Synthesis of Norcarbovir Analogues, the First Examples of Cyclobutene Nucleosides Unsubstituted at the Vinylic Position

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Received July 30, 1996 (Revised Manuscript Received January 8, 1997[⊗]*)*

Two cyclobutene nucleosides, **27** and **29**, analogous to the yet unknown norcarbovir, and with adenine and hypoxanthine as the base moieties, respectively, were synthesized starting from *cis*-3-cyclobutene-1,2-dicarboxylic anhydride (**6**). Its reduction to lactone **9** followed by reaction with ammonia and then Hofmann rearrangement led to cyclic carbamate **15** which was the key intermediate of these syntheses. Its *tert*-butoxycarbonyl derivative **17** led to the ring opening of the heterocyclic moiety at low temperature. Compound **18** was thus obtained, and the successive benzylation and then treatment with hydrochloric acid yielded hydrochloride **21**. Construction of bases was achieved in satisfying overall yields provided that mild experimental conditions from **21** to **27** or **29** were used to restrict the unwanted electrocyclic ring opening. Nitropyrimidine **31** was also prepared from **21** *via* the intermediate **23**.

Introduction

The recognition that nucleosides and nucleoside analogues can possess interesting antitumor and antiviral properties has led to a great interest of chemists during the past years.[1] Peculiarly, (−)-carbovir (**1**), the carbocyclic analogue of 2′,3′-didehydro-2′,3′-dideoxyguanosine in which the furan ring oxygen is replaced by a methylene, was reported to be a potent inhibitor of reverse transcriptase of HIV-1.[2] This interesting biological activity gave rise to a number of synthetical works from research laboratories.[3] As a further step in the evaluation of the analogues of carbovir, we planned to remove this methylene and to obtain norderivatives. Besides the possible interest of these compounds on the biological point of view, we anticipated that special conditions would be needed to synthesize these compounds. Cyclobutene compounds with two *cis* substituents at the allylic position have indeed almost never been prepared as target molecules, and they rather are intermediates to acyclic[4] and cyclic[5] (*Z*,*E*)-dienes. On the other hand only one cyclobutene nucleoside (**2**) has been previously prepared[6a,7] as well as a few cyclobutane nucleosides with an exocyclic double bond (**3**, **4**)[6] (Figure 1).

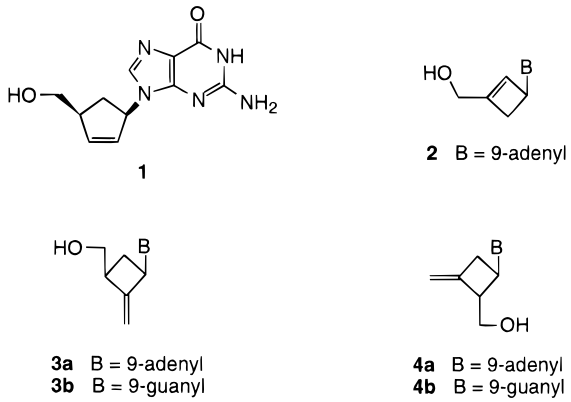

Figure 1.

Result and Discussion

This paper deals with the first synthesis of cyclobutene nucleosides unsubstituted at the vinylic position (**5**). The synthetic way started from anhydride **6** prepared by photocycloaddition of acetylene to maleic anhydride.[8] In early experiments the carboxylic group of the hemiester **7**, obtained by methanolysis of **6**, was converted into amide or acyl azide in the usual experimental conditions but the subsequent Hofmann or Curtius rearrangements failed to yield the amino ester **8**, or a protected related product, due to the high thermal unstability of the intermediates and the product. Fortunately replacement of the methoxycarbonyl group by an hydroxymethyl group resulted in an increased stability and the amido alcohol **10** was obtained in fair yield by reduction of anhydride

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1997.

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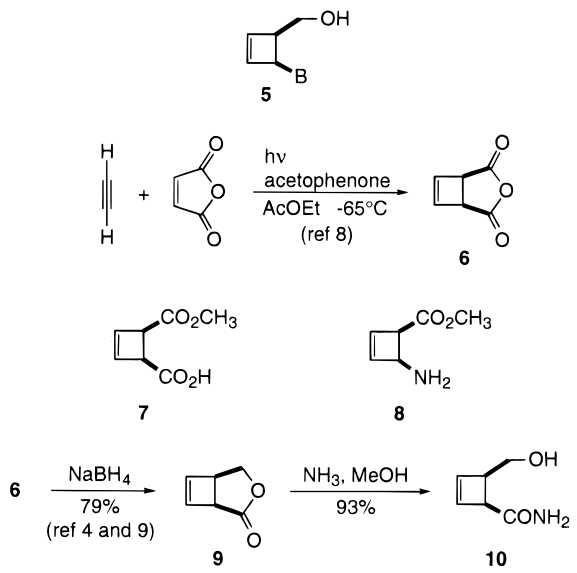
S0022-3263(96)01451-X CCC: $14.00

Scheme 1



6 to lactone **9**[4,9] followed by treatment with ammonia (Scheme 1).

Reaction of the silyl or tetrahydropyranyl derivative, **11a** or **11b**, respectively, with bis(acetoxy)iodobenzene[10] led to the expected methyl carbamates **12a** and **12b** together with small amounts of the electrocyclic ring-opening products. Attempts of separation by column chromatography on silica gel failed and led to higher yields of the opening products. On the other hand heating of cyclobutene **12a** at 110 °C in toluene for 12 min gave rise to **13** as the sole electrocyclic ring-opening product. Other similar outward conrotation preferences for nitrogen substituents were pointed out previously.[11] In these experimental conditions, a part of compound **13** was isomerized into **14** (Scheme 2). These dienes were characterized by ^{1}H NMR (**13**, $J_{H-1/H-2} = 12.9$ Hz; $J_{H-3/H-4} = 9.9$ Hz; strong NOE enhancement of H-4 upon saturation of H-3 + H-4 at 5.95 ppm; **14**, $J_{H-1/H-2} = 13.8$ Hz; $J_{H-3/H-4} = 15.3$ Hz). The cyclobutene/diene ratio for the reaction from **11a** was measured by integration of ^{1}H NMR signals corresponding to methylene groups of both compounds (3.79 and 4.20 ppm for **12a** and **13**, respectively). The same method was used for the following products.

Compounds **12a** and **12b** were submitted to the usual hydrolytic methods for methyl carbamates (e.g., heating in basic or acidic conditions). However we could not thus obtain the expected amino alcohols, and either recovery of the starting materials or formation of unidentified products occurred.

On the other hand the same reaction from the unprotected **10** led to an interesting result. Cyclic carbamate **15** was thus obtained in high yield provided that the reaction was run in a concentrated medium to reduce the amount of methyl carbamate **16**. When this compound (**15**) was submitted to reaction with di-*tert*-butyl dicarbonate,[12] the expected product **17** was easily obtained. Its basic treatment in mild conditions led to compound **18**, and only a small amount of the electrocyclic ring-opening occurred. *tert*-Butoxycarbonyl derivative **18** reacted with hydrochloric acid at 0 °C and yielded the pure crystallized hydrochloride **20**. Similarly, benzylation of **18** followed by the same hydrochloric acid treatment led to compound **21**. Compounds **20** and **21** were thus obtained in high purity and in 41% and 38% overall yields, respectively, from **6**, and difficulties due to the unwanted thermal electrocyclic reactions were thus practically circumvented.

