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Synthesis of (±)-9-[*c*-4, *t*-5-bis(hydroxymethyl)cyclopent-2-en-*r*-1-yl]-9*H*-adenine (BCA) derivatives branched at the 4′-position based on intramolecular S_H2' cyclization

Hiroki Kumamoto [a,*], Nonoko Takahashi [a], Tomomi Shimamura [a], Hiromichi Tanaka [a], Kazuo T. Nakamura [a], Takayuki Hamasaki [b], Masanori Baba [b], Hiroshi Abe [c], Masahiko Yano [d], Nobuyuki Kato [d]

[a] *School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan*
[b] *Division of Antiviral Chemotherapy, Center for Chronic Viral Diseases, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima 890-8544, Japan*
[c] *Nanomedical Engineering Laboratory, Discovery Research Institute, Riken, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan*
[d] *Department of Molecular Biology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan*

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Abstract

Synthesis of 4′-branched BCA analogues (**5**) was carried out. Stereospecific construction of the cis-disposed 4′-carbon-substituents and 5′-hydroxymethyl group was secured by employing the bicyclo[3.3.0]lactone **16** as a key intermediate, which was prepared by radical-mediated intramolecular S_H2' cyclization of the phenylselenomethyl ester **15**. After manipulation of the double bond of **16**, bis(Boc)adenine was introduced based on the Mitsunobu reaction of the allyl alcohol **24**. Transformation of the lactone function of **27** allowed preparation of the 4′-hydroxymethyl (**31**), the 4′-vinyl (**32**), the 4′-cyano (**34**), and the 4′-ethynyl (**35**) derivatives. Anti-HIV and anti-HCV activities of the free nucleosides **36**–**38** were also examined.

Keywords: Carbocyclic nucleoside; Radical cyclization; Mitsunobu reaction

1. Introduction

Since the discovery of carbovir (**1**)[1] and its prodrug abacavir (**2**)[2] as anti-HIV agents, carbocyclic nucleosides have been recognized as a source of new antiviral agents. An anti-HIV active compound (±)-9-[*c*-4, *tert*-5-bis(hydroxymethyl)cyclopent-2-en-*r*-1-yl]-9*H*-adenine [(±)-BCA (**4**)] synthesized by Katagiri et al.[3] was designed as a hybrid of **1** and COXT (**3**),[4] which is a carbocyclic analogue of antibiotic oxetanocin.[5]

On the other hand, nucleosides having a 4′-carbon-substituent have attracted much attention due to the reported potent anti-HIV activity of 4′-cyanothymidine (**6**) and 4′-ethynyl-2′-deoxycytidine (**7**).[6] Also, in our recent study, the 4′-ethynyl analogue **9** (4′-Ed4T)[7] of anti-HIV agent stavudine (**8**, d4T)[8] was found to show a higher activity against HIV than the parent compound **8**. Based on these facts, we were interested in synthesizing 4′-branched (±)-BCA derivatives (**5**) that can be regarded as a hybrid of **4** and 4′-carbon-substituted nucleosides (**6**, **7**, and **9**).

2. Result and discussion

A synthetic plan for the title compounds is depicted in Scheme 1 as a retrosynthetic analysis. Manipulation of the lactone function of **I** ensures cis-disposition between the

* Corresponding author. Tel.: +81 3 3784 8187; fax: +81 3 3784 8252.
E-mail address: kumamoto@pharm.showa-u.ac.jp (H. Kumamoto).

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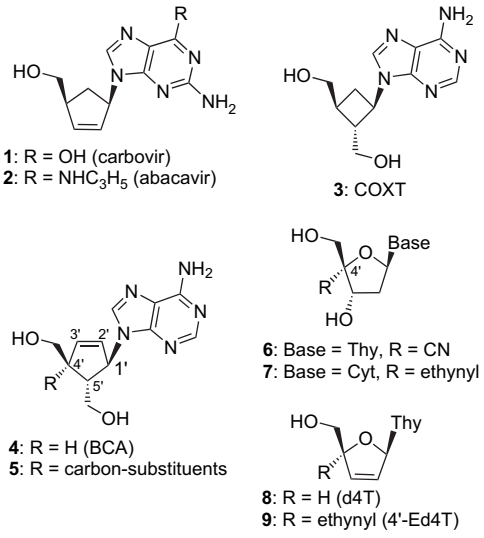
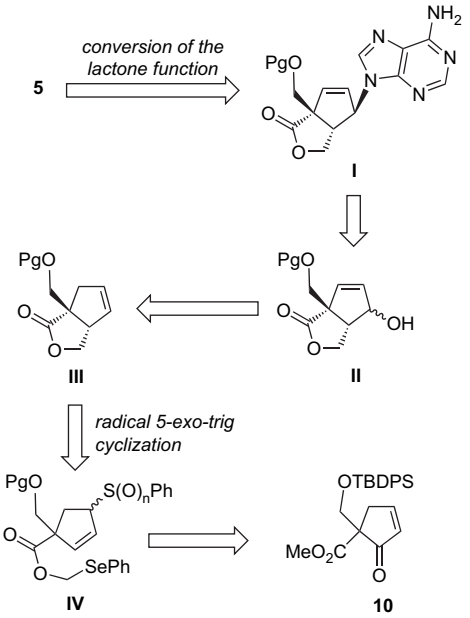


5′-hydroxymethyl group and a variety of 4′-carbon-substituents (R in **5**). Compound **I** can be prepared by condensation of adenine base with the allyl alcohol **II**, which would be obtained from **III** by a series of reactions: epoxidation, ring opening with a selenide anion, and selenoxide elimination.

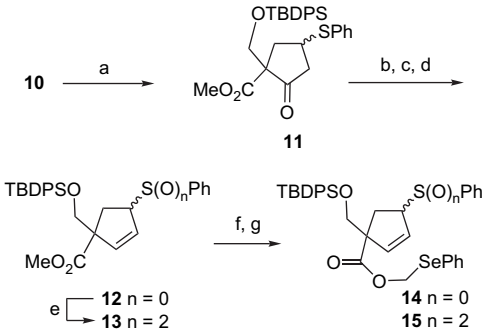


Scheme 1. Retrosynthesis of **5**.

The bicyclic system of **III** could be constructed by radical-mediated 5-*exo-trig* cyclization of the phenylselenomethyl ester **IV**, which would take place through an S_H2' process with elimination of $S(O)_nPh$ (n=0 or 2) radical.[9] We anticipated that the enone **10**[10] can be employed for the preparation of **IV**.

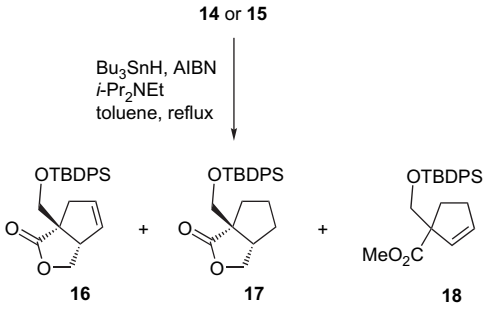
2.1. Radical-mediated 5-exo-trig cyclization of *14* and *15*

Preparation of the substrates (**14** and **15**) for the radical cyclization was performed as shown in Scheme 2. The enone **10**[10] was transformed to the phenylthio derivative **11** by 1,4-addition of PhSH. Its conversion to the allyl sulfide **12** was performed by initial reduction of the ketone followed by trifluoromethanesulfonylation of the resulting secondary alcohol, and then by β-elimination of the triflate with DBN. The allyl sulfone **13** was also prepared by *m*-CPBA oxidation of **12**. After saponification of **12** and **13**, the radical precursors **14** and **15** were prepared in 68 and 81% yields, respectively, by treatment with $PhSeCH_2Cl$[11] in the presence of *i*-Pr_2NEt and NaI.



Scheme 2. Reagents and conditions: (a) PhSH, Et_3N, CH_2Cl_2; (b) $NaBH_4$, MeOH; (c) Tf_2O, pyridine, CH_2Cl_2; (d) DBN, MeCN (87% from **10**); (e) *m*-CPBA, CH_2Cl_2 (96%); (f), KOH, MeOH, H_2O; (g) $PhSeCH_2Cl$, NaI, *i*-Pr_2NEt, DME (68% for **14**, 81% for **15**).

Radical-mediated cyclization of **14** was first carried out by adding a mixture of Bu_3SnH and AIBN over 5 h to a refluxing toluene solution of **14** containing *i*-Pr_2NEt (Scheme 3). Although the lactone **16** was obtained as a major product in 61% yield, this reaction also gave the saturated lactone **17** (5%) and the non-cyclized doubly reduced product **18** (18%). In contrast to this, the reaction of **15** under the same reaction conditions gave **16** in a much higher yield of 94%.

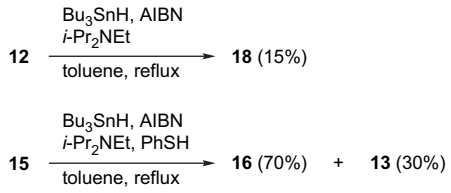


Scheme 3. Radical reactions of **14** and **15**.

Although the observed different outcome between the sulfide **14** and the sulfone **15** in this cyclization reaction could be, in part, due to the lower electrophilicity of the π bond of the former as compared with that of the latter,[12] at least two factors are likely to be involved in the formation of the byproducts (**17** and **18**) from **14**.

One is susceptibility of the phenylthio group in the allylic position to the attack of a tin radical. When **12**, lacking the phenylseleno group, was reacted under the same reaction conditions, a 15% yield of **18** was obtained, apparently via radical reduction of the phenylthio group with Bu_3SnH (Scheme 4). In contrast, the corresponding sulfone derivative **13** completely

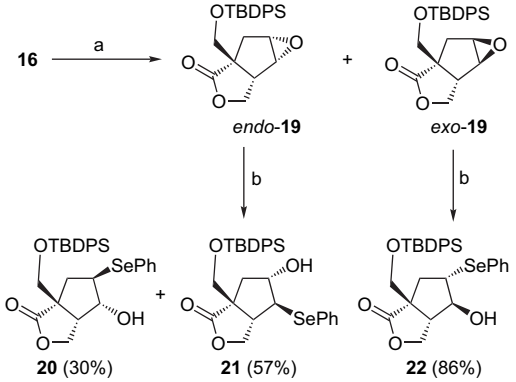
survived in these reaction conditions. It has been reported that PhSH serves as an excellent hydrogen donor in the reaction with carbon-centered radicals, whereas benzenesulfinic acid does not.[13] The other factor is an efficient reducing character of the generated PhSH to radical intermediates. In fact, when cyclization reaction of the allyl sulfone **15** was carried out in the presence of PhSH (0.5 equiv), the methyl ester **13** was formed in 30% yield.



