h at room temperature, then acetic acid (5 ml) was added. The solution was evaporated to dryness and the residue was partitioned between bezene (200 ml) and water (120 ml). The organic layer was washed with water (120 ml), dried over $MgSO_4$ and evaporated. The resulting syrup was evaporated azeotropically with toluene (50 ml) three times and chromatographed over a column of Silica gel G (3.0 × 15 cm) with benzene (1 l) to give a cara-

NII-Electronic Library Service

mel (3.64 g, 87%). MS *m/z*: 194 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 4.97 (2H, m, $=CH_2$), 4.43 (1H, dt, $J=5.8$, 1.8 Hz, H1), 3.97 (1H, dd, $J=11.6$, 5.1 Hz, one of 2-CH_2O–), 3.84 (1H, dd, $J=11.6$, 4.0 Hz, one of 2-CH_2O–), 2.92 (2H, m, H4a, H2), 2.62 (1H, double quintet, $J=15.7$, 2.0 Hz, H4b), 1.3—1.9 (*ca.* 10H, C_6H_{10}).

Addition of 4 with Silver Fluoride and Iodine Compound **4** (470 mg, 2.42 mmol) was dissolved in pyridine (0.5 ml) and CH_3CN (100 ml), then silver fluoride (2.12 g, 16.7 mmol) was suspended to the solution, and the whole was cooled in an ice-bath. A solution of iodine (2.08 g, 8.2 mmol) in CH_3CN (52 ml) was added dropwise (*ca.* 1 h), and the mixture was stirred for 1 d at 45 °C. Usual work-up as described for **10** gave a gum, which was dissolved in $CHCl_3$ (3 ml) and chromatographed over a column of Silica gel G (3.0 × 40 cm) with 0—7% AcOEt in hexane (2 l). The starting material (83 mg, 18%) was recovered from the first fraction. Concentration of the second fraction to a small volume gave *O*-cyclohexylidene-(1*S**,2*S**,3*S**)-3-fluoro-3-iodomethyl-2-hydroxymethyl-1-cyclobutanol (**6**) as a white solid (317 mg, 38%), mp 112—118 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.39 (1H, dt, $J=6.7$, 8.0 Hz, H1), 4.00 (1H, dd, $J=11.9$, 37.5 Hz, one of 3-CH_2I), 4.00 (2H, m, 2-CH_2O–), 3.76 (1H, dt, $J=11.9$, 2.0 Hz, one of 3-CH_2I), 2.61 (1H, dt, $J=5.4$, 18.1 Hz, H2), 2.45 (1H, m, H4a), 2.20 (1H, dd, $J=6.4$, 13.4 Hz, H4b), 1.3—1.9 (10H, C_6H_{10}). *Anal.* Calcd for $C_{12}H_{18}FIO_2$: C, 42.37; H, 5.33. Found: C, 42.51; H, 5.39. Evaporation of the third fraction gave *O*-cyclohexylidene-(1*S**,2*S**,3*R**)-3-fluoro-3-iodomethyl-2-hydroxymethyl-1-cyclobutanol (**5**) as a caramel (51 mg, 6.2%). ^{1}H-NMR ($CDCl_3$) δ: 4.17 (1H, m, H1), 4.13 (1H, dd, $J=5.9$, 12.8 Hz, one of 2-CH_2O–), 3.90 (1H, dd, $J=7.4$, 12.8 Hz, one of 2-CH_2O–), 3.42 (1H, dt, $J=5.9$, 10.9 Hz, one of 3-CH_2I), 3.29 (1H, t, $J=10.9$ Hz, one of 3-CH_2I), 2.55—2.8 (3H, m, H2, H4a, H4b), 1.3—1.8 (*ca.* 10H, C_6H_{10}).

***O*-Cyclohexylidene-(1*S**,2*S**,3*S**)-3-benzoyloxymethyl-3-fluoro-2-hydroxymethyl-1-cyclobutanol (7)** A solution of **6** (34 mg, 0.1 mmol) and sodium benzoate (72 mg) in DMF (3 ml) was stirred at 120 °C for 2 h, then cooled. Usual work-up and separation of the resulting syrup using Silica gel G (2.2 × 20 cm) gave a caramel (26.7 mg, 80%). ^{1}H-NMR ($CDCl_3$) δ: 8.09 (m, 2H of $C_6H_5CO_2$–), 7.5 (m, 3H of $C_6H_5CO_2$–), 4.98 (1H, q, $J=10.8$, one of 3-CH_2OBz), 4.82 (1H, q, $J=11.1$ Hz), 4.49 (1H, m, H1), 4.10 (1H, d, $J=13.2$ Hz, one of 2-CH_2O–), 4.04 (1H, dd, $J=5.5$, 13.2 Hz, one of 2-CH_2O–), 2.60 (1H, dt, $J=5.5$, 19.4 Hz, H2), 2.52 (1H, ddd, $J=5.9$, 13.2, 18.7 Hz, H4a), 2.37 (1H, dd, $J=5.5$, 13.2 Hz, H4b).

