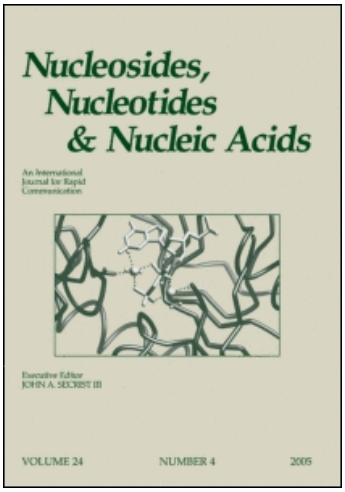

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Sato, Yoshiko , Ueyama, Kenji , Maruyama, Tokumi and Richman, Douglas D.(1996) 'Synthesis of the Fluoromethyl Derivatives of Carbocyclic Oxetanocin A', Nucleosides, Nucleotides and Nucleic Acids, 15: 1, 109 — 119
To link to this Article: DOI: 10.1080/07328319608002374
URL: http://dx.doi.org/10.1080/07328319608002374

NUCLEOSIDES & NUCLEOTIDES, 15(1-3), 109-119 (1996)

SYNTHESIS OF THE FLUOROMETHYL DERIVATIVES OF CARBOCYCLIC OXETANOCIN A

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ABSTRACT: Treatment of the 2,3-di-*O*-benzoate **1** with sodium boronhydride mainly afforded the 3-*O*-benzoate **2** accompanied with isomers **3a,b** and fully deprotected product **4**. Compound **2** was converted to **5**, from which **8** was obtained. The 1-cyclobutanols **8** and **5** were successfully condensed with 6-chloropurine by Mitsunobu reaction to give **9** and **11**, respectively. After partial deprotection, the cyclobutyl nucleosides **10** and **15** were subjected to fluorination using DAST to afford the fluoromethyl analogs **12** and **16** from which target compounds **14** and **17** were obtained in good yields, respectively.

INTRODUCTION

3'-Azido-3'-deoxythymidine (zidovudine) and 2',3'-dideoxyionosine (ddI) have been used in the treatment of the acquired immunodeficiency syndrome (AIDS). Recently, a number of the fluoro derivatives have demonstrated antiviral activity against human immunodeficiency virus (HIV). For example, 3'-deoxy-3'-fluorothymidine (FLT) is a candidate anti-AIDS compound in clinical trial.[1] 9-[(2*RS*)-3-Fluoro-2-phosphonylmethoxypropyl]adenine [(*RS*)-FPMP] is also a interesting anti-HIV agent,[2] because the parent compound 9-[(2*S*)-3-hydroxyl-2-phosphonylmethoxypropyl]adenine [(*S*)-HPMPA] exhibited strong antiviral activity against DNA viruses but little anti-HIV activity *in vitro*.[3] The difference of antiviral spectrum between [(*RS*)-FPMP] and [(*S*)-HPMPA] could be explainable from their structure that (*RS*)-FPMP is a complete chain terminator but (*S*)-HPMPA is a non-obligated chain terminator. Synthesis of carbocyclic analogs of oxetanocins (C.OXTs) and evaluation of their antiviral activity has been reported from

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This paper is dedicated to Dr. Yoshihisa Mizuno, Emeritus Professor of Hokkaido University, in celebration of his 75th birthday.

several groups, including ours.[4] The C.OXTs have shown the strong antiviral activity against several DNA viruses, but activity against HIV were not satisfactory.[4c] By analogy with (*RS*)-FPMP,[3] therefore, we planned to change the 2'-CH_2OH group of C.OXT-A to CH_2F. In this paper, a new synthetic route to prepare fluorine derivatives of C.OXT-A is described and their anti-HIV activity is also presented.