We anticipated that the following steps would also need mild experimental conditions for the same reasons. Therefore, we used, in the first step of construction of adenine, 4,6-dichloro-5-nitropyrimidine,[13] which is more reactive that the corresponding amino derivative. The reactions worked at room temperature from hydrochlorides **20** or **21**, in the presence of triethylamine, and gave the substitution products **22** and **23** in satisfactory yields. Compound **22** was obtained in lower yield than **23**. Moreover the subsequent reduction of the nitro group of **22**, in several experimental conditions, proved to give complex mixtures instead of the expected product. Therefore we pursued the synthesis from benzylated derivative **23**. Its reduction with sodium hydrosulfite[14] gave the expected product **24** that could be easily purified; however, in these conditions, the yield was low (27%).[15] Other reagents such as $NaBH_4-Pd/C$[16] and H_3PO_2-Pd/C[17] gave bad results. An attempt of reduction in the presence of bakers' yeast[18] also failed. Finally the best result was obtained with $SnCl_2 \cdot 2H_2O$[13a,19] in ethanol. Compound **24** was thus prepared in 62% yield at 60 °C for 10 min. Further cyclization with triethyl orthoformate gave the expected product **25** at room temperature. It was treated with ammonia under pressure in a stainless steel bomb for 48 h at 40 °C, and the reaction yielded **26** in high yield. Subsequent debenzylation with boron trichloride[13a] gave norcabovir A (**27**) (Scheme 3) in 12 steps from **6** and in 15% overall yield. Fortunately compounds **24**, **25**, **26**, and **27** were less sensitive to heating than the previous ones of this synthesis. For instance, preparation of **24** needed a short heating at 60 °C, and only a small amount of the electrocyclic ring-opening product was detected by ^{1}H NMR of the crude product. It was removed in the course of the purification by column chromatography.

Compound **29** with hypoxanthine as the base was obtained by acidic hydrolysis of **25** followed by debenzylation. We also prepared compound **31** by nucleophilic substitution of ammonia to **23**, followed by debenzylation (Scheme 4). Compounds **30** and **31** were obtained

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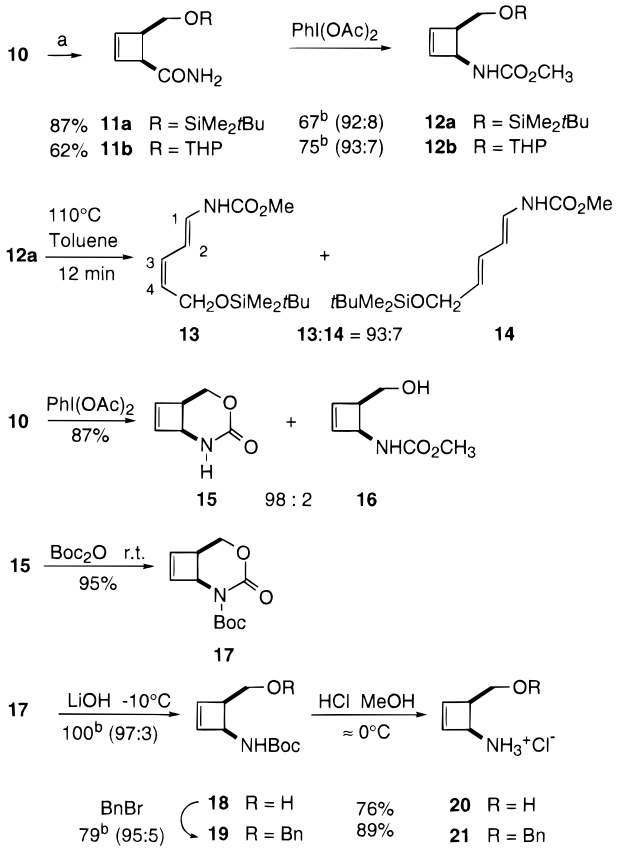
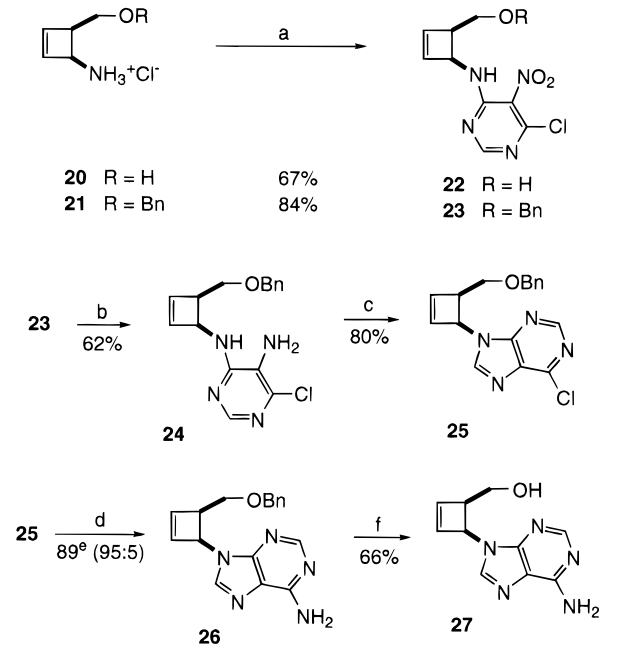
Scheme 2



[a] ^{t}BuMe$_2$SiCl, imidazole, DMF (**11a**) or dihydropyrane, PPTS (**11b**). [b] Total yields (%) for the cyclobutene compounds and the resulting electrocyclic ring-opening products that could not be separated from this mixture. The numbers in parentheses refer to the ratio cyclobutenes/dienes measured by ^{1}H NMR.

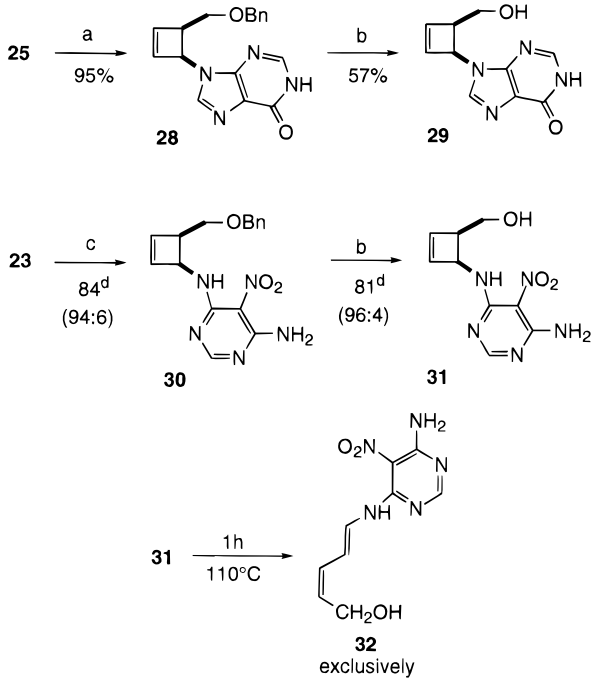
Scheme 3



[a] 4,6-Dichloro-5-nitropyrimidine, Et_3N, CH_2Cl_2, rt, 30 min. [b] $SnCl_2 \cdot 2H_2O$, EtOH, 60 °C, 10 min. [c] $HC(OEt)_3$, HCl, rt. [d] NH_3, MeOH, 10−11 bars, 48 h, 40 °C. [e] See *b*, Scheme 2. [f] BCl_3, CH_2Cl_2, −78 °C.

together with small amounts of dienes. The total conversion of **31** into diene **32** was achieved in 1 h at 110 °C in

Scheme 4



[a] CF_3CO_2H, H_2O, rt. [b] BCl_3, CH_2Cl_2, −78 °C. [c] NH_3, MeOH, rt. [d] See *b*, Scheme 2.

DMSO-d_6. NMR results and NOE experiments[11] are in agreement with the 1′*Z*,3′*E* stereochemistry.

Compounds **27**, **29**, and **31** have been evaluated as inactive in *in vitro* anti HIV-1 and HIV-2 screens (CEM 4 cells) and in *in vitro* antitumor tests (KB cells).

