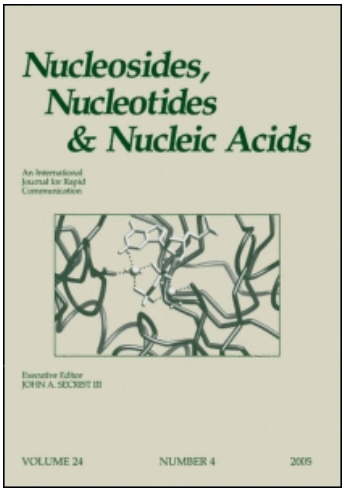


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

A Convenient Synthesis of Acyclic Adenosines with an Unsaturated Side Chain by Modification of 9-(2,3-*O*-Isopropylidene-D-Ribityl)Adenine

Kosaku Hirota[a]; Yasunari Monguchi[a]; Hironao Sajiki[a]; Chizuko Yatome[b]; Akio Hiraoka[b]; Yukio Kitade[b]
[a] Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University, Mitahora-higashi, Gifu, Japan [b] Department of Biomolecular Science, Faculty of Engineering, Gifu University, Yanagido, Gifu, Japan

To cite this Article Hirota, Kosaku , Monguchi, Yasunari , Sajiki, Hironao , Yatome, Chizuko , Hiraoka, Akio and Kitade, Yukio(1998) 'A Convenient Synthesis of Acyclic Adenosines with an Unsaturated Side Chain by Modification of 9-(2,3-*O*-Isopropylidene-D-Ribityl)Adenine', Nucleosides, Nucleotides and Nucleic Acids, 17: 8, 1333 — 1345
To link to this Article: DOI: 10.1080/07328319808003472
URL: http://dx.doi.org/10.1080/07328319808003472

NUCLEOSIDES & NUCLEOTIDES, 17(8), 1333-1345 (1998)

A CONVENIENT SYNTHESIS OF ACYCLIC ADENOSINES WITH AN UNSATURATED SIDE CHAIN BY MODIFICATION OF 9-(2,3-*O*-ISOPROPYLIDENE-D-RIBITYL)ADENINE

Kosaku Hirota,*[a] Yasunari Monguchi,[a] Hironao Sajiki,[a]
Chizuko Yatome,[b] Akio Hiraoka,[b] and Yukio Kitade[b]

[a] *Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University, Mitahora-higashi, Gifu 502-0003, Japan*
[b] *Department of Biomolecular Science, Faculty of Engineering, Gifu University, Yanagido, Gifu 501-1112, Japan*

ABSTRACT : In expectation of discovering their antiviral activity, acyclic adenosine derivatives **7**, **11**, **12**, and **16** were designed as analogs of neplanocin A (NPA) and L-eritadenine which are strong inhibitors of *S*-adenosyl-L-homocysteine hydrolase. The 1',5'-*seco*-analog of 4'-deoxymethyl-NPA (DHCA) **7** was synthesized by dideoxygenation of 9-(2,3-*O*-isopropylidene-D-ribityl)adenine (**2**). Acyclic DHCA analogs **11** and **16** were obtained by Wittig reaction of the aldehyde **3** with $Ph_3P{=}CHCO_2Et$ and $Ph_3P{=}CHCN$, respectively. Hydrolysis of the ester **11** afforded a vinylog of L-eritadenine **12**. The synthesized acyclic nucleosides **7**, **10**, and **11** were evaluated for antiviral activity, however, none of them showed any significant antiviral activity.

S-Adenosyl-L-homocysteine (AdoHcy) hydrolase, which catalyses the hydrolysis of AdoHcy to adenosine and L-homocysteine, has been recognized as an attractive target for the development of antiviral agents.[1] This enzyme plays an important role in regulating the *S*-adenosyl-L-methionine-dependent transmethylation reaction which is involved in the maturation of viral mRNA. Naturally occurring adenosine analogs, D-eritadenine[2] and neplanocin A (NPA)[3], have exhibited antiviral activities through the strong and irreversible inhibition of this enzyme. Recently, we have reported a convenient method for the

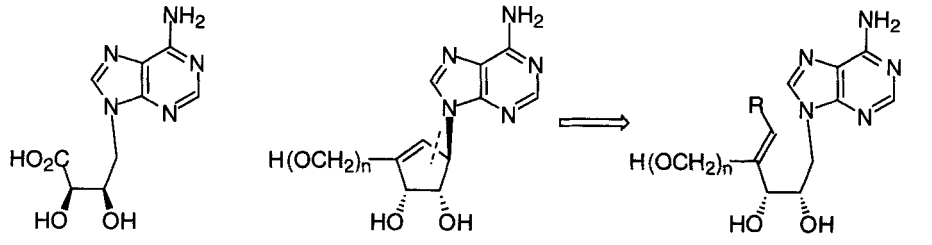
*Kosaku Hirota: Phone: +81-58-237-3931 (ext. 224), Fax: +81-58-237-5979, e-mail: hirota@gifu-pu.ac.jp

synthesis of acyclic purine nucleosides from commercially available purine nucleosides.[4, 5] The 9-D-ribityladenine **2**,[4] easily prepared by the DIBAL-H reduction of 2',3'-*O*-isopropylideneadenosine (**1**), was applied[5, 6] to the synthesis of several acyclic adenosine derivatives, an acyclic NPA analog **A**[5a] and L-eritadenine.[7] The latter was obtained *via* a useful aldehyde intermediate **3**[5b] (SCHEME 1). On the other hand, 4'-dehydroxymethyl-NPA (DHCA) has been shown to be a more selective inhibitor of AdoHcy hydrolase than NPA, because lack of the 4'-hydroxymethyl group causes the substrate inactivity for adenosine kinase.[8] Therefore, we planed to synthesize the acyclic DHCA analogs **B**, though the carboxylic acid **B** (R = CO_2H) can be also regarded as a vinylog of L-eritadenine.[6]

In this paper, the synthesis of acyclic adenosines **7**, **11**, **12**, and **16** with an unsaturated side chain according to our methods utilizing the 9-D-ribityadenine derivative **2** is described.

