Approaches to Unsaturated Analogues of Nucleosides Comprising Four- and Six-Membered Rings

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Unsaturated nucleoside analogues **21**, **22**, **46**, and **54**, comprising four- and six-membered rings, were synthesized using two different approaches. The 2-benzyloxycycloalkanones **23a** and **23b** served as starting materials for both methods. Conversion to methylenecyclobutanes **29a** and **29b** was followed by addition of bromine via pyridinium perbromide to give vicinal dibromides **30a** and **30b**. Reaction of **29a** with Br_2 gave a ring-contracted cyclopropane derivative **31**. Alkylation−elimination of adenine with **30a** gave bromoalkene **32** as the major product and adenine-containing unsaturated derivatives **33**, **34**, and **35** as minor components. Vicinal dibromide **30b** gave the Zaitsev cyclohexene **45** as the only product. Epoxidation of **29a** and **29b** afforded oxiranes **36a** and **36b** which were used in alkylation of adenine to furnish hydroxy derivatives **37a**, **37b**, **38a**, and **38b**. β-Elimination via mesylates **39a** and **40a** using tBuOK/DMF gave *Z*- and *E*-methylenecyclobutanes **34** and **35**. With an excess of base the *E*-bis-methylenecyclobutane **41** was obtained. Mesylation of cyclohexane derivatives **37b** and **38b** gave the *Z*- and *E*-N^6-mesylated product **48**. By contrast, the N^6-benzoyl derivatives **49** and **50** afforded *O*-mesyl intermediates **51** and **52**. β-Elimination gave both Hofmann and Zaitsev products **53** and **45**. *O*-Debenzylation of **34** and **35**, **45**, and **53** afforded analogues **21**, **22**, **46**, and **54**. The *E*-isomer **22** was also obtained by hydroboration procedure from *E*-bis-methylenecyclobutane **41**.

Introduction

Unsaturated analogues of nucleosides are in the center of current interest as potential antiviral and antitumor agents. This diverse class of compounds includes antibiotics decoyinine (angustmycin A)[1] (**1**) and neplanocin[2] A (**2**), AIDS drug stavudine[3] (**3a**), anti-HIV agents carbovir[4] (**3b**) and (−)-BCA[5] **4**, antitumor agent 2′-deoxy-2′-methylenecytidine[6] (DMDC, **5**), and carbocyclic analogue BMS 200475 (**6**)[7] effective against hepatitis B virus (HBV). The 3′,4′-unsaturated nucleosides **7** are also known.[8] Likewise, significant attention has been paid to the development of synthetic methods for four-membered ring structures with exocyclic or endocyclic double bonds such as compounds[9−11] **8**−**11**. This effort was undoubtedly motivated by the antiviral activity of antibiotic oxetanocin A (**12a**) and the carbocyclic guanine analogue[12] **12b**. Syntheses of cyclohexene analogues **13**−**15** related to carbovir[4] (**3b**) were also subjects of several investigations.[13−15] Structures of **1**−**22** are shown in Chart 1.

It is noteworthy that most of the unsaturated nucleoside analogues studied thus far are substituted at an allylic position of the unsaturated carbohydrate (carbocyclic) moiety by a nucleic acid base (compounds **2**−**6**, **8**, **10**, **11**, and **13**−**15**). Nevertheless, analogues of an enamine type, with a double bond attached to a heterocyclic base, such as 1′,2′-unsaturated nucleosides[16] **16**, *N*-vinyl nucleic acid bases[17a] **17**, and derivatives thereof[17b,c] **18** are known. In this group of analogues, methyl-

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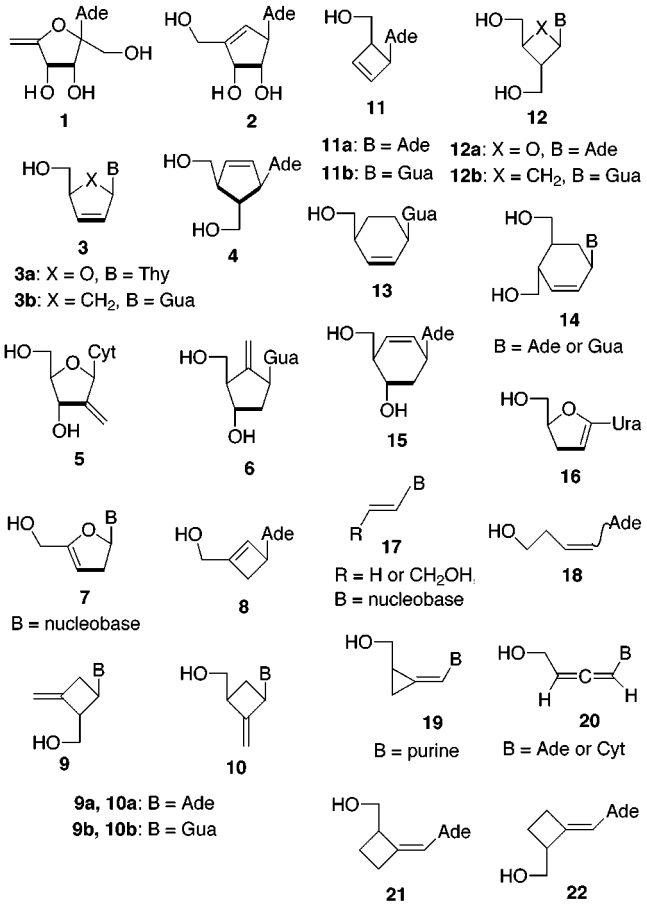
Chart 1. Structures 1−22

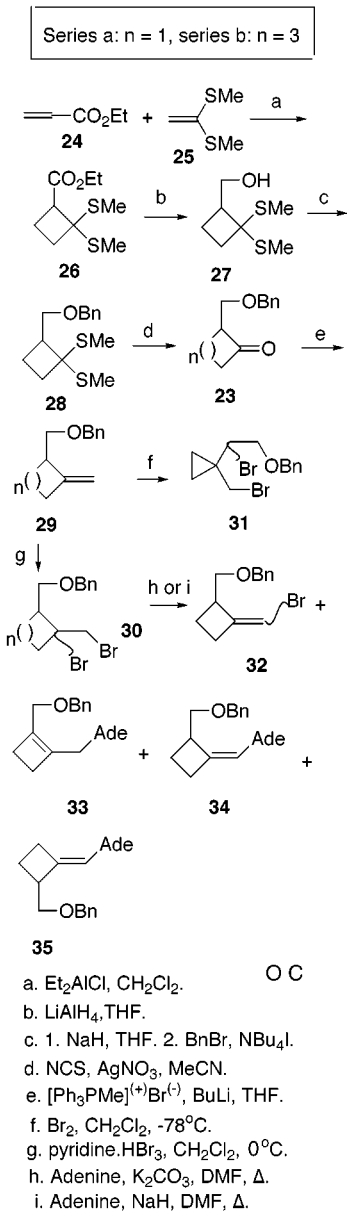


enecyclopropanes[18] **19** and allenes[19] **20** exhibited potent antiviral activity. Previously, the alkylation−elimination procedure proved advantageous[18b,20] for synthesis of methylenecyclopropanes **19**. It was therefore of interest to investigate the scope and limitations of this procedure for synthesis of unsaturated analogues comprising larger than three-membered rings. Alternate approaches for synthesis of such compounds were also in the focus of our attention. The results obtained with four- and six-membered ring systems are the subject of this communication.

Results and Discussion

Two approaches for synthesis of the *Z*- and *E*-methylenecyclobutane analogues **21** and **22** were investigated. Both approaches made use of 2-(benzyloxymethyl)cyclobutanone (**23a**) as a key intermediate. The latter was obtained by a modification of the procedure described for the corresponding *O*-benzoate.[21] Reaction of ethyl acrylate (**24**) and ketene dimethyl thioacetal[22] (**25**) furnished

Scheme 1



ethyl 2,2-(bismethylthio)-1-cyclobutanecarboxylate (**26**) in 82% yield (Scheme 1). Reduction[23] with $LiAlH_4$ in THF gave hydroxymethyl derivative **27** (93%). Benzylation afforded the *O*-benzyl thioacetal **28** which, in turn, was hydrolyzed using *N*-chlorosuccinimide and $AgNO_3$ in aqueous MeCN[20] to give the key intermediate **23a** in a total yield of 70%. The Wittig methylenation led then to methylenecyclobutane **29a** (73%). Surprisingly, addition of bromine in CH_2Cl_2 at low temperature (−78 °C) did not give any expected vicinal dibromocyclobutane **30a** but a ring-contracted derivative **31** in 70% yield. Formation of cyclopropylmethyl, cyclobutyl, and open-chain compounds was previously observed in solvolysis of cyclobutyl derivatives.[24] In our case, the reaction which proceeds most likely via the respective bromonium cation gives **31** as a major product. By using a less reactive agent, pyridinium hydrobromide perbromide at 0 °C, a ring