Scheme 4. Radical reactions of **12** and **15**.

2.2. Synthesis of adenine nucleoside *I*

When *m*-CPBA oxidation of **16** was carried out as the first step to prepare the allylic alcohol (**II** in Scheme 1), the epoxide **19** was formed as a mixture of two diastereomers (2.6:1) in 69% yield (Scheme 5, method A). NOE experiments (Fig. 1) of both products showed that the major isomer is the *endo*-**19** compound (NOE: H-5/H-6, 8.6%; H-5/H-8β, 0.5%; H-8β/H-7, 13.0%; H-8α/H-7, 1.0%), and the minor one is the *exo*-**19** compound (NOE: H-4/H-6, 3.4%; H-7/H-8α, 5.0%; H-1′/H-8β, 3.2%; H-5/H-4β, 6.3%; H-4α/H-6, 3.2%). While ring opening of the *endo*-**19** compound with phenylselenide anion generated from $(PhSe)_2/NaBH_4$ resulted in poor



Scheme 5. Reagents and conditions: (a) method A: *m*-CPBA, CH_2Cl_2 (69%, *endo*/*exo*=2.6:1), method B: NIS, AcOH, CH_2Cl_2 then NaOMe, MeOH (90%, *endo*/*exo*=1:7); (b) $(PhSe)_2$, $NaBH_4$, EtOH, rt.

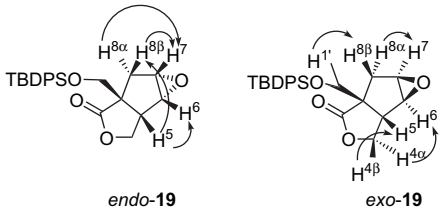


Figure 1. NOE experiments of the *endo*- and *exo*-**19**.

regioselectivity forming the selenide **20** (30%) as well as the undesired **21** (57%), the reaction of the *exo*-**19** compound gave **22** exclusively in 86% yield.

As shown in Scheme 5 by method B, the *exo*-epoxide **19** can be obtained as the major isomer upon reacting **16** with NIS/AcOH followed by NaOMe. The resulting mixture of the two epoxides, when reacted with $(PhSe)_2/NaBH_4$, furnished the desired selenide **22** in 83% yield from **16** after chromatographic purification.

It is interesting that both *m*-CPBA and NIS favor an approach from the more hindered concave face of **16**. Although there have been several precedents on the similar curious observation regarding electrophilic reaction in bicyclo[3.3.0] systems,[14,15] we have no clear explanation for the observed stereochemical outcome at the present time.

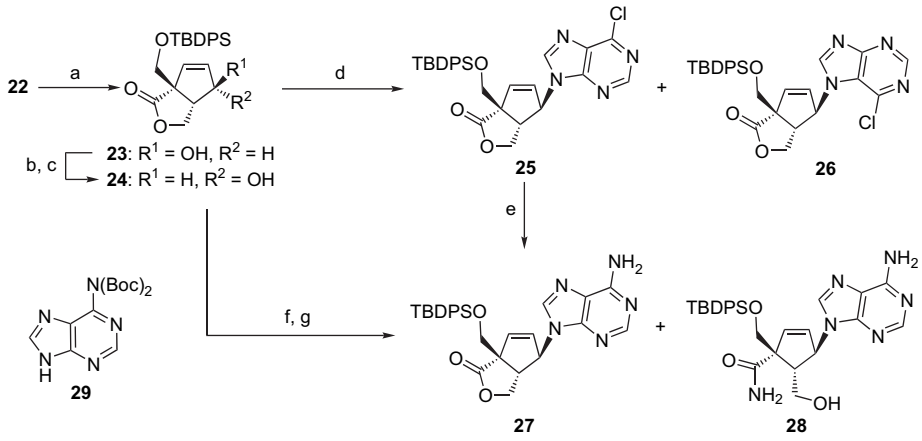
After oxidation of the selenide **22** with *m*-CPBA, selenoxide *syn*-elimination was effected in refluxing CH_2Cl_2 in the presence of Et_3N. This gave the allyl alcohol **23** in 90% yield in two steps (Scheme 6). For the introduction of the adenine base, we initially considered that the Pd-catalyzed glycosylation reported by Trost[16] could be employed. However, neither the acetate nor the carbonate derived from **23** gave **I** upon reacting with N^6-benzoyladenine/NaH in the presence of $Pd(PPh_3)_4$ in DMF. We then selected the Mitsunobu reaction. Requisite inversion of the hydroxyl group of **23** was also carried out by this reaction (DEAD/PPh_3/AcOH). Subsequent methanolysis gave the inverted allyl alcohol **24** in 98% yield.

As a precursor of the adenine base, 6-chloropurine was initially used in the Mitsunobu reaction of **24** (DIAD/PPh_3/THF). In this step, as shown in Scheme 6, the desired **25** was accompanied by the N^7-glycoside **26** (9%). Also, ammonolysis of the crude **25** by heating in a sealed tube gave the amide **28** (5%) as a byproduct (the yield of **27**: 68% from **24**). These observations led us to examine the use of bis(Boc)adenine (**29**)[17] instead of 6-chloropurine.

The reaction between **24** and **29** under the Mitsunobu conditions was followed by removal of the Boc-protecting group with 50% aqueous HCO_2H. Compound **27** was obtained in 83% overall yield from **24**. Formation of N^7-glycosylated product was not detected in this reaction. Since **29** is more soluble in THF than 6-chloropurine, and since use of a sealed tube can be avoided, we feel this method is suitable for the preparation of carbocyclic adenine nucleosides in general. Stereochemistry of **27** was confirmed by X-ray crystallographic analysis as shown in Figure 2.

2.3. Conversion of the lactone nucleoside *27* to 4′-branched BCA derivatives

To prepare BCA derivatives with a variety of carbon-functionalities at the 4′-position, the lactone nucleoside **27** was first converted to the cyclic hemiacetal **30** (98%) by reacting with DIBALH. Reduction of **30** with $NaBH_4$ gave the 4′-hydroxymethyl derivative **31** in 86% yield. The Wittig reaction of **30** with $PPh_3{=}CH_2$ proceeded well at low temperature in THF to give the vinyl derivative **32** in 96% yield. The reaction



Scheme 6. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2 then Et_3N, CH_2Cl_2, reflux (90%); (b) AcOH, DEAD, Ph_3P, THF, 0 °C; (c) K_2CO_3, MeOH, rt (98% from **23**); (d) 6-chloropurine, DIAD, Ph_3P, THF, −40 °C to rt; (e) NH_3/MeOH, 120 °C in a sealed tube, **27** (68% from **24**) and **28** (5% from **24**); (f) **29**, DIAD, Ph_3P, THF, −40 °C to rt; (g) aq 50% HCO_2H, THF, 50 °C, **27** (83% from **24**).

with a stable ylide such as $PPh_3{=}CHCO_2Me$, on the other hand, was very sluggish and required refluxing in xylene. Furthermore, the product formed in this reaction was not the expected one but the bicyclic nucleoside **33** (72% as a single stereoisomer, the stereochemistry of the 8-position was not determined), which apparently resulted from intramolecular 1,4-addition of the 5′-hydroxymethyl group to the initially formed Wittig product.

The 4′-cyano derivative (**34**) was prepared from **30** in 84% yield by the following sequence of reactions: oxime formation, O-acetylation, and finally elimination of AcOH at 100 °C in the presence of NaOAc. Several attempts to synthesize the 4′-ethynyl derivative (**35**) from **30** met with failure: $Ph_3P^+CH_2BrBr^-$/*tert*-BuOK,[18] $Ph_3P^+CH_2ClCl^-$/LHMDS,[19] and $P(O)(OMe)_2C(N_2)COMe/K_2CO_3$.[20] Compound **35** was formed only when **30** was reacted with $TMSCHN_2$/LDA,[21] albeit in a low yield (31%) (Scheme 7).

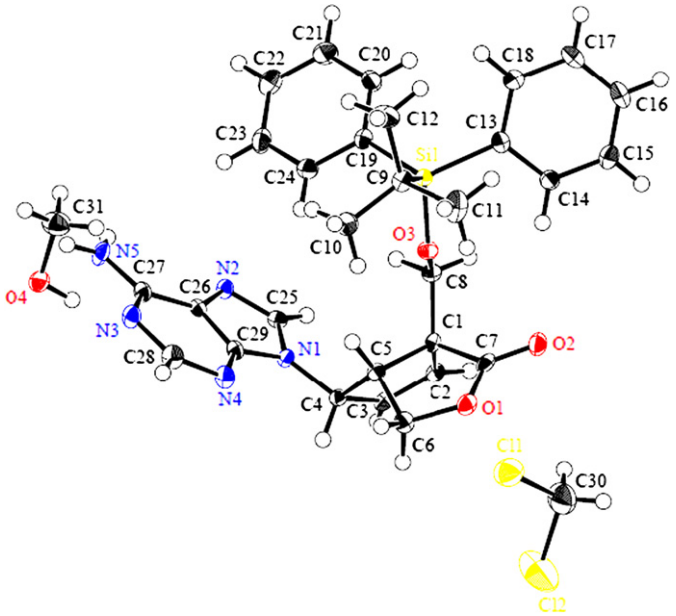
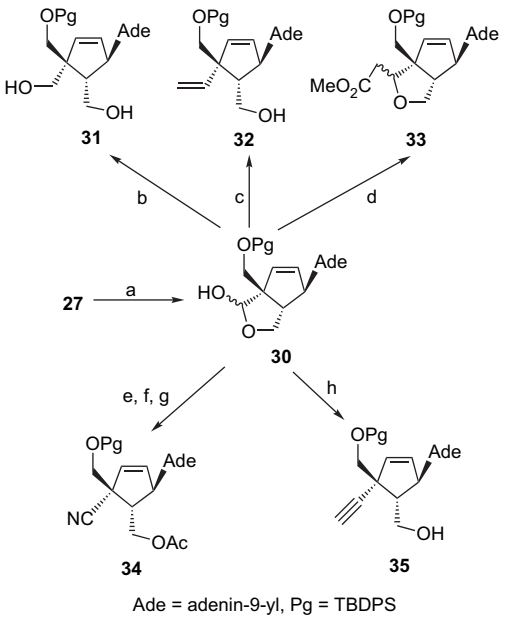


Figure 2. ORTEP drawing of compound **27**.