SYNTHESIS

Katagiri *et al.* reported the synthesis of 2'-protected oxetanocin A, in which selective deprotection by enzymatic and photo-chemical methods have been described.[5] We also have prepared the 3-*O*-benzoate **2** from the dibenzoate **1**[6] via *O*-cyclohexylidine derivative in 4 steps.[4c] But a new method to shorten the pathway should be developed for a large scale preparation of the C.OXT derivatives. Thus the dibenzoate **1** was treated with $NaBH_4$ in MeOH-*i*-PrOH at 40° for 5 h. After separation by the column chromatography, the 3-*O*-benzoate **2** was obtained in 57% yield and recovered the starting material in 12% yield. A minor product was isolated as a third fraction, which was proved as a non-separable mixture of the 2-*O*-benzoate **3a** and its migration product **3b** (4.0%). Also fully deprotected triol **4** was also observed on thin-layer chromatography (TLC). Formation of methyl benzoate was confirmed by the characteristic odor and spot on TLC of the reaction mixture. No reduction product (benzyl alcohol) was detected. This result suggests that the reagent act as a base. The 3-preference are explainable by the neighboring group participation of 1-OH group as follows: At first 1-alcoholic anion was formed by deprotonation of **1** with $NaBH_4$. The counter cation (Na^+) of 1-alcoholic anion would cause the electrostatic interaction with C=O of 2-$CH_2OCOC_6H_5$ group. This electrostatic effect facilitate the nucleophilic attack with methoxide ion to form the 3-*O*-benzoate **2**. A similar alcoholysis of **1** in the presence of a catalytic amount of NaOH (0.06 eq.) also afforded the 3-*O*-benzoate **2** as a main product but the yield was not satisfactory because of the formation of the triol **4**.[7] The primary alcohol moiety of **2** was protected with trityl group by conventional way to give **5**. Introduction of the purine base was attempted via the tosylate **6**.[6] Thus, compound **5** was reacted with tosyl chloride to afford **6**, which was subjected to a nucleophilic displacement with adenylate ion in DMF. But the spot of the desired product was not observed on TLC. The Mitsunobu reaction was chosen as a next trial.