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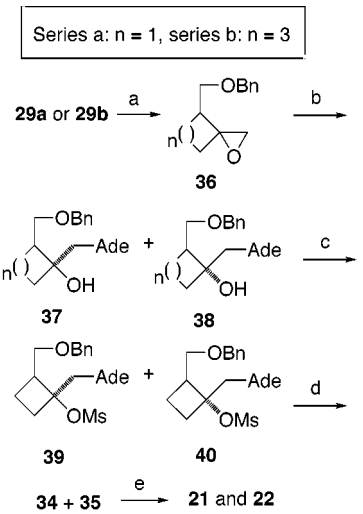
Scheme 2

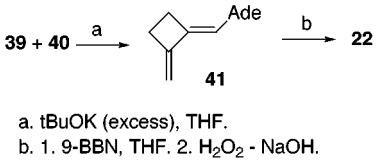


contraction was not observed and dibromocyclobutane **30a** was obtained in 95% yield. Alkylation of adenine with **30a**, using K_2CO_3 in DMF at 110 °C (18 h), led predominantly to an elimination of elements of HBr to give the *E*/*Z*-bromomethylenecyclobutanes **32** (70%). Products of alkylation−elimination **33** (3.5%), and **34** and **35** (4.6%, ratio 2:1) were obtained as minor components. Interestingly, this ratio corresponded to the values observed in the methylenecyclopropane series[18b,20] (*Z*/*E* = 2:1 or 1:1). Reaction of **30a** using sodium salt of adenine in DMF at 100 °C for 10 h afforded a similar distribution of the reaction products.

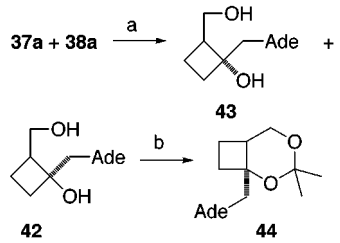
Because of low yields of intermediates **34** and **35** we sought an alternate approach (Scheme 2). Protected methylenecyclobutane **29a** was converted to oxirane **36a** in quantitative yield. Opening of the epoxide ring with adenine afforded readily separable *Z*- and *E*-hydroxy derivatives **37a** and **38a** in 34 and 32% yield, respectively. Mesylation of the tertiary hydroxy groups of **37a** and **38a** by a routine mesyl chloride−pyridine procedure proved difficult but catalysis with DMAP gave the *Z*- and *E*-mesylates **39** and **40** in 50 and 69% yield. The $Sc(OTf)_3$/DMAP method[25] recommended for acylation of tertiary hydroxy groups was not applicable for mesylation of **37a** and **38a**. It should be noted that separated isomers of **39** and **40** are not necessary for the next step. Thus, an elimination of mesyloxy function was performed with a mixture of mesylates **39** and **40** using a 50% excess of tBuOK in THF to give the mixture of *Z*- and *E*-isomers **34** and **35** in 87% yield. Surprisingly, with a 2 M excess of tBuOK, the benzyloxy group was also eliminated to give diene **41** (Scheme 3) as an *E*-isomer in 78% yield.

O-Debenzylation of isomeric mixture **34** and **35** was performed with BCl_3 in CH_2Cl_2 at −78 °C to give target compounds **21** and **22**. The separation of both isomers could not be accomplished on silica gel, but chromatography on alumina led to a smooth resolution of the *E*- and *Z*-isomers **22** and **21** which were obtained in 68 and

Scheme 3



Scheme 4



11% yield, respectively. It is interesting to note that the ratio of isomers differs significantly from that obtained by the alkylation−elimination procedure (Scheme 1, ratio **34**/**35** = 2:1). Selective hydroboration of diene **41** with 9-BBN in THF and alkaline H_2O_2 gave the *E*-isomer **22** in 62% yield (Scheme 3). This result contrasts with a previously reported[26] lack of success with selective hydroboration of conjugated dienes. An absence of enamine reduction[27] (loss of heterocyclic base) is also noteworthy.

Deprotection of intermediates **37a** and **38a** afforded diols **42** and **43** in 78 and 75% yield, respectively (Scheme 4). Although neither **42** nor **43** formed borate complexes as indicated by paper electrophoresis in 0.1 M $Na_2B_4O_7$ (pH 9), compound **42** was smoothly transformed (77% yield) to a 1,3-dioxane derivative **44** using acetone dimethyl ketal and TsOH in DMF. This established the *Z*-isomeric structure of **42**.

As expected, the UV spectra of compounds **21** and **22** were very similar to those of the corresponding *Z*-methylenecyclopropane analogue **19** (B = Ade) and its *E*-isomer.[18b] The assignment of the *Z*- and *E*-isomers **21** and **22** and structure of diene **41** followed from the NMR spectra and, particularly, from the NOE data (Chart 2). A significant difference between the H_8 chemical shifts of **21** and **22** ($\Delta\delta$ 0.24 vs 0.26 found for the *Z*- and *E*-isomers of synadenol[18b]) suggested the *Z*-isomeric structure of **21**. This was corroborated by NOE enhancement (6.4%) between the H_8 and $H_{5'(6')}$ absent in the *E*-isomer **22**. By contrast, the *E*-isomer **22** exhibited NOE enhancements of 1.3 and 3.1% of the $H_{1'}$ and $H_{5'}$ as well as 1.0 and 2.4% of $H_{1'}$ and $H_{6'}$ that were not found in the *Z*-isomer **21**. Interestingly, the NOE was observed between the $H_{1'}$ and both H_8 and H_2 (2.0−2.3 and 0.6%, respectively) in the *Z*-isomer **21** indicating, on an NMR time-scale, some freedom of rotation of the heterocyclic base. No such interactions were observed in the *E*-isomer **22** where such a rotation is much less hindered. The structure of diene **41** was confirmed by the UV spectrum (ϵ_{max} 23 500 vs 13 600 for the *E*-isomer **22**) which is compatible with the presence of a conjugated system of double bonds attached to a heterocyclic base. The ^1H

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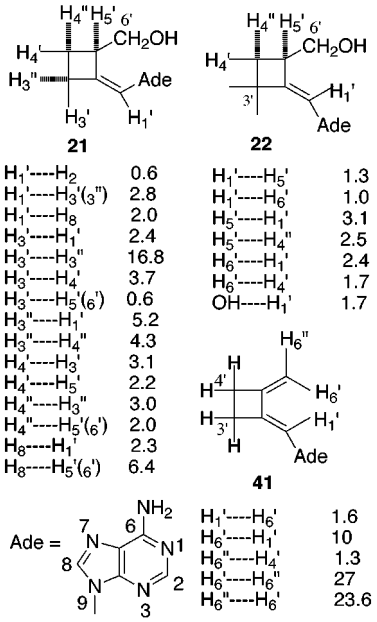
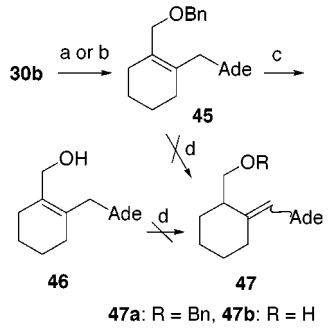
Chart 2. NOE Data of 21, 22, and 41



Scheme 5

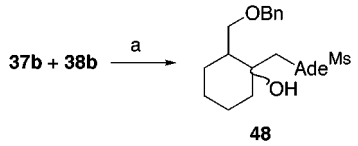


a. Adenine, K_2CO_3, DMF, Δ.
b. Adenine, NaH, DMF, Δ.
c. Na, NH_3 (l).
d. tBuOK, DMF, Δ.

NMR spectrum showed the presence of exomethylene protons $H_{6'}$ and $H_{6''}$ (δ 5.40 and 4.86, respectively). The NOE data confirmed the *E*-isomeric structure of **41** as based on enhancements between the $H_{1'}$ and $H_{6'}$ of 1.6 and 10%, respectively.