Scheme 7. Reagents and conditions: (a) *i*-Bu_2AlH, CH_2Cl_2, −78 °C (98%); (b) $NaBH_4$, MeOH (86%); (c) Ph_3PCH_3Br, BuLi, THF, −78 °C to rt (96%); (d) $Ph_3P{=}CHCO_2Me$, xylene, reflux (72%); (e) $NH_2OH{\cdot}HCl$, pyridine; (f) Ac_2O, *i*-Pr_2NEt, MeCN; (g) NaOAc, AcOH, 100 °C (84% from **30**); (h) $TMSCHN_2$, LDA, THF, −78 °C to rt (31%).

Removal of the silyl group in **31**, **32**, and **35** was performed by treatment with Bu_4NF in THF to give the corresponding free carbocyclic nucleosides **36**–**38** (Fig. 3). Deprotection of the cyano derivative (**34**) with Bu_4NF/THF followed by NH_3/MeOH gave the bicyclic iminoether **39** as a result of nucleophilic addition of the 5′-hydroxylmethyl group to the 4′-cyano group.

The 4′-carbon-substituted BCA analogues **36**–**38** did not show any activity against HIV-1 ($HTLV\text{-}III_B$ strain) replication at their non-toxic concentrations to the host cell (data not shown). We also examined their effects on genome-length HCV RNA replication using the OR6 cell-based assay system.[22,23] However, at 10 μM concentration, these compounds exerted no effects on HCV RNA replication without concomitant cytotoxicity.

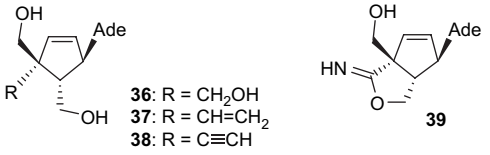


Figure 3. Structures of **36**–**39**.

3. Conclusion

The synthesis of novel 4′-branched BCA analogues was carried out using a radical-mediated 5-*exo-trig* cyclization as a key step, which takes place through a S_H2' process. The allyl sulfone **15** was found to give a higher yield of the cyclized product (**16**) than the allyl sulfide **14**. Several experiments were carried out to see why **15** acts as a better substrate in this cyclization reaction. Transformation of **16** to the allyl alcohol **23** was effected by a series of reactions: stereoselective epoxide formation, regioselective ring opening with phenylselenide anion, and selenoxide elimination. For glycosylation under Mitsunobu conditions, the inverted allyl alcohol **24** prepared from **23** was reacted with bis(Boc)adenine (**29**). Manipulation of the lactone function of the resulting **27** allowed preparation of the 4′-hydroxymethyl (**31**), the 4′-vinyl (**32**), the 4′-cyano (**34**), and the 4′-ethynyl (**35**) derivatives, which were deprotected to give the corresponding free nucleosides (**36**–**38**). Deprotection of the 4′-cyano derivative (**34**) led to the formation of the bicyclic iminoether (**39**).

Compounds **36**–**38** were tested for their potential to inhibit replication of HIV-1 and HCV in cell culture, but no significant inhibition was observed.

4. Experimental

4.1. General

Melting points were determined on a Yanaco micro melting point apparatus, and are uncorrected. ^{1}H NMR and ^{13}C NMR were measured on a JEOL JNM-GX 400 (400 MHz). Chemical shifts are reported relative to Me_4Si. Mass spectra (MS) were taken in FAB mode with *m*-nitrobenzyl alcohol as a matrix on a JEOL JMS-700. Infrared spectra (IR) were recorded on a JASCO FT/IR-410 spectrophotometer. Column chromatography was carried out on silica gel (Micro Bead Silica Gel PSQ 100B, Fuji Silysia Chemical Ltd). Thin layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254}, Merck). Where necessary, analytical samples were purified by high-performance liquid chromatography (HPLC). HPLC was carried out on a Shimadzu LC-6AD with a Shim-pack PREP-SIL (H)• KIT column (2×25 cm). THF was distilled from benzophenone ketyl.

4.2. 1-(tert-Butyldiphenylsilyloxy)methyl-4-phenylthio-2-cyclopentenecarboxylic acid methyl ester (*12*)

To a mixture of **10**[10] (5.0 g, 12.2 mmol) and PhSH (1.5 mL, 14.6 mmol) in CH_2Cl_2 (60 mL) was added Et_3N (68 μL, 0.49 mmol) at room temperature. After stirring for 12 h, the reaction mixture was partitioned between 1 M HCl and CH_2Cl_2. After evaporation, the resulting **11** (6.13 g) was used for the next reaction without further purification. To a MeOH (160 mL) solution of the crude **11** (6.13 g) was added $NaBH_4$ (923 mg, 24.4 mmol) at −40 °C. The reaction mixture was stirred for 2 h. Quenching the reaction by adding acetone (40 mL)/AcOH (1.4 mL) was followed by partition between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was evaporated and the residue was dissolved in CH_2Cl_2 (65 mL). To this solution were added pyridine (1.97 mL, 24.4 mmol) and Tf_2O (3.08 mL, 18.3 mmol) at −40 °C. After being stirred for 0.5 h at room temperature, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was evaporated and the residue was dissolved to MeCN (65 mL). To this solution was added DBN (3.02 mL, 24.4 mmol) at 0 °C and the mixture was stirred for 0.5 h at room temperature. The mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. Silica gel column chromatography (hexane/AcOEt=50:1) of the organic layer gave **12** (5.31 g, 87% from **10**, isomeric mixture ca. 2:1) as an oil. The two isomers were separated by HPLC (hexane/AcOEt=10:1, t_R 9.2 min for the minor isomer; t_R 10.9 min for the major isomer) for their NMR measurement.

4.2.1. NMR spectra of the major isomer

^{1}H NMR ($CDCl_3$) δ 1.01 (9H, s, SiBu-*tert*), 2.04 (1H, dd, J=14.4 and 4.4 Hz, H-5), 2.94 (1H, dd, J=14.4 and 8.4 Hz, H-5), 3.68 (3H, s, OMe), 3.73 (1H, d, J=9.3 Hz, CH_2OSi), 3.85 (1H, d, J=9.3 Hz, CH_2OSi), 4.33–4.37 (1H, m, H-4), 5.86 (1H, dd, J=5.6 and 1.5 Hz, H-2), 5.89 (1H, dd, J=5.6 and 2.0 Hz, H-3), 7.16–7.63 (15H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.3, 26.7, 37.6, 51.5, 52.1, 63.2, 69.3, 126.7, 127.6, 128.9, 129.6, 129.7, 131.1, 133.1, 133.2, 133.3, 134.3, 135.4, 135.6, 135.7, 178.5; FABMS *m/z* 503 (M^++H).

4.2.2. NMR spectra of the minor isomer

^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s, SiBu-*tert*), 2.41–2.43 (2H, m, H-5), 3.66 (3H, s, OMe), 3.70 (1H, d, J=9.3 Hz, CH_2OSi), 3.75 (1H, d, J=9.3 Hz, CH_2OSi), 4.18–4.22 (1H, m, H-4), 5.88 (1H, dd, J=5.6 and 2.0 Hz, H-3), 5.94 (1H, dd, J=5.6 and 1.7 Hz, H-2), 7.20–7.63 (15H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.3, 26.7, 37.8, 51.5, 52.0, 62.6, 69.1, 126.8, 127.7, 128.8, 129.7, 131.5, 133.1, 133.2, 133.3, 134.0, 135.2, 135.5, 135.8, 174.5; FABMS *m/z* 503 (M^++H). Anal. Calcd for $C_{30}H_{34}O_3SSi$: C, 71.67; H, 6.82. Found: C, 71.38; H, 6.86.

4.3. Benzenesulfonyl-1-(tert-butyldiphenylsilyloxy)-methyl-2-cyclopentenecarboxylic acid methyl ester (*13*)

To a CH_2Cl_2 (30 mL) solution of **12** (865 mg, 1.72 mmol) was added *m*-CPBA (>65%, 1.0 g, 3.78 mmol). The reaction mixture was stirred for 3 h at room temperature, treated with Et_3N (527 μL, 3.78 mmol), and then partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. Silica gel column chromatography (hexane/AcOEt=5:1) of the organic layer gave

13 (879 mg, 96%, inseparable mixture of two isomers ca. 2:1) as an oil.

4.3.1. NMR spectra of the major isomer

^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s, SiBu-*tert*), 2.26 (1H, dd, J=15.0 and 5.2 Hz, H-5), 2.82 (1H, dd, J=15.0 and 9.5 Hz, H-5), 3.62 (1H, d, J=9.5 Hz, CH_2OSi), 3.65 (3H, s, OMe), 3.77 (1H, d, J=9.5 Hz, CH_2OSi), 4.41–4.44 (1H, m, H-4), 5.83 (1H, dd, J=5.7 and 1.7 Hz, H-3), 6.06 (1H, dd, J=5.7 and 2.3 Hz, H-2), 7.37–7.47 (8H, m, Ph), 7.54–7.62 (5H, m, Ph), 7.80–7.82 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.3, 26.6, 30.5, 52.3, 63.7, 69.1, 71.6, 126.6, 127.6, 127.7, 128.9, 129.1, 129.7, 129.8, 133.1, 133.8, 135.5, 135.6, 137.3, 138.6, 173.6.

4.3.2. NMR spectra of the minor isomer

^{1}H NMR ($CDCl_3$) δ 0.99 (9H, s, SiBu-*tert*), 2.22 (1H, dd, J=15.0 and 9.2 Hz, H-5), 2.69 (1H, dd, J=15.0 and 5.2 Hz, H-5), 3.56 (3H, s, OMe), 3.62 (1H, d, J=9.2 Hz, CH_2OSi), 3.68 (1H, d, J=9.2 Hz, CH_2OSi), 4.27–4.29 (1H, m, H-4), 5.85 (1H, dd, J=5.7 and 2.3 Hz, H-3), 6.15 (1H, dd, J=5.7 and 2.3 Hz, H-2), 7.34–7.37 (4H, m, Ph), 7.40–7.43 (2H, m, Ph), 7.54–7.57 (6H, m, Ph), 7.63–7.66 (1H, m, Ph), 7.85–7.87 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.6, 30.4, 52.2, 62.9, 69.0, 71.2, 126.1, 127.7, 129.0, 129.3, 129.8, 132.7, 132.8, 133.7, 135.4, 135.5, 136.7, 139.5, 173.1; FABMS *m/z* 535 (M^++H). Anal. Calcd for $C_{30}H_{34}O_5SSi$: C, 67.38; H, 6.41. Found: C, 67.39; H, 6.54.

