Purines. LXV. Preparatory study for the syntheses of the marine sponge purines agelasimines-A and -B: Synthesis and acetylation of their N(7)-benzyl analogues

December 1994 Chem. Pharm. Bull. 42(12) 2461—2466 (1994)

Purines. LXV.[1] Preparatory Study for the Syntheses of the Marine Sponge Purines Agelasimines-A and -B: Synthesis and Acetylation of Their N(7)-Benzyl Analogues

Tozo FUJII,* Tohru SAITO, Jun CHIKAZAWA, Yuko NAKAMURA, and Masashi OHBA

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan.

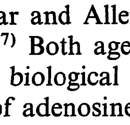
Received June 30, 1994; accepted July 26, 1994

Four-step synthetic routes from 3-methyladenine (10) to 7-benzyl-N^6,3-dimethyladenine (1b) and 7-benzyl-1,2-dihydro-1,3-dimethyladenine (2b), selected as models for the marine sponge alkaloids agelasimine-A (1a) and agelasimine-B (2a), respectively, have been established. The key steps involved are regioselective methylations of 7-benzyl-3-methyladenine (8) and 7-benzyl-1,2-dihydro-3-methyladenine (11). The reaction of 1b with acetic anhydride in pyridine was found to give the monocyclic imidazole derivative 29b. A similar acetylation of 2b yielded the N^6-acetyl derivative 20b. When treated with boiling H_2O, 20b afforded 7-benzyl-2,3-dimethylhypoxanthine (21b) and a compound inferred to be the dihydrohypoxanthine derivative 30. Probable pathways to 29b from 1b and to 21b and 30 from 20b are proposed.

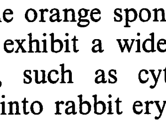
Keywords agelasimine-A N(7)-benzyl analogue; agelasimine-B model; adenine methylation; adenine trisubstituted acetylation; adenine 1,2-dihydro acetylation; Dimroth rearrangement 1,3-dimethyladenine

Certain genera of marine sponges are rich sources of biologically active purine alkaloids; more than 15 unusual purine derivatives, based mainly on the adenine nucleus, have so far been isolated from them.[2-6] Among these purine derivatives are agelasimine-A (**1a**) and agelasimine-B (**2a**), novel adenine-related bicyclic diterpenoids isolated, along with three bromine-containing alkaloids, by Fathi-Afshar and Allen from the orange sponge *Agelas mauritiana*.[7] Both agelasimines exhibit a wide range of interesting biological activities, such as cytotoxicity, inhibition of adenosine transfer into rabbit erythrocytes, Ca^{2+}-channel antagonistic action, α_1 adrenergic blockade, and others.[7,8] Chemical structures (**1a** and **2a**), featuring trisubstituted adenine nuclei and a $C_{20}H_{35}O$ portion at N(7), have been proposed on the basis of interpretation of their spectral data.[7] In an attempt to confirm the correctness of these proposals by chemical synthesis, we sought possible synthetic routes to the N(7)-benzyl analogues **1b** and **2b** in the present study as preliminaries to total syntheses of **1a** and **2a**. In connection with the reported acetylations of **1a** and **2a**, those of our model compounds **1b** and **2b** were also investigated. Brief accounts of the results reported here have been published in preliminary form.[9]

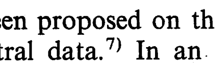
In designing a synthetic route to the first target 7-benzyl-N^6,3-dimethyladenine (**1b**), the following knowledge was used as a guide. Montgomery and Thomas reported that treatment of either 3-benzyladenine (**3**: $R = PhCH_2$) or 7-benzyladenine (**4**: $R = PhCH_2$) with benzyl chloride in $AcNMe_2$ in the presence of K_2CO_3 at 110°C overnight afforded N^6,3,7-tribenzyladenine (**5**).[10] The reaction in both cases is likely to proceed through the intermediate 3,7-dibenzyladenine (**6**: $R^1 = R^2 = PhCH_2$), because alkylation of either 3-alkyladenines (**3**) or 7-alkyladenines (**4**) is known to furnish 3,7-dialkyladenines (**6**).[10,11] Taking into consideration such an assumed preference for N^6-benzylation of **6** ($R^1 = R^2 = PhCH_2$), we planned to employ a similar sequence of reactions for synthesis of **1b** (Chart 1).

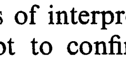


1



2

a: R = 

b: R = 

Treatment of 7-benzyl-3-methyladenine hydrobromide (**7**), obtained from 3-methyladenine (**10**) by benzylation according to the previously reported procedure,[11c] with 10% aqueous NaOH in hot H_2O produced the free base **8** in 80% yield. Methylation of **8** with MeI in $AcNMe_2$ was then effected at room temperature for 5 h, giving 7-benzyl-N^6,3-dimethyladenine hydriodide (**9**) in 89% yield. Finally, basification of a warm solution of the hydriodide salt **9** in H_2O with 10% aqueous NaOH provided the desired model **1b** in 86% yield. The UV spectra of **1b** in various solvents were similar to those[10,12] reported for N^6,3,7-trisubstituted adenines, supporting the correctness of the assigned substitution pattern. Furthermore, the stability of **1b** under alkaline conditions may rule out the possibility that the product from the methylation of **8** was not the N^6,3-dimethyl derivative **9**, but the alternative 1,3- or 3,9-dimethyl isomer, since the latter is considered to be very unstable under alkaline conditions.[13,14] The model compound **1b** thus synthesized was found to exhibit similarity in ^1H- and ^{13}C-NMR spectra, except for signals arising from the N(7)-substituent, to agelasimine-A (**1a**). This supports the correctness of the substitution pattern proposed[7] for the adenine moiety in agelasimine-A.