Conclusion

The main difficulty in obtaining the target molecules was the easy thermal electrocyclic ring opening of cyclobutene compounds, which could even partly occur at room temperature (e.g., **12a**,**b**, **18**, and **19**). Cyclobutene−diene isomerization has already been studied.[20] It has been shown that the rate and the stereoselectivity of the conrotatory electrocyclic reaction of cyclobutenes are influenced to a large extent by the electronic effects of the allylic substituents.[11,21] In this paper, we describe the first syntheses of carbocyclic nucleosides analogous to carbovir but with a cyclobutene ring. These compounds were obtained in fair overall yield when mild experimental conditions were used.

Experimental Section

NMR spectra were recorded at 400 and 100 MHz for ^{1}H and ^{13}C, respectively. Multiplicities in the ^{13}C spectra were determined by DEPT experiments, and numerous assignments were obtained by ^{13}C/^{1}H cosy experiments. IR spectra were recorded with a FT infrared spectrophotometer. Melting points are uncorrected. Isomerization can occur in the course of these measurements for cyclobutene compounds. Elemental analyses were performed by the service de microanalyse, CNRS ICSN, Gif sur Yvette. High-resolution mass measurements were performed at the CRMPO (Rennes). The column

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chromatographies were run on silica gel Gerudan SI 60, 230−400 mesh, under 1−2 bars. The silica gel/crude product ratio is indicated for each separation.

2-(Hydroxymethyl)cyclobut-3-enecarboxamide (10). Ammonia dried on KOH was bubbled for 1 h through a solution, cooled to 0 °C, of lactone **9**[4,9] (3.77 g, 34.24 mmol) in MeOH (175 mL). The reaction mixture was stirred overnight at room temperature. Evaporation led to crude **10**, and recrystallization in acetone provided **10** as white crystals (4.045 g, 93%): mp 148−150 °C; ^{1}H NMR (DMSO-d_6) δ 7.25 (s, 1H of NH_2), 6.99 (s, 1H of NH_2), 6.23 (ddd, 1H, H-3, $J_{H-3/H-4}$ = 2.8 Hz, $J_{H-3/H-1}$= 1.0 Hz, $J_{H-3/H-2}$ = 0.9 Hz), 6.17 (dd, 1H, H-4, $J_{H-4/H-3}$= 2.8 Hz, $J_{H-4/H-1}$ = 0.9 Hz), 3.64 (t, 1H, OH, J = 5.5 Hz), 3.55 (ddd, 1H, H-1, $J_{H-1/H-2}$ = 4.6 Hz, $J_{H-1/H-3}$ = 1.0 Hz, $J_{H-1/H-4}$ = 0.9 Hz), 3.53 (m, 1H, H-5, $J_{H-5/H-5'}$ = 10.8 Hz, $J_{H-5/H-2}$ = 7.2 Hz, $J_{H-5/OH}$ = 5.5 Hz), 3.39 (m, 1H, H-5′, J = 10.8, 7.5, 5.5 Hz), 3.09 (m, 1H, H-2, J = 7.5, 7.2, 4.6, 0.9 Hz); ^{13}C NMR (DMSO-d_6) δ 173.07 (*C*═O), 140.02 (C-3), 135.63 (C-4), 62.06 (C-5), 48.94 (C-1), 48.12 (C-2); IR (KBr disc) cm^{-1} 3365, 3282, 3162, 3052, 1649, 1623, 1560, 1415, 1114, 1039, 746. Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.80; H, 7.01; N, 11.08.

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)cyclobut-3-enecarboxamide (11a). ^{t}BuMe$_2$SiCl (4.268 g, 28.31 mmol) and imidazole (4.016 g, 58.98 mmol) were added to a solution of amido alcohol **10** (3 g, 23.59 mmol) in DMF (5.5 mL). The reaction mixture was stirred overnight at room temperature, and water (13 mL) was added. Extraction with Et$_2$O (4 × 30 mL), drying ($MgSO_4$), evaporation, and column chromatography on silica gel (60:1, cyclohexane/Et$_2$O 3:7) led to **11a** as white crystals (4.939g, 87%): mp 79−80 °C; ^{1}H NMR ($CDCl_3$) δ 6.35 (br s, 1H of NH_2), 5.47 (br s, 1H of NH_2), 6.24 (s, 2H, H-3 and H-4), 3.79 (d, 2H, H-5, J = 7.0 Hz), 3.73 (d, 1H, H-1, $J_{H-1/H-2}$ = 4.5 Hz), 4.25 (td, 1H, H-2, J = 7.0, 4.5 Hz), 0.89 (s, 9H, ^{t}Bu), 0.07 (s, 3H, Me), 0.06 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 173.89 (*C*═O), 139.93 (C-3), 135.35 (C-4), 63.67 (*C*H$_2$), 49.90 (C-1), 48.83 (C-2), 25.83 (C(*C*H$_3$)$_3$), 18.21 (*C*(CH$_3$)$_3$), −5.41 (*C*H$_3$), −5.44 (*C*H$_3$); IR (KBr disc) cm^{-1} 3384, 3195, 3054, 2965, 2929, 2857, 1648, 1471, 1417, 1259, 1095, 1068, 836, 795. Anal. Calcd for $C_{12}H_{23}NO_2Si$: C, 59.71; H, 9.60; N, 5.80; Si 11.63. Found: C, 59.56; H, 9.53; N, 5.86; Si 10.90.

2-((Tetrahydropyranyloxy)methyl)cyclobut-3-enecarboxamide (11b). Pyridinium *p*-toluenesulfonate (200 mg) and a small amount of CH_2Cl_2 were added to a suspension of amido alcohol **10** (1g, 7.87 mmol) in 3,4-dihydropyran (10 mL). The reaction mixture was heated to 50 °C with stirring until it became homogeneous (≈20 min). It was then cooled, and brine (5 mL) and water (5 mL) were added. Extraction with AcOEt (4 × 15 mL), drying ($MgSO_4$), and evaporation led to **11b** together with another tetrahydropyranyl derivative in a 79:21 ratio, respectively. Recrystallization (AcOEt/light petroleum ether 1:1) led to pure **11b** as white crystals (0.998 g, 62%): mp = 116−117 °C, ^{1}H NMR ($CDCl_3$) δ 6.31/6.29 (2d, 1H, H-3 or H-4), 6.21 (s, 1H, H-4 or H-3), 5.97/5.70 (2s, 2H, NH_2), 4.58/4.55 (2s, 1H, H-6), 3.94 (m, 1H), 3.85 (m, 1H), 3.73 (m, 1H), 3.50 (m, 3H), 1.75 (m, 2H), 1.53 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 174.09 (*C*═O), 140.95/140.53 (C-3), 135.03/134.64 (C-4), 99.33/99.14 (C-6), 68.02/67.56 (C-10), 62.50/62.34 (C-5), 49.62/49.55 (C-1), 46.83/46.35 (C-2), 30.48/30.43 (C-7), 25.24 (C-9), 19.61/19.50 (C-8). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.41; H, 7.96; N, 6.63.