*4.4. 1-(tert-Butyldiphenylsilyloxy)methyl-4-phenylthio-2-cyclopentenecarboxylic acid (phenylseleno)methyl ester (**14**)*

To a mixture of **12** (4.01 g, 7.98 mmol), THF (60 mL), and MeOH (90 mL) was added aqueous KOH [KOH (2.24 g, 39.9 mmol)/H_2O (30 mL)]. After being stirred at room temperature for 2 days, the reaction mixture was partition between 1 M HCl and CH_2Cl_2. The organic layer was evaporated and the residue was dissolved in DME (26 mL), to which $PhSeCH_2Cl$ (1.9 g, 9.24 mmol), NaI (1.39 g, 9.24 mmol), and *i*-Pr_2NEt (1.6 mL, 9.24 mmol) were added. The whole mixture was refluxed for 24 h and partitioned between $NaHCO_3$ and Et_2O. Flash silica gel column chromatography (hexane/AcOEt=80:1) of the organic layer gave **14** (3.57 g, 68% from **12**, a mixture of two isomers ca. 10:4) as an oil. Compound **14** was used for the radical reaction without further purification due to its instability to silica gel. ^{1}H NMR ($CDCl_3$) δ 1.01 (12.6H, s, SiBu-*tert*), 2.01 (1H, dd, J=14.4 and 4.6 Hz, H-5), 2.40–2.42 (0.8H, m, H-5×2), 2.89 (1H, dd, J=14.4 and 8.3 Hz, H-5), 3.71 (0.4H, d, J=9.5 Hz, CH_2OSi), 3.75 (1H, d, J=9.5 Hz, CH_2OSi), 3.76 (0.4H, d, J=9.5 Hz, CH_2OSi), 3.86 (1H, d, J=9.5 Hz, CH_2OSi), 4.18–4.23 (0.4H, m, H-4), 4.29–4.33 (1H, m, H-4), 5.49–5.61 (2.8H, m, CH_2Se×4), 5.81 (1H, dd, J=5.4 and 1.7 Hz, H-2), 5.88–5.90 (1.8H, m, H-2 and H-3), 7.16–7.63 (20H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.3, 26.7, 37.5, 37.7, 51.5, 62.5, 62.6, 62.7, 63.3, 68.6, 68.9, 126.8, 127.6, 127.7, 128.9, 129.2, 129.7, 129.8, 131.1, 131.4, 132.5, 132.8, 133.0, 133.1, 133.2, 133.3, 134.5, 134.9, 135.3, 135.6, 135.7, 173.2, 173.3; FABMS *m/z* 697 (M^++H).

*4.5. 4-Benzenesulfonyl-1-(tert-butyldiphenylsilyloxy)-methyl-2-cyclopentenecarboxylic acid (phenylseleno)methyl ester (**15**)*

Compound **13** (9.95 g, 18.6 mmol) was treated by the procedure described for the preparation of **14**. This gave **15** (10.4 g, 81% from **13**, a mixture of two isomers ca. 10:7) as an oil. Compound **15** was used for the radical reaction without further purification due to its instability to silica gel. ^{1}H NMR ($CDCl_3$) δ 0.98 (9H, s, SiBu-*tert*), 1.00 (6.3H, s, SiBu-*tert*), 2.21–2.27 (1.7H, m, H-5×2), 2.67 (1H, dd, J=15.0 and 5.4 Hz, H-5), 2.75 (0.7H, dd, J=15.0 and 9.3 Hz, H-5), 3.62–3.80 (3.4H, m, CH_2OSi×4), 5.38–5.59 (3.4H, m, CH_2Se×4), 5.82 (0.7H, dd, J=5.6 and 2.2 Hz, H-2 or H-3), 5.86 (1H, dd, J=5.6 and 2.2 Hz, H-2 or H-3), 6.00 (0.7H, dd, J=5.6 and 2.2 Hz, H-2 or H-3), 6.06 (1H, dd, J=5.6 and 2.2 Hz, H-2 or H-3), 7.22–7.85 (34H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.3, 19.4, 26.7, 30.2, 30.4, 62.7, 62.8, 63.0, 63.8, 68.4, 68.7, 71.3, 71.5, 126.8, 127.2, 127.7, 127.8, 128.9, 129.0, 129.1, 129.2, 129.3, 129.7, 129.8, 129.9, 132.6, 132.7, 133.0, 133.1, 133.2, 133.8, 133.9, 135.5, 135.6, 135.7, 137.3, 138.1, 138.8, 171.7, 172.4; FABMS *m/z* 729 (M^++K).

*4.6. Radical reaction of **14***

To a refluxing toluene (190 mL) solution of **14** (4.99 g, 7.58 mmol) and *i*-Pr_2NEt (2.18 mL, 12.5 mmol) was added dropwise a toluene (20 mL) solution of Bu_3SnH (4.77 mL, 1.77 mmol) and AIBN (245 mg, 1.52 mmol) over 5 h under positive pressure of dry Ar. After evaporation of the solvent, the reaction mixture was purified by silica gel chromatography (hexane/AcOEt=30:1). This gave **16** (1.96 g, 61% as a solid), **17** (150 mg, 5% as an oil), and **18** (538 mg, 18% as an oil).

*4.6.1. Physical data for **16***

Mp 77–78 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s, SiBu-*tert*), 2.20–2.26 (1H, m, CH_2CH=CH), 2.65–2.71 (1H, m, CH_2CH=CH), 3.57–3.60 (1H, m, H-5), 3.66 (1H, d, J=9.6 Hz, CH_2OSi), 4.11(1H, d, J=9.6 Hz, CH_2OSi), 4.19 (1H, dd, J=8.7 and 1.7 Hz, CH_2OCO), 4.56 (1H, dd, J=8.7 and 7.6 Hz, CH_2OCO), 5.63–5.65 and 5.72–5.75 (2H, each as m, CH=CH), 7.36–7.47 (6H, m, Ph), 7.62–7.73 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.7, 39.3, 50.3, 56.7, 67.3, 71.8, 127.9, 129.9, 130.0, 131.0, 132.2, 133.1, 135.5 135.7, 181.9; FABMS *m/z* 431 (M^++K). Anal. Calcd for $C_{24}H_{28}O_3Si$: C, 73.43; H, 7.19. Found: C, 73.39; H, 7.29.

*4.6.2. Physical data for **17***

^{1}H NMR ($CDCl_3$) δ 1.04 (9H, s, SiBu-*tert*), 1.40–1.48 (1H, m, $-CH_2CH_2-$), 1.56–1.70 (3H, m, $-CH_2CH_2-$), 1.89–2.00 (2H, m, $-CH_2CH_2-$), 2.91–2.93 (1H, m, H-5), 3.50 (1H, d, J=9.5 Hz, CH_2OSi), 3.99 (1H, dd, J=9.0 and 3.2 Hz, CH_2OCO), 4.05 (1H, d, J=9.5 Hz, CH_2OSi), 4.54 (1H, t, J=9.0 Hz, CH_2OCO), 7.37–7.47 (6H, m, Ph), 7.63–7.65

(4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.2, 25.5, 26.7, 33.7, 34.4, 42.7, 58.5, 67.5, 73.3, 127.8, 129.8, 129.9, 132.5, 133.2, 135.5, 135.7, 181.8; FABMS *m/z* 395 (M^++H). Anal. Calcd for $C_{24}H_{30}O_3Si$: C, 73.05; H, 7.66. Found: C, 72.78; H, 7.68.

4.6.3. Physical data for ***18***

^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s, SiBu-*tert*), 1.89–1.95 (1H, m, $-CH_2CH_2-$), 2.31–2.43 (3H, m, $-CH_2CH_2-$), 3.69 (3H, s, OCH_3), 3.72 (1H, d, *J*=9.3 Hz, CH_2OSi), 3.81 (1H, d, *J*=9.3 Hz, CH_2OSi), 5.74–5.76 and 5.86–5.88 (2H, each as m, $-CH{=}CH-$), 7.36–7.44 (6H, m, Ph), 7.62–7.65 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 18.9, 26.3, 29.6, 31.2, 51.5, 62.6, 68.6, 127.2, 129.2, 130.7, 133.1, 133.5, 135.2, 135.3, 175.2; FABMS *m/z* 395 (M^++H). Anal. Calcd for $C_{24}H_{30}O_3Si$: C, 73.05; H, 7.66. Found: C, 72.99; H, 7.87.

4.7. Radical reaction of ***15***

Compound **15** (4.50 g, 6.52 mmol) was treated by the procedure described for the reaction of **14**. This gave **16** (2.40 g, 94%).

4.8. Radical reaction of ***12*** *(depicted in Scheme 4)*

Compound **12** (99 mg, 0.917 mmol) was treated by the procedure described for the reaction of **14**. After evaporation of the solvent, the reaction mixture was analyzed by ^{1}H NMR (**12/18**=85:15, calculated by integrating OMe).

4.9. Radical reaction of ***15*** *(depicted in Scheme 4)*

To a refluxing toluene (5 mL) solution of **15** (138 mg, 0.20 mmol), *i*-Pr_2NEt (105 μL, 0.60 mmol), and PhSH (10.3 μL, 0.10 mmol) was added dropwise a toluene (1 mL) solution of Bu_3SnH (108 μL, 0.40 mmol) and AIBN (6.6 mg, 0.04 mmol) over 5 h under positive pressure of dry Ar. After evaporation of the solvent, the reaction mixture was analyzed by ^{1}H NMR (**16/13**=70:30, calculated by integrating CH_2OSi).

4.10. Preparation of the epoxide ***19***

4.10.1. Method A

To a CH_2Cl_2 (5 mL) solution of **16** (341 mg, 0.87 mmol) was added *m*-CPBA (>65%, 242 mg, 0.91 mmol) and the mixture was stirred for 17 h at room temperature. The reaction mixture was treated with Et_3N (0.127 mL, 0.91 mmol) and then partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. Preparative TLC (hexane/AcOEt=2:1) of the organic layer gave *endo*-**19** (176 mg, 50%, foam) and *exo*-**19** (69 mg, 19%, foam).