[4d] To exclude the possibility that the 6-chloro function undergoes nucleophilic substitution under deprotection condition, the 3-*O*-benzoyl group of **5** was altered to *tert*-butyldimethylsilyl (TBDMS) group prior to condensation with 6-chloropurine. Thus, the 3-*O*-benzoyl group of **5** was selectively hydrolyzed with NaOH and TBDMS group was introduced again to afford **8**. Then, compound **8** was condensed with 6-chloropurine in the presence of triphenylphosphine and diisopropyl azodicarboxylate in tetrahydrofuran (THF)

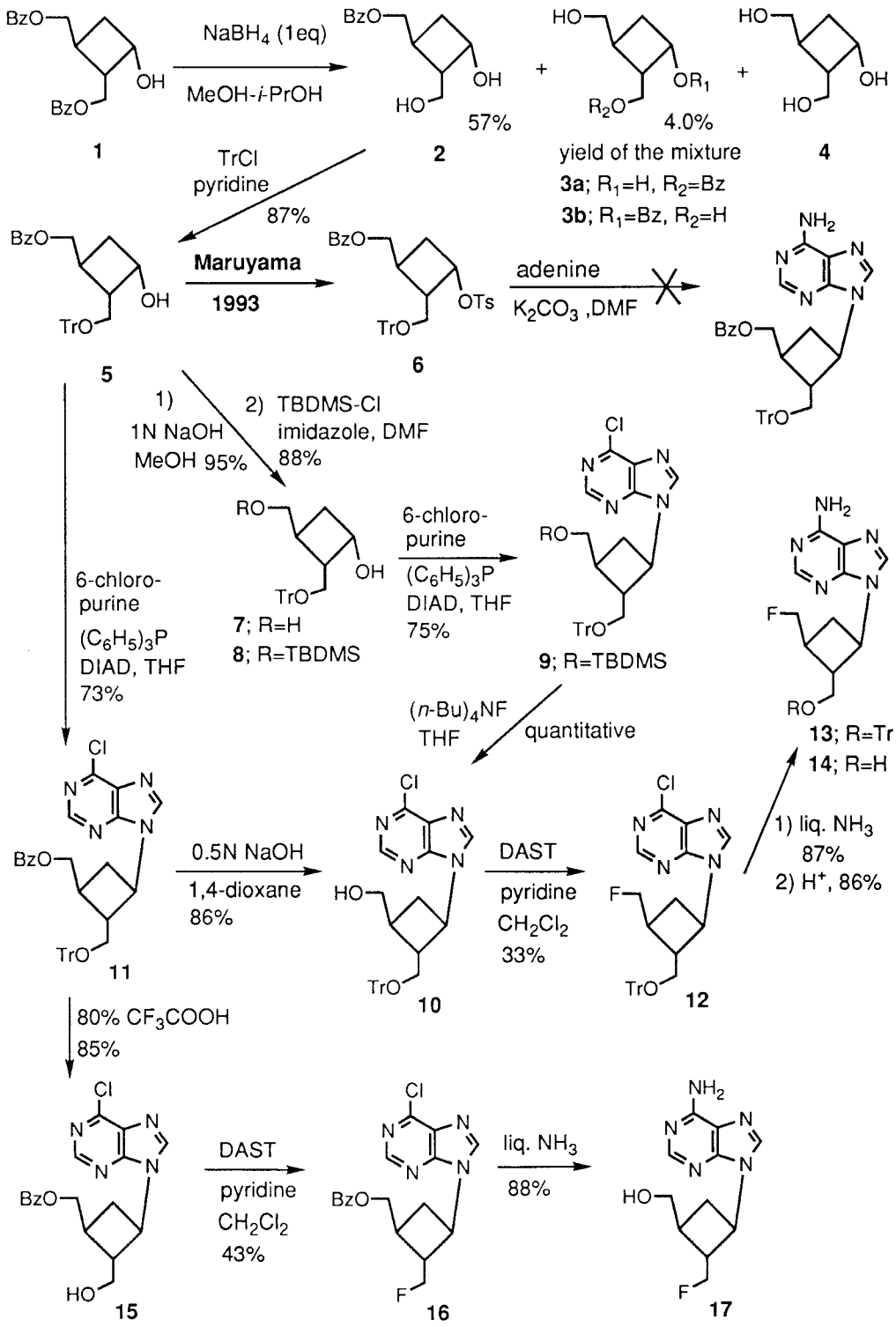
to give **9** in 75% which was superior to the tosylate method in the preparation of C.OXTs.[6] The nuclear Overhauser effect (NOE) was observed between down-site H4'a and H1' as well as H4'a and H3' on the two-dimensional NOE (NOESY) spectrum of **9** and its configuration was identified as the *trans-trans* structure (FIG.). The TBDMS group of **9** was removed to give **10** in quantitative yield. An alternative way to prepare **10** was also examined. Compound **5** was condensed with 6-chloropurine by the Mitsunobu reaction to give **11**. Hydrolysis of the 3'-*O*-benzoyl group of **11** with 0.5N NaOH was carried out without nucleophilic substitution of 6-chloro group to give **10**. The spectroscopic data of the product was identical with the former sample in any respect. The trityl group of **11** was removed by treatment with acid to give the 3'-*O*-benzoate **15**. Reactions using DAST (diethylaminosulfur trifluoride) were performed to both protected C.OXT analogs **10** and **15**. Fluorination of the 3'-*O*-benzoate **15** gave **16** in 53% yield. A similar reaction of **10** gave **12** in 33% yield. Deprotection of **13** and **16** gave the target compounds **14** and **17**, respectively (CHART). The ^{1}H-NMR spectrum of **17** indicated that the fluorine of the 2'-CH_2F caused a severe down field shift and large geminal coupling constant of 2'-methylene protons (FIG.). Also **14** was determined as 3'-CH_2F structure by the spectroscopic methods.