(Methoxycarbonyl)(2-((*tert*-butyldimethylsiloxy)methyl)cyclobut-3-enyl)amine (12a). Amido ether **11a** (0.400 g, 1.66 mmol) and then bis(acetoxy)iodobenzene (≈90% of purity, 587 mg, 1.64 mmol) were added to a stirred solution of KOH (85% of purity, 232 mg, 3.51 mmol) in MeOH (13 mL), cooled by an ice−water bath. The reaction mixture was progressively warmed up to room temperature. After 1.15 h MeOH was evaporated and then water (10 mL) and CH_2Cl_2 (5 mL) were successively added to the residue with stirring. Decantation, extraction (CH_2Cl_2, 3 × 5 mL), washing of the combined organic phases (brine, 5 mL), drying ($MgSO_4$), and then evaporation gave the crude product that was chromatographed on silica gel (60:1, cyclohexane then cyclohexane/AcOEt 92:8). An oil (376 mg, 67%) consisting of **12a** together with a small amount of the electrocyclic reaction product (92:8) was thus obtained: ^{1}H NMR ($CDCl_3$) δ 6.11 (d, 1H, H-3 or H-4, $J_{H-3/H-4}$= 2.4 Hz), 6.01 (d, 1H, H-4 or H-3, J = 2.4 Hz), 5.75 (br d, 1H, NH), 4.81 (dd, 1H, H-1, $J_{H-1/H-2}$ = 4.2 Hz), $J_{H-1/NH}$ = 9.6 Hz), 3.79 (m, 2H, H-5), 3.66 (s, 3H, CO_2Me), 3.24 (m, 1H, H-2), 0.89 (s, 9H, Si(Me)$_2$C*Me*$_3$), 0.06 and 0.04 (2s, 6H, Si(*Me*)$_2$CMe$_3$); ^{13}C NMR ($CDCl_3$) δ 157.00 (*C*═O), 138.60 and 138.03 (C-3 and C-4), 61.48 (C-5), 54.03 (C-1), 51.92 (CO_2CH_3), 50.47 (C-2), 25.80 (Si(CH$_3$)$_2$ C(*C*H$_3$)$_3$), 18.14 (Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), −5.46 and −5.49 (Si(*C*H$_3$)$_2$ C(CH$_3$)$_3$).

Refluxing of **12a** in toluene during 12 min gave rise to dienes **13** and **14** in a 93:7 ratio.

Methyl (1*E*,3*Z*)-[5-((*tert*-butyldimethylsilyl)oxy)penta-1,3-dienyl]carbamate (13): ^{1}H NMR (DMSO-d_6) δ 9.62 (br d, 1H, NH, $J_{NH/H-1}$ = 10.5 Hz), 6.67 (dd, 1H, H-1, $J_{H-1/H2}$ = 12.9 Hz, $J_{H-1/NH}$ = 10.5 Hz), 5.95 (m, 2H, H-2 and H-3), 5,23 (dt, 1H, H-4, $J_{H-4/H-3}$ = 9.9 Hz, $J_{H-4/H-5}$ = 6.5 Hz), 4.20 (d, 2H, H-5, J = 6.5 Hz), 3.62 (s, 3H, CO_2Me), 0.86 (s, 9H, Si-(Me)$_2$C*Me*$_3$), 0.04 (s, 6H, Si(*Me*)$_2$CMe$_3$); ^{13}C NMR ($CDCl_3$) δ 153.87 (*C*═O), 127.65, 127.17 and 126.59 (C-1, C-2, and C-3), 106.69 (CO_2CH_3), 59.71 (C-5), 25.94 (Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 18.35 (Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), −5.08 (Si(*C*H$_3$)$_2$C(CH$_3$)$_3$).

Methyl (1*E*,3*E*)-[5-((*tert*-butyldimethylsilyl)oxy)penta-1,3-dienyl]carbamate (14): ^{1}H NMR (DMSO-d_6) δ 9.57 (br d, 1H, NH, $J_{NH/H-1}$ = 10.3 Hz), 6.60 (dd, 1H, H-1, $J_{H-1/H2}$ = 13.8 Hz, $J_{H-1/NH}$ = 10.3 Hz), 6.14 (dd, 1H, H-3, $J_{H-3/H4}$ = 15.3 Hz, $J_{H-3/H-2}$ = 11.8 Hz), 5.72 (dd, 1H, H-2, J = 13.8, 11.8 Hz), 5.50 (dt, 1H, H-4, J = 15.3, 5.4 Hz), 4.13 (d, 2H, H-5, $J_{H-5/H-4}$ = 5.4 Hz), 3.61 (s, 3H, CO_2CH_3), 0.86 (s, 9H, Si(Me)$_2$C*Me*$_3$), 0.03 (s, 6H, Si(*Me*)$_2$CMe$_3$).

(Methoxycarbonyl)((2-tetrahydropyranyloxy)methyl)-cyclobut-3-enyl)amine (12b). The same experimental procedure as above from 100 mg (0.47 mmol) of **11b** and with cyclohexane and then cyclohexane/AcOEt 8:2 as the chromatography eluent led to an oil (86 mg, 75%) consisting of **12b** together with a small amount of the electrocyclic reaction product (97:3): ^{1}H NMR ($CDCl_3$) δ 6.13 (m, 2H, H-3 and H-4), 5.61/5.55 (2 br d, 1H, NH), 4.86 (m, 1H, H-1), 4.63/4.57 (m, 1H, H-6), 3.92/3.84 (2m, 2H, H-5 and H-10), 3.66 (s, 3H, CH_3), 3.50 (m, 2H, H-5′ and H-10′), 3.36 (m, 1H, H-2), 1.79/1.70 (2m, 2H), 1.56 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 156.68 (*C*═O), 138.94/138.82 and 138.19 (C-3 and C-4), 99.22/98.61 (C-6), 66.40/65.79 (C-10), 62.28 (C-5), 53.92 (C-1), 49.15 (*C*H$_3$), 48.60 (C-2), 30.67/30.36 (C-7), 25.97/25.31 (C-9), 19.50/19.41 (C-8).

2-Aza-4-oxabicyclo[4.2.0]oct-7-en-3-one (15). Amido alcohol **10** (4.014 g, 32.09 mmol) and then bis(acetoxy)-iodobenzene (≈90% of purity, 11.481 g, 32.09 mmol) were added to a stirred solution of KOH (85% of purity, 4.5 g, 68.21 mmol) in MeOH (40 mL), cooled by an ice−water bath. The reaction mixture was progressively warmed up to room temperature. After 1.3 h MeOH was evaporated and then CH_2Cl_2 (100 mL) and water (60 mL) were successively added to the residue under stirring. Decantation, extraction (CH_2Cl_2, 4 × 80 mL), drying ($MgSO_4$), and then evaporation left a white paste. Iodobenzene was removed under reduced pressure. Recrystallization (AcOEt, light petroleum ether) provided **15** as white crystals (3.43 g, 87%): mp 95−96 °C; ^{1}H NMR ($CDCl_3$) δ 6.22 (dd, 1H, H-7 or H-8, $J_{H-7/H-8}$ = 3.0 Hz), 6.17 (dd, 1H, H-8 or H-7, J = 3.0 Hz), 5.99 (br s, 1H, NH), 4.31 (m, 1H, H-1), 4.25 (dd, 1H, H-5, $J_{H-5/H-5'}$ = 11.8 Hz, $J_{H-5/H-6}$ = 1.5 Hz), 4.14 (dd, 1H, H-5′, J = 11.8, 3.4 Hz), 3.44 (m, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 157.05 (*C*═O), 139.55 and 137.82 (C-7 and C-8), 66.45 (C-5), 53.04 (C-1), 43.18 (C-6). IR (KBr disc) cm^{-1} 3288, 3068, 1710, 1673, 1465, 1448, 1411, 1365, 1263, 1193, 1105, 1000, 811, 763. Anal. Calcd for $C_6H_7NO_2$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.36; H, 5.45; N, 11.02

***N*-(*tert*-Butoxycarbonyl)-2-aza-4-oxabicyclo[4.2.0]oct-7-en-3-one (17).** Triethylamine (4.2 mL, 30.09 mmol) and 4-(dimethylamino)pyridine (334 mg, 2.74 mmol) were added under argon to a solution of carbamate **15** (3.422g, 27.35 mmol) in THF (7 mL). The mixture was cooled to 0 °C, and a solution of di-*tert*-butyl dicarbonate (7.162g, 41.16 mmol) in THF (7 mL) was added dropwise at the same temperature. The reaction mixture was stirred for 2 h at room temperature. Evaporation, stirring of residue with CH_2Cl_2 (80 mL), washing successively with 0.3 M $KHSO_4$ (2 × 15 mL), water (15 mL), and brine (30 mL), drying ($MgSO_4$), and evaporation left the crude product.