The 1',5'-*seco*-type of DHCA **7** had been synthesized from D-ribonolactone as a chiral pool by Jäger and coworkers.[9] However, their method included non-regioselective condensation of adenine with a side chain after a multi-step procedure, and biological evaluation of **7** was not described. In our first attempt to synthesize **7**, the Wittig methylenation of the aldehyde **3** with Ph_3PCH_3Br/BuLi gave a diastereomeric mixture of (2'*S*,3'*R*)-*erythro*-isomer **4** and (2'*S*,3'*S*)-*threo*-isomer **5** in low yield (16%, **4** : **5** = 77 : 23).[10, 11] However, the two products could not be separated by column chromatography. In order to obtain **4** as a single diastereomer in high yield, the dideoxygenation at the 4', 5'-position of **2** was investigated alternatively. Among numerous studies on the conversion of 1,2-diols into olefins, we adopted Lerner's method[12] for the preparation of **7**. *O*-Mesylation of **2** followed by the treatment with sodium iodide afforded **4** *via* the 4',5'-di-*O*-mesylate **6** in good yield. Deprotection of **4** by heating in 80% aqueous AcOH gave the target product **7** in 82% yield.

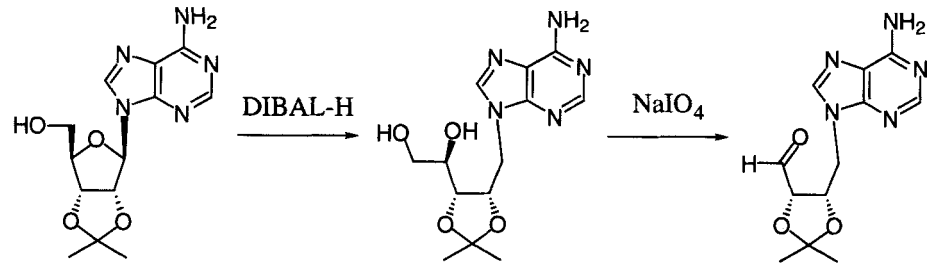
The Wittig reaction of the aldehyde **3** with $Ph_3P{=}CHCO_2Et$ at room temperature afforded a mixture of the α,β-unsaturated ester **8** (*E*) and **9** (*Z*) with the ratio of 67 : 33[11] in 72% yield, whereas the reaction under reflux resulted in the predominant formation of the (*E*)-isomer **8** in the ratio of 86 : 14.[11] The mixture itself was employed for the preparation of the desired eritadenine vinylog **12** because the respective products could not be isolated. When the mixture was treated under basic conditions and subsequently acidified with 1N HCl to pH 3–4, the obtained product was not the expected carboxylic acid **12**, but a γ-keto-acid **10** with retention of the 2'-configuration (optical activity $[\alpha]_D^{26}$ (*c* 0.07, DMF) was



D-eritadenine

n = 1 : NPA
n = 0 : DHCA

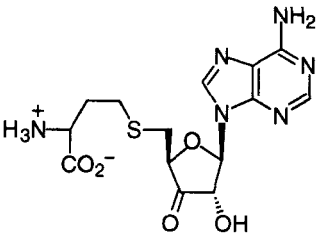
A : n = 1, R = H
B : n = 0, R = H, CO_2R', CN



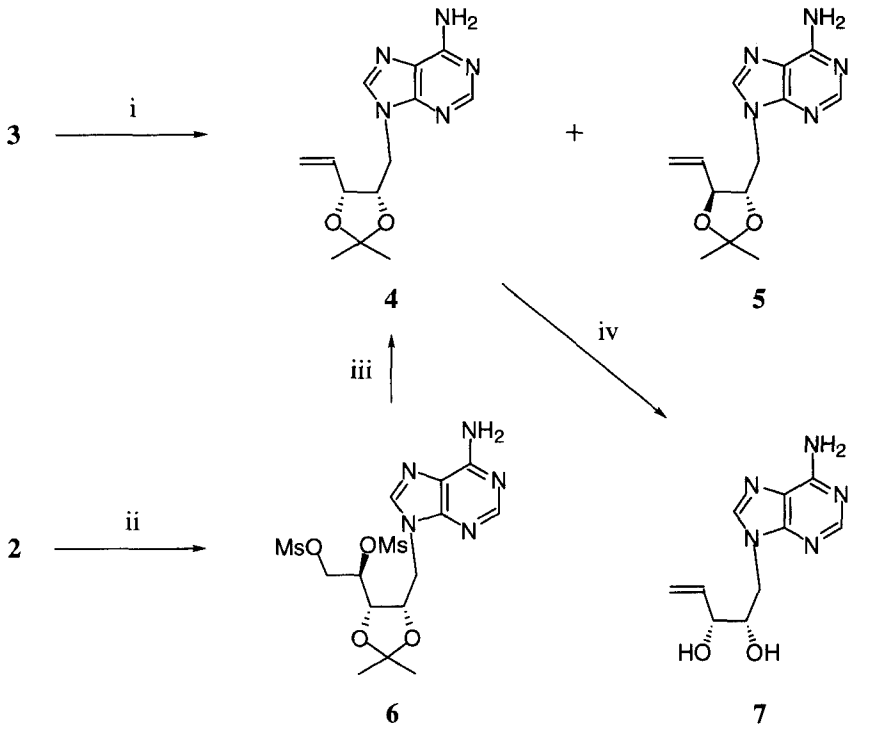
1 **2** **3**

SCHEME 1

–25.7) in 79% yield. The keto-acid **10**, which could form *via* an isomerization of the olefins into enolate intermediates under the basic conditions, is of interest in relation to a structural analogy to the 3'-keto-intermediate **C**[13] proposed for the AdoHcy hydrolase-catalyzed reaction mechanism. On the other hand, the mixture (**8** : **9** =86 : 14) was treated with trifluoro-acetic acid prior to base–treatment to afford the 2',3'-deprotected (*E*)-isomer **11** derived from **8** in 83% yield. Another (*Z*)-isomer derived from **9** was not isolated.[14] The saponification of **11** with LiOH gave an α,β-unsaturated carboxylic acid **12** in 89% yield. Furthermore, Pd/C-catalyzed hydrogenation of **12** furnished the two-carbon elongated L-eritadenine **13** in 82% yield.