***cis*-2-Trityloxymethyl-3-methylene-1-cyclobutanol (8)** A solution of **4** (1.19 g, 6.13 mmol) in methanol (50 ml) was stirred in the presence of Amberlite IR 120B (H^+ form, 10 ml) for 1 h at room temperature and the resin was removed by filtration. After evaporation of the solution, the residue was dissolved in water (100 ml) and the aqueous layer was washed with benzene (50 ml) twice, then evaporated to dryness. The residue was evaporated azeotropically with pyridine (20 ml) twice and dissolved in dry pyridine (10 ml). Triphenylmethyl chloride (2.0 g, 7.2 mmol) was added to this solution and the mixture was kept at room temperature overnight. A usual work-up of the solution and chromatography using silica gel gave a caramel, 1.82 g (83%). ^{1}H-NMR ($CDCl_3$) δ: 7.2—7.55 (*ca.* 15H, m, $(C_6H_5)_3C$–), 4.95, 5.05 (each 1H, m, $=CH_2$), 4.47 (1H, quintet, $J=7.3$ Hz, H1), 3.56 (1H, m, one of $TrOCH_2$–), 3.15—3.3 (2H, m, one of $TrOCH_2$–, H2), 3.0—3.1 (2H, m, 1-OH, H4a), 2.88 (1H, m, H4b). MS *m/z*: 356 (M^+).

Mitsunobu Reaction of 8 with 6-Chloropurine Triphenylphosphine (1.28 g, 4.89 mmol) was added to a solution of **8** (580 mg, 1.63 mmol) and 6-chloropurine (378 mg, 2.45 mmol) in tetrahydrofuran (THF) (35 ml), and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (1 ml, 4.8 mmol) was added and the whole was stirred at room temperature overnight. After concentration to a small volume, the solution was chromatographed over a column of Silica gel G (2.6 × 30 cm) with 0—10% AcOEt in benzene (1 l). Evaporation of the first faction gave an unstable product as a caramel (306 mg, 56%). This product appeared to be a cyclobutenyl derivative from the mass spectrum (*m/z* = 338, molecular ion peak). Evaporation of the second fraction gave 6-chloro-9-(*trans*-2-trityloxymethyl-3-methylenecyclobutyl)purine (**9**) as a caramel (268 mg, 33.4%). UV λ_{max}^{MeOH} nm: 265.5; $\lambda_{max}^{0.05\,N\,HCl}$ nm: 265; $\lambda_{max}^{0.05\,N\,NaOH}$ nm: 263. ^{1}H-NMR ($CDCl_3$) δ: 8.70 (1H, s, H8), 8.24 (1H, s, H2), 7.2—7.35 (15H, m $(C_6H_5)_3C$–), 4.97, 5.04 (each 1H, $=CH_2$), 4.85 (1H, q, $J=8.0$ Hz, H1′), 3.80 (1H, m, H2′), 3.42 (1H, dd, $J=5.0$, 9.8 Hz, one of –CH_2OTr), 3.51 (1H, dd, $J=7.5$, 9.8 Hz, one of –CH_2OTr), 3.4 (1H, m, H4′a), 3.3 (1H, m, H4′b). MS *m/z*: 492, 494 (M^+), 415, 417 ($M^+ - C_6H_5$), 249, 251 ($M^+ - Tr$).