Recrystallization led to 5.840 g (95%) of **17** as yellow crystals: mp 86−87 °C; ^{1}H NMR ($CDCl_3$) δ 6.21 (s, 2H, H-7 and H-8), 5.05 (d, 1H, H-1, $J_{H-1/H-6}$ = 4.4 Hz), 4.23 (dd, 1H, H-5, $J_{H-5/J-5'}$ = 11.3 Hz, $J_{H-5/H-6}$ = 2.0 Hz), 4.16 (dd, 1H, H-5′, J = 11.3, 3.4 Hz), 3.55 (br s, 1H, H-6), 1.53 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$) δ 152.31 and 151.63 (*C*═O), 138.45 and 138.37 (C-7 and C-8), 83.59 (*C*(CH_3)$_3$), 66.03 (C-5), 55.06 (C-1), 44.85 (C-6), 27.90 (*C*(CH_3)$_3$); IR (KBr disc) cm^{-1} 3060, 2983, 2970, 2940, 1750, 1718, 1558, 1394, 1367, 1303, 1265, 1151, 1116, 1089, 806, 761. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.85; H, 6.76; N, 6.25.

(*tert*-Butoxycarbonyl)(2-(hydroxymethyl)cyclobut-3-enyl)amine (18). Lithium hydroxide (0.93 g, 22.20 mmol) was added to a suspension of **17** (1g, 4.44 mmol) in a 1:1 MeOH/H_2O mixture (20 mL) at −10 °C. The reaction mixture was stirred for 1.5 h at the same temperature, and then CH_3CO_2H (11 mL) was added. Partial evaporation, extraction (AcOEt, 4 × 20 mL), drying, and evaporation led to white crystals (885 mg, 100%) consisting of **18** together with a small amount of the electrocyclic reaction product (97:3): mp (for the mixture) 72 °C; ^{1}H NMR ($CDCl_3$) δ 6.13 (dd, 1H, H-4, $J_{H-4/H-3}$ = 2,8 Hz, $J_{H-4/H-1}$ = 0,9 Hz), 6.09 (dd, 1H, H-3, J = 2.8, 0.9 Hz), 5.33 (br s, 1H, NH), 4.70 (dd, 1H, H-1, $J_{H-1/NH}$ = 7.8 Hz, $J_{H-1/H-2}$ = 3.4 Hz), 3.74 (m, 2H, H-5), 3.32 (m, 1H, H-2), 2.28 (br s, 1H, OH), 1.45 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$) δ 156.18 (*C*═O), 138.50 and 138.19 (C-3 and C-4), 79.82 (*C*(CH_3)$_3$) , 61.35 (C-5), 53.64 (C-1), 51.79 (C-2), 28.30 (C(*C*H_3)$_3$); IR (KBr disc) cm^{-1} 3359, 3052, 2983, 2935, 1675, 1567, 1511, 1270, 1168, 1052, 1027, 738. The crude product gave good analytical data. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.15; H, 8.51; N, 6.85.

(*tert*-Butoxycarbonyl)(2-((benzyloxy)methyl)cyclobut-3-enyl)amine (19). NaH (60% dispersion in oil, 1.809 g, 45.2 mmol) and ^{n}Bu_4NI (1.894 g, 5.13 mmol) were added under argon and with stirring to a cooled solution (−15 °C) of compound **18** (5.11g, 25.64 mmol) in dry THF (40 mL). Benzyl bromide (3.75 mL, 30.77 mmol) was then added dropwise at the same temperature. The reaction was allowed to proceed for 4 h with a progressive increasing of temperature (−15 → 5 °C). MeOH (40 mL) was then added. Evaporation and then chromatography on silica gel (20:1, cyclohexane/AcOEt 95:5 then 8:2) led to a colorless oil (5.85 g, 79%) that crystallized on standing. It consisted of **19** together with a small amount of the electrocyclic reaction product (94:6): mp (for the mixture) 36−37 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5H, Ph), 6.13 (d (AB system), H-3 or H-4, $J_{H-3/H-4}$ = 3.0 Hz), 6.10 (d (AB system), H-4 or H-3, J = 3.0 Hz), 5.31 (br s, 1H, NH), 4.79 (m, 1H, H-1), 4.53 (m, 2H, H-6), 3.63 (dd, 1H, H-5, $J_{H-5/H-5'}$ = 9.8 Hz, $J_{H-5/H-2}$ = 4.9 Hz), 3.57 (dd, 1H, H-5′, J = 9.8, 3.9 Hz), 3.34 (m, 1H, H-2), 1.45 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$) δ 155.57 (*C*═O), 138.80 and 138.28 (C-3 and C-4), 138.02 (quat C of Ph); 128.40, 127.80 and 127.68 (*C*H of Ph), 79.07 (*C*(CH_3)$_3$), 73.36 (C-6) , 69.27 (C-5), 53.61 (C-1), 49.13 (C-2), 28.39 (C(*C*H_3)$_3$). IR (KBr disc) cm^{-1} 3415, 3345, 3031, 2977, 2929, 2859, 1714, 1506, 1455, 1367, 1245, 1164, 736, 698; HRMS calcd for $C_{17}H_{23}NO_3$ 289.1678, found 289.1683.

(2-(Hydroxymethyl)cyclobut-3-enyl)amine Hydrochloride (20). Compound **18** (1.5 g, 7.53 mmol) was added to a 2 M solution of HCl in MeOH (150 mL). The mixture was stirred for 4 h (−5 → 15 °C), and then argon was bubbled through the solution. Evaporation and several additions of Et_2O followed by evaporation, drying under vacuum (P_2O_5), and two successive recrystallizations (EtOH/Et_2O 1:1) yielded **20** as a powder (0.78 g, 76%): mp 119−120 °C; ^{1}H NMR (D_2O) δ 6.35 (d, 1H, H-3, $J_{H-3/H-4}$ = 2.7 Hz), 6.20 (d, 1H, H-4, J = 2.7 Hz), 4.35 (d, 1H, H-1, J = 3.9 Hz), 3.89 (d, 2H, H-5, J = 4.9 Hz), 3.37 (dt, 1H, H-2); ^{13}C NMR (D_2O) δ 142.12 (C-3), 134.60 (C-4), 59.45 (C-5), 52.41 (C-1), 47.19 (C-2); IR (KBr disc) cm^{-1} 3400, 2400, 1619, 1589, 1469, 1374, 1301, 1151, 1114, 1056, 1037, 973, 844, 786, 736. Anal. Calcd for $C_5H_{10}ClNO$: C, 44.29; H, 7.43; N, 10.33; Cl, 26.15. Found: C, 44.22; H, 7.13; N, 10.19; Cl, 26.41.

(2-((Benzyloxy)methyl)cyclobut-3-enyl)amine Hydrochloride (21). Compound **19** (5.83 g, 20.14 mmol) reacted under the same experimental conditions as **18**, except that a 3 M solution of HCl was used. Recrystallization (CH_2Cl_2/Et_2O) led to **21** as a powder (4.07 g, 89%): mp 129−130 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (br s, 3H, NH_3^+), 7.32 (m, 5H, Ph), 6.25 (s, 1H, H-3 or H-4), 6.23 (s, 1H, H-4 or H-3), 4.67 (d (AB system), 1H, H-6, J = 11.8 Hz), 4.53 (d (AB system), 1H, H-6′, J = 11.8 Hz), 4.44 (br s, 1H, H-1), 4.05 (br d, 1H, H-5), 3.84 (dd, 1H, H-5′, $J_{H-5'/H-5}$ = 10.6 Hz, $J_{H-5'/H-2}$ = 4.2 Hz), 3.38 (br s, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 141.25 (C-3 or C-4), 137.24 (quat C of Ph), 134.74 (C-4 or C-3); 128.40, 127.83 and 127.79 (aromatic *C*H), 73.14 (C-6), 67.38 (C-5), 52.88 (C-1), 46.11 (C-2); IR (KBr disc) cm^{-1} 3100−2700, 1608, 1481, 1455, 1374, 1087, 748, 701; HRMS calcd for the corresponding amine ($C_{12}H_{15}NO$) 189.1154, found 189.1148.