The synthesis of the second target 7-benzyl-1,2-dihydro-1,3-dimethyladenine (**2b**) started from **7**, as shown in Chart 1. Reduction of **7** with $NaBH_4$ in H_2O at room

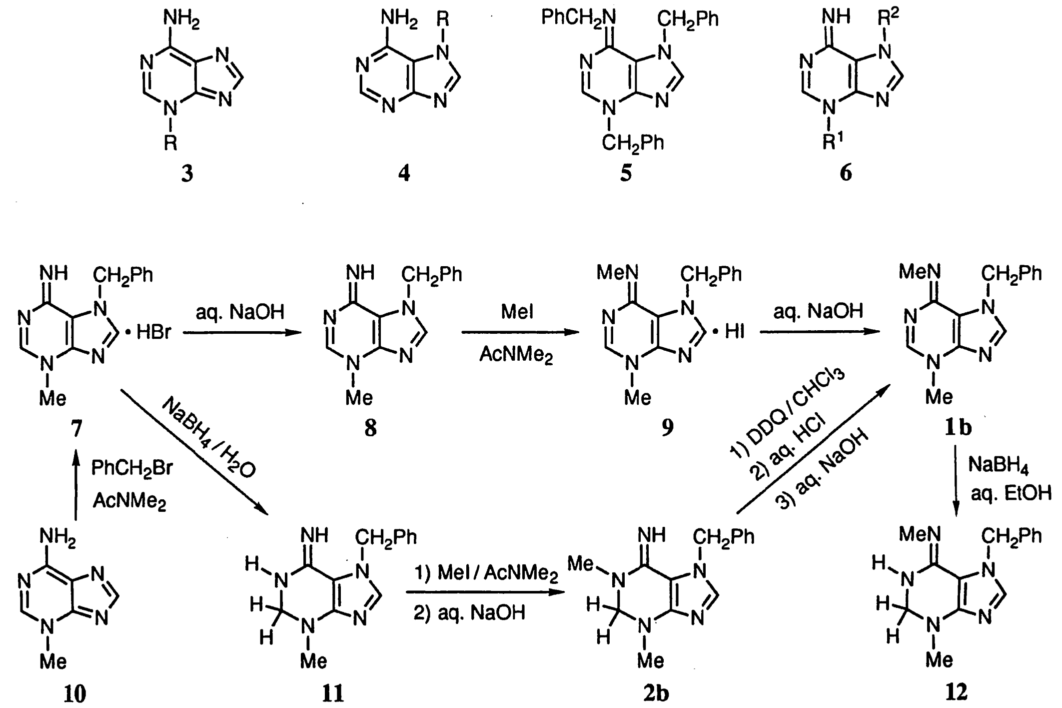


Chart 1

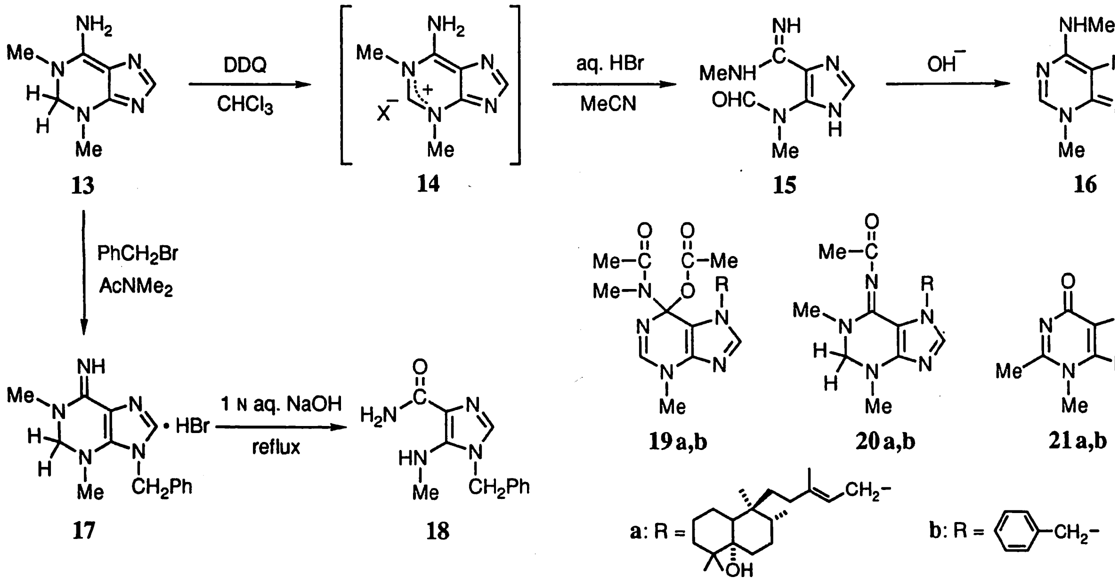


Chart 2

temperature for 30 min gave the 1,2-dihydro derivative **11** as an unstable oil.[15] On methylation with MeI in $AcNMe_2$ at room temperature for 4.5 h, **11** yielded the 1-methyl derivative as the crude salt (**2b**·HI). Treatment of the crude salt with aqueous NaOH furnished the desired free base **2b** in 15% overall yield (from **7**). The 1,2-dihydro-1,3-dimethyladenine structure was assignable to **2b** on the basis of its ^{1}H-NMR spectrum in $CDCl_3$: the nuclear Overhauser effects (NOE's) (4% each) observed for the two *N*-Me signals (at δ 2.90 and 2.91) on irradiation of the C(2)-protons signal (at δ 4.13) revealed the proximity of these three groups.

Meanwhile, the N^6,3-dimethyl isomer **12** was prepared in 84% yield from **1b** by $NaBH_4$ reduction in 50% aqueous EtOH at room temperature for 20 min. The ^{1}H- and ^{13}C-NMR spectra of the 1,3-dimethyl isomer **2b** were similar, except for signals arising from the N(7)-substituent, to those reported[7] for agelasimine-B (**2a**). This lends support to the structure (**2a**) proposed for agelasimine-B.