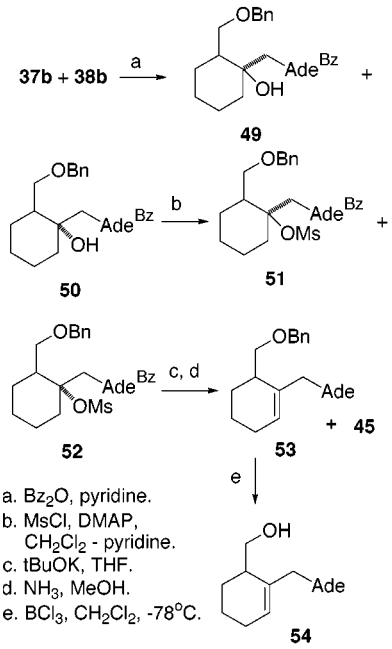
It was then of interest to investigate the applicability of both approaches for synthesis of unsaturated nucleoside analogues comprising a six-membered ring. The known[28] 2-(benzyloxymethyl)cyclohexanone (**23b**) was converted by a Wittig methylenation to compound **29b** (88%, Scheme 1). Addition of bromine, effected by pyridinium hydrobromide perbromide in CH_2Cl_2 at 0 °C, gave the corresponding vicinal dibromide **30b** in 98% yield. Alkylation−elimination of adenine with **30b** using K_2CO_3 or NaH in DMF gave the cyclohexene derivative **45** in 60 and 41% yield, respectively (Scheme 5). Attempted deprotection of **45** with BCl_3 in CH_2Cl_2 at −78 °C was not successful, possibly, because the cleavage can occur at benzylic and allylic sites of the molecule. However, debenzylation with Na in liquid NH_3 was uneventful in giving the target analogue **46** in 53% yield. Attempted isomerization of **45** and **46** with tBuOK in DMF to give

Scheme 6



a. MsCl, DMAP, CH_2Cl_2 - pyridine.

Scheme 7



a. Bz_2O, pyridine.
b. MsCl, DMAP, CH_2Cl_2 - pyridine.
c. tBuOK, THF.
d. NH_3, MeOH.
e. BCl_3, CH_2Cl_2, -78°C.

exocyclic alkenes **47a** and **47b** failed. Similar isomerization was effected without difficulty in the acyclic series.[17c] It is clear, then, that the stability of the endocyclic double bond in a six-membered ring prevails over any possible energy gain from conjugation with a heteroaromatic system.

An alternate approach also followed the methods described for methylenecyclobutane analogues (Scheme 2, $n = 2$). Methylenecyclohexane **29b** was converted to oxiranes **36b**, by reaction with m-CPBA in $NaHCO_3$ in CH_2Cl_2, in 84% yield. Alkylation of adenine with **36b** using NaH in DMF at 110 °C afforded a 1:1 mixture of the *Z*- and *E*-isomers **37b** and **38b** in 45% yield. Attempted *O*-mesylation of this product with MsCl and DMAP in pyridine gave only the *N*-mesylated product **48**. The latter was obtained as an inseparable mixture of *Z*- and *E*-isomers in 46% yield (Scheme 6). No *O*-mesylated products were detected even if the reaction was performed with 6 equiv of MsCl. The structure of **48** followed from the UV, NMR, and mass spectra. The UV maximum (273 nm) is indicative of N-substitution of the adenine moiety. As expected, the CH_3 signal of the mesyl group in the ^1H NMR spectrum of **48** (δ 3.28) is shifted downfield from that of the *O*-mesylates **39** and **40** (δ 3.08 and 3.14, respectively). Surprisingly, no N^6-mesylation was observed in the cyclobutane series (Scheme 2). Apparently, the tertiary hydroxy groups of cyclobutanes **38a** and **38b** are less sterically hindered than in cyclohexanes **37b** and **38b**.

Therefore, compounds **37b** and **38b** were selectively benzoylated using Bz_2O in pyridine to give the N^6-benzoyl derivatives **49** and **50** (69%, Scheme 7). Mesylation gave *O*-mesylates **51** and **52** in 50% yield. Interestingly, it

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seems that introduction of the benzoyl group at a distant N^6 position led to a relief of steric hindrance at the tertiary hydroxy groups. β-Elimination effected with tBuOK in THF and debenzoylation with NH_3/MeOH were perfomed in one pot. The products were separated by silica gel chromatography to give isomeric cyclohexenes **53** (46%) and **45** (22%). The latter was identical to the product obtained from an alkylation−elimination procedure with dibromides **30b**. Both products are clearly differentiated by the ^{1}H NMR spectra (lack or presence of an olefinic proton). Apparently, Hofmann-type orientation of the double bond predominates with mesylates **51** and **52**, whereas dibromides **30b** afforded exclusively Zaitsev product **45**. *O*-Debenzylation of cyclohexene **53** smoothly afforded compound **54** in 70% yield.

Compounds **21**, **22**, **42**, **43**, and **46** were tested against HCMV, HSV-1, HSV-2, EBV, HBV, VZV, and HIV-1 using the assays described previously.[18b] None of them had a significant antiviral activity. A moderate effect of **21** against EBV in Daudi cells (IC_{50} 39 μM) was not separated from cytotoxicity (CC_{50} 40 μM). These analogues were also ineffective as substrates for adenosine deaminase.

Experimental Section

General Methods. See reference 18b. The ^{1}H and ^{13}C NMR spectra were recorded with the 300 and 400 MHz instruments. For the FAB-MS thioglycerol matrix was used, and 2-methylpropane was employed as an ionization gas in CI-MS. (Benzyloxymethyl)cyclohexanone (**23b**) was prepared from cyclohexanone and dibenzyloxymethane[29] as described.[28]

Ethyl 2,2-Bis(methylthio)-1-cyclobutanecarboxylate (26). Diethylaluminum chloride (1.0 M in hexane, 125 mL) was added dropwise with stirring at 0 °C to a solution of 1,1-bis(methylthio)ethylene[22] (**25**, 10 g, 84 mmol) and ethyl acrylate (**24**, 13.5 mL, 186 mmol) in CH_2Cl_2 (150 mL). The mixture was stirred under N_2 for 1 h and then at room temperature for another 1 h. The reaction was quenched by the careful addition of Et_3N (9 mL) and 10% aqueous sodium bicarbonate (50 mL) at 0 °C. The inorganic salt was removed by filtration and it was washed with CH_2Cl_2. The combined organic phase was washed with H_2O and dried over Na_2SO_4. After evaporation of solvents, the crude product was purified on a silica gel column (hexanes/ethyl acetate, 20:1) to give the pure product **26** as an oil (16.0 g, 82%).

2,2-Bis(methylthio)-1-cyclobutylmethanol (27). A solution of compound **26** (14.0 g, 6.46 mmol) in THF (80 mL) was added to a suspension of $LiAlH_4$ (3.55 g, 9.54 mmol) in THF (100 mL) at 0 °C with stirring. The mixture was stirred at 0 °C for 1 h and the reaction was quenched carefully by saturated aqueous Na_2SO_4. The precipitate was filtered off and it was washed with ether. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate, 9:1) to give product **27** as a colorless oil (12.0 g, 93%). The ^{1}H NMR spectrum corresponded to that described for the *S*-enantiomer.[23]

2-(Benzyloxymethyl)cyclobutanone (23a). To a solution of [2,2-bis(methylthio)-1-cyclobutyl]methanol (**27**, 5.0 g, 28 mmol) in THF (160 mL) cooled to 0 °C, NaH (50% in mineral oil, 2.69 g, 56 mmol) was added in portions with stirring under N_2. The mixture was stirred for 30 min at room temperature, and benzyl bromide (33.6 mmol, 4.0 mL) was added dropwise followed by tetrabutylammonium iodide (0.1 g, 0.27 mmol). The stirring was continued for 16 h. The reaction was quenched with saturated aqueous NH_4Cl (150 mL) and the mixture was extracted with ethyl acetate/hexanes (1:1). The organic phase was washed with aqueous $NaHCO_3$ and brine and it was dried over Na_2SO_4. Evaporation of solvents gave the crude 2-(benzyloxymethyl)cyclobutanone bis(methylthio)ketal **28** which was added dropwise into a stirred solution of *N*-chlorosuccinimide (NCS, 11.2 g, 84 mmol) and $AgNO_3$ (16.1 g, 95 mmol) in 90% acetonitrile at 0 °C. After the mixture was stirred for 10 min at room temperature, saturated aqueous Na_2SO_3, $NaHCO_3$, and brine were added successively. The solids were removed by filtration. The filtrate was extracted with ethyl acetate; the organic phase was washed with brine and it was dried over Na_2SO_4. The solvent was evaporated and the crude product was chromatographed on a silica gel column using hexanes/ethyl acetate (10:1) to give **23a** as a colorless oil 3.74 g (70%). ^{1}H NMR ($CDCl_3$): δ 7.35 (5H, m), 4.54 (2H, s,), 3.74 (1H, dd, J = 5.4 and 9.9 Hz) and 3.60 (1H, dd, J = 4.5 and 9.6 Hz), 3.55 (1H, m), 3.04 (2H, m), 2.18 and 2.06 (2H, m). ^{13}C NMR: 210.5, 138.10, 128.34, 127.64, 127.57, 73.16, 67.56, 60.63, 45.71, 14.29. EI-MS: 190 (M, 2.0), 91 (100.0). HRMS: calcd for $C_{12}H_{14}O_2$, 190.0994; found, 190.0992.