BIOLOGICAL RESULTS

The antiviral activities of **14** and **17** were assayed by HIV plaque reduction in CD4-expressing HeLa cell monolayers as previously described.[8] Compound **17** showed no activity against HIV-1. This result indicates that the displacement of a hydroxyl group at the 2'-position to fluorine diminishes the moderate anti-HIV-1 activity of C.OXT-A (EC_{50} = 1.8 μM[4c]). Reduced affinity to cellular nucleoside kinase or weak activity against HIV reverse transcriptase of the test compounds would explain these results. Compound **14** was also proved to be inactive against HIV-1.

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.



CHART

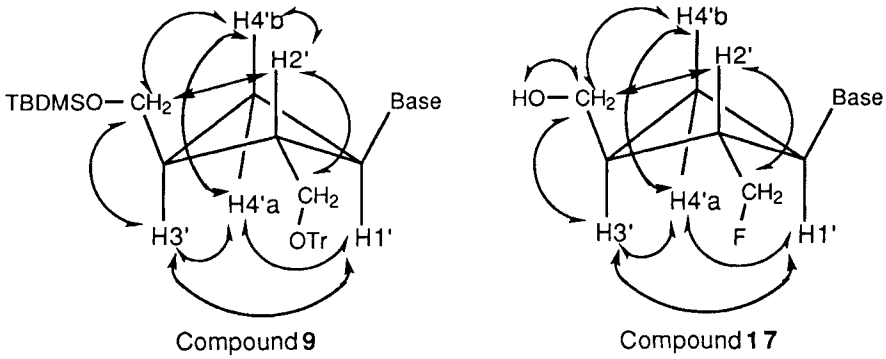


FIG. NOESY Results of compounds **9** and **17**

Selective debenzoylation of the di-*O*-benzoate 1. To a ice-cooled solution of **1** (4.08 g,12 mmol) in a mixture solution of MeOH (30 ml) and *i*-PrOH (30 ml) was added $NaBH_4$ (454 mg, 12 mmol). The solution was stirred at 40° for 5 h, then acetic acid was added. At that time emergence of methyl benzoate was detected by TLC (C_6H_6-AcOEt = 10 : 1, *Rf* 0.79) or its characteristic odor. The solution was evaporated and the residue was dissolved in $CHCl_3$ (300 ml) and the organic layer was washed with water twice (240 ml), dried over $MgSO_4$ and concentrated to a small volume. The solution was chromatographed over a column of silica gel G (4.2 × 38 cm) with 0 - 6.3% EtOH in $CHCl_3$ (4.0 l). The first fraction was evaporated to give the starting material (0.50 g, 12%). Evaporation of the second fraction gave *trans-cis*-3-benzoyloxymethyl-2-hydroxymethyl-1-cyclobutanol (**2**, 1.61 g, 57%) as a caramel. MS *m/z*: 237 (M^+ + 1). ^{1}H-NMR ($CDCl_3$) δ: 7.38-7.6, 8.0-8.08 (5H, m, benzoyl), 4.61 (1H, quintet, *J* = 5.1 Hz, H1), 4.34 (1H, dd, *J* = 6.3, *J* = 11.0 Hz, one of 3-CH_2OBz), 4.31 (1H, dd, *J* = 6.6, *J* = 11.0 Hz, one of 3-CH_2OBz), 3.96 (1H, m, one of 2-C*H*$_2$OH), 3.89 (1H, m, one of 2-C*H*$_2$OH), 3.19 (1H, d, *J* = 5.1 Hz, 1-OH), 2.87 (1H, br s, 2-CH_2O*H*), 2.61 (1H, m, H3), 2.54 (1H, m, H2), 2.25 (1H, dddd, *J* = 12.7, *J* = 7.5, *J* = 5.4, *J* = 2.0 Hz, H4a), 2.18 (1H, dddd, *J* = 12.7, *J* = 10.0, *J* = 5.4, *J* = 1.0 Hz, H4b).

The third fraction was evaporated to give a mixture of *trans-cis*-3-hydroxymethyl-2-benzoyloxymethyl-1-cyclobutanol (**3a**) and its migration product *trans-cis*-2,3-bis(hydroxymethyl)-1-benzoyloxycyclobutane (**3b**) as a syrup (114 mg, 4.0%). ^{1}H-NMR ($CDCl_3$) δ: 5.38 (q, *J* = 5.6 Hz, H1 of **3b**), 4.78 (dd, *J* = 11.3, *J* = 8.9 Hz, one of 2-CH_2OBz of **3a**), 4.29 (dd, *J* = 11.3, *J* = 4.0 Hz, one of 2-CH_2OBz of **3a**), 4.43 (m, H1 of **3a**). Ratio of **3a** and **3b** was approximately 3 : 1 on the basis of the ^{1}H-NMR spectrum.

***trans-cis*-3-Benzoyloxymethyl-2-trityloxymethyl-1-cyclobutanol (5).** A solution of **2** (1.57 g, 6.67 mmol) and trityl chloride (2.8 g, 10 mmol) in pyridine (20 ml) was kept at 4° overnight, and the reaction was continued at room temperature for 6 h. The solution was subjected to a usual work-up and silica gel column chromatography to give a caramel (2.78 g, 87%). MS *m/z*: 401 (M^+-C_6H_5). ^{1}H-NMR ($CDCl_3$) δ: 8.0 - 8.05 (2H, m, two of C_6H_5CO-), 7.2 - 7.6 (ca 18H, complex, three of C_6H_5CO-, trityl), 4.55 (1H, quintet, J = 6.3 Hz, H1'), 4.36 (2H, dd, J = 2.8, J = 6.1 Hz, 3-CH_2OBz), 3.56 (2H, m, 2-CH_2OTr), 2.6 - 2.8 (3H, m, H2, H3, H4a), 2.25 (1H, m, H4b).

***trans-cis*-3-Hydroxymethyl-2-trityloxymethyl-1-cyclobutanol (7).** To a solution of **5** (700 mg, 1.46 mmol) in MeOH (14 ml) was added 1N NaOH (7 ml) and the solution was stirred at 50° for 1 h. After neutralization with acetic acid, the solution was evaporated and the residual solid was partitioned between $CHCl_3$ (50 ml) and water (20 ml). The organic layer was washed with water twice (40 ml), dried over $MgSO_4$ and concentrated to a small volume. The solution was chromatographed over a column of silica gel G (2.5 × 25 cm) with 0 - 6.6% AcOEt in benzene (800 ml) to give a caramel (518 mg, 95%). ^{1}H-NMR ($CDCl_3$) δ: 7.2-7.5 (ca 15H, complex, trityl), 4.40 (1 H, quintet, J = 5.9 Hz, H1), 3.6 (2H, m, 3-CH_2OH and 1-OH), 3.44 (1H, dd, J = 10.7, J = 6.1 Hz, one of 3-CH_2OH), 3.35 (1H, dd, J = 10.7, J = 5.2 Hz, one of 3-CH_2OH), 2.35-2.55 (3H, complex, 2-CH_2OTr, H2), 2.06 (2H, m, H4), 1.69 (1H, m, H3). MS *m/z*: 297 (M^+ - C_6H_5).