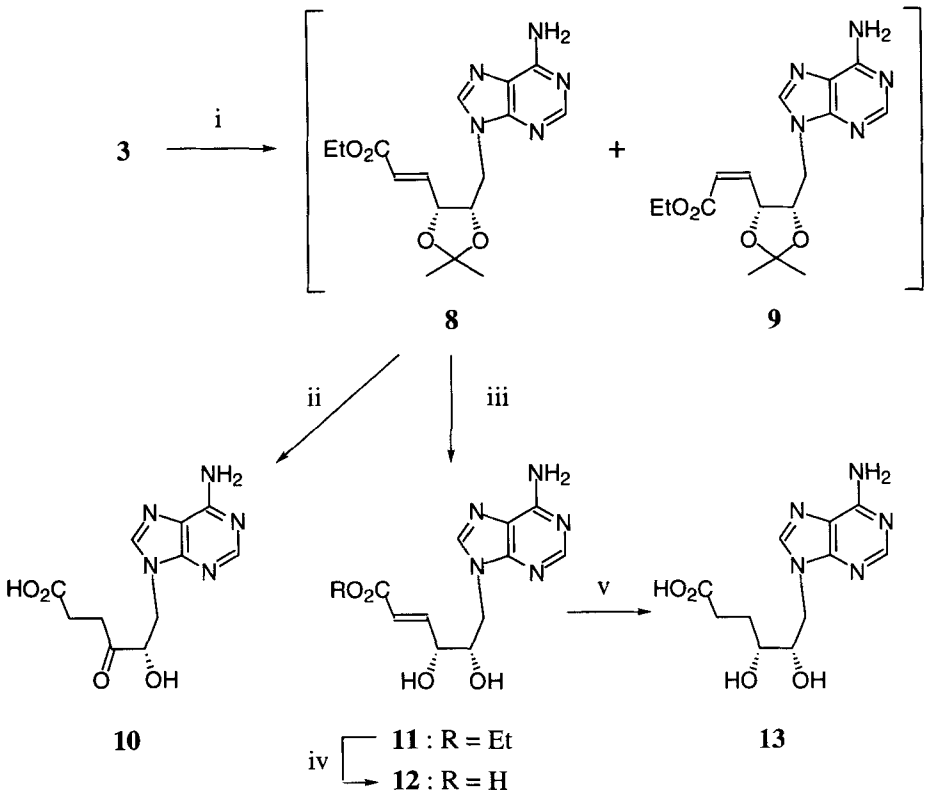
C



SCHEME 2 *Reagents and conditions:* i) Ph_3PCH_3Br, BuLi, THF, 0 °C–r. t.; ii) MsCl, pyridine, 0 °C–r. t.; iii) NaI, acetone, reflux; iv) 80% AcOH, 70 °C.

The synthesis of an acyclic DHCA analog **16** bearing a terminal nitrile group in the side chain was conducted in a similar manner to that described for the synthesis of **12** (SCHEME 4). The Wittig reaction of **3** using Ph_3P=CHCN in refluxing THF and the subsequent separation by column chromatography led to successful isolation of the α,β-unsaturated nitriles **14** (*E*) and **15** (*Z*), each in 37% yield. Removal of the isopropylidene group of **14** was accomplished by heating in 30% aqueous AcOH to give the target (*E*)-α,β-unsaturated nitrile **16** in 67% yield. Similar treatment of **15**, however, afforded a complicated mixture, and isolation of the corresponding deprotected-nitrile was unsuccessful.

The synthesized compounds **7**, **10**, and **11** showed no significant activities against influenza A, respiratory syncytial virus, human immunodeficiency virus, herpes simplex virus type 1, and human cytomegarovirus.

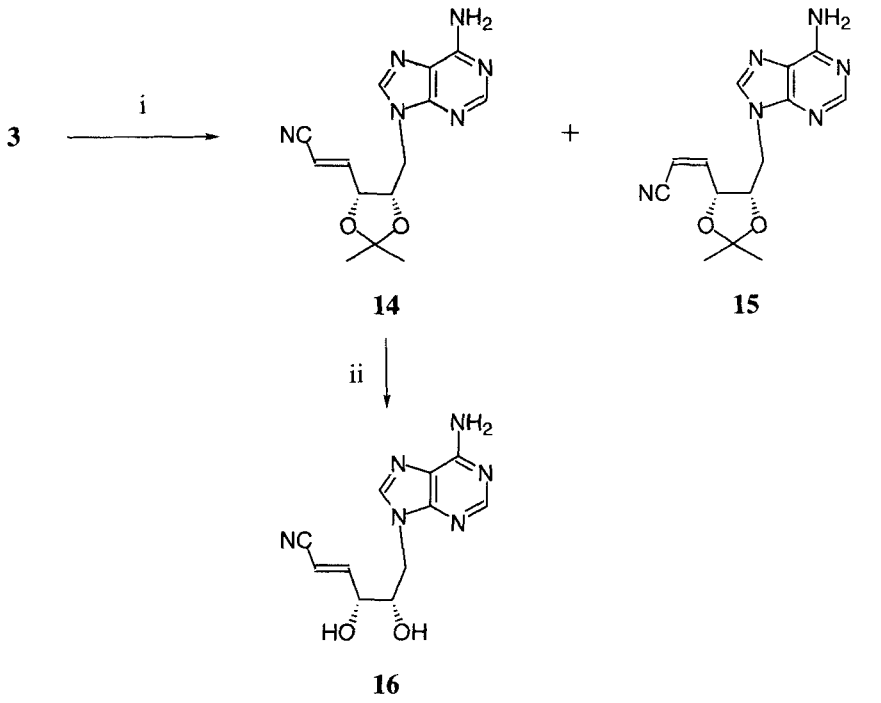


SCHEME 3 *Reagents and conditions:* i) $Ph_3P{=}CHCO_2Et$, THF, reflux; ii) KOH, EtOH then 1N HCl to pH 3–4, r. t.; iii) CF_3CO_2H, r. t.; iv) $LiOH{\cdot}H_2O$, $MeOH–H_2O$ (3 : 1), 0 °C–r. t.; v) 10% Pd/C, H_2, H_2O–AcOH (25 : 1), r. t..