*4.10.1.1. Physical data for endo-****19****.* ^{1}H NMR ($CDCl_3$) δ 1.04 (9H, s, SiBu-*tert*), 1.70 (1H, dd, *J*=14.6 and 2.2 Hz, H-8), 2.45 (1H, d, *J*=14.6 Hz, H-8), 2.81–2.84 (1H, m, H-5), 3.54–3.57 (2H, m, CH_2OSi and H-6), 3.65 (1H, t, *J*=2.2 Hz, H-7), 3.91 (1H, d, *J*=9.8 Hz, CH_2OSi), 4.48 (1H, dd, *J*=9.0 and 7.1 Hz, H-4), 4.53 (1H, dd, *J*=9.0 and 1.7 Hz, H-4), 7.37–7.48 (6H, m, Ph), 7.59–7.63 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.7, 34.3, 44.3, 54.9, 58.3, 60.4, 66.6, 68.4, 127.9, 130.0, 130.1, 135.4, 135.7, 180.0; FABMS *m/z* 409 (M^++H). Anal. Calcd for $C_{24}H_{28}O_4Si$: C, 70.55; H, 6.91. Found: C, 70.22; H, 6.89.

*4.10.1.2. Physical data for exo-****19****.* ^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s, SiBu-*tert*), 1.82 (1H, d, *J*=15.0 Hz, H-8), 2.16 (1H, dd, *J*=15.0 and 2.2 Hz, H-8), 3.45 (1H, dd, *J*=9.5 and 5.6 Hz, H-5), 3.51 (1H, d, *J*=9.3 Hz, CH_2OSi), 3.52 (1H, d, *J*=2.2 Hz, H-6), 3.56 (1H, t, *J*=2.2 Hz, H-7), 3.96 (1H, d, *J*=9.3 Hz, CH_2OSi), 4.15 (1H, dd, *J*=9.5 and 5.6 Hz, H-4), 4.40 (1H, t, *J*=9.5 Hz, H-4), 7.37–7.46 (6H, m, Ph), 7.61–7.64 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 18.7, 26.2, 34.1, 43.9, 57.3, 57.6, 61.4, 66.3, 67.2, 127.3, 127.4, 129.4, 131.9, 132.5, 135.0, 135.2, 179.7; FABMS *m/z* 409 (M^++H). Anal. Calcd for $C_{24}H_{28}O_4Si$: C, 70.55; H, 6.91. Found: C, 70.40; H, 6.93.

4.10.2. Method B

To a mixture of **16** (837 mg, 2.13 mmol) and AcOH (1.23 mL, 21.3 mmol) in CH_2Cl_2 (20 mL) wad added NIS (1.92 g, 8.52 mmol). The resulting mixture was stirred for 87 h at room temperature in the dark. After addition of saturated aqueous $Na_2S_2O_3$ (50 mL), the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was evaporated and treated with NaOMe (345 mg, 6.39 mmol) in MeOH (18 mL) for 30 min at room temperature. The reaction mixture was partitioned between 0.5 M HCl and CH_2Cl_2. Silica gel column chromatography (hexane/AcOEt=4:1) of the organic layer gave **19** (785 mg, 90%, *exo*/*endo*=7:1, calculated by integrating CH_2OSi). Compound **19** was used for the next ring opening reaction without separation.

*4.11. Epoxide ring cleavage of endo-****19*** *by phenylselenide anion*

The phenylselenide anion was prepared from $(PhSe)_2$ (131 mg, 0.41 mmol)/EtOH (10 mL) and $NaBH_4$ (31 mg, 0.83 mmol) with stirring for 10 min at room temperature. To this solution, an EtOH (3 mL) solution of *endo*-**19** (215 mg, 0.52 mmol) was added. After being stirred for 5 h at room temperature, the reaction mixture was partitioned between 0.5 M HCl and CH_2Cl_2. Preparative TLC (hexane/AcOEt=2:1) of the organic layer gave **20** (87 mg, 30%, foam) and **21** (169 mg, 57%, solid).

4.11.1. Physical data for ***20***

^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s, SiBu-*tert*), 1.60 (1H, dd, *J*=13.6 and 10.9 Hz, H-8), 2.31 (1H, br, OH), 2.38 (1H, dd, *J*=13.6 and 6.6 Hz, H-8), 3.14–3.18 (1H, m, H-5), 3.22–3.27 (1H, m, H-7), 3.52 (1H, d, *J*=9.7 Hz, CH_2OSi), 3.93 (1H, d, *J*=9.7 Hz, CH_2OSi), 4.05 (1H, t, *J*=8.0 Hz, H-6), 4.31 (1H, t, *J*=9.7 Hz, H-4), 4.62 (1H, dd, *J*=9.7 and 3.4 Hz, H-4), 7.24–7.32 (3H, m, Ph), 7.37–7.46 (6H, m, Ph), 7.50–7.52 (2H, m, Ph), 7.59–7.63 (4H, m, Ph); ^{13}C NMR ($CDCl_3$)

δ 19.2, 26.7, 36.6, 44.6, 46.5, 55.8, 65.8, 67.0, 77.5, 126.6, 127.8, 128.4, 129.4, 129.9, 132.2, 132.9, 135.3, 135.5, 135.6, 180.8; FABMS *m/z* 605 (M^++K). Anal. Calcd for $C_{30}H_{34}O_4SeSi$: C, 63.70; H, 6.06. Found: C, 63.33; H, 6.04.

*4.11.2. Physical data for **21***

Mp 127–128 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s, SiBu-*tert*), 1.99–2.09 (2H, m, H-8), 2.27 (1H, br, OH), 2.90–2.93 (1H, m, H-5), 3.45–3.47 (2H, m, H-6 and CH_2OSi), 4.00 (1H, d, *J*=9.2 Hz, CH_2OSi), 4.12–4.15 (1H, m, H-7), 4.27 (1H, dd, *J*=9.2 and 2.9 Hz, H-4), 4.50 (1H, t, *J*=9.2 Hz, H-4), 7.25–7.32 (3H, m, Ph), 7.35–7.53 (6H, m, Ph), 7.58–7.59 (2H, m, Ph), 7.60–7.62 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.7, 39.3, 47.8, 54.5, 56.3, 68.0, 72.7, 77.3, 127.8, 127.9, 128.3, 129.4, 129.9, 132.2, 132.8, 134.7, 135.5, 136.6, 181.5; FABMS *m/z* 567 (M^++H). Anal. Calcd for $C_{30}H_{34}O_4SeSi$: C, 63.70; H, 6.06. Found: C, 63.44; H, 6.08.

*4.12. Epoxide ring cleavage of exo-**19** by phenylselenide anion: formation of the allyl alcohol **22***

Compound **22** was prepared from *exo*-**19** (110 mg, 0.22 mmol) by the procedure described for the reaction of *endo*-**19**. Silica gel column chromatography (CH_2Cl_2) gave **22** (131 mg, 86%) as a foam.

Compound **22** was also obtained in 83% yield from **16** through method B in Scheme 5 without isolating *exo*-**19**.

*4.12.1. Physical data for **22***

^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s, SiBu-*tert*), 1.93 (1H, dd, *J*=14.4 and 10.2 Hz, H-8), 2.08 (1H, dd, *J*=14.4 and 8.1 Hz, H-8), 2.33 (1H, d, *J*=3.2 Hz, OH), 2.78–2.82 (1H, m, H-5), 3.22–3.29 (1H, m, H-7), 3.57 (1H, d, *J*=9.5 Hz, CH_2OSi), 3.80–3.85 (1H, m, H-6), 3.94 (1H, d, *J*=9.5 Hz, CH_2OSi), 4.33 (1H, dd, *J*=9.3 and 1.9 Hz, H-4), 4.50 (1H, dd, *J*=9.3 and 7.3 Hz, H-4), 7.26–7.63 (15H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 18.9, 26.4, 35.7, 47.7, 49.9, 53.5, 67.7, 70.2, 81.7, 127.6, 127.7, 128.3, 129.2, 129.8, 131.7, 132.4, 135.2, 135.3, 135.4, 180.4; FABMS *m/z* 605 (M^++K). Anal. Calcd for $C_{30}H_{34}O_4SeSi$: C, 63.70; H, 6.06. Found: C, 63.54; H, 6.14.

*4.13. (±)-c-1-(tert-Butyldiphenylsilyloxy)methyl-4-hydroxy-7-oxabicyclo-[3.3.0]oct-2-en-8-one (**23**)*

To a CH_2Cl_2 (50 mL) solution of **22** (1.9 g, 3.36 mmol) was added *m*-CPBA (>65%, 1.07 g, 4.03 mmol) and the mixture was stirred for 0.5 h at room temperature. After addition of Et_3N (2.34 mL, 16.8 mmol), the reaction mixture was refluxed for 1 h and then partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. Silica gel column chromatography (hexane/AcOEt=1:2) of the organic layer gave **23** (1.23 g, 90%, solid). Mp 120–121 °C; ^{1}H NMR ($CDCl_3$) δ 1.06 (9H, s, SiBu-*tert*), 2.43 (1H, d, *J*=10.3 Hz, OH), 3.04 (1H, dd, *J*=9.5 and 6.9 Hz, H-5), 3.82 (1H, d, *J*=10.3 Hz, CH_2OSi), 3.89 (1H, dd, *J*=9.5 and 6.9 Hz, H-4), 3.91 (1H, d, *J*=10.3 Hz, CH_2OSi), 4.54 (1H, dd, *J*=10.3 and 2.3 Hz, H-6), 4.61 (1H, t, *J*=9.5 Hz, H-4), 5.73 (1H, d, *J*=5.2 Hz, H-8), 6.12 (1H, dd, *J*=5.2 and 2.3 Hz, H-7), 7.38–7.47 (6H, m, Ph), 7.61–7.64 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.8, 51.5, 63.5, 65.1, 69.6, 81.3, 127.9, 130.1, 131.9, 132.0, 132.1, 135.6, 136.3, 175.8; FABMS *m/z* 409 (M^++H). Anal. Calcd for $C_{24}H_{28}O_4Si$: C, 70.55; H, 6.91. Found: C, 70.41; H, 6.95.