***trans-cis*-3-*tert*-Butyldimethylsilyloxymethyl-2-trityloxymethyl-1-cyclobutanol (8).** *tert*-Butyldimethylsilyl chloride (416 mg, 2.76 mmol) was added to a solution of **7** (840 mg, 2.25 mmol) and imidazole (280 mg, 4.12 mmol) in DMF (20 ml) and the solution was stirred for 1 h at room temperature. The mixture solution was diluted with benzene (60 ml) and the solution was washed with water, dried over $MgSO_4$ and concentrated to a small volume. The solution was chromatographed over a column of silica gel G (3.0 × 30 cm) with 0 - 20% AcOEt in benzene (1.8 l) to give a caramel (968 mg, 88%). MS *m/z* : 245 (M^+ -Tr) . ^{1}H-NMR ($CDCl_3$) δ: 7.1 - 7.5 (15H, m, trityl), 4.42 (1H, q, J = 6.5 Hz, H1), 3.58 (2H, m, 3-CH_2O-), 3.35 (2H, m, 2-CH_2OTr), 2.68 (1H, d, J = 7.5 Hz, 1-OH), 2.54 (1H, m, H2), 2.34 (1H, m, H3), 2.08 (2H, m, H4), 0.90 (9H, s, $(CH_3)_3CSi(CH_3)_2$-), 0.08 (6H, s, $(CH_3)_3CSi(CH_3)_2$-).

9-[*trans-trans*-3-(*tert*-Butyldimethylsilyloxymethyl)-2-(trityloxymethyl)-cyclobutyl]-6-chloropurine (9). A mixture of compound **8** (330 mg, 0.68 mmol), 6-chloropurine (157 mg, 1.02 mmol) and triphenylphosphine (535 mg, 2.04 mmol) were dissolved in dry THF (20 ml), then cooled to 0° under argon atmosphere. After addition of diisopropyl azodicarboxylate (0.4 ml, 2.04 mmol), the solution was stirred for at 0° for 15 min and the stirring was continued at 45° overnight. The solution was concentrated to a

small volume and chromatographed over a column of silica gel G (3.0 × 32 cm) with 0 - 20% AcOEt in benzene (1.8 l) to give a caramel (315 mg, 75%). MS *m/z*: 609, 611 (M^+ - CH_3), 567, 569 (M^+ - $C(CH_3)_3$), 381, 383 (M^+ -Tr). ^{1}H-NMR ($CDCl_3$) δ: 8.68, 8.28 (each 1H, s, H2 and H8), 7.19-7.30 (15H, m, trityl), 4.85 (1H, q, *J* = 8.8 Hz, H-1'), 3.69 (1H, dd, *J* = 10.3, *J* = 3.9 Hz, one of 3'-CH_2O-), 3.66 (1H, dd, *J* = 10.3, *J* = 4.4 Hz, one of 3'-CH_2O-), 3.33 (1H, dd, *J* = 9.8, *J* = 4.9 Hz, one of 2'-CH_2OTr), 3.22 (1H, dd, *J* = 9.8, *J* = 6.6 Hz, one of 2'-CH_2OTr), 3.06 (1H, m, H2'), 2.58 (1H, dt, *J* = 11.0, *J* = 8.1 Hz, H4'a), 2.46 (1H, q, *J* = 9.7 Hz, H4'b), 2.27 (1H, m, H3'), 0.90 (9H, s, $(CH_3)_3CSi(CH_3)_2$-), 0.08 (6H, s, $(CH_3)_3CSi(CH_3)_2$-), UV: λmax (MeOH) 265 nm.