In conclusion, 9-(2,3-*O*-isopropylidene-D-ribityl)adenine (**2**) and (2*S*,3*S*)-4-(adenin-9-yl)-2,3-dihydroxy-2,3-*O*-isopropylidenebutanal (**3**) are versatile chiral precursors for the synthesis of biologically interesting acyclic adenosine analogs.

EXPERIMENTAL

Melting points (uncorrected) were determined with a Yanagimoto melting point apparatus. Optical rotations were measured on a Jasco DIP-370 polarimeter and $[\alpha]_D$ values are given in $10^{-1}deg{\cdot}cm^2{\cdot}g^{-1}$. UV absorption spectra were recorded on a Shimadzu 260 spectrophotometer. IR spectra were measured using a Perkin Elmer 1640 FT-IR spectrometer. ^1H NMR spectra were recorded on a JEOL JNM GX-270 (270 MHz) or a JNM EX-400 (400 MHz) spectrometer. Chemical shifts (δ) are expressed in



SCHEME 4 *Reagents and condition:* i) Ph_3P=CHCN,THF, reflux; ii) 30% AcOH, reflux.

ppm relative to tetramethylsilane in $CDCl_3$ as a solvent or internally referenced to the residual protonated solvent resonances (δ 2.49) in DMSO-d_6 as a solvent. ^{13}C NMR spectra were recorded on a JEOL JNM EX-400 spectrometer (100 MHz). Solvent peak ($CDCl_3$: δ 77.0; DMSO-d_6: δ 39.5) was used as an internal standard for ^{13}C NMR. Mass spectra and high-resolution mass spectra were taken on a JEOL JMS-D 300 or a JMS-SX 102A machine. Elemental analyses were performed by the microanalytical laboratory of our university.

Thin-layer chromatographic (TLC) analyses were carried out on precoated Silicagel 60 F_{254} plates (Merck, Art 5715). The silica gel used for column chromatography was Wakogel C-300 or Fujigel BW-200. Reversed phase chromatography was accomplished by Sep-Pak® (C_{18}) cartridge (Waters).

Reaction of (2*S*,3*S*)-4-(adenin-9-yl)-2,3-dihydroxy-2,3-*O*-isopropylidenebutanal (3) with Ph_3CH_3Br/BuLi. To a suspension of methyltriphenylphos-

phonium bromide (1.786 g, 5 mmol) in anhydrous THF under argon atmosphere at 0 ℃ was added butyl lithium (2.41 mL of a 1.66 M solution in hexane, 4 mmol) dropwise and the mixture was stirred for 30 min. To the mixture was added a suspension of **3** (277 mg, 1 mmol) in anhydrous THF at 0 ℃. The mixture was warmed up to room temperature over a night and stirred for 3 days. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 50 : 1–40 : 1) to give a diastereomeric mixture of (2'*S*,3'*R*)-isomer **4** and (2'*S*,3'*S*)-isomer **5** (44 mg, 16%, **4** : **5** = 77 : 23). *For* **5** ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 and 1.42 (each 3H, s, isopropylidene), 3.97–4.07 and 4.38–4.45 (4H, m, 1'-H × 2, 2'-H and 3'-H, overlapped with peaks for 1'-H of **15** at 3.95 and 4.38 ppm), 5.32 (1H, d, *J* = 10.3 Hz, 5'-H), 5.47 (1H, d, *J* = 17.1 Hz, 5'-H), 5.70 (2H, brs, 6-NH_2), 5.83 (1H, ddd, *J* = 17.1, 10.3 and 6.8 Hz, 4'-H), 7.98 (1H, s, 2-H or 8-H), 8.37 (1H, s, 2-H or 8-H).

9-[(2*S*, 3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-4-penten-1-yl]adenine (4). To a solution of 9-(2,3-*O*-isopropylidene-D-ribityl)adenine (**2**) (309 mg, 1 mmol) in pyridine (16 mL) at 0 ℃ was added methanesulfonyl chloride (464 μL, 6 mmol) dropwise. After being stirred at 0 ℃ for 1 h and then at room temperature for 3 h, the mixture was poured into a saturated aqueous $NaHCO_3$ solution at 0 ℃. To a resulting mixture was added $CHCl_3$ and the organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 35 : 1) to give 9-(2,3-*O*-isopropylidene-4,5-bis-*O*-methansulfonyl-D-ribityl)adenine **6** (465 mg, quantitatively) as a pale yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 and 1.54(each 3H, s, isopropylidene), 3.15 and 3.32 (each 3H, s, CH_3SO_2), 4.20 (1H, dd, *J* = 14.2 and 10.3 Hz, 1'-H), 4.46 (1H, dd, *J* = 8.8 and 5.9 Hz, 3'-H), 4.51 (1H, dd, *J* = 12.2 and 3.4 Hz, 5'-H), 4.61 (1H, ddd, *J* = 10.3, 5.9 and 2.0 Hz, 2'-H), 4.78 (1H, dd, *J* = 14.2 and 2.0 Hz, 1'-H), 4.79 (1H, dd, *J* = 12.2 and 2.4 Hz, 5'-H), 5.05 (1H, ddd, *J* = 8.8, 3.4 and 2.4 Hz, 4'-H), 5.86 (2H, brs, 6-NH_2), 7.91 (1H, s, 2-H or 8-H), 8.32 (1H, s, 2-H or 8-H); ^{13}C NMR ($CDCl_3$) δ 25.26, 27.90, 37.75, 39.55, 43.62, 67.56, 73.36, 74.39, 75.37, 110.21, 119.37, 141.34, 149.91, 152.93, 155.46; MS (EI) *m/z* 465 (M^+, 4%), 450 (16), 312 (100), 135 (28). HRMS (EI) Calcd for $C_{15}H_{23}O_8N_5S_2$ (M^+): 465.0988. Found: 465.1001. To a solution of **6** (303 mg, 0.65 mmol) in acetone (5 mL) was added sodium iodide (968 mg, 6.5 mmol) and the mixture was heated under reflux for 5.5 h and diluted with $CHCl_3$. After H_2O was added to the mixture, the organic layer was separated and the aqueous layer was

extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was triturated with ether to give **4** (162 mg, 91%) as a colorless solid, which was recrystallized from EtOH. mp 225–227 ℃; UV (MeOH) λ_{max} 260 nm; IR (KBr) ν_{max} 3281, 3130, 2986, 2935, 2749, 2684, 1677, 1607, 1573, 1478, 1419, 1371, 1326, 1307, 1244, 1216, 1163, 1065, 1011, 936, 884, 852, 721, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 and 1.60 (each 3H, s, isopropylidene), 3.95 (1H, dd, *J* = 14.2 and 10.3 Hz, 1'-H), 4.38 (1H, dd, *J* = 14.2 and 2.4 Hz, 1'-H), 4.56 (1H, ddd, *J* = 10.3, 6.8 and 2.4 Hz, 2'-H), 4.78 (1H, t, *J* = 6.8 Hz, 3'-H), 5.39 (1H, d, *J* = 10.3 Hz, 5'-H), 5.53 (1H, d, *J* = 17.1 Hz, 5'-H), 5.60 (2H, brs, 6-NH_2), 5.91 (1H, ddd, *J* = 17.1, 10.3 and 6.8 Hz, 4'-H), 7.92 (1H, s, 2-H or 8-H), 8.36 (1H, s, 2-H or 8-H); ^{13}C NMR ($CDCl_3$) δ 25.28, 28.04, 45.03, 75.76, 78.02, 109.53, 119.48, 119.67, 131.96, 141.47, 150.04, 152.91, 155.33; MS (EI) *m/z* 275 (M^+, 9%), 260 (100), 148 (29), 136 (32). *Anal.* Calcd for $C_{13}H_{17}O_2N_5 \cdot 1/10H_2O$: C, 56.34; H, 6.26; N, 25.28. Found: C, 56.17; H, 6.19; N, 25.27. The existence of water in this product was confirmed by ^1H NMR analysis.

9-[(2*S*,3*R*)-2,3-Dihydroxy-4-penten-1-yl]adenine (7). A solution of **4** (10 mg, 36.3 μmol) in 80% aqueous AcOH was stirred at 70 ℃ for 8 h. The solvent was evaporated *in vacuo* and the residure was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 20 : 1–12 : 1) to give **7** (7 mg, 82%) as a colorless solid. UV (MeOH) λ_{max} 260 nm; IR (KBr) ν_{max} 3462, 3406, 3321, 3263, 3190, 2905, 2718, 2656, 1659, 1603, 1575, 1483, 1418, 1336, 1306, 1247, 1205, 1094, 1049, 1005, 924, 724, 650 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) and ^{13}C NMR (DMSO-d_6) data are identical with those reported in the litetreture[9b]; MS (EI) *m/z* 235 (M^+, 28%), 217 (20), 178 (100), 148 (76), 135 (97). HRMS (EI) Calcd for $C_{10}H_{13}O_2N_5$ (M^+): 235.1069. Found: 235.1080.

Ethyl (4*R*,5*S*)-6-(Adenin-9-yl)-4,5-dihydroxy-4,5-*O*-isopropylidene-2-hexenoates (8 and 9). A mixture of **3** (122 mg, 0.44 mmol) and (carbethoxymethylene)triphenylphosphorane (460 mg, 1.32 mmol) in anhydrous THF (30 mL) under argon atmosphere was heated under reflux for 4 h. The solvent was evaporated *in vacuo* and the residure was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 45 : 1) to give a geometrical mixture of *E*-isomer **8** and *Z*-isomer **9** (152 mg, 99%, **8** : **9** = 86 : 14) as a colorless solid, which was recrystallized from EtOH. ^1H NMR (400 MHz, $CDCl_3$) *for* **8** (*E*-isomer), δ 1.31 (3H, t, *J* = 7.3 Hz, CH_3CH_2), 1.36 and 1.61 (each 3H, s, isopropylidene), 3.95 (1H, dd, *J* = 14.2 and 9.8 Hz, 6-H), 4.22 (2H, q, *J* = 7.3 Hz,

CH_3CH_2), 4.37 (1H, dd, J = 14.2 and 2.9 Hz, 6-H), 4.67 (1H, ddd, J = 9.8, 6.8 and 2.9 Hz, 5-H), 4.93 (1H, ddd, J = 6.8, 5.4 and 1.5 Hz, 4-H), 5.77 (2H, brs, adenine 6-NH_2), 6.23 (1H, dd, J = 15.6 and 1.5 Hz, 2-H), 6.90 (1H, dd, J = 15.6 and 5.4 Hz, 3-H), 7.88 (1H, s, adenine 2-H or 8-H), 8.35 (1H, s, adenine 2-H or 8-H); *for* **9** (Z-isomer), δ 1.31 (3H, t, J = 7.3 Hz, CH_3CH_2), 1.37 and 1.59 (each 3H, s, isopropylidene), 3.99 (1H, dd, J = 14.2 and 9.8 Hz, 6-H), 4.22 (2H, q, J = 7.3 Hz, CH_3CH_2), 4.35 (1H, dd, J = 14.2 and 2.9 Hz, 6-H), 4.86 (1H, ddd, J = 9.8, 6.8 and 2.9 Hz, 5-H), 5.71 (1H, td, J = 6.8 and 1.5 Hz, 4-H), 5.73 (2H, brs, adenine 6-NH_2), 5.96 (1H, dd, J = 11.7 and 1.5 Hz, 2-H), 6.27 (1H, dd, J = 11.7 and 6.8 Hz, 3-H), 7.97 (1H, s, adenine 2-H or 8-H), 8.34 (1H, s, adenine 2-H or 8-H); MS (EI) *m/z* 347 (M^+, 11%), 332 (100), 148 (42), 135 (49). *Anal.* Calcd for $C_{16}H_{21}O_4N_5 \cdot 1/10H_2O$: C, 55.03; H, 6.12; N, 20.06. Found: C, 55.13; H, 6.12; N, 19.85. The existence of water in this product was confirmed by ^1H NMR analysis.