6-Chloro-9-[(1*R,2*S**,3*R**)-3-fluoro-3-iodomethyl-2-(trityloxymethyl)-cyclobutyl]purine (10)** Compound **9** (643 mg, 1.3 mmol) was dissolved in pyridine (0.5 ml) and CH_3CN (76 ml), then silver fluoride (1.3 g, 10.2 mmol) was suspended in the solution, and the mixture was cooled. A solution of iodine (1.3 g, 5.1 mmol) in CH_3CN (30 ml) was added dropwise (*ca.* 1 h), and the whole was stirred for 1 d at 45 °C. Insoluble material was removed by filtration and the solution was evaporated to give a residue, which was partitioned between $CHCl_3$ (200 ml) and water (150 ml). The organic layer was washed successively with 5% $NaHCO_3$ (150 ml), 5% NaCl (150 ml), 5% $Na_2S_2O_3$ (150 ml) and water (150 ml), dried over $MgSO_4$, and concentrated to a small volume. The solution was chromatographed over a column of Silica gel G (3.0 × 70 cm) with 0—17% AcOEt in benzene (4 l), and evaporation of the fraction gave a caramel (184.5 mg, 22.1%). UV λ_{max}^{MeOH} nm: 265; $\lambda_{max}^{0.05\,N\,HCl}$ nm: 265; $\lambda_{max}^{0.05\,N\,NaOH}$ nm: 264. ^{1}H-NMR (C_6D_6) δ: 8.4 (1H, s, H8), 6.95—7.32 (16H, m, H2, $(C_6H_5)_3C$–), 3.98 (1H, q, $J=8.6$ Hz, H1′), 3.64 (1H, dd, $J=7.4$, 9.7 Hz, one of –CH_2OTr), 3.52 (1H, ddd, $J=1.2$, 7.9, 9.7 Hz, one of –CH_2OTr), 3.31 (1H, dd, $J=11.6$, 13.9 Hz, one of 3′-CH_2I), 3.08 (1H, dd, $J=11.6$, 28.6 Hz, one of 3′-CH_2I), 2.84 (1H, dq, $J=8.1$, 18.5 Hz, H2′), 2.42 (1H, ddd, $J=8.8$, 12.9, 26.6 Hz, H4′a), 2.28 (1H, ddd, $J=8.8$, 12.9, 19.4 Hz, H4′b). MS *m/z*: 638, 640 (M^+), 561, 563 ($M^+ - C_6H_5$), 395, 397 ($M^+ - Tr$).

6-Chloro-9-[(1*R,2*S**,3*R**)-3-benzoyloxymethyl-3-fluoro-2-(trityloxymethyl)cyclobutyl]purine (11)** Sodium benzoate (210 mg, 1.46 mmol) was added to a solution of **10** (222 mg, 0.348 mmol) in DMF (15 ml) and the mixture was stirred at 55 °C for 12 h, then cooled. The solution was evaporated *in vacuo* to dryness and the residue was partitioned between benzene (100 ml) and water (50 ml). The organic layer was washed with water (50 ml) twice, dried over $MgSO_4$ and concentrated to a small volume. The solution was chromatographed over a column of Silica gel G (3.0 × 43 cm) with 0—20% AcOEt in benzene (2 l) to give a caramel, which was crystallized from ether to afford a white solid (153 mg, 69%), mp 194—196 °C. UV λ_{max}^{MeOH} nm: 265.5; $\lambda_{max}^{0.05\,N\,HCl}$ nm: 265; $\lambda_{max}^{0.05\,N\,NaOH}$ nm: 265. ^{1}H-NMR ($CDCl_3$) δ: 8.58 (1H, s, H8), 8.05 (1H, s, H2), 7.3—8.0 (5H, m, $C_6H_5CO_2$–), 7.1—7.3 (15H, m, $(C_6H_5)_3C$–), 4.92 (1H, q, $J=8.6$ Hz, H1′), 4.66 (2H, d, $J=9.0$ Hz, 3′-CH_2OBz), 3.15—3.7 (4H, m, H2′, H4′a, 2-CH_2OTr), 2.85 (1H, ddd, $J=8.6$, 13.8, 19.2 Hz, H4′b). MS *m/z*: 555, 557 ($M^+ - C_6H_5$), 389, 391 ($M^+ - Tr$).