1-(Benzyloxymethyl)-2-methylenecyclobutane (29a). Butyllithium (1.6 M in hexane, 13.82 mL, 22 mmol) was added to a suspension of methyltriphenylphosphonium bromide (7.89 g, 22 mmol) in THF (100 mL) at room temperature with stirring under N_2. After 2 h, ketone **23a** (3.0 g, 16 mmol) in THF (50 mL) was added dropwise and the resulting mixture was stirred another 14 h. The reaction was quenched with saturated aqueous NH_4Cl (150 mL) and it was extracted with ether. The organic phase was washed with aqueous $NaHCO_3$ and brine, and it was dried over Na_2SO_4. The crude product obtained after evaporation was chromatographed on a silica gel column (hexanes/ethyl acetate, 100:0.5 → 100:1.5) to give compound **29a** as a colorless oil (2.20 g, 73%). ^{1}H NMR ($CDCl_3$): δ 7.37 (5H, m), 4.90 (1H, m) and 4.82 (1H, m, CH_2═), 4.60 (2H, s), 3.60 (2H, m), 3.32 (1H, m), 2.70 (2H, m), 2.17 (1H, m), and 1.80 (1H, m). ^{13}C NMR: 151.36, 138.62, 128.38, 127.65, 127.55, 105.33, 73.11, 73.06, 44.05, 29.30, 21.26. EI-MS: 188 (M, 0.3), 91 (100.0). HRMS: calcd for $C_{13}H_{16}O$, 188.1201; found, 188.1198.

1-(Benzyloxymethyl)-2-methylenecyclohexane (29b). The procedure described above for compound **29a** was followed starting from ketone **23b** (3.8 g, 17.4 mmol), methyltriphenylphosphonium bromide (9.35 g, 26.2 mmol), and BuLi (1.6 M in hexane, 16.4 mL, 26.2 mmol) to give product **29b** as an oil (3.3 g, 88%). ^{1}H NMR ($CDCl_3$): δ 7.38 and 7.32 (5H, m), 4.74 (1H, s) and 4.61 (1H, s, CH_2═), 4.56 (2H, s), 3.67 (1H, dd, J = 6.3 and 9.0 Hz) and 3.49 (1H, dd, J = 7.5 and 9.0 Hz), 2.42 (1H, m), 2.28 and 2.25 (1H, m), 2.27 (1H, m), 1.90 (1H, s), 1.70 (2H, m), 1.47 (2H, m), 1.32 (1H, s). ^{13}C NMR: 150.30, 138.66, 128.34, 127.66, 127.49, 106.02, 73.09, 72.23, 43.00, 35.62, 31.17, 28.57, 24.72. EI-MS: 216 (M, 2.1), 91 (100.0). HRMS: calcd for $C_{15}H_{20}O$, 216.1514; found, 216.1514.

(*Z*)- and (*E*)-(2-Benzyloxymethyl)-1-bromo-1-bromomethylcyclobutane (30a). Pyridinium hydrobromide perbromide (3.4 g, 10.6 mmol) was added in portions to a solution of methylenecyclobutane **29a** (2.0 g, 10.6 mmol) in CH_2Cl_2 (80 mL) at 0 °C with stirring. The stirring was continued at 0 °C for 3 h whereupon the reaction was quenched with saturated aqueous $NaHSO_3$ (50 mL). The product was extracted with ether; the combined organic phase was washed with brine and it was dried over Na_2SO_4. Evaporation afforded the crude product which was chromatographed on a silica gel column (hexanes/ethyl acetate, 100:1 → 50:1) to give compound **30a** as an oil (3.50 g, 95%). ^{1}H NMR ($CDCl_3$): δ 7.40 (5H, m), 4.55 (2H, m), 4.08 and 3.74 (1H, J_{AB} = 11.4 Hz) and 3.90 (1H, s, 1:1), 3.62 (2H, m), 3.44 (m) and 2.82 (1H, m, 1:1), 2.61 (m) and 2.46 (2H, m, 3:1), 2.20 (m), 1.98 (m) and 1.88 (2H, m, 1:2:1). EI-MS: 350 (M, 0.1), 348 (M, 0.2), 346 (M, 0.1), 91 (100.0). HRMS: calcd for $C_{13}H_{16}O^{79}Br_2$, 345.9568; found 345.9564. Anal. Calcd for $C_{13}H_{16}OBr_2$: C, 44.86; H, 4.63. Found: C, 44.67; H, 4.57.

(*E*)-2-(Benzyloxymethyl)-1-bromo-1-bromomethylcyclohexane (30b). The procedure described for compound **30a** was followed using methylenecyclohexane **29b** (1.6 g, 7.4 mmol) and pyridinium hydrobromide perbromide (2.4 g, 7.5 mmol) in CH_2Cl_2 (50 mL) to give product **30b** as an oil (2.70 g, 98%). ^{1}H NMR ($CDCl_3$): δ 7.40 (5H, m), 4.56 (2H, s), 4.32

(29) Laskina, E. D. *Zh. Prikl. Khim.* **1959**, *32*, 878−882; *Chem. Abstr.* **1959**, *53*, 17039b.

and 3.86 (2H, J_{AB} = 10.2 Hz), 3.71 (1H, dd, J = 5.8 and 9.7 Hz) and 3.30 (1H, dd, J = 6.4 and 9.7 Hz), 2.17 (1H, m), 2.05 (1H, m), 1.74 (5H, m), 1.35 (2H, m). ^{13}C NMR: 138.34, 128.39, 127.54, 127.42, 73.45, 73.21, 42.37, 42.59, 39.44, 26.59, 24.83, 22.77. EI-MS: 297 (0.2) and 295 (0.3, M − Br), 91 (100.0). HRMS: calcd for $C_{15}H_{20}O^{79}Br$ (M − Br), 295.0692; found, 295.0697. Anal. Calcd for $C_{15}H_{20}Br_2O$: C, 47.90; H, 5.36; Br, 42.49. Found: C, 48.07; H, 5.46; Br, 42.61.

1-(2-Benzyloxy-1-bromo)ethyl)-1-bromomethylcyclopropane (31). Bromine was added dropwise with stirring to a solution of compound **29a** (200 mg, 1.06 mmol) in CH_2Cl_2 (20 mL) at −78 °C till the color did not fade. The reaction was quenched with saturated aqueous $NaHSO_3$ (10 mL) and the product was extracted with ether. The combined organic phase was washed with brine and dried over Na_2SO_4. Evaporation gave the crude product, which was chromatographed on a silica gel column (hexanes/ethyl acetate, 100:1 → 50:1) to give compound **31** as an oil (260 mg, 70%). ^{1}H NMR ($CDCl_3$): δ 7.40 (5H, m), 4.60 (2H, s), 4.20 (1H, t, J = 6.4 Hz), 3.92 (2H, d, J = 6.5 Hz), 3.70 and 3.54 (2H, J_{AB} = 11.1 Hz), 1.15−0.95 (4H, m). ^{13}C NMR: 137.77, 128.53, 127.80, 127.76, 73.19, 72.59, 68.48, 59.73, 40.75, 19.28, 17.44. EI-MS: 350 (M, 0.1), 348 (M, 0.2), 346 (M, 0.1), 91 (100.0). HRMS: calcd for $C_{13}H_{16}Br_2O$, 345.9568; found, 345.9568.

(*Z*)- and (*E*)-1-(Benzyloxymethyl)-2-bromomethylenecyclobutane (32), 9-{[2-(Benzyloxymethyl)cyclobut-1-en-1-yl]methyl}adenine (33), and Compounds 34 and 35. Method A. A mixture of compound **30a** (180 mg, 0.52 mmol), adenine (180 mg, 0.73 mmol), and flame-dried K_2CO_3 (800 mg, 5.8 mmol) in DMF (8 mL) was stirred at 110 °C for 18 h. The solids were filtered off and washed with DMF. The solvent was evaporated and the crude product was chromatographed on a silica gel column (CH_2Cl_2/MeOH, 30:1 → 20:1) to give first compound **32** (97 mg, 70%) as an oil, followed by a mixture of isomers **34** + **35** (39 mg, 4.6%) as a gum, and cyclobutene **33** (30 mg, 3.5%) as a solid.

The ^{1}H NMR spectrum of **34** and **35** indicated a *Z*/*E* ratio of 2:1.

Compound 32. ^{1}H NMR ($CDCl_3$): δ 7.30 (5H, m), 6.10 (s) and 5.95 (s, 2:1, 1H), 4.56 (2H, s), 4.60 (dd, J = 6.3 and 4.0 Hz) and 4.40 (2H, m, 1:2), 3.23 (m, 1H), 2.75 (m) and 2.62 (2H, m, 1:2), 2.23 (1H, m), 1.92 (1H, m). CI-MS: 269 (M + H, 3.4), 267 (M + H, 3.8), 91 (100.0). HRMS: calcd for $C_{13}H_{15}O$ (M − Br), 187.1123; found, 187.1121.