9-[*trans-trans*-3-Hydroxymethyl-2-(trityloxymethyl)cyclobutyl]-6-chloropurine (10). Method A. Tetrabutylammonium fluoride (1M solution, 3.0 ml) was added to a solution of **9** (750 mg, 1.2 mmol) in the mixture of acetic acid (0.2 ml) and THF (15 ml) and the solution was stirred for 1 h at room temperature, then concentrated to a small volume. The solution was chromatographed over a column of silica gel G (2.8 × 30 cm) with 0 - 6.3% EtOH in $CHCl_3$ (1.5 l) to give a caramel (711 mg, quantitative). MS *m/z*: 511, 513 (M^++1), 433, 435 (M^+- C_6H_5), 267, 269 (M^+ - Tr), 243 (Tr^+). ^{1}H-NMR ($CDCl_3$) δ: 8.13, 8.71 (each 1H, s, H2, H8), 7.19-7.47(15H, m, trityl), 4.71 (1H, q, *J* = 8.7 Hz, H1'), 3.72 (2H, m, 3'-CH_2OH), 3.40 (2H, m, 2'-CH_2OTr), 2.92 (1H, quintet, *J* = 7.4 Hz, H3'), 2.2-2.7 (4H, m, H4', H2', 3'-CH_2OH), UV: λmax (MeOH) 265 nm.

Method B. A solution of **11** (614 mg, 1 mmol) in 1,4-dioxane (30 ml) and 0.5 N NaOH (8 ml) was kept at 4° for 2 days, then neutralized with 0.5 N HCl. The solution was subjected to a usual work-up to give a caramel (438 mg, 86%), which was identical in any respect with that obtained by method A.

9-[*trans-trans*-3-Benzoyloxymethyl-2-(trityloxymethyl)cyclobutyl]-6-chloropurine (11). A mixture of compound **5** (1.08g, 2.26 mmol), 6-chloropurine (524 mg, 1.5 eq.) and triphenylphosphine (888 mg, 1.5 eq.) were dissolved in dry THF (80 ml), then cooled to 0° under argon atmosphere. After addition of diisopropyl azodicarboxylate (0.7 ml, 1.5 eq.), the solution was stirred for 15 min and the reaction was continued at 45° overnight. The mixture solution was subjected to a similar treatment and silica gel column chromatography as described in the section of **9** to give a caramel. Crystallization of the product form ether gave a white solid (1.01 g, 73%). MS *m/z*: 615, 617 (M^+ + 1) UV: λmax (MeOH) 266 nm. ^{1}H-NMR ($CDCl_3$) δ: 8.60 (1H, s, H8), 8.09 (1H, s, H2), 7.2-7.64, 8.0-8.1 (ca 20 H, m, benzoyl, trityl), 4.87 (1H, q, *J* = 5.9 Hz, H1'), 4.48 (2H, m, 3'-CH_2OBz), 3.39 (2H, m, 2'-CH_2OTr), 3.21 (1H, m, H2'), 2.6-2.8 (3H, m, H3', H4').

9-[*trans-trans*-3-Fluoromethyl-2-(trityloxymethyl)cyclobutyl]-6-chloropurine (12). To a ice-cooled solution of **10** (420 mg, 0.82 mmol) in a mixture solution

of CH_2Cl_2 (25 ml) and pyridine (1.5 ml) was added DAST (0.7 ml, 5.3 mmol). The mixture solution was gradually warmed to room temperature and refluxed for 10 h. The whole was added dropwise to saturated $NaHCO_3$ (30 ml) and the organic layer was diluted with additional CH_2Cl_2 (50 ml). The aqueous layer was washed with CH_2Cl_2 (30 ml) and the combined organic layer was washed with water twice (60 ml), dried over $MgSO_4$. The solution was evaporated and pyridine was removed by azeotropical evaporation with toluene three times (30 ml). The residue was dissolved in a small amount of $CHCl_3$ and the solution was chromatographed over a column of silica gel G (2.8 × 42 cm) with 0 - 25% AcOEt in C_6H_6 (2.4 l) to give a caramel, which was crystallized from ether (2 ml) to afford a solid (138 mg, 33%). MS *m/z*: 513, 515 (M^+), 435, 437 (M^+ - C_6H_5), 269, 271 (M^+ - Tr). ^{1}H-NMR ($CDCl_3$) δ: 8.69, 8.18 (each 1H, s, H2, H8), 7.15-7.5 (ca 15H, trityl), 4.88 (1H, q, J = 8.4 Hz, H1'), 4.50 (2H, dd, J_{HF} = 47.3, J = 3.2 Hz, 3'-CH_2F), 3.35 (2H, m, 2'-CH_2OTr), 3.05 (1H, m, H2'), 2.35-2.8 (3H, m, H3', H4'). UV: λmax (MeOH) 265 nm.