4-[[2′-(Hydroxymethyl)cyclobut-3′-enyl]amino]-6-chloro-5-nitropyrimidine (22). Triethylamine (290 μL, 2.07 mmol) was added dropwise and with stirring to a cooled suspension (0 °C) of hydrochloride **20** (140 mg, 1.034 mmol) and of 4,6-dichloro-5-nitropyrimidine (413 mg, 2.07 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was allowed to slowly warm up to room temperature. After 0.5 h, evaporation then chromatography on silica gel (60:1, CH_2Cl_2/Et_2O 95:5 then 8:2) led to **22** as orange crystals (179 mg, 67%): mp 96−98 °C; ^{1}H NMR ($CDCl_3$) δ 8.39 (br s, 2H, NH and H-2), 6.27 (d (AB system), 1H, H-3′ or H-4′, $J_{H-3'/H-4'}$ = 2.5 Hz), 6.23 (d (AB system), 1H, H-4′ or H-3′, J = 2.5 Hz); 5.42 (dd, 1H, H-1′, $J_{H-1'/H-2'}$ = 4.2 Hz, $J_{H-1'/NH}$ = 7.6 Hz), 3.93 (dd, 1H, C*H*$_2$OH, J = 11.3, 4.9 Hz), 3.86 (br d, 1H, C*H*$_2$OH), 3.48 (ddd, 1H, H-2′), 1.94 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 157.92 (C-2), 155.46 and 154.64 (C-4 and C-6), 138.65 and 138.54 (C-3′ and C-4′), 127.35 (C-5), 61.00 (*C*H_2), 54.12 (C-1′), 50.32 (C-2′); IR (KBr disc) cm^{-1} 3361, 3228, 2954, 2940, 2898, 2879, 1596, 1525, 1482, 1330, 1222, 1068, 970, 858, 784, 752. Anal. Calcd for $C_9H_9ClN_4O_3$: C, 42.12; H, 3.54; N, 21.83; Cl, 13.81. Found: C, 42.09; H, 3.54; N, 21.67; Cl, 14.11.

4-[[2′-((Benzyloxy)methyl)cyclobut-3′-enyl]amino]-6-chloro-5-nitropyrimidine (23). Triethylamine (620 μL, 4.44 mmol) was added dropwise and with stirring to a cooled suspension (0 °C) of hydrochloride **21** (500 mg, 2.22 mmol) and of 4,6-dichloro-5-nitropyrimidine (885 mg, 4.44 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was allowed to warm up to room temperature. After 15 min, evaporation then chromatography on silica gel (60:1, cyclohexane/AcOEt 95:5 and then 9:1) led to **23** as an orange oil (768 mg, 84%): ^{1}H NMR ($CDCl_3$) δ 8.35 (s, 1H, H-2), 8.30 (br s, 1H, NH), 7.31 (m, 5H, Ph), 6.22 (s, 2H, H-3′ and H-4′), 5.36 (dd, 1H, H-1′), $J_{H-1'/NH}$ = 7.4 Hz, $J_{H-1'/H-2'}$ = 3.9 Hz), 4.63 (d (AB system), 1H, benzylic, J = 11.8 Hz), 4.49 (d (AB system), 1H, benzylic, J = 11.8 Hz), 3.65 (m, 2H, C*H*$_2$O), 3.49 (m, 1H, H-2′); ^{13}C NMR ($CDCl_3$) δ 157.86 (C-2), 155.53 and 154.63 (C-4 and C-6), 139.55 and 137.29 (C-3′ and C-4′), 137.48 (quat C of Ph); 128.38, 127.82 and 127.80 (*C*H of Ph), 127.21 (C-5), 73.36 (benzylic C), 68.73 (*C*H_2O), 54.26 (C-1′), 48.49 (C-2′); IR (film) cm^{-1} 3326, 3060, 3031, 1594, 1519, 1492, 1334, 1224, 1062, 858, 786, 750, 698; HRMS calcd for $C_{16}H_{15}ClN_4O_3$ 346.0833, found 346.0848.

4-[[2′-((Benzyloxy)methyl)cyclobut-3′-enyl]amino]-5-amino-6-chloropyrimidine (24). A solution of **23** (1.187 g, 3.423 mmol) and of $SnCl_2$·$2H_2O$ (3.864 g, 17.12 mmol) in EtOH (7 mL) was heated for 10 min at 60 °C. The reaction mixture was then cooled and poured into cooled water (250 mL). The suspension thus obtained was neutralized (pH 7−8) by adding a $NaHCO_3$ aqueous solution (≈45 mL). Extraction (AcOEt, 4 × 160 mL), drying ($MgSO_4$), evaporation, and chromatography on silica gel (60:1, CH_2Cl_2/Et_2O 95:5 and then 8:2) yielded **22** as an oil (0.676, 62%): ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1H, H-2), 7.33 (m, 5H, Ph), 6.23 (s, 2H, H-3′ and H-4′), 5.84 (br d, 1H, NH, $J_{NH/H-1'}$ = 8.4 Hz), 5.31 (dd, 1H, H-1′, J = 8.4, 3.9 Hz), 4.54 (s, 2H, benzylic), 3.74 (dd, 1H, C*H*$_2$O, J = 10.3, 4.9 Hz), 3.69 (dd, 1H, C*H*$_2$O, J = 10.3, 3.5 Hz), 3.49 (m, 1H, H-2′), 3.15 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 149.10 (C-2); 154.30, 142.08 and 121.98 (quat C of base), 139.01 and 138.09 (C-3′ and C-4′), 137.73 (quat C of Ph); 128.44, 127.83 and 127.66 (*C*H of Ph), 73.33 (benzylic C), 69.27 (*C*H_2O), 54.23 (C-1′), 48.96 (C-2′); IR (film) cm^{-1} 3357, 3249, 3060, 3031, 1643, 1573, 1494, 1455, 1419, 1218, 740, 698; HRMS calcd for $C_{16}H_{17}ClN_4O$ 316.1091, found 316.1094.

9-[2′-((Benzyloxy)methyl)cyclobut-3′-enyl]-6-chloropurine (25). A solution of **24** (667 mg, 2.08 mmol) and of 12

M HCl (210 μL) in triethyl orthoformate (5.6 mL) was stirred for 5 h at room temperature. The reaction mixture was cooled and then poured into cooled water (15 mL). Neutralization (pH 7−8) by adding a $NaHCO_3$ aqueous solution (≈3 mL), extraction (AcOEt 4 × 25 mL), drying ($MgSO_4$), evaporation and chromatography on silica gel (60:1, cyclohexane/AcOEt 8:2 and then 7:3) led to **25** as an oil that crystallized on standing (white crystals; 550 mg, 80%): mp 76−77 °C; ^{1}H NMR ($CDCl_3$) δ 8.65 and 8.18 (2s, 2H, H-2 and H-8), 7.21 (m, 3H, Ph), 6.82 (m, 2H, Ph), 6.51 (d (AB system), 1H, H-3′ or H-4′, $J_{H-3'/H-4'}$ = 3.0 Hz), 6.42 (d (AB system), 1H, H-4′ or H-3′, J = 3.0 Hz), 5.78 (d, 1H, H-1′, $J_{H-1'/H-2'}$ = 3.5 Hz), 4.07 (d (AB system), 1H, benzylic, J = 11.8 Hz), 3.86 (d (AB system), 1H, benzylic, J = 11.8 Hz), 3.75 (ddd, 1H, H-2′), 3.45 (dd, 1H, CH_2O, J = 10.3, 4.2 Hz), 3.16 (dd, 1H, CH_2O, J = 10.3, 8.9 Hz); ^{13}C NMR δ 151.73 and 144.50 (C-2 and C-8), 142.80 and 133.28 (C-3′ and C-4′), 136.84 (quat C of Ph); 152.10, 150.72 and 131.67 (quat C of base); 128.18, 127.69 and 127.46 (*C*H of Ph), 73.13 (benzylic C), 68.32 (*C*H_2O), 55.75 (C-1′), 50.00 (C-2′); IR (KBr disc) cm^{-1} 3124, 3064, 3029, 2859, 2833, 2784, 1590, 1560, 1550, 1488, 1455, 1332, 1218, 950, 821, 744, 694. Anal. Calcd for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.14; Cl, 10.85. Found: C, 62.21; H, 4.84; N, 16.95; Cl, 10.81.