***Z*- and *E*-Isomers 34** and **35.** UV max (EtOH): 261 nm (ϵ 13 700), 209 (ϵ 23 900). ^{1}H NMR ($CDCl_3$): δ 8.39 (1H, s), 8.22 (s) and 7.90 (1H, s, 1:2), 7.38, 7.27 and 7.20 (5H, m), 6.98 (s) and 6.77 (1H, s, 2:1), 5.89 (2H, s), 4.59 (s) and 4.40 (2H, s, 2:1), 3.66 (m) and 3.50 (3H, m), 2.94 (2H, m), 2.31 (1H, m), 1.99 (m) and 1.85 (1H, m, 2:1). The *Z*/*E* ratio (2:1) was determined from integration of the appropriate ^{1}H NMR signals.

Compound 33. Mp 187−190 °C. UV max (EtOH): 261 nm (ϵ 13 500), 207 (ϵ 23 800). ^{1}H NMR ($CDCl_3$): δ 8.37 (1H, s) and 7.81 (1H, s, H_8 and H_2), 7.34 (5H, m), 5.81 (2H, s, NH_2), 4.87 (2H, s), 4.51 (2H, s), 3.99 (2H, s), 2.39 (2H, s), 2.34 (2H, s). ^{13}C NMR: 155.68, 153.41, 153.04, 142.76, 140.81, 138.47, 136.25, 128.72, 128.05, 127.93, 112.68, 73.21, 41.47, 27.90, 27.57. FAB-MS: 322 (M + H, 100.0).

Method B. A mixture of adenine (180 mg, 0.73 mmol) and NaH (50% in mineral oil, 35 mg, 0.73 mmol) in DMF (6 mL) was stirred at room temperature under N_2 for 4 h. A solution of compound **30a** (180 mg, 0.52 mmol) in DMF (10 mL) was added. The resulting mixture was then stirred at 100 °C for 10 h. Evaporation of all solvents and workup as described above gave compound **32** (100 mg, 72%), isomers **34** and **35** (35 mg, 4%), and cyclobutene **33** (30 mg, 3.5%).

(*E*)- and (*Z*)-4-(Benzyloxymethyl)-1-oxaspiro[2,3]hexanes (36a). *m*-Chloroperoxybenzoic acid (m-CPBA, 85%, 1.96 g, 9.7 mmol) was added in portions to a stirred mixture of compound **29a** (1.4 g, 7.4 mmol) and $NaHCO_3$ (0.87 g, 10.36 mmol) in CH_2Cl_2 (80 mL) at 0 °C. The mixture was stirred at 0 °C for 4 h whereupon saturated aqueous Na_2SO_3 was added to quench the reaction. The product was extracted with ether (3 × 50 mL). The organic phase was washed with aqueous $NaHCO_3$ and brine and then dried over Na_2SO_4. Evaporation of the solvent gave the crude product which was chromatographed on a silica gel column (hexanes/ethyl acetate, 20:1 → 15:1 → 10:1) to give compound **36a** (1.50 g, 100%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.37 (5H, m), 4.58 and 4.50 (2H, 2s, 1.2:1), 3.63 (d, J = 5.1 Hz) and 3.42 (2H, d, J = 4.8 Hz, 1.2:1), 3.06 and 2.95 (1H, m, 1.2:1), 2.90 and 2.65 (J_{AB} = 4.5 Hz), 2.75 and 2.73 (2H, J_{AB} = 4.5 Hz, 1:1.2,), 2.42 (m) and 2.22 (m, 2H), 2.03 (m), 1.84 (m) and 1.70 (m, 2H). EI-MS: 204 (M, 0.8), 91 (100.0). HRMS: calcd for $C_{13}H_{16}O_2$, 204.1150; found, 204.1151.

(*E*)- and (*Z*)-4-(Benzyloxymethyl)-1-oxaspiro[2,5]octanes (36b). The procedure for compound **36a** was followed using methylenecyclohexane **29b** (3.0 g, 13.9 mmol), $NaHCO_3$ (1.75 g, 20.8 mmol), and m-CPBA (3.34 g, 19.43 mmol) to give **36b** (2.7 g, 84%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.38 (5H, m), 4.43 (2H, m), 2.00 (1H, m), 1.85−1.44 (8H, m). Resolved signals of isomers: isomer A, 3.50 (dd, J = 5.4 and 8.9 Hz) and 3.25 (2H, dd, J = 5.4 and 9.1 Hz), 2.94 (1H, d, J = 4.5 Hz) and 2.76 (1H, d, J = 4.5 Hz); isomer B, 3.40 and 3.34 (2H, J_{AB} = 8.4 Hz), 2.54 (2H, d, J = 4.2 Hz). The isomeric ratio was 1:1. EI-MS: 232 (M, 0.5), 91 (100.0). HRMS: calcd for $C_{15}H_{20}O_2$, 232.1463; found, 232.1464.

(*Z*)-9-{[2-(Benzyloxymethyl)-1-hydroxycyclobutyl]methyl}adenine (37a) and (*E*)-9-{[2-(Benzyloxymethyl)-1-hydroxycyclobutyl]methyl}adenine (38a). A mixture of adenine (1.5 g, 11.1 mmol) and NaH (50% in mineral oil, 0.45 g, 9.3 mmol) in dry DMF (50 mL) was stirred at room temperature for 4 h under N_2. Compound **36a** (1.6 g, 7.8 mmol) in DMF (5 mL) was then added and the stirring was continued at 110 °C for 10 h. After cooling, the solvent was evaporated and the crude product was chromatographed on silica gel (CH_2Cl_2/MeOH, 30:1 → 20:1 → 10:1) to give the *Z*-isomer (0.9 g, 34%) and *E*-isomer (0.85 g, 32%) as foams.

***Z*-Isomer 37a.** UV max (EtOH): 261 nm (ϵ 13 900), 209 (ϵ 25 000). ^{1}H NMR ($CDCl_3$): δ 8.40 (1H, s) and 8.08 (1H, s, H_8 and H_2), 7.37 (5H, m), 6.00 (2H, s, NH_2), 4.50 (1H, brs, OH), 4.43 (2H, s), 4.37 and 4.28 (2H, J_{AB} = 14 Hz), 3.63 (m) and 3.52 (2H, m), 2.50 (1H, m), 2.10 (2H, m), 1.95 (1H, m), 1.77 (1H, m). ^{13}C NMR: 155.97, 152.74, 150.34, 141.76, 137.72, 128.39, 127.70, 127.50, 118.74, 75.13, 73.13, 69.97, 51.66, 41.25, 32.40, 16.01. FAB-MS: 340 (M, 100.0).

***E*-Isomer 38a.** UV max (EtOH): 261 nm (ϵ 14 200), 210 (ϵ 23 900). ^{1}H NMR ($CDCl_3$): δ 8.40 (1H, s) and 8.00 (1H, s, H_8 and H_2), 7.37 (5H, m), 6.00 (2H, s, NH_2), 4.50 (1H, brs, OH), 4.37 (2H, s), 4.52 and 4.25 (2H, J_{AB} = 14 Hz), 3.60 (2H, m), 2.75 (1H, m), 1.94 (1H, m), 1.80 (2H, m), 1.55 (1H, s). ^{13}C NMR: 155.88, 152.58, 150.32, 142.14, 137.93, 128.41, 127.75, 118.72, 75.46, 73.13, 69.03, 47.87, 41.75, 31.57, 15.40. FAB-MS: 340 (M, 100.0).

(*Z*)- and (*E*)-9-{[2-(Benzyloxymethyl)-1-hydroxycyclohexyl]methyl}adenine (37b and 38b). The procedure for compounds **37a** and **38a** was followed using compound **36b** (2.7 g, 11.6 mmol), adenine (2.35 g, 17 mmol), and NaH (50% in mineral oil, 0.72 g, 15 mmol) to give *Z*- and *E*-isomers **37b** and **38b** as a gum (1.9 g, 45%). The *E*/*Z* ratio was 1:1. UV max (EtOH): 261 nm (ϵ 14 700), 209 (ϵ 20 600). ^{1}H NMR (DMSO-d_6): δ 8.20 (1H, s), 8.08 and 8.06 (2s, 1H, 1:1, H_8 and H_2), 7.40 (2H, NH_2), 7.37 and 7.20 (5H, m), 5.05 and 4.80 (1H, s, 1:1, OH), 4.45 (3H, m), 4.29 and 4.24 (1H, J_{AB} = 14.4 Hz), 3.97 (d, J = 14.4 Hz), 3.81 (m) and 3.74 (m, 2H), 3.60 (1H, m), 1.1−1.8 (8H, m). FAB-MS: 369 (M, 100.0).