Similar treatment of **3** (139 mg, 0.5 mmol) with (carbethoxymethylene)triphenylphosphorane (523 mg, 1.5 mmol) at room temperature for 17 h gave a geometrical mixture of **8** and **9** (125 mg, 72%, **8** : **9** = 67 : 33).

(5*S*)-6-(Adenin-9-yl)-5-hydroxy-4-oxo-2-hexanoic Acid (10). A mixture of **8** and **9** (38 mg, 0.109 mmol, **8** : **9** = 67 : 33) was stirred with KOH (61 mg, 1.09 mmol) in EtOH (8 mL) at room temperature for 2 days. The pH of the reaction mixture was adjusted to 3–4 with 1N HCl and the solvent was removed *in vacuo*. The residue was purified by reversed phase column chromatography (H_2O/MeCN, 19 : 1–9 : 1) to give **10** (24 mg, 79%) as a colorless solid. $[\alpha]_D^{26}$ (*c* 0.07, DMF) –25.7; UV (MeOH) λ_{max} 259 nm; IR (KBr) ν_{max} 3452, 3320, 3258, 3197, 3073, 2937, 1719, 1685, 1652, 1583, 1482, 1418, 1292, 1214, 1120, 1087, 1021, 907, 797, 707, 641 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.41 (2H, t, J = 6.3 Hz, 2-H or 3-H), 2.85 (2H, t, J = 6.3 Hz, 2-H or 3-H), 4.20 (1H, dd, J = 15.2 and 9.3 Hz, 6-H), 4.40–4.44 (2H, m, 5-H and 6-H), 6.01 (1H, d, J = 5.4 Hz, 5-OH), 7.17 (2H, brs, adenine 6-NH_2), 8.01 (1H, s, adenine 2-H or 8-H), 8.12 (1H, s, adenine 2-H or 8-H), 12.11 (1H, brs, 1-CO_2H); ^{13}C NMR (DMSO-d_6) δ 27.25, 33.17, 45.52, 74.30, 118.52, 141.46, 149.50, 152.25, 155.87, 173.64, 210.27; MS (FAB, NBA) *m/z* 280 (M^++H, 10%). HRMS (FAB) Calcd for $C_{11}H_{14}O_4N_5$ (M^++H): 280.1046. Found: 280.1055.

Ethyl (4*R*,5*S*)-6-(Adenin-9-yl)-4,5-dihydroxy-2-hexenoate (11). A mixture of **8** and **9** (145 mg, 0.417 mmol, **8** : **9** = 86 : 14) was stirred in CF_3CO_2H (3 mL)

at room temperature for 4 h. The solvent was evaporated *in vacuo* and the residure was purified by column chromatography on silica gel ($CHCl_3$/EtOAc/MeOH, 10 : 5 : 1–8 : 4 : 1) to give **11** (106 mg, 83%) as a colorless solid, which was recrystallized from EtOH. mp 183–185 ℃; UV (MeOH) λ_{max} 260 nm; IR (KBr) ν_{max} 3385, 3185, 1703, 1642, 1604, 1478, 1420, 1369, 1306, 1259, 1183, 1065, 1036, 983, 722, 647 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.20 (3H, t, J = 7.3 Hz, CH_3CH_2), 3.76 (1H, m, 5-H), 4.02–4.08 (2H, m, 4-H and 6-H), 4.11 (2H, q, J = 7.3 Hz, CH_3CH_2), 4.37 (1H, dd, J = 14.2 and 2.9 Hz, 6-H), 5.40 (1H, d, J = 6.3 Hz, 5-OH), 5.66 (1H, d, J = 5.4 Hz, 4-OH), 6.01 (1H, dd, J = 15.6 and 1.5 Hz, 2-H), 7.02 (1H, dd, J = 15.6 and 4.4 Hz, 3-H), 7.17 (2H, brs, adenine 6-NH_2), 8.02 (1H, s, adenine 2-H or 8-H), 8.12 (1H, s, adenine 2-H or 8-H); ^{13}C NMR (DMSO-d_6) δ 14.12, 46.21, 59.82, 71.60, 71.69, 118.58, 120.33, 141.73, 148.99, 149.61, 152.08, 155.83, 165.63; MS (EI) *m/z* 307 (M^+, 13%), 290 (12), 178 (100), 148 (45), 135 (53). *Anal.* Calcd for $C_{13}H_{17}O_4N_5 \cdot 1/2H_2O$: C, 49.36; H, 5.74; N, 22.14. Found: C, 49.41; H, 5.52; N, 22.17. The existence of water in this product was confirmed by ^1H NMR analysis.

(*E*)-(4*R*, 5*S*)-6-(Adenin-9-yl)-4,5-dihydroxy-2-hexenoic Acid (12). To a suspension of **11** (57 mg, 0.185 mmol) in MeOH–H_2O (8 mL, 3 : 1) at 0 ℃ was added LiOH·H_2O (12 mg, 0.278 mmol). The mixture was warmed up to room temperature, stirred for 11 h, neutralized by the addition of Amberlite CG-50 and then filterd. The filtrate was concentrated *in vacuo* and the residue was purified by reversed phase column chromatography (H_2O) to give **12** (46 mg, 89%) as a colorless solid. UV (MeOH) λ_{max} 260 nm; IR (KBr) ν_{max} 3397, 3219, 2926, 2855, 1655, 1606, 1579, 1561, 1546, 1407, 1306, 1251, 1205, 1089, 1064, 1021, 724, 652 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.69 (1H, m, 5-H), 3.95 (1H, m, 4-H), 4.01 (1H, dd, J = 14.2, 9.3 Hz, 6-H), 4.31 (1H, dd, J = 14.2 and 2.4 Hz, 6-H), 5.40 (br, OH), 5.85 (1H, d, J = 15.6 Hz, 2-H), 6.43 (1H, dd, J = 15.6 and 5.9 Hz, 3-H), 7.13 (2H, brs, adenine 6-NH_2), 8.02 (1H, s, adenine 2-H or 8-H), 8.11 (1H, s, adenine 2-H or 8-H); MS (FAB, NBA) *m/z* 280 (M^++H, 22%). HRMS (FAB) Calcd for $C_{11}H_{14}O_4N_5$ (M^++H): 280.1046. Found: 280.1040.