*4.14. (±)-t-1-(tert-Butyldiphenylsilyloxy)methyl-4-hydroxy-7-oxabicyclo-[3.3.0]oct-2-en-8-one (**24**)*

To a stirred THF (2 mL) solution containing **23** (105 mg, 0.257 mmol), PPh_3 (202 mg, 0.771 mmol), and AcOH (73.6 μL, 1.29 mmol) was added DEAD (2.2 M in toluene, 352 μL, 0.771 mmol) at 0 °C. After stirring for 15 min, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was evaporated and the resulting residue was dissolved in MeOH (4 mL) containing K_2CO_3 (80 mg, 0.514 mmol). After being stirred for 15 min at 0 °C, the reaction mixture was partitioned between 0.5 M HCl and CH_2Cl_2. Silica gel column chromatography (hexane/AcOEt=3:1) of the organic layer gave **24** (103 mg, 98%, solid). Mp 139–140 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s, SiBu-*tert*), 1.68 (1H, d, *J*=7.3 Hz, OH), 3.21–3.26 (1H, m, H-5), 3.55 (1H, d, *J*=9.8 Hz, CH_2OSi), 4.12 (1H, d, *J*=9.8 Hz, CH_2OSi), 4.40 (1H, t, *J*=9.0 Hz, H-4), 4.64 (1H, dd, *J*=9.0 and 4.9 Hz, H-4), 5.00–5.04 (1H, m H-6), 5.67 (1H, dd, *J*=5.6 and 1.5 Hz, H-8), 5.94 (1H, dd, *J*=5.6 and 2.0 Hz, H-7), 7.37–7.47 (6H, m, Ph), 7.62–7.66 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.0, 26.5, 44.6, 64.0, 65.6, 65.8, 76.9, 127.6, 129.7, 130.8, 132.1, 132.7, 135.3, 135.4, 136.9, 177.5; FABMS *m/z* 409 (M^++H). Anal. Calcd for $C_{24}H_{28}O_4Si$: C, 70.55; H, 6.91. Found: C, 70.45; H, 6.98.

*4.15. Mitsunobu reaction between **24** and 6-chloropurine, and subsequent ammonolysis*

To a stirred THF (100 mL) solution containing **24** (2.0 g, 4.90 mmol), PPh_3 (3.91 g, 12.2 mmol), and 6-chloropurine (1.13 g, 7.34 mmol) was added dropwise DIAD (6.42 mL, 12.2 mmol) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was purified by silica gel column chromatography. Elution with hexane/AcOEt=3:1 gave a mixture of **25** and triphenylphosphine oxide. Elution with hexane/AcOEt=1:1 gave **26** (240 mg, 9%, foam). The crude **25** dissolved in THF (10 mL) was transferred in a sealed tube containing NH_3/MeOH (200 mL) and the whole mixture was heated at 120 °C for 6 h. After evaporation, the reaction mixture was purified by silica gel column chromatography. Elution with $CHCl_3$/MeOH=80:1 gave **27** (1.75 g, 68% from **24**, solid), which was recrystallized from MeOH/CH_2Cl_2. Elution with $CHCl_3$/MeOH=30:1 gave **28** (120 mg, 5% from **24**, solid).

*4.15.1. Physical data for **26***

^{1}H NMR ($CDCl_3$) δ 0.97 (9H, s, SiBu-*tert*), 3.02–3.03 (1H, m H-5′), 3.48 (1H, d, *J*=10.0 Hz, CH_2OSi), 4.38 (1H, d,

J=10.0 Hz, CH_2OSi), 4.41 (1H, dd, J=10.0 and 5.2 Hz, H-4′), 4.76 (1H, t, J=10.0 Hz, H-4′), 5.92–5.93 (1H, m, H-6′), 6.11 (1H, dd, J=5.2 and 2.3 Hz, H-8′), 6.23 (1H, dd, J=5.2 and 1.7 Hz, H-7′), 7.12–7.20 (3H, m, Ph), 7.28–7.31 (2H, m, Ph), 7.34–7.38 (3H, m, Ph), 7.49–7.51 (2H, m, Ph), 7.80 (1H, s, H-8), 8.95 (1H, s, H-2); ^{13}C NMR ($CDCl_3$) δ 19.0, 26.6, 49.8, 65.5, 68.8, 70.2, 121.8, 127.7, 127.8, 129.5, 129.9, 130.0, 131.8, 132.2, 135.0, 135.4, 137.2, 142.5, 145.6, 152.6, 162.3, 174.6; FABMS m/z 545 (M^++H). Anal. Calcd for $C_{29}H_{29}ClN_4O_3Si$: C, 63.90; H, 5.36; N, 10.28. Found: C, 63.62; H, 5.32; N, 10.21.

4.15.2. Physical data for ***27***

Mp 229–231 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (9H, s, SiBu-*tert*), 3.13–3.15 (1H, m, H-5′), 3.72 (1H, d, J=10.0 Hz, CH_2OSi), 4.32 (1H, d, J=10.0 Hz, CH_2OSi), 4.58 (1H, dd, J=9.7 and 3.4 Hz, H-4′), 4.70 (1H, t, J=9.7 Hz, H-4′), 5.89 (2H, br, NH_2), 6.02 (1H, dd, J=5.4 and 2.0 Hz, H-8′), 6.05 (1H, dd, J=5.4 and 2.0 Hz, H-7′), 6.59–6.60 (1H, m, H-6′), 7.25–7.58 (10H, m, Ph), 7.59 (1H, s, H-8), 8.33 (1H, s, H-2); ^{13}C NMR ($CDCl_3$) δ 19.1, 26.7, 50.3, 65.2, 65.9, 67.1, 71.7, 120.1, 127.8, 127.9, 129.9, 130.0, 130.7, 131.9, 132.5, 135.0, 135.3, 135.6, 137.0, 149.7, 153.2, 155.5, 175.9; FABMS m/z 526 (M^++H). Anal. Calcd for $C_{29}H_{31}N_5O_3Si$: C, 66.26; H, 5.94; N, 13.32. Found: C, 66.06; H, 5.85; N, 13.44.

4.15.3. Physical data for ***28***

Mp 200–202 °C; ^{1}H NMR (DMSO-d_6) δ 1.00 (9H, s, SiBu-*tert*), 2.64 (1H, dd, J=14.5 and 7.2 Hz, H-5′), 3.53–3.59 (1H, m, CH_2OH), 3.68–3.74 (1H, m, CH_2OH), 3.90 (1H, d, J=9.7 Hz, CH_2OSi), 4.11 (1H, d, J=9.7 Hz, CH_2OSi), 4.54 (1H, dd, J=5.7 and 4.5 Hz, OH), 5.52–5.55 (1H, m, H-1′), 6.10 (1H, dd, J=5.7 and 1.8 Hz, C*H*=CH), 6.22 (1H, dd, J=5.7 and 2.0 Hz, C*H*=CH), 6.98 (1H, br, NH_2), 7.22 (2H, br, NH_2), 7.34 (1H, br, NH_2), 7.40–7.48 (6H, m, Ph), 7.64–7.68 (4H, m, Ph), 7.94 (1H, s, H-8), 8.06 (1H, s, H-2); ^{13}C NMR (DMSO-d_6) δ 19.0, 26.6, 52.4, 60.7, 62.7, 63.2, 67.4, 79.2, 119.0, 127.8, 127.9, 129.8, 132.8, 132.9, 135.1, 135.2, 136.5, 138.9, 149.4, 152.2, 156.0, 173.0; FABMS m/z 543 (M^++H). Anal. Calcd for $C_{29}H_{34}N_6O_3Si\cdot H_2O$: C, 62.12; H, 6.47; N, 14.99. Found: C, 62.39; H, 6.12; N, 14.91.

4.16. Mitsunobu reaction between ***24*** *and bis(Boc)-adenine (****29****), and subsequent hydrolysis*

To a THF (50 mL) solution containing **24** (2.89 g, 7.07 mmol), Ph_3P (2.36 g, 8.98 mmol), and bis(Boc)adenine (**29**)[18] (3.01 g, 8.98 mmol) was added dropwise DIAD (1.77 mL, 8.98 mmol) at −40 °C. The resulting mixture was stirred for 18 h at −40 °C. After evaporation of the solvent, the reaction mixture was purified by flash silica gel column chromatography (hexane/AcOEt=1:1). The crude product obtained was dissolved in THF (25 mL) containing 50% aqueous HCO_2H (50 mL) and the whole mixture was heated at 50 °C for 9 h. After evaporation, the residue was treated with 26% NH_4OH (2 mL) and then evaporated to dryness. Silica gel column chromatography ($CHCl_3$/MeOH=11:1) of the residue gave **27** (3.09 g, 83%).

4.17. (±)-c-4-(Adenine-9-yl)-1-(tert-butyldiphenylsilyloxy)methyl-7-oxabicyclo-[3.3.0]oct-2-en-8-ol: the cyclic hemiacetal ***30***

To a CH_2Cl_2 (10 mL) solution of **27** (200 mg, 0.49 mmol) was added *i*-Bu_2AlH (1.01 M in toluene, 1.46 mL, 1.47 mmol) at −70 °C. The resulting mixture was stirred for 15 min at −70 °C and the reaction was quenched by adding saturated aqueous NH_4Cl. The reaction mixture was partitioned between 0.5 M HCl and CH_2Cl_2. Silica gel column chromatography ($CHCl_3$/MeOH=10:1) of the organic layer gave **30** (194 mg, 97%, a mixture of two isomers ca. 4:1) as a foam.

4.17.1. Physical data for ***30***

^{1}H NMR (DMSO-d_6) δ 0.96 and 0.97 (11.25H, each as s, SiBu-*tert*), 2.60–2.64 (1H, m, H-5′), 3.68 (1H, d, J=10.0 Hz, CH_2OSi), 3.74–3.75 (0.5H, m, CH_2OSi), 3.93–4.02 (2.5H, m, CH_2OSi and H-4′), 5.19 (1H, d, J=4.4 Hz, OC*H*OH), 5.24 (0.25H, d, J=5.0 Hz, OC*H*OH), 5.35–5.37 (1.25H, m, H-6′), 5.97 (0.25H, dd, J=5.6 and 2.0 Hz, C*H*=CH), 6.01 (0.25H, dd, J=5.6 and 1.7 Hz, C*H*=CH), 6.11 (1H, dd, J=5.6 and 2.2 Hz, C*H*=CH), 6.30 (1H, dd, J=5.6 and 1.7 Hz, C*H*=CH), 6.33 (1H, d, J=4.4 Hz, OH), 6.50 (0.25H, d, J=5.0 Hz, OH), 7.20 (2.5H, br, NH_2), 7.33–7.64 (12.5H, m, Ph), 7.75 (1H, s, H-8), 7.82 (0.25H, s, H-8), 8.07 (0.25H, s, H-2), 8.10 (1H, s, H-2); ^{13}C NMR (DMSO-d_6) δ 18.9, 26.6, 26.7, 51.7, 52.5, 64.8, 66.0, 66.3, 67.9, 68.0, 68.4, 70.5, 99.1, 99.5, 118.8, 118.9, 127.9, 128.9, 129.1, 129.8, 129.9, 130.0, 132.6, 132.7, 132.8, 139.5, 140.0, 141.3, 148.3, 148.4, 148.6, 153.0; FABMS m/z 528 (M^++H). Anal. Calcd for $C_{29}H_{33}N_5O_3Si$: C, 66.01; H, 6.30; N, 13.27. Found: C, 65.99; H, 6.18; N, 13.27.