(*Z*)-9-{[2-(Benzyloxymethyl)-1-methylsulfonylcyclobutyl]methyl}adenine (39). Methylsulfonyl chloride (MsCl, 0.43 mL, 5.4 mmol) was added dropwise to a stirred mixture of compound **37a** (0.61 g, 1.8 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 0.26 g, 2.15 mmol) in CH_2Cl_2 (25 mL) and pyridine (5 mL) at 0 °C. The stirring was continued at room temperature for 24 h whereupon MeOH/H_2O (2:1, 1 mL) was added. After 1 h, the solvents were evaporated and the crude product was chromatographed on a silica gel column (CH_2Cl_2/MeOH, 40:1 → 30:1 → 20:1) to give compound **39** as a gum (256 mg, 50%) and recovered starting material **37a** (180 mg, 30%). ^{1}H NMR ($CDCl_3$): δ 8.36 (1H, s) and 8.18 (1H, s, H_8 and H_2, adenine), 7.37 (5H, m), 6.60 (2H, s, NH_2), 4.65 (2H, d, J = 2.4 Hz), 4.46 (2H, s), 3.50 (2H, s),

3.08 (3H, s, CH_3), 2.75 (1H, m), 2.46 (1H, m), 2.0 (3H, m). ^{13}C NMR: 155.84, 153.03, 150.69, 141.62, 141.71, 137.95, 128.41, 127.75, 118.85, 89.55, 73.09, 69.44, 49.59, 42.31, 30.10, 17.54. FAB-MS: 418 (M, 62.0), 136 (100.0).

(*E*)-9-{[2-(Benzyloxymethyl)-1-methylsulfonylcyclobutyl]methyl}adenine (40). The procedure described above was used with compound **38a** (0.80 g, 2.36 mmol), DMAP (0.346 g, 2.83 mmol), MsCl (0.553 mL, 7.1 mmol), CH_2Cl_2 (30 mL), and pyridine (5 mL) to give gummy product **40** (678 mg, 69%). ^1H NMR ($CDCl_3$): δ 8.36 (1H, s) and 8.12 (1H, s, H_2 and H_8), 7.37 (5H, m), 6.50 (2H, s, NH_2), 4.94 and 4.63 (2H, J_{AB} = 15.3 Hz), 4.50 and 4.47 (2H, J_{AB} = 12 Hz), 3.75 (1H, dd, J = 10.4 and 4.7 Hz) and 3.66 (1H, dd, J = 6.0 and 10.5 Hz), 3.50 (1H, m), 3.14 (3H, s, CH_3), 2.35 (2H, m), 2.00 (2H, m). ^{13}C NMR: 155.85, 152.79, 150.71, 141.68, 141.70, 137.81, 127.78, 127.68, 118.80, 89.58, 73.27, 67.64, 45.54, 44.61, 40.45, 30.15, 16.04. FAB-MS: 418 (M, 58.7), 136 (100.0).

(*Z*)- and (*E*)-9-{[2-(Benzyloxymethyl)cyclobutylidene]methyl}adenine (34 and 35). Freshly sublimed tBuOK (842 mg, 7.5 mmol) was added to a mixture of compounds **39** and **40** (2.08 g, 5 mmol) in THF (50 mL) with stirring at 0 °C. The stirring was continued at room temperature for 6 h, the reaction mixture was cooled to 0 °C, and 1 M HCl (1.0 mL) was added dropwise. The volatile components were evaporated and the crude product was chromatographed on a silica gel column (CH_2Cl_2/MeOH, 30:1 → 20:1) to give products **34** and **35** as a solid (1.40 g, 87%). ^1H NMR spectrum was identical, except the isomeric ratio, with that of the product obtained from dibromo derivatives **30a**. EI-MS: 321 (M, 21.0), 91 (100.0). HRMS: calcd for $C_{18}H_{19}N_5O$, 321.1590; found, 321.1587.

(*E*)-9-[(2-Methylenecyclobutylidene)methyl]adenine (41). The procedure described above was employed using a two molar excess of tBuOK (840 mg, 7.5 mmol) and mesylates **39** and **40** (1.04 g, 2.5 mmol) in THF (30 mL) to give product **41** (414 mg, 78%). Mp 229−230 °C. UV max (EtOH): 260 nm (ϵ 23 500), 205 (ϵ 17 500). ^1H NMR (DMSO-d_6): δ 8.27 (1H, s) and 8.17 (1H, s, H_8 and H_2), 7.39 (2H, s, NH_2), 7.34 (1H, m, $H_{1'}$), 5.40 (1H, m, $H_{6'}$), 4.86 (1H, m, $H_{6''}$), 2.99 (2H, m, $H_{3'}$), 2.71 (2H, m, $H_{4'}$). ^{13}C NMR: 157.23, 154.20, 149.59, 147.20, 138.99, 133.45, 119.09, 111.43, 106.09, 29.55, 27.55. EI-MS: 213 (M, 100.0). HRMS: calcd for $C_{11}H_{11}N_5$, 213.1014; found, 213.1020. Anal. Calcd for $C_{11}H_{11}N_5$: C, 61.96; H, 5.20; N, 32.84. Found: C, 61.79; H, 5.25; N, 33.01.

(*Z*)-9-{[2-(Hydroxymethyl)cyclobutylidene]methyl}adenine (21) and (*E*)-9-{[2-(Hydroxymethyl)cyclobutylidene]methyl}adenine (22). Method A. Deprotection of *O*-Benzyl Derivatives 34 and 35. Boron trichloride (1 M in CH_2Cl_2, 25.8 mL, 25.8 mmol) was added dropwise with stirring to a solution of isomeric mixture **34** and **35** (1.38 g, 4.3 mmol) obtained from mesylates **39** and **40** in CH_2Cl_2 (100 mL) at −78 °C under N_2. The stirring was continued for 4 h. A 1:1 mixture of MeOH/CH_2Cl_2 (10 mL) was then added. The solvents were evaporated and the syrupy product was stirred with MeOH (30 mL) and $NaHCO_3$ (2.2 g, 25.8 mmol) for 2 h. The solids were filtered off and washed with MeOH/CH_2Cl_2 (1:1, 2 × 10 mL). The combined filtrates were evaporated and the crude product was chromatographed on a silica gel column using CH_2Cl_2/MeOH (30:1 → 20:1 → 15:1) to give a mixture of **21** and **22** (824 mg, 83%) as a solid. Chromatography on a column of neutral alumina (CH_2Cl_2/MeOH, 40:1 → 30:1 → 20:1) gave the *E*-isomer **22** (676 mg, 68%) followed by *Z*-isomer **21** (109 mg, 11%).

***E*-Isomer 22.** Mp 231−233 °C. UV max (EtOH): 261 nm (ϵ 13 600), 227 (ϵ 24 400). ^1H NMR (DMSO-d_6): δ 8.14 (2H, s, H_8 and H_2), 7.33 (2H, s, NH_2), 6.90 (1H, m, $H_{1'}$), 4.77 (1H, t, J = 3.6 Hz, OH), 3.54 (2H, t, J = 5.4 Hz, $H_{6'}$), 3.20 (1H, m, $H_{5'}$), 2.87 (2H, m, $H_{3'}$), 2.10 (1H, m, $H_{4''}$), 1.79 (1H, m, $H_{4'}$). ^{13}C NMR: 156.46, 153.25, 148.69, 138.48, 136.15, 118.36, 112.31, 64.06, 44.25, 27.69, 21.14. EI-MS: 231 (M, 100.0). HRMS: calcd for $C_{11}H_{13}N_5O$, 231.1120; found, 231.1121. Anal.Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 57.29; H, 5.79; N, 30.40.

***Z*-Isomer 21.** Mp 229−231 °C. UV max (EtOH): 261 nm (ϵ 15 200), 227 (ϵ 24 000). ^1H NMR (DMSO-d_6): δ 8.38 (1H, s, H_8), 8.14 (1H, s, H_2), 7.29 (2H, s, NH_2), 6.72 (1H, m, $H_{1'}$), 4.83 (1H, t, J = 3.0 Hz, OH), 3.42 (3H, m, $H_{5'}$ + $H_{6'}$, overlapped with H_2O), 2.81 (1H, m, $H_{3'}$), 2.71 (1H, m, $H_{3''}$), 2.14 (1H, m, $H_{4''}$), 1.77 (1H, m, $H_{4'}$). ^{13}C NMR: 157.10, 153.88, 149.77, 140.10, 137.84, 119.18, 113.92, 63.36, 46.04, 28.05, 21.78. EI-MS: 231 (M, 100.0). HRMS: calcd for $C_{11}H_{13}N_5O$, 231.1120; found, 231.1120. Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 57.00; H, 5.73; N, 30.30.