9-[(1*R,2*S**,3*R**)-3-Fluoro-3-hydroxymethyl-2-(trityloxymethyl)cyclobutyl]adenine (12)** Compound **11** (103 mg, 0.16 mmol) was treated with liquid NH_3 (2 ml) in a sealed tube (steel, 20 ml) at 60 °C for 2 d, then cooled to −60 °C. Volatile material was removed carefully and the residue was dissolved in $CHCl_3$. The organic solution was washed with water (20 ml), dried over $MgSO_4$ and concentrated to a small volume. The solution was chromatographed over a column of Silica gel G (2.0 × 14 cm) with 0—10% EtOH in $CHCl_3$ (400 ml) to give a caramel, which was crystallized from ether to afford a white solid (75.5 mg, 91.4%), mp 192—194 °C. UV λ_{max}^{MeOH} nm: 260; $\lambda_{max}^{0.05\,N\,HCl}$ nm: 260; $\lambda_{max}^{0.05\,N\,HaOH}$ nm: 260. ^{1}H-NMR ($CDCl_3$) δ: 8.31 (1H, s, H8), 7.66 (1H, s, H2), 7.20—7.35 (15H, m, $(C_6H_5)_3C$–), 5.64 (2H, br s, NH_2), 4.73 (1H, q, $J=8.7$ Hz, H1′), 3.91 (2H, dd, $J=3.8$, 18.9 Hz, 3′-C<u>H</u>$_2$OH), 3.61 (1H, dd, $J=8.6$, 9.4 Hz, one of 2′-CH_2OTr), 3.47 (1H, dd, $J=6.5$, 9.4 Hz, one of 2′-CH_2OTr), 3.37 (1H, m, H2′), 3.21 (1H, m, 3′-CH_2O<u>H</u>), 3.09 (1H, ddd, $J=8.6$, 13.5, 27.5 Hz, H4′a), 2.74 (1H, ddd, $J=9.2$, 13.5, 20.5 Hz, H4′b). MS *m/z*: 509 (M^+), 266 ($M^+ - Tr$).

3′-Fluorocarbocyclic Oxetanocin A (F-C.OXT-A, 1b) A solution of **12** (71 mg, 0.14 mmol) in MeOH (10 ml) and 1 N HCl (0.6 ml) was stirred at 55 °C for 80 min and Amberlite IR 400 (AcO^- form, 7 ml) was added to the solution. The mixture was stirred for 10 min, then the resin was filtered off and the solution was evaporated. The residue was dissolved in water (20 ml) and the aqueous layer was washed with benzene (10 ml) twice. The solution was evaporated to dryness and the residue was crystallized from EtOH to give a white solid (31.3 mg, 84%), mp 184—186 °C. UV λ_{max}^{MeOH} nm: 261; $\lambda_{max}^{0.05\,N\,HCl}$ nm: 260; $\lambda_{max}^{0.05\,N\,NaOH}$ nm: 261. ^{1}H-NMR (DMSO-d_6) δ: 8.23 (1H, s, H8), 8.14 (1H, s, H2), 7.23 (2H, s, –NH_2), 5.15 (1H, t, $J=5.7$ Hz, 3′-CH_2O<u>H</u>), 4.88 (1H, q, $J=8.7$ Hz, H1′), 4.66 (1H, t, $J=5.3$ Hz, 2′-CH_2O<u>H</u>), 3.6—3.72 (4H, m, 2′-C<u>H</u>$_2$OH, 3′-C<u>H</u>$_2$OH), 3.26 (1H, dq, $J=7.6$, 19.6 Hz, H2′), 2.89 (1H, ddd, $J=8.8$, 14.2, 29.1 Hz, H4′a), 2.62 (1H, ddd, $J=8.1$, 14.2, 19.0 Hz, H4′b). MS *m/z*: 267 (M^+), 250 ($M^+ - OH$), 162 ($M^+ - C_4H_6FO_2$). *Anal.* Calcd for $C_{11}H_{14}FN_5O_2 \cdot 0.5H_2O$: C, 47.82; H, 5.47; N, 25.35. Found: C, 48.14; H, 5.26; N, 25.30.

***O*-Cyclohexylidene-(1*S**,2*S**,3*S**)-1,2-bis(hydroxymethyl)cyclobutane-1,3-diol (13)** A 0.7 N NaOH solution (14 ml) was dissolved in a solution

NII-Electronic Library Service

of **4** (850 mg, 4.38 mmol) in 1,4-dioxane (60 ml) and 0.3 M $KMnO_4$ was added. The mixture was stirred for 30 min at room temperature. After neutralization with AcOH, the insoluble material was filtered off and the filtrate was evaporated to dryness. The residue was partitioned between CH_2Cl_2 (30 ml) and water (30 ml) and the aqueous layer was extracted with CH_2Cl_2 (25 ml) ten times. The combined organic layer was dried over $MgSO_4$ and concentrated to a small volume. The solution was chromatographed over a column of Silica gel G (2.2 × 20 cm) with 0—10% EtOH in $CHCl_3$ (400 ml) to give a caramel. Concentration of the fraction afforded a white solid (567 mg, 57%), mp 117—118 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.41 (1H, t, J=6.1 Hz, H3), 4.25 (1H, dd, J=5.0, 11.1 Hz, one of 2-CH_2O–), 4.02 (3H, m, one of 2-CH_2O–, 1-C<u>H</u>$_2$OH), 3.06 (1H, s, 1-OH), 2.31 (2H, m, 1-CH_2O<u>H</u>, H2), 2.21 (1H, dd, J=5.86, 12.9, H4a), 2.12 (1H, d, J=12.9 Hz, H4b), 1.35—1.9 (10H, C_6H_{10}). MS m/z: 228 (M^+). *Anal.* Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.00; H, 8.96.