(4*R*,5*S*)-6-(Adenin-9-yl)-4,5-dihydroxy-2-hexanoic Acid (13). A mixture of **12** (27.9 mg, 0.1 mmol) and 10% Pd/C (1.5 mg) in H_2O–AcOH (10.4 mL, 25 : 1) was stirred under hydrogen atmosphere (balloon) at room temperature for 3 h, filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by reversed phase column chromatography (H_2O/MeCN, 24 : 1) to give **13** (23.0 mg, 82%) as a colorless solid. UV (H_2O) λ_{max} 260 nm; IR (KBr) ν_{max} 3424, 3333, 3272, 3220, 3121, 2963, 2920, 1688, 1643, 1605, 1488, 1421, 1366, 1328, 1252, 1187, 1070, 936, 891,

798, 772, 725, 646, 573 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.50 (1H, m, 3-H), 1.90 (1H, m, 3-H), 2.24 (1H, ddd, J = 15.6, 8.8 and 6.8 Hz, 2-H), 2.36 (1H, ddd, J = 15.6, 9.8 and 5.4 Hz, 2-H), 3.23 (1H, m, 4-H), 3.54 (1H, m, 5-H), 3.99 (1H, dd, J = 14.2, 8.3 Hz, 6-H), 4.41 (1H, dd, J = 14.2 and 2.9 Hz, 6-H), 5.15 (br, OH), 7.15 (2H, brs, adenine 6-NH_2), 8.00 (1H, s, adenine 2-H or 8-H), 8.12 (1H, s, adenine 2-H or 8-H) 11.93 (1H, brs, 1-CO_2H); ^{13}C NMR (DMSO-d_6) δ 28.45, 30.10, 46.47, 71.29, 72.27, 118.54, 141.79, 149.58, 152.08, 155.87, 174.79; MS (FAB, NBA) *m/z* 282 (M^++H, 11%). HRMS (FAB) Calcd for $C_{11}H_{16}O_4N_5$ (M^++H): 282.1202. Found: 282.1200.

(*E*)-(4*R*, 5*S*)-6-(Adenin-9-yl)-4,5-dihydroxy-4,5-*O*-isopropylidene-2-hexenonitrile (14) and (*Z*)-(4*R*,5*S*)-6-(Adenin-9-yl)-4,5-dihydroxy-4,5-*O*-isopropylidene-2-hexenonitrile (15). A mixture of **3** (416 mg, 1.5 mmol) and (cyanomethylene)triphenylphosphorane (1.356 g, 4.5 mmol) in anhydrous THF (40 mL) was heated under reflux for 2.5 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 30 : 1) to give *E*-isomer **14** (168 mg, 37%) as the first fraction and *Z*-isomer **15** (167 mg, 37%) as the second fraction, each of which was recrystallized from MeOH.

For **14**: mp 276–278 °C; UV (MeOH) λ_{max} 260 nm; IR (KBr) ν_{max} 3310, 3152, 2988, 2941, 2733, 2677, 2225 (CN), 1670, 1605, 1570, 1477, 1418, 1384, 1330, 1303, 1245, 1211, 1063, 1010, 970, 894, 798, 709, 663, 592 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36 and 1.60 (each 3H, s, isopropylidene), 3.96 (1H, dd, J = 14.7 Hz and 9.3 Hz, 6-H), 4.38 (1H, dd, J = 14.7 and 2.9 Hz, 6-H), 4.68 (1H, m, 5-H), 4.90 (1H, m, 4-H), 5.52 (2H, brs, adenine 6-NH_2), 5.82 (1H, dd, J = 16.1 and 2.0 Hz, 2-H), 6.73 (1H, dd, J = 16.1 and 4.4 Hz, 3-H), 7.88 (1H, s, adenine 2-H or 8-H), 8.37 (1H, s, adenine 2-H or 8-H); MS (EI) *m/z* 300 (M^+, 30%), 285 (100), 242 (25), 148 (42), 135 (46). *Anal.* Calcd for $C_{14}H_{16}O_2N_6$: C, 55.99; H, 5.37; N, 27.98. Found: C, 55.95; H, 5.43; N, 27.78.

For **15**: mp 265–267 °C; UV (MeOH) λ_{max} 260 nm; IR (KBr) ν_{max} 3102, 2942, 2941, 2747, 2685, 2228 (CN), 1676, 1598, 1478, 1417, 1386, 1327, 1243, 1063, 1015, 976, 914, 886, 858, 798, 757, 723 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 and 1.61 (each 3H, s, isopropylidene), 4.05 (1H, dd, J = 14.7 and 9.3 Hz, 6-H), 4.38 (1H, dd, J = 14.7 and 2.9 Hz, 6-H), 4.74 (1H, ddd, J = 9.3, 6.8, and 2.9 Hz, 5-H), 5.21 (1H, ddd, J = 8.8, 6.8, and 1.5 Hz, 4-H), 5.51 (2H, brs, adenine 6-NH_2), 5.59 (1H, dd, J = 11.2 and 1.5 Hz, 2-H), 6.47 (1H, dd, J =11.2 and 8.8 Hz, 3-H), 7.94 (1H, s, adenine 2-H or 8-H) 8.36 (1H, s, adenine 2-H or 8-H); MS (EI) *m/z* 300 (M^+, 27%), 285 (99), 242 (100), 149 (69), 135 (65). *Anal.* Calcd for $C_{14}H_{16}O_2N_6$: C, 55.99; H, 5.37; N, 27.98. Found: C, 55.99; H, 5.40; N, 27.95.