Interestingly, oxidation of **2b** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in $CHCl_3$ at room temperature for 10 min, followed by successive treatment with aqueous HCl and 10% aqueous NaOH, was found to give **1b** in 30% yield. This conversion is analogous to the previously reported transformation[13] of 1,2-dihydro-1,3-dimethyladenine (**13**) into N^6,3-dimethyladenine (**16**) *via* **14** and **15** (Chart 2); it is suggestive of a possible bio-

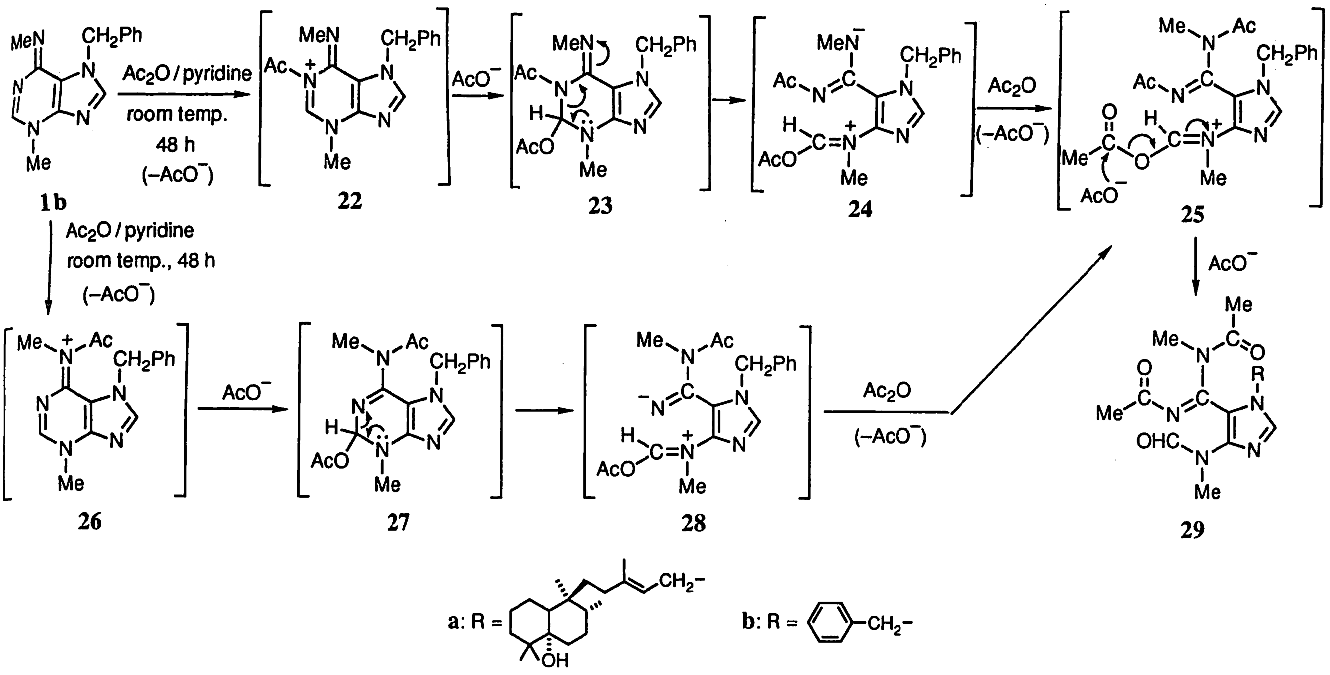


Chart 3

genetic pathway to agelasimine-A (**1a**) from agelasimine-B (**2a**).

With a view to finding an alternative access to **2b**, **13** was benzylated with $PhCH_2Br$ in $AcNMe_2$ at 75—85 °C for 9 h. However, the only product that could be isolated (in 12% yield) from the reaction mixture was not the desired 7-benzylated derivative (**2b**·HBr), but the 9-benzylated derivative **17** (Chart 2). The location of the benzyl group in **17** was established by alkaline hydrolysis (1 N aqueous NaOH, reflux, 1 h), which led to the formation of a known compound,[16] 1-benzyl-5-methylaminoimidazole-4-carboxamide (**18**).

In connection with the structure determination of the above two marine sponge alkaloids, the Canadian authors[7] further described the reactions of **1a** and **2a** with acetic anhydride in pyridine to form diacetylagelasimine-A and N^6-acetylagelasimine-B (**20a**), respectively. They assigned structure **19a** to diacetylagelasimine-A on the basis of ^{1}H-NMR and mass spectral data, although its exact nature has not been firmly established (mixture of isomers).[7] Because structure **19a** corresponds to a very reactive tetrahedral intermediate, presumably difficult to isolate, in the acetolysis of the C(6)=NMe group in **1a**, the correctness of their assignment should be verified. This led us next to explore similar acetylations of our model compounds **1b** and **2b**.

The model **1b** for agelasimine-A (**1a**) was first treated with an excess of acetic anhydride in pyridine at room temperature for 48 h (Chart 3). Work-up of the reaction mixture gave a crystalline product (10% yield) corresponding to a 1 : 1 adduct ($C_{14}H_{15}N_5 \cdot C_4H_6O_3$) of **1b** and acetic anhydride. Provided the reaction with acetic anhydride had occurred only in the pyrimidine moiety, the isomeric structures **19b**, **23**, **27**, and **29b** would be candidates for the adduct. However, it was difficult to determine which structure is correct on the basis of the spectral data alone. We therefore subjected the adduct to an X-ray crystallographic analysis and were able to establish its structure to be the monocycle **29b**; an imidazole-5-carboxamidine derivative bearing an *N*-methylformamido group at C(4), two acetyl groups attached separately to nitrogens in the *N*-methylamidine moiety, and a benzyl group at N(1).[17] The ^{1}H-NMR spectrum of **29b** in $CDCl_3$ at 27 °C exhibited two sets of signals, all with a 3 : 1 ratio of relative integral intensities, for most of the different species of protons. Similarly, two sets of signals were also observed in Me_2SO-d_6 at 27 °C, but they coalesced into one set at 100 °C. The complexity of these signals is probably a result of *cis–trans* equilibration of the amido groups, most likely that of the *N*-methylformamido group at C(4), as we have experienced previously in similar structures.[14a,18] The formation of **29b** from **1b** by acetylation may be assumed to proceed through the intermediates **22**, **23**, **24**, and **25** and/or through **26**, **27**, **28**, and **25**, as depicted in Chart 3. Thus, it is likely that the "diacetylagelasimine-A" obtained by a similar acetylation of agelasimine-A (**1a**) has the analogous imidazole structure **29a** instead of the proposed[7] purine structure **19a**.