9-[2′-((Benzyloxy)methyl)cyclobut-3′-enyl]adenine (26). A mixture of NH_3 and MeOH (1:1) was prepared at −78 °C. It was introduced into a cooled stainless steel bomb containing chloropurine **25** (361 mg, 1.11 mmol). The bomb was closed, and the reaction mixture was heated to 40 °C for 48 h under 10−11 bars of pressure. Evaporation led to a mixture of **26** and of the electrocyclic reaction product in a 92:8 ratio, respectively. This ratio became 95:5 after chromatography on silica gel (60:1, CH_2Cl_2, CH_2Cl_2/MeOH 98:2 and then 95:5). White crystals (302 mg, 89%) corresponding to this mixture were thus obtained: mp (for a pure sample obtained after several triturations in the CH_2Cl_2/Et_2O mixture) 150−151 °C; ^{1}H NMR ($CDCl_3$) δ 8.34 and 7.87 (2s, 2H, H-2 and H-8), 7.22 (m, 3H, Ph), 6.93 (m, 2H, Ph), 6.50 (d (AB system), 1H, H-3′ or H-4′, $J_{H-3'/H-4'}$ = 3.0 Hz), 6.39 (d (AB system), 1H, H-4′ or H-3′, J = 3.0 Hz), 5.75 (br s, 2H, NH_2), 5.71 (d, 1H, H-1′, $J_{H-1'/H-2'}$ = 3.9 Hz), 4.09 (d (AB system), 1 H, benzylic, J = 11.8 Hz), 3.98 (d (AB system), 1H, benzylic, J = 11.8 Hz), 3.72 (ddd, 1H, H-2′), 3.38 (dd, 1H, CH_2O, J = 9.8, 4.9 Hz), 3.23 (dd, 1H, CH_2O, J = 9.8, 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 152.90 and 139.90 (C-2 and C-8), 142.67 and 133.68 (C-3′ and C-4′), 137.42 (quat C of Ph); 155.48, 150.38 and 119.72 (quat C of base); 128.16 and 127.47 (*C*H of Ph); 73.08 (benzylic C), 68.69 (*C*H_2O), 55.31 (C-1′), 49.96 (C-2′); IR (KBr disc) cm^{-1} 3278, 3120, 3033, 1675, 1602, 1573, 1307, 1211, 744, 696; HRMS calcd for $C_{17}H_{17}N_5O$ 307.1433, found 307.1420.

9-[2′-(Hydroxymethyl)cyclobut-3′-enyl]adenine (27). A solution of compound **26** (202 mg, 0.66 mmol) in dry CH_2Cl_2 (42 mL) was cooled under argon to −78 °C. A 1 M solution of BCl_3 in CH_2Cl_2 (5.25 mL) was then added. The reaction mixture was stirred at the same temperature for 4 h. The cooling bath was removed, and MeOH (30 mL) was added slowly. Evaporation and three successive MeOH additions and evaporations led to the crude product. MeOH (20 mL) was added, and the resulting solution was neutralized by a saturated solution of NH_3 in MeOH. The suspension thus obtained was evaporated. Chromatography on silica gel (60:1, CH_2Cl_2, CH_2Cl_2/MeOH 95:5 and then 8:2) led to a white solid that was recrystallized in MeOH (93 mg, 66%): mp 164−165 °C; ^{1}H NMR (DMSO-d_6) δ 8.12 and 8.03 (2 s, 2H, H-2 and H-8), 7.21 (br s, 2H, NH_2), 6.53 (d (AB system), 1h, H-3′ or H-4′, $J_{H-3'/H-4'}$ = 3.0 Hz), 6.49 (d (AB system), 1H, H-4′ or H-3′, J = 3.0 Hz), 5.50 (d, 1H, H-1′, $J_{H-1'/H-2'}$ = 3.9 Hz), 4.33 (t, 1H, OH, J = 4.9 Hz), 3.39 (m, 1H, H-2′), 3.16 (m, 2H, CH_2O); adding of CF_3CO_2H led to 3.23 (dd, 1H, CH_2O, J = 10.8, 6.4 Hz), 3.15 (dd, 1H, CH_2O, J = 10.8, 5.9 Hz); ^{13}C NMR (DMSO-d_6) δ 152.24 and 139.71 (C-2 and C-8), 142.58 and 134.37 (C-3′ and C-4′), 155.86, 149.67 and 118.75 (quat C of base), 60.23 (CH_2O), 54.33 (C-1′), 51.23 (C-2′); IR (KBr disc) cm^{-1} 3411, 3289, 3124, 1675, 1608, 1338, 1299, 1045, 796, 736, 647; HRMS calcd for $C_{10}H_{11}N_5O$ 217.0963, found 217.0969.

9-[2′-((Benzyloxy)methyl)cyclobut-3′-enyl]hypoxanthine (28). Compound **25** (300 mg, 0.92 mmol) was added to 8 mL of a 3:1 CF_3CO_2H/H_2O mixture cooled to 0 °C. The reaction mixture was stirred at room temperature for 48 h. Partial evaporation, neutralization by 30 mL of a 10:1 MeOH/NH_4OH mixture cooled to 0 °C, evaporation, and then chromatography on silica gel (40:1, CH_2Cl_2/MeOH 98:2 to 9:1) led to **28** as white crystals (270 mg, 95%): mp 155−156 °C; ^{1}H NMR (DMSO-d_6) δ 12.26 (br s, 1H, NH), 8.01 and 7.97 (2s, 2H, H-2 and H-8), 7.20 (m, 3H, Ph), 6.88 (m, 2H, Ph), 6.48 (d (AB system), 1H, H-3′ or H-4′, $J_{H-3'/H-4'}$ = 2.5 Hz), 6.45 (d (AB system), 1H, H-4′ or H-3′, J = 2.5 Hz), 5.57 (d, 1H, H-1′, $J_{H-1'/H-2'}$ = 3.9 Hz), 4.10 (d (AB system), 1H, benzylic, J = 11.8 Hz), 3,89 (d (AB system), 1H, benzylic, J = 11.8 Hz), 3.56 (m, 1H, H-2′), 3.42 (dd, 1H, CH_2O, J = 10.3, 3.9 Hz), 3.15 (dd, 1H, CH_2O, J = 10.3, 9.3 Hz); ^{13}C NMR (DMSO-d_6) δ 156.73, 148.61 and 124.17 (quat C of base), 145.24 and 139.15 (C-2 and C-8), 141.45 and 134.71 (C-3′ and C-4′), 137.85 (quat C of Ph); 127.91, 127.18 and 126.99 (*C*H of Ph); 71.93 (benzylic C), 68.72 (*C*H_2O), 54.88 (C-1′), 49.19 (C-2′); IR (KBr disc) cm^{-1} 1698, 1589, 1415, 1342, 1207, 1097; HRMS calcd for $C_{17}H_{16}N_4O_2$ 308.1273, found 308.1269.