9-[*trans-trans*-3-Fluoromethyl-2-(trityloxymethyl)cyclobutyl]adenine (13). Compound **12** (105 mg, 0.21 mmol) was treated with liquid NH_3 (2 ml) in a sealed tube (steel, 20 ml) at 60° for 2 days, then cooled to - 78°. Volatile material was removed carefully and the residue was dissolved in $CHCl_3$ (50 ml). 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 (2.2 × 30 cm) with 0 - 6.3% EtOH in $CHCl_3$ (400 ml) to give a caramel, which was crystallized from ether to afford a white solid (88 mg, 87%). mp 95-97°. *Anal.* Calcd. for $C_{30}H_{28}FN_5O$: C, 73.00; H, 5.72; N, 14.19. Found: C, 72.87; H, 5.83; N, 14.25. MS *m/z*: 494 (M^+ + 1), 250 (M^+ - Tr). ^{1}H-NMR ($CDCl_3$) δ: 8.31, 7.86 (each 1H, s, H2, H8), 7.15-7.4 (ca 15H, trityl), 5.60 (2H, br s, 6-NH_2), 4.81, (1H, q, J = 8.9 Hz, H1'), 4.50 (2H, dd, J_{HF} = 46.5, J = 3.4 Hz, 3'-CH_2F), 3.33 (2H, m, 2'-CH_2OTr), 3.04 (1H, m, H2'), 2.25 - 2.75 (3H, m, H3', H4'). UV: λmax (MeOH) 260 nm, λmax (0.05N HCl) 259 nm, λmax (0.05N NaOH) 260 nm.

9-[*trans-trans*-3-Fluoromethyl-2-(hydroxymethyl)cyclobutyl]adenine (14). A solution of **13** (75 mg, 0.15 mmol) in MeOH (10 ml) and 1N HCl (0.7 ml) was stirred at 55° for 1.5 h, then Amberlite IR400 (OAc^- form, 7 ml) was added. After removal of the resin, the solution was evaporated to dryness and the residue was dissolved in water (30 ml). The aqueous layer was washed with ether twice (20 ml) and evaporated to give a caramel, which was crystallized from EtOH to afford white crystallines (32.7 mg, 86%). mp 160-162°. *Anal.* Calcd. for $C_{11}H_{14}FN_5O$: C, 52.58; H, 5.62; N, 27.87. Found: C, 52.28; H, 5.68; N, 27.95. MS *m/z*: 251 (M^+), 234 (M^+ - OH), 135 (adenine). ^{1}H NMR (DMSO-d_6) δ: 8.30 (1H, s, H8), 8.27 (1H, s, H2), 7.21 (2H, br s, 6-NH_2), 4.81 (1H, t,

J = 5.2 Hz, 2'-CH_2OH), 4.71 (1H, q, J = 8.5 Hz, H1'), 4.56 (2H, dd, J_{HF} = 47.9, J = 5.4 Hz, 3'-CH_2F), 3.52 (2H, t, J = 5.1 Hz, 2'-CH_2OH), 2.89 (1H, m, H2'), 2.47-2.54 (1H, m, H4'a), 2.36 (1H, m, H3'), 2.33 (1H, m, H4'b). UV: λmax (MeOH) 260 nm, λmax (1N HCl) 258 nm, λmax (1N NaOH) 260 nm.

9-[*trans-trans*-3-Benzoyloxymethyl-2-(hydroxymethyl)cyclobutyl]-6-chloropurine (15). Compound **11** (448 mg, 0.73 mmol) was dissolved in 80% CF_3COOH (6 ml) and the solution was kept at room temperature for 10 min, then the mixture solution was added dropwise to 5% $NaHCO_3$ (240 ml). The solution was extracted from CH_2Cl_2 twice (320 ml) and the organic layer was washed with water (400 ml), dried over $MgSO_4$ and concentrated to a small volume. The solution was chromatographed over a column of silica gel G (3.0 × 25 cm) with 0 - 9.1% EtOH in $CHCl_3$ (1.5 l) to give a caramel, which was crystallized from ether to afford white crystallines (230 mg, 85%). mp 127-128°. *Anal.* Calcd. for $C_{18}H_{17}ClN_4O_3$: C, 57.99; H, 4.60; N, 15.03. Found: C, 57.74; H, 4.71; N, 15.03. MS *m/z*: 372, 374 (M^+), 251, 253 (M^+ - $C_6H_5CO_2$). ^{1}H-NMR($CDCl_3$) δ: 8.66, 8.20 (each 1H, s, H2, H8), 7.40-7.63, 8.03-8.07 (5H, m, benzoyl), 4.71-4.85 (1H, q, J = 8.6 Hz, H1'), 4.55 (1H, dd, J = 11.2, J = 4.6 Hz, one of 3'-CH_2O-), 4.44 (1H, dd, J = 11.2, J = 5.3 Hz, one of 3'-CH_2O-), 3.85 (2H, t, J = 5.3 Hz, 2'-CH_2OH), 3.39 (1H, t, J = 5.0 Hz, 2'-CH_2OH), 3.05 (1H, m, H2'), 2.45-2.85 (3H, m, H4', H3'). UV: λmax (MeOH) 265 nm.