Finally, we investigated the acetylation of **2b**, a model for agelasimine-B (**2a**). Treatment of **2b** with an excess of acetic anhydride in pyridine at room temperature for 1 h gave the N^6-acetyl derivative **20b** in 80% yield (Chart 4). Support for the correctness of the assigned structure came from the mass and ^{1}H-NMR spectra and chemical properties of **20b**. Its ^{1}H-NMR spectrum in $CDCl_3$ was similar to that[7] of **20a**, except for signals arising from the N(7)-substituent. When treated with boiling H_2O, **20b** was found to produce 7-benzyl-2,3-dimethylhypoxanthine (**21b**) and a compound inferred to be the dihydrohypoxanthine **30** in 23% and 35% yields, respectively. The formation of **21b** and **30** from **20b** may be explained in terms of the sequence of reactions delineated in Chart 5. Interesting-

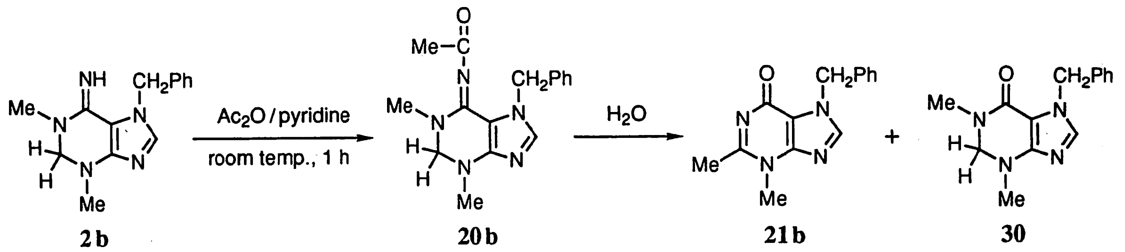


Chart 4

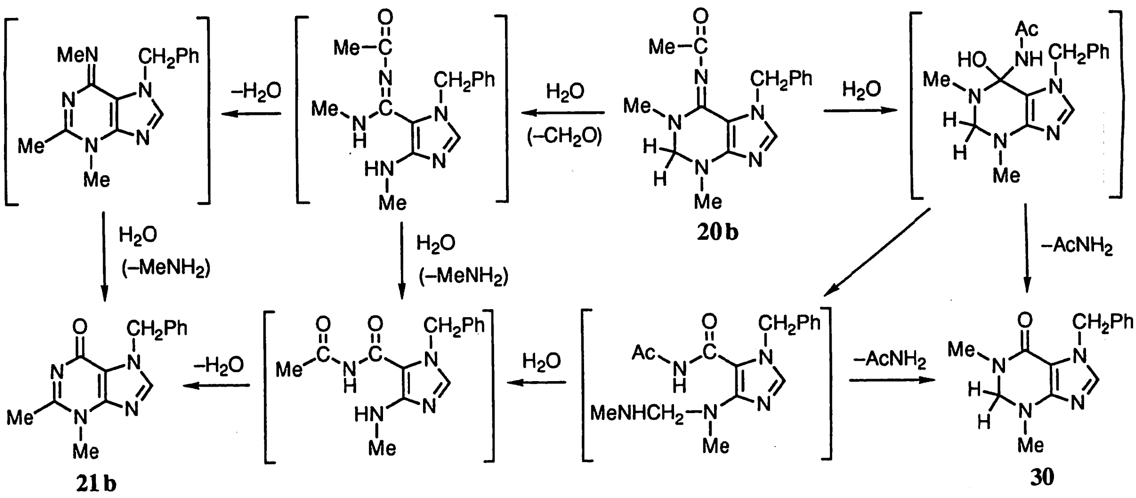


Chart 5

ly, **21b** was found to be a minor product in the above acetylation of **2b**; it was obtained more efficiently (64% yield) when **2b** was treated with acetic anhydride in the absence of pyridine at room temperature for 50 h.

In conclusion, the success in the above four-step synthetic routes to **1b** and **2b** from 3-methyladenine (**10**) appears to open ways for chemical syntheses of the structurally analogous marine sponge alkaloids, agelasimine-A (**1a**) and agelasimine-B (**2a**). The structures of **20b** and **21b** partially correspond, respectively, to those of N^6-acetylagelasimine-B (**20a**) and the artifact purino-diterpene **21a**, both isolated by Faulkner and co-workers[19] from the acetylated mixture of the crude extract of the same sponge (*Agelas mauritiana*).[7] Accordingly, the present results suggest that **21a** might have originated from agelasimine-B (**2a**) *via* N^6-acetylagelasimine-B (**20a**). They also suggest that the structure of "diacetylagelasimine-A" is not **19a**, but **29a**.

Experimental

General Notes All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. TLC was run on Merck silica gel 60 F_{254} plates (0.25-mm thickness), Merck aluminum oxide F_{254} (type E) plates (0.25 mm), or Funakoshi Avicel SF-2020F plates, and spots were located under UV light (254 nm). Flash chromatography[20] was carried out by using Merck silica gel 60 (No. 9385). UV spectra reported herein were recorded on a Hitachi 320 UV spectrophotometer on solutions in MeOH, 95% (v/v) aqueous EtOH, 0.1 N aqueous HCl (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous NaOH (pH 13). Other spectra were measured with a JASCO A-202 IR spectrophotometer; a Hitachi M-80 mass spectrometer; or any of a JEOL JNM-FX-100 (^{1}H 100 MHz), a JEOL JNM-EX-270 (^{1}H 270 MHz, ^{13}C 67.8 MHz), and a JEOL JNM-GSX-500 (^{1}H 500 MHz) NMR spectrometer. Chemical shifts are reported in δ values relative to internal Me_4Si. Elemental analyses and MS measurements were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, m = multiplet, s = singlet, sh = shoulder.