*4.18. (±)-9-[c-4-(tert-Butyldiphenylsilyloxy)methyl-t-4,t-5-bis(hydroxymethyl)-cyclopent-2-en-r-1-yl]-9H-adenine (****31****)*

To a MeOH (40 mL) solution of **30** (200 mg, 0.38 mmol) was added $NaBH_4$ (43 mg, 1.14 mmol) at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was partitioned between 0.5 M HCl and $CHCl_3$. Silica gel column chromatography ($CHCl_3$/MeOH=20:1) of the organic layer gave **31** (173 mg, 86%) as an oil.

^{1}H NMR ($CDCl_3$) δ 1.00 (9H, s, SiBu-*tert*), 2.56–2.62 (1H, m, H-5′), 3.57–3.83 (6H, m, CH_2OSi and CH_2OH), 4.58 (1H, t, J=4.8 Hz, OH), 4.70 (1H, t, J=5.0 Hz, OH), 5.42–5.45 (1H, m, H-1′), 5.92 (1H, dd, J=5.7 and 1.5 Hz, H-2′ or H-3′), 6.00 (1H, dd, J=5.7 and 2.1 Hz, H-2′ or H-3′), 7.20 (2H, br, NH_2), 7.39–7.48 (6H, m, Ph), 7.61–7.64 (4H, m, Ph), 7.94 (1H, s, H-8), 8.09 (1H, s, H-2); ^{13}C NMR ($CDCl_3$) δ 18.7, 26.4, 52.5, 57.6, 59.0, 61.6, 62.1, 66.8, 118.6, 127.6, 127.7, 129.6, 130.2, 130.7, 132.7, 134.9, 138.4, 138.8, 149.3, 152.1, 155.7; FABMS m/z 530 (M^++H). Anal.

Calcd for $C_{29}H_{35}N_5O_3Si\cdot 1/5H_2O$: C, 65.31; H, 6.69; N, 13.13. Found: C, 65.02; H, 6.70; N, 12.90.

4.19. (±)-9-[c-4-(tert-Butyldiphenylsilyloxy)methyl-t-5-hydroxymethyl-t-4-vinylcyclopent-2-en-r-1-yl]-9H-adenine (32)

To a suspension of methyltriphenylphosphonium bromide (1.04 g, 2.91 mmol) in THF (30 mL) was added dropwise BuLi (1.67 M in hexane, 1.57 mL, 2.62 mmol) at −78 °C. The resulting suspension was allowed to warm to 0 °C and stirred for 1 h. To this, a THF (4 mL) solution of **30** (154 mg, 0.29 mmol) was added at −78 °C. The reaction mixture was stirred at room temperature for 12 h, and then partitioned between saturated aqueous NH_4Cl and Et_2O. Silica gel column chromatography ($CHCl_3$/MeOH=80:1) of the organic layer gave **32** (146 mg, 96%) as a foam.

^{1}H NMR ($CDCl_3$) δ 1.00 (9H, s, SiBu-*tert*), 2.68−2.73 (1H, m H-5′), 3.50−3.54 (1H, m, CH_2OH), 3.60−3.65 (1H, m, CH_2OH), 3.82 (1H, d, J=9.7 Hz, CH_2OSi), 3.84 (1H, d, J=9.7 Hz, CH_2OSi), 4.56 (1H, t, J=4.6 Hz, OH), 5.01 (1H, dd, J=17.8 and 1.7 Hz, CH=CH_2), 5.19 (1H, dd, J=10.6 and 1.7 Hz, CH=CH_2), 5.23 (1H, d, J=8.0 Hz, H-1′), 5.98 (1H, dd, J=17.8 and 10.6 Hz, CH=CH_2), 6.02−6.04 (2H, m, H-2′ and H-3′), 7.24 (2H, br, NH_2), 7.40−7.48 (6H, m, Ph), 7.61−7.64 (4H, m, Ph), 7.97 (1H, s, H-8), 8.08 (1H, s, H-2); ^{13}C NMR ($CDCl_3$) δ 19.0, 26.6, 53.4, 58.8, 60.5, 61.7, 68.8, 115.9, 118.9, 127.9, 129.8, 129.9, 130.6, 132.9, 135.2, 138.4, 138.6, 138.8, 149.4, 152.3, 156.0; FABMS *m/z* 526 (M^++H). Anal. Calcd for $C_{30}H_{35}N_5O_2Si\cdot 1/10H_2O$: C, 68.31; H, 6.73; N, 13.28. Found: C, 68.04; H, 6.72; N, 13.11.

4.20. (±)-c-4-(Adenine-9-yl)-1-(tert-butyldiphenylsilyloxy)methyl-7-oxabicyclo-[3.3.0]oct-2-en-8-ylacetic acid methyl ester (33)

A mixture of **30** (38 mg, 0.07 mmol) and Ph_3P=$CHCO_2Me$ (60 mg, 0.18 mmol) in xylene (8 mL) was refluxed for 24 h. The reaction mixture was partitioned between H_2O and $CHCl_3$. Silica gel column chromatography ($CHCl_3$/MeOH=50:1) of the organic layer gave **33** (30 mg, 72%, a single isomer, stereochemistry not known) as a foam.

^{1}H NMR ($CDCl_3$) δ 1.06 (9H, s, SiBu-*tert*), 2.45−2.47 (2H, m, H-5′ and CHCH_2CO_2Me), 2.68 (1H, dd, J=15.2 and 4.0 Hz, CHCH_2CO_2Me), 3.71 (3H, s, OMe), 3.78−3.84 (3H, m, CH_2OSi and CH_2O−), 4.21 (1H, dd, J=9.7 and 4.0 Hz, CHCH_2CO_2Me), 4.29 (1H, d, J=9.7 Hz, CH_2O−), 5.49−5.51 (1H, m, H-1′), 5.76 (2H, br, NH_2), 5.95 (1H, dd, J=5.7 and 2.2 Hz, CH=CH), 6.03 (1H, dd, J=5.7 and 2.2 Hz, CH=CH), 7.34−7.47 (6H, m, Ph), 7.59−7.63 (5H, m, Ph and H-8), 8.30 (1H, s, H-2); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.9, 37.1, 51.9, 55.6, 66.6, 67.1, 67.5, 72.8, 80.2, 120.0, 127.8, 130.0, 130.8, 132.6, 135.5, 135.6, 137.3, 138.1, 149.8, 153.0, 153.7, 155.3, 171.5; FABMS *m/z* 584 (M^++H). Anal. Calcd for $C_{32}H_{37}N_5O_4Si$: C, 65.84; H, 6.39; N, 12.00. Found: C, 65.85; H, 6.39; N, 12.12.

4.21. (±)-9-[t-5-Acetoxymethyl-c-4-(tert-butyldiphenylsilyloxy)methyl-t-4-cyanocyclopent-2-en-r-1-yl]-9H-adenine (34)

A mixture of **30** (197 mg, 0.37 mmol) and $NH_2OH\cdot HCl$ (520 mg, 7.48 mmol) in pyridine (5 mL) was stirred at room temperature for 3 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. The organic layer was evaporated to leave the crude oxime. The crude oxime was dissolved in MeCN (12 mL) and reacted with Ac_2O (106 μL, 1.12 mmol) in the presence of *i*-Pr_2NEt (195 μL, 1.12 mmol) and DMAP (137 mg, 1.12 mmol) for 1 h. The reaction mixture was partitioned between 0.5 M HCl and $CHCl_3$. After evaporation of the organic layer, the residue was dissolved in AcOH (6 mL) containing NaOAc (27 mg, 0.33 mmol) and the whole mixture was heated at 100 °C for 3 h. The reaction mixture was evaporated, and then partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. Silica gel column chromatography ($CHCl_3$/MeOH=60:1) of the organic layer gave **34** (178 mg, 84% from **30**) as a foam. IR (neat) 2236 cm^{-1} (C≡N); ^{1}H NMR ($CDCl_3$) δ 1.10 (9H, s, SiBu-*tert*), 1.83 (3H, s, Ac), 2.94 (1H, dd, J=14.3 and 7.4 Hz, H-5′), 3.93 (1H, d, J=9.7 Hz, CH_2OSi), 4.01 (1H, d, J=9.7 Hz, CH_2OSi), 4.49−4.58 (2H, m, CH_2OAc), 5.67−5.69 (1H, m, H-1′), 6.02 (2H, br, NH_2), 6.10 (1H, dd, J=5.7 and 1.7 Hz, CH=CH), 6.14 (1H, dd, J=5.7 and 2.3 Hz, CH=CH), 7.27−7.49 (6H, m, Ph), 7.65−7.70 (5H, m, Ph and H-8), 8.26 (1H, s, H-2); ^{13}C NMR ($CDCl_3$) δ 19.3, 20.4, 26.7, 49.1, 53.3, 62.3, 63.4, 67.2, 117.8, 119.8, 127.9, 130.2, 132.0, 132.1, 133.2, 133.5, 135.5, 135.6, 138.4, 149.8, 153.1, 155.6, 170.2; FABMS *m/z* 567 (M^++H). Anal. Calcd for $C_{31}H_{34}N_6O_3Si\cdot 3/10H_2O$: C, 65.08; H, 6.10; N, 14.69. Found: C, 64.86; H, 5.93; N, 14.54.