(1*S,2*S**,3*S**)-3-*O*-Trityl-1,2-bis(trityloxymethyl)cyclobutane-1,3-diol (14)** Amberlite IR 120B (H^+ form, 3 ml) was added to a solution of **13** (363 mg, 1.59 mmol) and the mixture was stirred for 1 h at room temperature. After removal of the resin, the solution was evaporated to dryness and the residue was dissolved in water (50 ml). This solution was washed with $CHCl_3$ (30 ml) five times. The syrup obtained by evaporation of the aqueous layer was distilled azeotropically with pyridine (30 ml) twice and dissolved in dry pyridine (15 ml). Trityl chloride (3.5 g, 12.6 mmol) was added to the solution and the mixture was stirred at 80 °C overnight. Usual work-up gave a caramel (945 mg, 85%). ^{1}H-NMR ($CDCl_3$) δ: 7.08—7.4 (*ca.* 45H, m, $(C_6H_5)_3C$–×3), 4.4 (1H, m, H3), 3.25—3.48 (3H, m, 1-CH_2OTr, one of 2-CH_2OTr), 2.83—2.98 (2H, m, H2, one of 2-CH_2OTr), 2.73 (1H, s, 1-OH), 1.5—1.63 (2H, m, H4a, H2a), 0.82 (1H, dd, J=3.9, 13.4 Hz, H4b). MS m/z: 631 ($M^+ - Tr$).

Reaction of 14 with DAST DAST (0.17 ml, 1.29 mmol) was added dropwise to a cooled solution (−60 °C) of **14** (130 mg, 0.15 mmol) in CH_2Cl_2 (5 ml) and pyridine (0.34 ml) and the mixture was stirred for 2 h at room temperature under an N_2 atmosphere. The solution was poured into a stirred solution of 10% $NaHCO_3$ (50 ml) and diluted with CH_2Cl_2 (25 ml). The organic layer was washed with water (50 ml × 3), dried over $MgSO_4$ and evaporated to a small volume. The solution was chromatographed over a column of Silica gel G (2.5 × 26 cm) with 0—20% AcOEt in hexane (2 l) to give 2,3-bis(trityloxymethyl)-3-buten-1-one as a caramel (**15**, 23.6 mg, 26%). ^{1}H-NMR ($CDCl_3$) δ: 9.53 (1H, d, –CHO), 7.2—7.4 (*ca.* 30H, m, $(C_6H_5)_3C$–×2), 5.44, 4.96 (each 1H, s, $=CH_2$), 3.53 (2H, s, 3-CH_2OTr), 3.55 (1H, m, one of 2-CH_2OTr), 3.30 (1H, dd, J=6.0, 9.1 Hz, one of 2-CH_2OTr), 3.15 (1H, m, –C<u>H</u>(CH_2OTr)CHO). MS m/z: 371 ($M^+ - Tr$).

Acknowledgments We thank Drs. T. Nagahata, J. Seki and R. Ikeda (Nippon Kayaku Co., Ltd.) for the antiviral data. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas, No. 05210211, from the Ministry of Education, Science and Culture, Japan.