9-[*trans-trans*-3-Benzoyloxymethyl-2-(fluoromethyl)cyclobutyl]-6-chloropurine (16). To a ice-cooled solution of **15** (410 mg, 1.10 mmol) in a mixture solution of CH_2Cl_2 (40 ml) and pyridine (1.7 ml) was added DAST (1.2 ml, 9.09 mmol). The mixture solution was gradually warmed to room temperature and refluxed for 10 h. The whole was added dropwise to saturated $NaHCO_3$ (50 ml) and the organic layer was diluted with additional CH_2Cl_2 (70 ml). The aqueous layer was washed with CH_2Cl_2 (30 ml) and the combined organic layer was washed with water twice (50 ml), dried over $MgSO_4$. The solution was evaporated and pyridine was removed by azeotropical evaporation with toluene three times (30 ml). The residue was dissolved in a small amount of $CHCl_3$ and the solution was chromatographed over a column of silica gel G (2.0 × 25 cm) with 0 - 50% AcOEt in benzene (1.0 l) to give a caramel, which was crystallized from ether (10 ml) to afford white crystallines (217 mg, 53%). mp 129-131°. *Anal.* Calcd. for $C_{18}H_{16}ClFN_4O_2 \cdot 1/2H_2O$: C, 56.33; H, 4.46; N, 14.60. Found: C, 56.55; H, 4.35; N, 14.74. MS *m/z*: 374, 376 (M^+), 355, 357 (M^+ - F), 253, 255 (M^+ - $C_6H_5CO_2$). ^{1}H-NMR ($CDCl_3$) δ: 8.52, 8.13 (each 1H, s, H2, H8), 8.05-8.2, 7.4-7.4 (5H, m, benzoyl), 4.90 (1H, q, J = 9.2 Hz, H1'), 4.59 (2H, d, J = 48.1 Hz, 2'-CH_2F), 4.56 (2H, m, 3'-CH_2OBz), 3.48 (1H, m, J_{HF} = 29.0 Hz, H2'), 2.65-2.72 (3H, m, H4', H3'), UV: λmax (MeOH) 265 nm.

9-[*trans-trans*-3-Hydroxymethyl-2-(fluoromethyl)cyclobutyl]adenine (17). Compound **16** (110 mg, 0.29 mmol) was treated with liquid NH_3 (2 ml) in a sealed tube (steel, 20 ml) at 60° for 2 days, then cooled to - 60°. Volatile material was removed carefully and the residue was dissolved in a small amount of MeOH. The solution was chromatographed over a column of silica gel G (2.2 × 32 cm) with 4.8 - 25% EtOH in $CHCl_3$ (1.5 l) to give a caramel, which was crystallized from EtOH to afford a white solid (65 mg, 88%). mp 145-147°. *Anal.* Calcd. for $C_{11}H_{14}FN_5O$: C, 52.58; H, 5.62; N, 27.87. Found: C, 52.29; H, 5.72; N, 27.83. MS *m/z*: 251 (M^+), 234 (M^+ - OH), 232 (M^+ - F), 135 (adenine). ^{1}H-NMR ($CDCl_3$) δ: 8.28 (1H, s, H8), 8.13 (1H, s, H2), 7.22 (2H, br s, 6-NH_2), 4.75 (1H, q, J = 8.8 Hz, H-1'), 4.71 (1H, t, J = 4.6 Hz, 3'-CH_2OH), 4.55 (2H, m, J_{HF} = 47.9, 2'-CH_2F), 3.56 (2H, t, J = 5.0 Hz, 3'-CH_2OH), 3.03 (1H, m, J_{HF} = 25.6 Hz, H-2'), 2.44 (1H, dt, J = 10.7, J = 8.1 Hz, H4'a), 2.33 (1H, q, J = 9.5 Hz, H4'b), 2.19 (1H, m, H3'). UV: λmax (MeOH), 260 nm, λmax (1N HCl), 259 nm, λmax (1N NaOH) 260 nm.

ACKNOWLEDGMENT

We are grateful to Professor Mitsuaki Kodama of Tokushima Bunri University for his useful suggestions concerning the manuscript. 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.

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