Method B. (*E*)-9-{[2-(Hydroxymethyl)cyclobutylidene]methyl}adenine (22) from Dimethylenecyclobutane 41. 9-Borabicyclo[3.3.1]nonane (9-BBN, 0.5 M in THF, 7.5 mL) was slowly added to a solution of compound **41** (400 mg, 4.7 mmol) in THF (5 mL) at 0 °C under N_2. The mixture was stirred for 30 min and then for 8 h at room temperature. A solution of 5% NaOH in 50% H_2O_2 (10 mL) was added, and the resulting mixture was stirred for 16 h and lyophilized. The residue was washed with CH_2Cl_2/MeOH (10:1) with the aid of a sonicator. The combined organic portions were evaporated and the residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH, 15:1 → 12:1) to give compound **22** (269 mg, 62%) identical (TLC, ^1H, and ^{13}C NMR) to the product obtained by method A.

(*Z*)-9-{[1-Hydroxy-2-(hydroxymethyl)cyclobutyl]methyl}adenine (42). The deprotection was performed as described for compounds **21** and **22** (method A), using the *Z*-isomer **37a** (226 mg, 0.67 mmol) and BCl_3 (1.0 M in CH_2Cl_2, 3.35 mmol, 3.35 mL) at −78 °C for 4 h. Chromatography (CH_2Cl_2/MeOH, 15:1 → 10:1) afforded product **42** (117 mg, 78%). Mp 208−211 °C. UV max (EtOH): 260 nm (ϵ 14 300), 209 (ϵ 18 600). ^1H NMR ($CDCl_3$): δ 8.09 (1H, s) and 8.02 (1H, s, H_8 and H_2), 7.39 (2H, s, NH_2), 5.30 (1H, brs, OH), 4.25 and 4.17 (2H, J_{AB} = 14 Hz), 3.70 (1H, brs, OH), 3.53 (1H, dd, J = 6.8 and 10.7 Hz) and 3.41 (1H, m), 2.27 (1H, m), 1.98 (1H, m), 1.82 (1H, m), 1.67 (1H, m), 1.50 (1H, m). ^{13}C NMR: 156.22, 152.74, 150.46, 142.21, 118.48, 74.35, 61.16, 51.27, 44.46, 31.27, 16.58. EI-MS: 249 (M, 6.9), 148 (100.0). HRMS: calcd for $C_{11}H_{15}N_5O_2$, 249.1226; found, 249.1224. Anal. Calcd for $C_{11}H_{15}N_5O_2$ x 0.6 H_2O: C, 50.80; H, 6.28; N, 26.93. Found: C, 50.84; H, 6.15; N, 27.39. 32.84.

(*E*)-9-{[1-Hydroxy-2-(hydroxymethyl)cyclobutyl]methyl}adenine (43). The reaction was carried out as described above for the *Z*-isomer **42**, starting from the *E*-isomer **38a** (204 mg, 0.6 mmol) and BCl_3 (1.0 M in CH_2Cl_2, 3.0 mmol, 3.0 mL) to give compound **43** (112 mg, 75%). Mp 207−209 °C. UV max (EtOH): 260 nm (ϵ 14 600), 210 (ϵ 18 900). ^1H NMR ($CDCl_3$): δ 8.14 (1H, s) and 8.05 (1H, s, H_8 and H_2), 7.25 (2H, s, NH_2), 5.58 (1H, s, OH), 4.56 (1H, s, OH), 4.53 and 4.06 (2H, J_{AB} = 14 Hz), 3.50 (2H, m), 2.43 (1H, m), 1.82 (1H, m), 1.70 (1H, m), 1.56 (1H, m), 1.43 (1H, m). ^{13}C NMR: 156.31, 152.86, 150.56, 142.56, 118.41, 75.04, 60.27, 49.97, 46.64, 31.27, 15.69. FAB-MS: 249 (M, 4.9), 148 (100.0). EI−HRMS: calcd for $C_{11}H_{15}N_5O_2$, 249.1226; found, 249.1224. Anal. Calcd for $C_{11}H_{15}N_5O_2$: C, 52.99; H, 6.07; N, 28.10. Found: C, 52.89; H, 6.09; N, 28.33.

Cyclic Ketal 44. A mixture of compound **42** (26 mg, 0.064 mmol), 2,2-dimethoxypropane (5 mL), and TsOH × H_2O (50 mg, 0.26 mmol) in DMF (1 mL) was stirred for 8 h at room temperature, and then it was cooled to 0 °C. Triethylamine (1 mL) was added and the mixture was evaporated. Chromatography on a column of silica gel (CH_2Cl_2/MeOH/NH_4OH, 100:2:0.1 → 90:2:0.1) gave product **44** (23 mg, 77%). Mp 244−247 °C. ^1H NMR ($CDCl_3$): δ 8.14 (1H, s) and 8.00 (1H, s, H_8 and H_2, adenine), 7.20 (2H, s, NH_2), 4.28 and 4.19 (2H, J_{AB} = 14 Hz), 3.83 (1H, dd, J = 5.1 and 12.3 Hz) and 3.53 (1H, dd, J = 3.0 and 12.1 Hz), 2.32 (1H, m), 1.98 (2H, m), 1.75 (2H, m), 1.34 (3H, s) and 1.30 (3H, s, Me_2C). ^{13}C NMR: 156.38, 152.91, 150.52, 142.0, 118.55, 97.97, 74.56, 60.94, 50.28, 33.90, 31.34, 29.52, 25.33, 17.94. EI-MS: 289 (M, 16.5), 55 (100.0). HRMS: calcd for $C_{14}H_{19}N_5O_2$, 289.1539; found, 289.1540. Anal. Calcd for $C_{14}H_{19}N_5O_2$: C, 58.12; H, 6.62; N, 24.20. Found: C, 57.89; H, 6.82; N, 24.62.

9-{[2-[(Benzyloxymethyl)cyclohex-1-en-1-yl]methyl}adenine (45). Method A. A mixture of adenine (468 mg, 3.47 mmol) and NaH (50% in mineral oil, 166 mg, 3.47 mmol) in DMF (30 mL)

was stirred at room temperature for 4 h. A solution of dibromide **30b** (1.30 g, 3.47 mmol) in DMF (10 mL) was then added. The resulting mixture was stirred at 100 °C for 10 h under N_2. Evaporation of all solvents and workup as described above gave product **45** (0.5 g, 41%). Mp 165−167 °C. UV max (EtOH): 260 nm (ϵ 14 700), 209 (ϵ 29 700). ^{1}H NMR (DMSO-d_6): δ 8.18 (1H, s) and 8.00 (1H, s, H_2 and H_8), 7.29 (7H, m, Ph and NH_2), 4.80 (2H, s), 4.45 (2H, s) 4.20 (2H, s), 2.07 (2H, m), 1.80 (2H, m) 1.40 (4H, m). ^{13}C NMR: 156.41, 152.98, 150.19, 141.05, 138.94, 133.43, 130.45, 128.64, 127.99, 127.82, 118.94, 71.68, 69.80, 44.28, 28.37, 27.44, 22.36, 22.31. EI-MS: 350 (M + H, 1.3), 91 (100.0). CI-MS: 351 (M + 2H, 22.1), 350 (M + H, 100.0). HRMS: calcd for $C_{20}H_{23}N_5O$, 349.1903; found, 349.1900. Anal. Calcd for $C_{20}H_{23}N_5O$: C, 68.75; H, 6.63; N, 20.04. Found: C, 68.65; H, 6.75; N, 20.18.

Method B. The mixture of dibromide **30b** (1.30 g, 3.47 mmol), adenine (0.61 g, 4.5 mmol), and flame-dried K_2CO_3 (2.8 g, 21 mmol) in DMF (30 mL) was stirred at 110 °C for 18 h. The solid was filtered off and washed with DMF. The filtrate was evaporated and the crude product was chromatographed on a silica gel column (CH_2Cl_2/MeOH, 30:1 → 20:1) to give product **45** (0.72 g, 60%) as a solid identical to compound prepared by method A.

9-{[2-(Hydroxymethyl)cyclohex-1-en-1-yl]methyl}-adenine (46). Sodium (92 mg, 4 mmol) was added to liquid NH_3 (20 mL) under N_2 with stirring at −78 °C. A solution of compound **45** (700 mg, 2 mmol) in THF (10 mL) was added dropwise over a period of 3 min. After an additional 15 min, the reaction was quenched with NH_4Cl (300 mg, 5.6 mmol). Ammonia was evaporated, and the solids were filtered off and washed with CH_2Cl_2/MeOH (10:1) with the aid of a sonicator. The combined filtrates were evaporated and the crude product was chromatographed on a silica gel column (CH_2Cl_2/MeOH, 20:1 → 15:1) to give compound **46** (274 mg, 53%) as a solid. Mp 216−218 °C. UV max (EtOH): 260 (ϵ 14 300), 208 (ϵ 24 400). ^{1}H NMR ($CDCl_3$): δ 8.10 (1H, s) and 8.05 (1H, s, H_2 and H_8), 7.23 (2H, s, NH_2), 5.01 (1H, t, J = 4.2 Hz, OH), 4.79 (2H, s), 4.12 (2H, d, J = 3.9 Hz), 2.08 (2H, m), 1.75 (2H, m), 1.45 (4H, m). ^{13}C NMR: 156.44, 152.74, 150.50, 142.35, 136.97, 127.70, 127.67, 61.12, 44.36, 28.05, 27.27, 22.55, 22.42. EI-MS: 259 (M, 2.7), 136 (100.0). HRMS: calcd for $C_{13}H_{17}N_5O$, 259.1433; found, 259.1432. Anal. Calcd for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.61; N, 27.01. Found: C, 60.32; H, 6.49; N, 27.26.