7-Benzyl-3-methyladenine (8) 7-Benzyl-3-methyladenine hydrobromide (**7**)[11c] (200 mg, 0.625 mmol) was dissolved in hot H_2O (1.5 ml), and 10% aqueous NaOH (*ca.* 1.5 ml) was added. The resulting mixture was cooled in an ice bath for 30 min. The colorless prisms that deposited were filtered off, washed with H_2O, and dried to give the free base **8**·H_2O (128 mg, 80%), mp 159—161.5 °C (dec.). Recrystallization from AcOEt and drying over P_2O_5 at 3 mmHg and room temperature for 18 h yielded an analytical sample of **8**·H_2O as colorless plates, mp 163—163.5 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 224 nm (sh) (ε 11000), 280 (15000); $\lambda_{max}^{H_2O}$ (pH 1) 224 (sh) (12400), 277 (15300); $\lambda_{max}^{H_2O}$ (pH 7) 224 (sh) (12400), 277 (15300); $\lambda_{max}^{H_2O}$ (pH 13) 283 (13200); ^{1}H-NMR (Me_2SO-d_6) δ: 3.54 [3H, s, N(3)-Me], 5.70 [2H, s, N(7)-C$\underline{H}_2$Ph], *ca.* 6.9 (br, NH), 7.2—7.5 [5H, m, N(7)-$CH_2\underline{Ph}$], 7.73 and 8.11 (1H each, s, purine protons). *Anal.* Calcd for $C_{13}H_{13}N_5 \cdot H_2O$: C, 60.69; H, 5.88; N, 27.22. Found: C, 60.92; H, 6.04; N, 26.84.

7-Benzyl-N^6,3-dimethyladenine Hydriodide (9) A solution of **8**·H_2O (1.80 g, 7 mmol) and MeI (4.97 g, 35 mmol) in $AcNMe_2$ (21 ml) was stirred at room temperature for 5 h. After dilution with ether (100 ml), the reaction mixture was cooled in an ice bath. The light yellow solid that deposited was filtered off, washed successively with EtOH and ether, and dried to afford **9** (2.38 g, 89%), mp 209—220 °C (dec.). Recrystallization from EtOH furnished an analytical sample as colorless plates, mp 229—230 °C (dec.); MS *m*/*z*: 253 ($M^+ - HI$); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 287 nm (ε 17300); $\lambda_{max}^{H_2O}$ (pH 1) 226 (24300), 285 (17400); $\lambda_{max}^{H_2O}$ (pH 7) 226 (24500), 285 (17500); $\lambda_{max}^{H_2O}$ (pH 13) 286 (6500); ^{1}H-NMR (Me_2SO-d_6) δ: 3.08 (3H, d, J = 4.5 Hz, N^6-Me), 3.99 [3H, s, N(3)-Me], 5.84 [2H, s, N(7)-C$\underline{H}_2$Ph], 7.15—7.42 [5H, m, N(7)-$CH_2\underline{Ph}$], 8.56 (1H, br, NH), 8.78 and 8.86 (1H each, s, purine protons). *Anal.* Calcd for $C_{14}H_{15}N_5 \cdot HI$: C, 44.11; H, 4.23; N, 18.37. Found: C, 43.96; H, 4.22; N, 18.28.

7-Benzyl-N^6,3-dimethyladenine (1b) A solution of **9** (200 mg, 0.525 mmol) in warm H_2O (1.5 ml) was made strongly basic by addition of 10% aqueous NaOH (*ca.* 1.5 ml) and then cooled in an ice bath. A slightly brownish solid that deposited was filtered off, washed with H_2O, and dried to yield **1b** (114 mg, 86%), mp 152.5—153.5 °C. Recrystallization from cyclohexane gave an analytical sample as colorless needles, mp 153—154.5 °C; MS *m/z*: 253 (M$^+$); UV $\lambda_{\max}^{\mathrm{MeOH}}$ 227 nm (sh) (ε 11000), 287 (17400); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 1) 225 (sh) (11000), 285 (17100); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 7) 225 (sh) (10900), 284 (17200); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 13) 285 (6600); ^{1}H-NMR (CDCl$_3$) δ: 3.25 [3H, s, N(3)-Me],[21] 3.61 (3H, s, *N*^{6}-Me),[21] 5.74 [2H, s, N(7)-C$\underline{\mathrm{H}}_2$Ph], 7.32 [5H, m, N(7)-CH$_2\underline{\mathrm{Ph}}$], 7.38 and 7.58 (1H each, s, purine protons); ^{13}C-NMR (CDCl$_3$) δ: 33.9 and 34.7 (two Me's), 49.9 (CH$_2$), 113.9 [C(5)], 128.0, 128.2, 128.8, and 136.7 (Ph), 137.7 [C(8)], 142.5 [C(4) or C(6)], 145.2 [C(2)], 150.1 [C(6) or C(4)]. *Anal.* Calcd for $C_{14}H_{15}N_5$: C, 66.38; H, 5.97; N, 27.65. Found: C, 66.28; H, 5.96; N, 27.73.