(*E*)-(4*R*,5*S*)-6-(Adenin-9-yl)-4,5-dihydroxy-2-hexenonitrile (16). A solution of **14** (194 mg, 0.646 mmol) in 30 % aqueous AcOH (20 mL) was heated under reflux for 3 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 10 : 1) followed by recrystallization from EtOH to give an analytically pure **16** (112 mg, 67%). mp 207–208 ℃; UV (MeOH) λ_{max} 260 nm; IR (KBr) ν_{max} 3119, 2228 (CN), 1646, 1606, 1489, 1420, 1338, 1304, 1247, 1091, 1071, 967, 797, 725, 646, 592 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.73 (1H, m, 5-H), 4.04 (1H, m, 4-H), 4.06 (1H, dd, *J* = 14.2 and 8.3 Hz, 6-H), 4.35 (1H, dd, *J* = 14.2 and 2.9 Hz, 6-H), 5.46 (1H, d, *J* = 6.4 Hz, 5-OH), 5.83 (1H, dd, *J* = 16.6 and 2.0 Hz, 2-H), 5.85 (1H, d, *J* = 5.4 Hz, 4-OH), 7.03 (1H, dd, *J* = 16.6 and 3.9 Hz, 3-H), 7.17 (2H, brs, adenine 6-NH_2), 8.01 (1H, s, adenine 2-H or 8-H), 8.12 (1H, s, adenine 2-H or 8-H); ^{13}C NMR (DMSO-d_6) δ 46.03, 71.41, 72.00, 99.06, 117.99, 118.56, 141.66, 149.58, 152.17, 155.90, 156.12; MS *m/z*: 260 (M^+, 24%), 178 (100), 148 (79), 135 (90). *Anal.* Calcd for $C_{11}H_{12}O_2N_6$: C, 50.76; H, 4.65; N, 32.29. Found: C, 50.89; H, 4.66; N, 32.20.

ACKNOWLEDGEMENT

We thank Dr. Machida of the Reseach and Development Division, Yamasa Corporation, for the antiviral assay.

REFERENCES AND NOTES

1. (a) De Clercq, E. *Biochem. Pharmacol.* **1987**, *36*, 2567–2575. (b) Wolfe, M. S.; Borchardt, R. T. *J. Med. Chem.* **1991**, *34*, 1521–1530. (c) Yuan, C. S.; Liu, S.; Wnuk, S. F.; Robins, M. J.; Borchardt, R. T. In *Advances in Antiviral Drug Design*; De Clercq, E., Ed.; JAI Press Inc.: Greenwich, 1996; Vol. 2, pp. 41–88.
2. (a) Votruba, I.; Holy, A. *Collect. Czech. Chem. Commun.* **1982**, *47*, 167–172. (b) Holy, A.; Votruba, I.; De Clercq, E. *ibid.* **1982**, *47*, 1392–1407. (c) Merta, A.; Votruba, I.; Vesely, J.; Holy, A. *ibid.* **1983**, *48*, 2701–2708.
3. (a) Borchardt, R. T.; Keller, B. T.; Patel-Thombre, U. *J. Biol. Chem.* **1984**, *259*, 4353–4358. (b) De Clercq, E. *Antimicrob. Agents Chemother.* **1985**, *28*, 84–89.
4. (a) Kitade, Y.; Hirota, K.; Maki, Y. *Tetrahedron Lett.* **1993**, *34*, 4835–4836. (b) Hirota, K.; Monguchi, Y.; Kitade, Y.; Sajiki, H. *Tetrahedron* **1997**, *53*, 16683–16698.
5. (a) Kitade, Y.; Monguchi, Y.; Hirota, K.; Maki, Y. *Tetrahedron Lett.* **1993**, *34*, 6579–6580. (b) Hirota, K.; Monguchi, Y.; Sajiki, H.; Kitade, Y. *Synlett*, **1997**, 697–698.

6. Recentry, Matsuda *et al.* have utilized the 9-ribityladenine **2** for the synthesis of neplanocin A: Niizuma, S.; Shuto, S.; Matsuda, A. *Tetrahedron* **1997**, *53*, 13621–13632.

7. L-Eritadenine exhibits the most inhibitory activity next to D-eritadenine among the four possible stereoisomers toward AdoHcy hydrolase: see, ref. 2a

8. (a) Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Org. Chem.* **1987**, *52*, 5457–5461. (b) Hasobe, M.; Mckee, J. G.; Borcherding, D. R.; Borchardt, R. T. *Antimicrob. Agents Chemother.* **1987**, *31*, 1849–1851. (c) Narayanan, S. R.; Keller, B. T.; Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Med. Chem.* **1988**, *31*, 500–503.

9. (a) Hümmer, W.; Gracza, T.; Jäger, V. *Tetrahedron Lett.* **1989**, *30*, 1517–1520. (b) Jäger, V.; Hümmer, W.; Stahl, U.; Gracza, T. *Synthesis*, **1991**, 769–776.

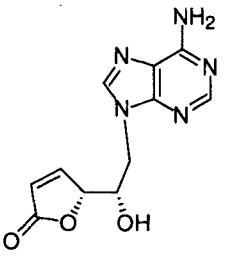
10. Lee *et al.* have reported that the easy epimerization of 2,3-*erythro*-aldose acetonide to 2,3-*threo*-aldose acetonide was observed under the basic conditions: (a) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, III, L. A.; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245–264. (b) Lee, A. W. M. *Magnetic Resonance in Chemistry* **1985**, *23*, 468–469.

11. The ratio of epimers was determined by ^{1}H NMR spectrum.

12. Lerner, L. M. *J. Org. Chem.* **1972**, *37*, 470–473.

13. (a) Palmer, J. L.; Abeles, R. H. *J. Biol. Chem.* **1976**, *251*, 5817–5819. (b) Palmer, J. L.; Abeles, R. H. *ibid.* **1979**, *254*, 1217–1226.

14. Chu *et al.* have reported that similar treatment of D-glyceraldehyde acetonide with $Ph_3P{=}CHCO_2Et$ and subsequent dilute HCl gave the α,β-unsaturated lactone *via* (*Z*)-α,β-unsaturated ester. However, we could not purify the lactone **D** corresponding to Chu's lactone: Chu, C. K.; Beach, J. W.; Ullas, G. V.; Kosugi, Y. *Tetrahedron Lett.* **1988**, *29*, 5349–5352.



D

Received 12/2/97
Accepted 1/19/98