(*E*)- and (*Z*)-9-{[2-(Benzyloxymethyl)-1-hydroxycyclohexyl]methyl}-*N*^{6}-mesyladenine (48). The method described for mesylates **39** and **40** was followed, using a mixture of isomers **37b** and **38b** (780 mg, 2.12 mmol), DMAP (337 mg, 2.76 mmol), MsCl (0.984 mL, 12.72 mmol, added in two equimolar portions), CH_2Cl_2 (30 mL), and pyridine (4 mL). Chromatography (CH_2Cl_2/MeOH, 100:1 → 60:1) afforded the N^6-mesyl derivatives **48** (440 mg, 46%). Mp 180−183 °C. UV max (EtOH): 273 nm (ϵ 14 300), 216 (ϵ 23 600). ^{1}H NMR (DMSO-d_6): δ 8.37 (1H, s) and 8.20 (1H, s, H_8 and H_2), 7.32 (4H, m) and 7.26 (1H, m, Ph), 4.92 and 4.70 (1H, 2s, ratio 1:1, OH), 4.47 (2.5 H, m), 4.37 and 4.23 (0.5H, J_{AB} = 13.8 Hz), 3.98 (0.5H, 1/2 of AB, J_{AB} = 13.0 Hz), 3.82 (0.5H, m), 3.73 (0.5H, m), 3.49 (0.5H, m), 3.28 (4H, CH_3 and CH_2), 1.86−1.08 (9H, m). EI-MS: 445 (M, 2.3), 91 (100.0). HRMS: calcd for $C_{11}H_{27}N_5O_4S$, 445.1784; found, 445.1782.

(*E*)- and (*Z*)-9-{[2-(Benzyloxymethyl)-1-hydroxycyclohexyl]methyl}-*N*^{6}-benzoyladenine (49 and 50). A mixture of isomers **37b** and **38b** (1.84 g, 5 mmol) and benzoic anhydride (Bz_2O, 9.0 g, 40 mmol) in pyridine (10 mL) was stirred at room temperature for 12 h and then at 40 °C for 24 h. The resultant solution was poured on ice (100 g) and $NaHCO_3$ (20 g) with stirring, whereupon it was extracted with $CHCl_3$. The organic phase was washed successively with saturated aqueous $NaHCO_3$, H_2O, 5% aqueous HCl, $NaHCO_3$, and brine, and then it was dried over Na_2SO_4. Solvents were evaporated and the residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH, 90:1 → 80:1) to give product **49** and **50** (1.63 g, 69%) as a solid. The *E*/*Z* ratio was 1:1. UV max (EtOH): 287 nm (ϵ 18 300), 235 (ϵ 13 900), 206 (ϵ 25 900). ^{1}H NMR (DMSO-d_6): δ 11.13 (1H, s, NHCO), 8.71 (1H, s), 8.32 and 8.31 (1H, 2s, H_8 and H_2), 8.04 and 8.02 (2H, 2s), 7.62 (1H, m), 7.53 (2H, m), 7.33 (4H, m) and 7.26 (1H, m, aromatic H's), 4.95 and 4.75 (1H, 2s, ratio 1:1, OH), 4.55 and 4.50 (1H, J_{AB} = 10.8 Hz), 4.48 (1H, s), 4.42 and 4.32 (1H, J_{AB} = 10.6 Hz), 4.04, 3.87, 3.77 and 3.58 (2H, m), 3.58 and 3.34 (1H, m), 1.60−1.90 (9H, m). EI-MS: 471 (M, 1.7), 91 (100.0). HRMS: calcd for $C_{27}H_{29}N_5O_3$, 471.2270; found, 471.2272.

(*E*)- and (*Z*)-9-{[2-(Benzyloxymethyl)-1-methylsulfonylcyclohexyl]methyl}-*N*^{6}-benzoyladenine (51 and 52). The method described for mesylates **39** and **40** was followed. A mixture of isomers **49** and **50** (1.60 g, 3.4 mmol), DMAP (0.5 g, 4.1 mmol), MsCl (0.79 mL, 10.2 mmol), CH_2Cl_2 (60 mL) and pyridine (10 mL) were used. Chromatography (CH_2Cl_2/MeOH, 60:1 → 50:1) afforded product **51** and **52** as a solid (0.93 g, 50%). ^{1}H NMR (DMSO-d_6): δ 9.42 (1H, s, NHCO), 8.71 (1H, s), 8.32 and 8.31 (1H, 2s, H_8 and H_2), 8.03 (2H, 2s), 7.60 (1H, m), 7.51 (2H, m), 7.32 (4H, m) and 7.26 (1H, m, aromatic H's), 4.95 and 4.55 (1H, J_{AB} = 10.8 Hz) and 4.75 (1H, m), 4.30 (2H, 2s), 3.80 and 3.48 (2H, m), 3.40 and 3.24 (1H, m), 3.15 and 3.10 (3H, 2s), 1.66−2.0 (9H, m). FAB-MS: 549 (M, 100.0).

9-{[3-(Benzyloxymethyl)cyclohex-1-en-2-yl]methyl}-adenine (53) and 9-{[2-(Benzyloxymethyl)cyclohex-1-en-1-yl]methyl}adenine (45). The procedure described for the *E*- and *Z*-isomers **34** and **35** was followed, using mesylates **51** and **52** (450 mg, 0.82 mmol) and tBuOK (184 mg, 1.65 mmol) in THF (5 mL) at 0 °C. A solution of the crude product in 20% NH_3 in methanol was then allowed to stand at room temperature for 4 h. Evaporation of volatile components and chromatography (CH_2Cl_2/MeOH, 30:1 → 20:1) gave compounds **53** (130 mg, 46%) and **45** (60 mg, 22%) as solids. Compound **45** was identical (TLC, ^{1}H, and ^{13}C NMR) to the product obtained from dibromo derivative **30b**.

Compound 53. ^{1}H NMR ($CDCl_3$): δ 8.35 (1H, s) and 7.74 (1H, s, H_2 and H_8, adenine), 7.28 (5H, m), 6.60 (2H, s, NH_2), 5.60 (1H, m, CH═), 4.88 and 4.64 (2H, J_{AB} = 15.1 Hz), 4.46 (2H, s), 3.50 (2H, m), 2.27 and 2.17 (1H, m), 1.99 (2H, m), 1.85 and 1.72 (1H, m) 1.56 (3H, m). ^{13}C NMR: 156.04, 153.19, 150.33, 140.96, 138.42, 133.75, 128.64, 127.99, 127.81, 119.57, 73.37, 72.83, 48.17, 35.92, 25.93, 25.37, 19.31.

9-{[3-(Hydroxymethyl)cyclohex-1-en-2-yl]methyl}-adenine (54). The deprotection was carried out as described for methylenecyclobutanes **21** and **22,** with compound **53** (100 mg, 0.22 mmol) and BCl_3 (1 M in CH_2Cl_2, 1.37 mL, 1.37 mmol) in CH_2Cl_2 (3 mL). The crude product was chromatographed on a silica gel column (CH_2Cl_2/MeOH, 20:1 → 15:1) to give 40 mg (70%) of **54**. Mp 184−187 °C after crystallization from CH_2Cl_2/MeOH (10:1). UV max (EtOH): 261 nm (ϵ 14 100), 209 (ϵ 25 700). ^{1}H NMR (DMSO-d_6): δ 8.14 and 8.05 (2H, s, H_8 and H_2), 7.22 (2H, s, NH_2), 5.40 (1H, s, CH═), 4.76 and 4.66 (2H, J_{AB} = 11.7 Hz), 4.64 (1H, brs, OH), 3.52 and 3.38 (2H, m), 2.01 (1H, m), 1.89 (2H, m), 1.70 (1H, m), 1.51 (1H, m), 1.42 (2H, m). ^{13}C NMR 156.44, 152.98, 150.10, 141.45, 134.98, 126.58, 119.04, 62.95, 47.30, 38.38, 25.15, 24.95, 18.87. EI-MS 259: (M, 5.4), 228 (100.0). HRMS: calcd for $C_{13}H_{17}N_5O$, 259.1433; found, 259.1433. Anal. Calcd for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.61; N, 27.01. Found: C, 60.12; H, 6.49; N, 27.18.

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