9-[2′-(Hydroxymethyl)cyclobut-3′-enyl]hypoxanthine (29). The same experimental procedure as for **26** starting from **28** (242 mg, 0.76 mmol) led to 224 mg of a white solid after chromatography on silica gel (60:1, CH_2Cl_2/MeOH 95:5 and then 8:2). Recrystallization in methanol yielded 88 mg (57%) of **29** (white crystals): mp 220−221 °C; ^{1}H NMR (DMSO-d_6) δ 12.17 (br s, 1H, NH), 8.02 and 7.98 (2 s, 2H, H-2 and H-8), 6.52 and 6.45 (2 s, 2H, H-3′ and H-4′), 5.50 (d, 1H, H-1′, $J_{H-1'/H-2'}$ = 3.4 Hz), 4.32 (t, 1H, OH, J = 4.43 Hz), 3.37 (m, 1H, H-2′), 3.18 (m, 2H, CH_2O); ^{13}C NMR (DMSO-d_6) δ 156.74, 148.59 and 124.09 (quat C of base), 145.30 and 139.24 (C-2 and C-8), 142.72 and 134.23 (C-3′ and C-4′), 60.22 (*C*H_2O), 54.74 (C-1′), 51.22 (C-2′); IR (KBr disc) cm^{-1} 3372, 3100, 3050, 1687, 1596, 1413, 1347, 1047, 609; HRMS calcd for $C_{10}H_{10}N_4O_2$ 218.0804, found 218.0817.

6-Amino-4-[[2′-((benzyloxy)methyl)cyclobut-3′-enyl]-amino]-5-nitropyrimidine (30). A saturated solution of NH_3 in MeOH (15 mL) was added to a cooled (−15 °C) solution of compound **23** (416 mg, 1,20 mmol) in MeOH (2 mL). The reaction mixture was stirred for 2 h (−15 → rt). Evaporation and then chromatography on silica gel (70:1, cyclohexane/AcOEt 8:2 and then 1:1) led to an orange solid (331 mg, 84%) consisting of **30** together with a small amount of the electrocyclic reaction product (94:6): mp (for the mixture) 155 °C; ^{1}H NMR ($CDCl_3$) δ 9.69 (br d, 1H, NH, J = 6.4 Hz), 8.55 and 6.30 (2 br s, 2H, NH_2), 8.03 (s, 1H, H-2), 7.29 (m, 5H, Ph), 6.26 (d (AB system), 1H, H-3′ or H-4′, $J_{H-3'/H-4'}$ = 3.0 Hz), 6.23 (d (AB sytem), 1H, H-4′ or H-3′, J = 3.0 Hz), 5.39 (dd, 1H, H-1′, $J_{H-1'/NH}$ = 6.9 Hz, $J_{H-1'/H-2'}$ = 4.18 Hz), 4.62 (d (AB system), 1H, benzylic, J = 12.3 Hz), 4.50 (d (AB system), 1H, benzylic, J = 12.3 Hz), 3.64 (m, 2H, CH_2O), 3.51 (m, 1H, H-2′); ^{13}C NMR ($CDCl_3$) δ 159.44 (C-2), 159.20 and 156.81 (C-4 and C-6), 139.49 and 137.64 (C-3′ and C-4′), 137.80 (quat C of Ph), 128.26, 127.76 and 127.57 (*C*H of Ph), 112.96 (C-5), 73.27 (benzylic C), 69.13 (*C*H_2O), 53.78 (C-1′), 48.67 (C-2′); IR (KBr disc) cm^{-1} 3446, 3336, 3280, 3108, 3033, 1654, 1596, 1513, 1353, 1290, 1234, 1112, 1002, 794, 750, 696. Anal. Calcd for $C_{16}H_{17}N_5O_3$: C, 58,71; H, 5.24; N, 21.39. Found: C, 58.37; H, 5.68; N, 21.42.

6-Amino-4-[[2′-(hydroxymethyl)cyclobut-3′-enyl]amino]-5-nitropyrimidine (31). The same experimental procedure as for **26** starting from **30** (270 mg, 0.76 mmol) led to the crude product that was added to 30 mL of MeOH and neutralized by a satured solution of NH_3 in MeOH. Evaporation and chromatography on silica gel (80:1, CH_2Cl_2 and then CH_2Cl_2/MeOH 99:1 to 95:5) led to an orange solid (159 mg, 81%) consisting of **31** together with a small amount of the electrocyclic reaction product (96:4): mp (for the mixture) 196−200 °C; ^{1}H NMR (DMSO-d_6) δ 9,69 (d, 1H, NH, J = 7.4 Hz), 8.60 and 8.54 (2 s, 2H, NH_2), 7.98 (s, 1H, H-2), 6.26 (s, 2H, H-3′ and H-4′), 5.27 (dd, 1H, H-1′, $J_{H-1'-NH}$ = 7.4 Hz, $J_{H-1'/H-2'}$ = 3.9 Hz), 4.79 (t, 1H, OH, J = 4.7 Hz), 3.61 (m, 2H, CH_2O), 3.28 (m, 1H, H-2′); ^{13}C NMR (DMSO-d_6) δ 159.41 (C-2), 158.81 and 156.46 (C-4 and C-6), 140.20 and 137.57 (C-3′ and C-4′), 111.90 (C-5), 60.31 (*C*H_2O), 53.02 (C-1′), 50.12 (C-2′); IR (KBr

disc) cm^{-1} 3446, 3330, 3286, 1654, 1596, 1513, 1353, 1288, 1236, 1043, 1002, 794; HRMS calcd for $C_9H_{11}N_5O_3$ 237.0862, found 237.0860.

6-Amino-4-[[(1′*E*,3′*Z*)-5′-hydroxypenta-1′,3′-dienyl]amino]-5-nitropyrimidine (32). Compound **31** was heated at 110 °C in DMSO-d_6 during 1 h and led only to diene **32**: ^{1}H NMR (DMSO-d_6) δ 10.72 (d, 1H, NH, $J_{NH/H-1'} = 10.5$ Hz), 8.65 (br s, 2H, NH_2), 8.05 (s, 1H, H-2), 7.48 (dd, 1H, H-1′, $J_{H-1'/H-2'} = 13.8$ Hz, $J_{H-1'/NH} = 10.5$ Hz), 6.67 (dd, 1H, H-2′, $J_{H-2'/H-1'} = 13.8$ Hz, $J_{H-2'/H-3'} = 11.5$ Hz), 6.07 (dd, 1H, H-3′, $J_{H-3'/H-2'} = 11.5$ Hz, $J_{H-3'/H-4'} = 10.8$ Hz), 5.43 (dt, 1H, H-4′, $J_{H-4'/H-3'} = 10.8$ Hz, $J_{H-4'/H-5'} = 6.6$ Hz), 4.66 (t, OH, $J_{OH/H-5'} = 5.3$ Hz), 4.13 (dd, 2H, H-5′, $J_{H-5'/H-4'} = 6.6$ Hz, $J_{H-5'/OH} = 5.3$ Hz); ^{13}C NMR (DMSO-d_6) δ 158.69, 152.54 and 112.14 (C-4, C-5 and C-6), 159.11 (C-2), 130.10, 126.55, 126.30 and 112.14 (C-1′, C-2′, C-3′, and C-4′), 57.33 (C-5′).

Acknowledgment. We thank Drs. E. Bisagni and M. Legraverend for useful suggestions and for one experiment, Dr. D. Planchenault for its participation to the beginning of this work, French MRE ministry for a fellowship (M.-E. G.-M.), and Drs. J.-F. Riou, A. Bousseau, and J.-F. Ferron (Rhône-Poulenc Rorer Co.) for the biological tests.

Supporting Information Available: ^{1}H NMR spectra of **12**−**14**, **19**, **21**, **23**, **24**, **26** to **29**, **31**, and **32** (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO961451Y