4.22. (±)-9-[c-4-(tert-Butyldiphenylsilyloxy)methyl-t-4-ethynyl-t-5-hydroxymethylcyclopent-2-en-r-1-yl]-9H-adenine (35)

To a LDA solution in THF (30 mL), prepared from diisopropylamine (626 μL, 4.47 mmol) and BuLi (1.66 M in hexane, 2.53 mL, 4.2 mmol) at 0 °C, $TMSCHN_2$ (0.6 M in hexane, 7.45 mL, 4.47 mmol) was added at −78 °C. The mixture was stirred at −78 °C for 0.5 h. Compound **30** (295 mg, 0.56 mmol) in THF (30 mL) was added to the mixture at −78 °C. The whole mixture was stirred for 0.5 h at −78 °C and then for 3 h at room temperature. The reaction was quenched by adding saturated aqueous NH_4Cl. Extraction with $CHCl_3$ followed by preparative TLC ($CHCl_3$/MeOH=20:1) gave **35** (92 mg, 31%) as a foam. IR (neat) 2220 cm^{-1} (C≡C); ^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s, SiBu-*tert*), 2.38 (1H, s, C≡CH), 2.57−2.62 (1H, m, H-5′), 3.76 (1H, d, J=10.0 Hz, CH_2OSi), 3.79 (1H, d, J=10.0 Hz, CH_2OSi), 3.80 (1H, br, OH), 3.97−4.07 (2H, m, CH_2OH), 5.62−5.64 (1H, m, H-1′), 5.68 (2H, br, NH_2), 5.96 (1H, dd, J=5.6 and 2.0 Hz, H-2′), 6.04 (1H, dd, J=5.6 and 2.0 Hz, H-3′), 7.34−7.45 (6H, m, Ph), 7.60−7.65 (4H, m, Ph), 7.75 (1H, s, H-8), 8.35 (1H, s, H-2); ^{13}C NMR ($CDCl_3$) δ 19.3, 26.9, 52.6,

53.8, 62.6, 62.9, 68.9, 74.1, 81.8, 119.9, 127.8, 129.2, 129.9, 132.7, 135.5, 135.6, 138.3, 138.9, 149.7, 152.9, 155.6; FABMS *m/z* 524 (M^++H). Anal. Calcd for $C_{30}H_{33}N_5O_2Si$: C, 68.80; H, 6.35; N, 13.37. Found: C, 68.54; H, 6.40; N, 13.35.

*4.23. (±)-9-[c-4,t-4,t-5-Tris(hydroxymethyl)-cyclopent-2-en-r-1-yl]-9H-adenine (**36**)*

To a THF (8 mL) solution of **31** (154 mg, 0.291 mmol) was added Bu_4NF (1 M solution in THF, 320 μL, 0.32 mmol). After being stirred for 0.5 h, the reaction mixture containing the free nucleoside was reacted with Ac_2O (110 μL, 1.16 mmol) in the presence of *i*-Pr_2NEt (210 μL, 0.32 mmol) and DMAP (143 mg, 1.16 mmol) for 1 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. Silica gel column chromatography (CH_2Cl_2/MeOH=100:1) of the organic layer gave the triacetate (99 mg). The triacetate was treated with NH_3/MeOH (5 mL) at 5 °C for 24 h. After evaporation, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=40:1). This gave **36** (48 mg, 74%) as a foam.

^{1}H NMR (CD_3OD) δ 2.54–2.60 (1H, m, H-5′), 3.61–3.96 (6H, m, C*H*$_2$OH), 5.58–5.61 (1H, m H-1′), 5.95 (1H, dd, *J*=5.6 and 1.7 Hz, H-2′ or H-3′), 6.00 (1H, dd, *J*=5.6 and 2.1 Hz, H-2′ or H-3′), 8.17 and 8.18 (2H, each as s, H-8 and H-2); ^{13}C NMR (DMSO-d_6) δ 53.8, 57.9, 59.1, 61.9, 62.3, 65.3, 118.9, 130.2, 139.1, 139.2, 149.5, 152.2, 155.9; FABMS *m/z* 292 (M^++H). Anal. Calcd for $C_{13}H_{17}N_5O_3\cdot 1/5H_2O$: C, 52.95; H, 5.95; N, 23.75. Found: C, 53.18; H, 6.03; N, 23.51.

*4.24. (±)-9-[c-4,t-5-Bis(hydroxymethyl)-t-4-vinylcyclopent-2-en-r-1-yl]-9H-adenine (**37**)*

Compound **37** (42 mg, 69%) was obtained as a foam from **32** (113 mg, 0.214 mmol) by the procedure described for the preparation of **36**. ^{1}H NMR (CD_3OD) δ 2.65–2.70 (1H, m, H-5′), 3.63–3.81 (4H, m, C*H*$_2$OH), 5.12 (1H, dd, *J*=17.6 and, 1.5 Hz, CH=C*H*$_2$), 5.25 (1H, dd, *J*=10.7 and 1.5 Hz, CH=C*H*$_2$), 5.39 (1H, d, *J*=7.6 Hz, H-1′), 5.96–6.03 (3H, m, H-2′, H-3′ and C*H*=CH$_2$), 8.18 (1H, s, H-8), 8.20 (1H, s, H-2); ^{13}C NMR (DMSO-d_6) δ 55.7, 60.5, 62.3, 64.1, 68.7, 117.0, 120.1, 131.3, 138.8, 140.7, 141.2, 150.6, 153.6, 157.3; FABMS *m/z* 288 (M^++H). Anal. Calcd for $C_{14}H_{17}N_5O_2\cdot 1/10H_2O$: C, 58.16; H, 6.00; N, 24.22. Found: C, 58.08; H, 5.94; N, 24.48.

*4.25. (±)-9-[t-4-Ethynyl-c-4,t-5-bis(hydroxymethyl)-cyclopent-2-en-r-1-yl]-9H-adenine (**38**)*

Compound **38** (44 mg, 70%, solid) was obtained from **35** (116 mg, 0.22 mmol) by the procedure described for the preparation of **36**. Mp 113–115 °C; IR (KBr) 2100 cm^{-1} (C≡C); ^{1}H NMR (DMSO-d_6) δ 2.60 (1H, q, *J*=7.5 Hz, H-5′), 3.16 (1H, s, ethynyl), 3.56–3.59 (1H, m, C*H*$_2$OH), 3.62–3.67 (2H, m, C*H*$_2$OH), 3.82–3.87 (1H, m, C*H*$_2$OH), 4.61–4.63 (1H, m, OH), 5.21–5.24 (1H, m, OH), 5.37 (1H, dt, *J*=7.5 and 2.3 Hz, H-1′), 5.88 (1H, dd, *J*=5.2 and 2.3 Hz, H-2′ or H-3′), 5.97 (1H, dd, *J*=5.2 and 2.3 Hz, H-2′ or H-3′), 7.19 (2H, br, NH_2), 8.05 (1H, s, H-8), 8.11 (1H, s, H-2); ^{13}C NMR (DMSO-d_6) δ 52.2, 52.4, 61.4, 62.3, 66.8, 75.7, 82.9, 118.8, 130.4, 137.3, 139.1, 149.2, 152.2, 155.9; FABMS *m/z* 286 (M^++H). Anal. Calcd for $C_{14}H_{15}N_5O_2\cdot 3/4H_2O$: C, 56.11; H, 5.58; N, 23.37. Found: C, 56.30; H, 5.35; N, 23.29.

*4.26. (±)-c-4-(Adenine-9-yl)-1-hydroxymethyl-7-oxabicyclo-[3.3.0]oct-2-en-8-ylideneamine (**39**)*

To a THF (8 mL) solution of **34** (135 mg, 0.238 mmol) was added Bu_4NF (1 M solution in THF, 262 μL, 0.262 mmol). After being stirred for 1 h, the reaction mixture containing the free nucleoside was reacted with Ac_2O (34 μL, 0.36 mmol) in the presence of *i*-Pr_2NEt (104 μL, 0.59 mmol) and DMAP (44 mg, 0.36 mmol) for 1 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. Silica gel column chromatography (CH_2Cl_2/MeOH=40:1) of the organic layer gave the diacetate (87 mg). The acetate was treated with NH_3/MeOH (5 mL) at 5 °C for 18 h. During evaporation of the solvent, precipitation occurred. The precipitate was washed with hot benzene (50 mL) to give an analytically pure **39** (38 mg, 79%, solid, mixture of two isomers ca. 6:4). Mp 237 °C; ^{1}H NMR (DMSO-d_6) δ 3.06–3.11 (1H, m, H-5′), 3.66–3.76 (2H, m, C*H*$_2$OH), 4.24–4.29 (1H, m, C*H*$_2$O), 4.41–4.47 (1H, m, C*H*$_2$O), 5.01–5.02 (0.6H, m, OH), 5.14–5.16 (0.4H, m, OH), 5.49–5.51 (1H, m, H-1′), 5.99–6.02 (1.6H, m, CH=CH), 6.09–6.11 (0.4H, m, CH=CH), 7.25 (2H, br, NH_2), 7.63 (0.6H, s, NH), 7.93 (0.4H, s, NH), 8.01 (0.4H, s, H-8), 8.03 (0.6H, s, H-8), 8.15 (1H, s, H-2); ^{13}C NMR (DMSO-d_6) δ 50.6, 50.7, 63.9, 64.4, 64.5, 65.5, 66.1, 71.5, 72.1, 119.0, 119.1, 129.2, 129.4, 136.8, 137.9, 138.7, 138.8, 149.1, 152.4, 156.0, 169.9, 174.6; FABMS *m/z* 287 (M^++H). Anal. Calcd for $C_{13}H_{14}N_6O_2\cdot 1/10H_2O$: C, 54.20; H, 4.97; N, 29.17. Found: C, 54.13; H, 4.89; N, 29.11.

4.27. Anti-HIV-1 assay

MT-4 cells (1×10^5 cells/mL) were infected with HIV-1 (HTLV-III$_B$ strain) at a multiplicity of infection (MOI) of 0.02 and were cultured in the presence of various concentrations of the test compounds. After a 4-day incubation at 37 °C, the number of viable cells was monitored by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide method. The cytotoxicity of the compounds was evaluated in parallel with their antiviral activity, based on the viability of mock-infected cells.

4.28. Anti-HCV assay

OR6 cells, a cell line cloned from ORN/C-5B/KE cells22) that supports genome-length HCV RNA (strain O of genotype 1b) encoding *Renilla* luciferase reporter gene, were cultured in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum in the presence of G418 (300 mg/mL: Geneticin; Invitrogen, Carlsbad, CA). To monitor the anti-HCV effects of the compounds, OR6 cells were plated onto

24-well plates in triplicate (1.5×10^4 cells per well) and cultured for 24 h. Then, the cells were treated with the compounds (10 μM each) for 72 h. After treatment, the cells were harvested with *Renilla* luciferase lysis reagent (Promega, Madison, WI) and subjected to the *Renilla* luciferase assay according to the manufacturer's protocol.

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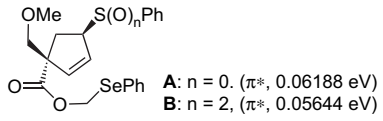

A: n = 0. (π*, 0.06188 eV)
B: n = 2, (π*, 0.05644 eV)

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