References and Notes

1) *a*) N. Shimada, S. Hasegawa, T. Harada, T. Tomisawa, A. Fujii, T. Takita, *J. Antibiot.*, **39**, 1623 (1986); *b*) H. Hoshino, N. Shimada, T. Takita, T. Takeuchi, *ibid.*, **40**, 1077 (1987).
2) M. Honjo, T. Maruyama, Y. Sato, T. Horii, *Chem. Pharm. Bull.*, **37**, 1413 (1989); *b*) T. Maruyama, Y. Sato, T. Horii, H. Shiota, K. Nitta, T. Sirasaka, H. Mitsuya, M. Honjo, *ibid.*, **38**, 2719 (1990); *c*) T. Maruyama, Y. Hanai, Y. Sato, R. Snoeck, G. Andrei, M. Hosoya, J. Balzarini, E. De Clercq, *ibid.*, **41**, 516 (1993).
3) W. A. Slusarchyk, G. S. Bisacchi, A. K. Field, D. R. Hockstein, G. A. Jacobs, B. McGeever-Rubin, F. A. Tino, A. V. Tuomari, G. A. Yamanaka, M. G. Young, R. Zahler, *J. Med. Chem.*, **35**, 1799 (1992) and the references cited therein.
4) *a*) J. P. H. Verheyden, I. D. Jenkins, G. R. Owen, S. D. Dimitrijevich, C. M. Richards, P. C. Srivastava, N. Le-Hong, J. G. Moffatt, *Ann. N.Y. Acad. Sci.*, **255**, 151 (1975); *b*) I. D. Jenkins, J. P. H. Verheyden, J. G. Moffatt, *J. Am. Chem. Soc.*, **98**, 3346 (1976); *c*) G. R. Owen, J. P. H. Verheyden, J. G. Moffatt, *J. Org. Chem.*, **41**, 3010 (1976); *d*) S. Ajmera, A. R. Bapat, E. Stephanian, P. Danenberg, *J. Med. Chem.*, **31**, 1094 (1988).
5) Part of this work was presented at the 114th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, Mar. 1994, Abstract of Papers, p. 102, 9-5; *b*) Recently, independent work was described by a group of E. R. Squibb and Sons. They reported the synthesis of (1α,2β,3β)-2-amino-9-[3-fluoro-2,3-bis(hydroxymethyl)cyclobutyl]-1,9-dihydro-6*H*-purine-2-one in a different manner, Jpn. Kokai Tokkyo Koho Japan. Patent 5-306243 (Cl. C07C 35/04), Nov. 1993/826,585, 26 Jan., 27/Jan. 1992; p. 32.
6) *a*) H. Maag, R. M. Rydzewski, M. J. McRoberts, D. Crawford-Ruth, J. P. H. Verheyden, E. J. Prisbe, *J. Med. Chem.*, **35**, 1440 (1992); *b*) J. P. H. Verheyden, J. G. Moffatt, *J. Am. Chem. Soc.*, **97**, 4386 (1975).
(1975).
7) T. Maruyama, Y. Hanai, Y. Sato, *Nucleosides & Nucleotides*, **11**, 855 (1992).
8) *a*) O. Mitsunobu, *Synthesis*, **1981**, 1; *b*) A. Toyota (née Mizutani), N. Katagiri, C. Kaneko, *Chem. Pharm. Bull.*, **40**, 1039 (1992).
9) L. L. Bennett, Jr., H. P. Schnebli, M. H. Vail, P. W. Alla, J. A. Montgomery, *Molecular Pharmacol.*, **2**, 432 (1966).
10) *a*) A. C. Richardson, *Carbohydr. Res.*, **10**, 395 (1969); *b*) D. H. Ball, F. W. Parrish, *Adv. Carbohydr. Res.*, **24**, 139 (1969), and references cited therein.
11) K. B. Wiberg, K. A. Saegebarth, *J. Am. Chem. Soc.*, **79**, 2822 (1957).
12) M. J. Middleton, *J. Org. Chem.*, **40**, 574 (1975).
13) Y. Nishiyama, N. Yamamoto, Y. Yamada, T. Daikoku, Y. Ichikawa, K. Takahashi, *J. Antibiot.*, **42**, 1854 (1989).
14) J. Seki, N. Shimada, K. Takahashi, T. Takita, T. Takeuchi, H. Hoshino, *J. Antibiot.*, **33**, 773 (1989).
15) T. Nagahata, K. Ueda, T. Tsurimoto, O. Chisaka, K. Matsubara, *J. Antibiot.*, **42**, 644 (1989).
16) *a*) W. H. Prusoff, T.-S. Lin, "Antiviral Drug Development," ed. by E. De Clercq, R. T. Walker, Plenum Press, New York, 1988; *b*) R. K. Robins, *Chemistry and Engineering News*, January 27, p. 28 (1986).
17) G. S. Bisacchi, A. Braitman, C. W. Cianci, J. M. Clark, A. K. Field, M. E. Hagen, D. R. Hockstein, M. F. Malley, T. Mitt, W. A. Slusarchyk, J. E. Sundeen, B. J. Terry, A. V. Tuomari, E. R. Weaver, M. G. Young, R. Zahler, *J. Med. Chem.*, **34**, 1415 (1991).
18) J. M. Cameron, P. Collis, M. Daniel, R. Storer, P. Wilcox, *Drugs of the Future*, **18**, 319 (1993).

NII-Electronic Library Service