7-Benzyl-1,2-dihydro-1,3-dimethyladenine (2b) A solution of **7** (4.80 g, 15 mmol) in H$_2$O (150 ml) was stirred at room temperature, and NaBH$_4$ (1.13 g, 29.9 mmol) was added in portions. After having been stirred at room temperature for 30 min, the reaction solution was saturated with K$_2$CO$_3$ and extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ extracts were combined, dried over anhydrous K$_2$CO$_3$, and concentrated *in vacuo* to leave crude **11** (3.23 g) as a yellow foam. A solution of the total amount of the crude **11** and MeI (8.52 g, 60 mmol) in AcNMe$_2$ (20 ml) was stirred at room temperature for 4.5 h. The reaction mixture was concentrated *in vacuo* to leave a brown oil, which was triturated with acetone–ether (2 : 1, v/v) under ice-cooling. The pale yellowish solid that deposited was filtered off, washed with acetone, and dried to yield a first crop (1.07 g) of **2b**·HI, mp 187—188.5 °C (dec.). The filtrate and washings were combined and concentrated *in vacuo*. Trituration of the residual oil with EtOH–acetone–ether (1 : 6 : 6, v/v) gave a second crop (461 mg) of **2b**·HI, mp 189.5—191.5 °C (dec.). The first and second crops of **2b**·HI were combined and dissolved in H$_2$O (10 ml). The aqueous solution was made strongly basic by addition of 10% aqueous NaOH (*ca.* 10 ml), saturated with K$_2$CO$_3$, and then extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ extracts were combined, washed with saturated aqueous NaCl, dried over anhydrous MgSO$_4$, and concentrated *in vacuo* to leave a yellow oil (757 mg). The oil crystallized from cyclohexane to afford **2b** (561 mg, 15%) as pale yellowish needles, mp 95—97 °C. Further recrystallization from cyclohexane gave an analytical sample of **2b** as slightly yellowish needles, mp 96—97 °C; MS *m/z*: 255 (M$^+$); UV $\lambda_{\max}^{\mathrm{MeOH}}$ 243 nm (sh) (ε 8000), 328 (6300); $\lambda_{\max}^{95\%\ \mathrm{aq.\,EtOH}}$ 244 (sh) (7700), 305 (4700); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 1) 226 (sh) (11900), 323 (5800); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 7) 325 (6000); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 13) 243 (7300), 290 (5800); ^{1}H-NMR (CDCl$_3$) δ: 2.90 and 2.91 (3H each, s, two NMe's), 4.13 [2H, s, C(2)-H's], 5.55 [2H, s, N(7)-C$\underline{\mathrm{H}}_2$Ph], 7.2—7.4 [6H, br s, C(8)-H and N(7)-CH$_2\underline{\mathrm{Ph}}$]; ^{13}C-NMR (CDCl$_3$) δ: 33.0 and 35.1 (two Me's), 49.9 [N(7)-CH$_2$], 71.1 [C(2)], 107.4 [C(5)], 127.2, 127.8, 128.7, and 136.4 (Ph), 138.1 [C(8)], 154.2 [C(4) or C(6)], 155.1 [C(6) or C(4)]. *Anal.* Calcd for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43. Found: C, 65.77; H, 6.60; N, 27.49.

Conversion of 2b into 1b A solution of **2b** (51 mg, 0.2 mmol) in CHCl$_3$ (2 ml) was stirred at room temperature, and DDQ (58 mg, 0.26 mmol) was added in portions. The resulting mixture was stirred at room temperature for 10 min. The reaction mixture was concentrated *in vacuo* to leave a dark green solid, which was suspended in H$_2$O (1 ml). The suspension was diluted with 10% aqueous HCl (1 ml), washed with CH$_2$Cl$_2$ (4 × 10 ml), and filtered. The aqueous filtrate was made strongly basic (pH > 11) with 10% aqueous NaOH and extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ extracts were combined, dried over anhydrous MgSO$_4$, and concentrated *in vacuo* to leave a slightly yellowish oil (41 mg). The oil was crystallized from cyclohexane to furnish **1b** (15 mg, 30%) as colorless needles, mp 151—153 °C. This sample was identical (by comparison of the IR spectrum) with the one prepared from **9** (*vide supra*).

7-Benzyl-1,2-dihydro-*N*^{6},3-dimethyladenine (12) A solution of **1b** (51 mg, 0.2 mmol) in 50% (v/v) aqueous EtOH (2 ml) was stirred at room temperature, and NaBH$_4$ (15 mg, 0.4 mmol) was added in portions. The mixture was stirred at the same temperature for 20 min and then concentrated *in vacuo* to leave a colorless oil, which was partitioned between H$_2$O and CH$_2$Cl$_2$. The CH$_2$Cl$_2$ extracts were combined, dried over anhydrous MgSO$_4$, and concentrated *in vacuo*, leaving **12** (43 mg, 84%) as a colorless oil; ^{1}H-NMR (CDCl$_3$) δ: 2.76 (3H, s, *N*^{6}-Me), 2.89 [3H, s, N(3)-Me],[22] 4.34 [2H, s, C(2)-H's], 5.34 [2H, s, N(7)-C$\underline{\mathrm{H}}_2$Ph], 7.2—7.4 [6H, br s, C(8)-H and N(7)-CH$_2\underline{\mathrm{Ph}}$]; high-resolution MS Calcd for $C_{14}H_{17}N_5$: 255.1484, Found: 255.1468.

9-Benzyl-1,2-dihydro-1,3-dimethyladenine Hydrobromide (17) A stirred mixture of 1,2-dihydro-1,3-dimethyladenine (**13**)[13] (330 mg, 2 mmol) and PhCH$_2$Br (680 mg, 4 mmol) in AcNMe$_2$ (9 ml) was heated in an oil bath kept at 75—85 °C for 9 h. The reaction mixture was cooled to room temperature, and the solid that deposited was filtered off, washed with acetone, and dried to give **17** (81 mg, 12%), mp 246.5—248 °C (dec.). Recrystallization from EtOH afforded an analytical sample of **17** as colorless needles, mp 248—250 °C (dec.); MS *m/z*: 255 (M$^+$ − HBr); UV $\lambda_{\max}^{95\%\ \mathrm{aq.\,EtOH}}$ 291 nm (ε 5900); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 1) 289 (5800); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 7) 289 (5800); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 13) 242 (11700); ^{1}H-NMR (Me$_2$SO-*d*$_6$) δ: 2.75 and 3.14 (3H each, s, two NMe's), 4.72 [2H, s, C(2)-H's]. 5.26 [2H, s, N(9)-C$\underline{\mathrm{H}}_2$Ph], 7.1—7.6 [5H, m, N(9)-CH$_2\underline{\mathrm{Ph}}$], 7.90 [1H, s, C(8)-H], 8.64 and 9.15 (1H each, br, NH's). *Anal.* Calcd for $C_{14}H_{17}N_5 \cdot HBr$: C, 50.01; H, 5.40; N, 20.83. Found: C, 49.80; H, 5.53; N, 20.86.

1-Benzyl-5-methylamino-1*H*-imidazole-4-carboxamide (18) A *stirred* mixture of **17** (17 mg, 0.051 mmol) and 1 N aqueous NaOH (2 ml) was heated under reflux for 1 h. After cooling, the reaction mixture was brought to pH 9 with 10% aqueous HCl and extracted with CH$_2$Cl$_2$ (4 × 10 ml). The CH$_2$Cl$_2$ extracts were combined, dried over anhydrous MgSO$_4$, and concentrated *in vacuo*. The residual solid (6 mg) was triturated with AcOEt (1 ml), and the insoluble solid that resulted was filtered off and dried to give **18** (2 mg, 17%) as a colorless solid, mp 180—181.5 °C. This sample was identical (by comparison of the IR spectrum) with authentic **18**[16] (mp 182—183 °C).

Acetylation of 1b to Form *N*^{1},*N*^{2}-Diacetyl-1-benzyl-*N*^{1}-methyl-4-(*N*-methylformamido)-1*H*-imidazole-5-carboxamidine (29b) A solution of **1b** (507 mg, 2 mmol) and acetic anhydride (4.08 g, 40 mmol) in pyridine (10 ml) was stirred at room temperature for 48 h. The reaction mixture was concentrated *in vacuo*, and the residual oil was partitioned between aqueous NaHCO$_3$ and CH$_2$Cl$_2$. The CH$_2$Cl$_2$ extracts were combined, dried over anhydrous MgSO$_4$, and concentrated *in vacuo* to leave a brown foam (460 mg). Purification of the foam by flash chromatography[20] [silica gel, CH$_2$Cl$_2$–EtOH (20 : 1, v/v)] gave **29b** (68 mg, 10%) as a slightly brownish oil. The oil was crystallized from AcOEt, and further recrystallization from AcOEt yielded an analytical sample of **29b** as almost colorless prisms, mp 152—153.5 °C; MS *m/z*: 355 (M$^+$); UV $\lambda_{\max}^{95\%\ \mathrm{aq.\,EtOH}}$ 241 nm (sh) (ε 11300); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 1) 266 (4900); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 7) 240 (sh) (10300); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 13) 245 (9700); IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 1692, 1670, and 1615 (amide CO's); ^{1}H-NMR (CDCl$_3$) (at 27°C) [major and minor peaks (3 : 1 in relative integral intensity)] δ: 2.03 and 2.10 (or 1.96) (3H, s each, COMe), 2.07 and 1.96 (or 2.10) (3H, s each, COMe), 2.96 and 2.95 (3H, s each, NMe), 3.25 and 3.37 (3H, s each, NMe), 5.23 and 5.16 (2H, s each, C$\underline{\mathrm{H}}_2$Ph), 7.2—7.5 [6H, m, CH$_2\underline{\mathrm{Ph}}$ and C(2)-H], 8.25 and 8.17 (1H, s each, HCON); ^{1}H-NMR (Me$_2$SO-*d*$_6$) (at 27 °C) [major and minor peaks (*ca.* 5 : 1)] δ: 1.67 and 1.92 (or 1.70) (3H, s each, COMe), 1.98 and 1.70 (or 1.92) (3H, s each, COMe), 2.97 and 2.80 (3H, s each, NMe), 3.03 and 3.22 (3H, s each, NMe), 5.22 (2H, s, C$\underline{\mathrm{H}}_2$Ph), 7.2—7.4 (5H, m, CH$_2\underline{\mathrm{Ph}}$), 8.05 [1H, s, C(2)-H], 8.16 (1H, s, HCON); ^{1}H-NMR (Me$_2$SO-*d*$_6$) (at 100 °C) δ: 1.83 (3H, s, COMe), 1.96 (3H, s, COMe), 2.94 (s, two NMe's and H$_2$O), 5.23 (2H, s, C$\underline{\mathrm{H}}_2$Ph), 7.2—7.4 (5H, m, CH$_2\underline{\mathrm{Ph}}$), 7.87 [1H, s, C(2)-H], 8.20 (1H, s, HCON). *Anal.* Calcd for $C_{18}H_{21}N_5O_3$: C, 60.83; H, 5.96; N, 19.71. Found: C, 60.82; H, 6.00; N, 19.67. The structure of **29b** was unequivocally established by an X-ray crystallographic analysis.[17]

Acetylation of 7-Benzyl-1,2-dihydro-1,3-dimethyladenine (2b) i) With Acetic Anhydride in Pyridine: A solution of **2b** (383 mg, 1.5 mmol) and acetic anhydride (3.83 g, 37.5 mmol) in pyridine (7.5 ml) was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* to leave a yellowish orange oil, which was dissolved in H$_2$O (1.5 ml). The aqueous solution was brought to pH 7—8 with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (4 × 20 ml). The CH$_2$Cl$_2$ extracts were combined, dried over anhydrous MgSO$_4$, and concentrated *in vacuo*. Purification of the residual oil (540 mg) by flash chromatography[20] [silica gel, CH$_2$Cl$_2$–EtOH (5 : 1, v/v)] afforded *N*^{6}-acetyl-7-benzyl-1,2-dihydro-1,3-dimethyladenine (**20b**) (359 mg, 80%) as a slightly yellow powder, mp 130—135.5 °C (dec.); UV $\lambda_{\max}^{\mathrm{MeOH}}$ 226 nm (sh) (ε 11100), 258 (7700), 347 (6800); $\lambda_{\max}^{95\%\ \mathrm{aq.\,EtOH}}$ 225 (sh) (11700), 258 (7900), 347 (7300); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 1) 229 (sh) (7500), 272 (7700), 377 (6500); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 7) 227 (sh) (10000), 257 (8600), 355 (6800); $\lambda_{\max}^{\mathrm{H_2O}}$ (pH 13) 224 (sh) (10000), 256 (8400), 354 (6500); IR $\nu_{\max}^{\mathrm{CHCl_3}}$ 1600 cm^{-1} (amide CO); ^{1}H-NMR (CDCl$_3$) δ: 2.14 (3H, s, COMe), 2.97 and 3.04 (3H each, s, NMe's), 4.41 [2H, s, C(2)-H's], 5.40 [2H, s, N(7)-C$\underline{\mathrm{H}}_2$Ph], 7.2—7.4 [6H, m, N(7)-CH$_2\underline{\mathrm{Ph}}$ and C(8)-H]; high-resolution MS Calcd for $C_{16}H_{19}N_5O$: 297.1589, Found: 297.1585.

In a separate run, it was also possible to isolate a small amount of 7-benzyl-2,3-dimethylhypoxanthine (**21b**) (*vide infra*) from the product mixture by means of similar flash chromatography[20] [CH$_2$Cl$_2$–EtOH (3 : 1, v/v)].

ii) With Acetic Anhydride Alone: A mixture of **2b** (255 mg, 1 mmol) and acetic anhydride (4 ml) was stirred at room temperature for 50 h.

The reaction mixture was concentrated *in vacuo* to leave a yellowish orange oil. Purification of the oil by means of flash chromatography[20] [silica gel, CH_2Cl_2–EtOH (10 : 1, v/v)] provided 7-benzyl-2,3-dimethylhypoxanthine (**21b**) (163 mg, 64%) as a slightly yellow solid, mp 195—199 °C. Recrystallization from AcOEt yielded an analytical sample of **21b** as colorless plates, mp 199.5—201 °C; MS *m/z*: 254 (M^+); UV λ_{max}^{MeOH} 221 nm (sh) (ε 14000), 268 (11900); $\lambda_{max}^{H_2O}$ (pH 1) 257 (11200); $\lambda_{max}^{H_2O}$ (pH 7) 267 (12300); $\lambda_{max}^{H_2O}$ (pH 13) 267 (12200); IR ν_{max}^{Nujol} 1640 cm^{-1} (CO); ^{1}H-NMR (Me_2SO-d_6) δ: 2.46 [3H, s, C(2)-Me], 3.74 [3H, s, N(3)-Me], 5.57 [2H, s, N(7)-C$\underline{H}_2$Ph], 7.2—7.4 [5H, m, N(7)-$CH_2$$\underline{Ph}$], 8.30 [1H, s, C(8)-H]. *Anal.* Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.00; H, 5.58; N, 22.02.

Hydrolysis of *N*^{6}-Acetyl-7-benzyl-1,2-dihydro-1,3-dimethyladenine (20b) A stirred solution of **20b** (10 mg, 0.034 mmol) in H_2O (0.5 ml) was kept at room temperature for 3 h, then at 45—55 °C for 24 h, and finally heated under reflux for a further 2 h. The reaction mixture was concentrated *in vacuo* to dryness to leave a colorless oil (*ca.* 10 mg), which was purified by preparative TLC (silica gel, CH_2Cl_2–EtOH (10 : 1, v/v)]. The slowest-running zone (*Rf* 0.4) gave **21b** (2 mg, 23%) as a colorless solid, which was identical with an authentic sample by comparison of the IR spectrum. The fastest-running zone (*Rf* 0.7) furnished a compound presumed to be 7-benzyl-1,2-dihydro-1,3-dimethylhypoxanthine (**30**), as colorless needles (3 mg, 35%); MS *m/z*: 256 (M^+); IR ν_{max}^{Nujol} 1640 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ: 2.92 and 2.98 (3H each, s, NMe's), 4.30 [2H, s, C(2)-H's], 5.42 [2H, s, N(7)-C$\underline{H}_2$Ph], 7.2—7.4 [6H, m, N(7)-$CH_2$$\underline{Ph}$ and C(8)-H].

References and Notes

1) Paper LXIV in this series, T. Saito, Y. Asahi, S. Nakajima, T. Fujii, *Chem. Pharm. Bull.*, **42**, 2263 (1994).
2) For a review on the purine alkaloids, see Atta-ur-Rahman, M. I. Choudhary, "The Alkaloids," Vol. 38, ed. by A. Brossi, Academic Press, New York, 1990, Chapter 3.
3) T. Fujii, T. Saito, S. Mori, *Chem. Pharm. Bull.*, **38**, 2146 (1990).
4) For aplysidine from *Aplysina* sp., see K. Kondo, H. Shigemori, M. Ishibashi, J. Kobayashi, *Tetrahedron*, **48**, 7145 (1992).
5) For agelasine G from *Agelas* sp., see K. Ishida, M. Ishibashi, H. Shigemori, T. Sasaki, J. Kobayashi, *Chem. Pharm. Bull.*, **40**, 766 (1992).
6) (−)-Agelasine B, isolated from *Agelas nakamurai*, has been synthesized by two research groups: *a*) H. Iio, K. Asao, T. Tokoroyama, *J. Chem. Soc., Chem. Commun.*, **1985**, 774; *b*) E. Piers, J. Y. Roberge, *Tetrahedron Lett.*, **33**, 6923 (1992).
7) R. Fathi-Afshar, T. M. Allen, *Can. J. Chem.*, **66**, 45 (1988).
8) R. Fathi-Afshar, T. M. Allen, C. A. Krueger, D. A. Cook, A. S. Clanachan, R. Vriend, H. P. Baer, C. E. Cass, *Can. J. Physiol. Pharmacol.*, **67**, 276 (1989).
9) *a*) T. Saito, J. Chikazawa, Y. Nakamura, T. Fujii, *Heterocycles*, **35**, 143 (1993); *b*) T. Fujii, T. Saito, J. Chikazawa, M. Ohba, T. Date, *ibid.*, **38**, 733 (1994).
10) J. A. Montgomery, H. J. Thomas, *J. Heterocycl. Chem.*, **1**, 115 (1964).
11) *a*) N. J. Leonard, T. Fujii, *J. Am. Chem. Soc.*, **85**, 3719 (1963); *b*) T. Fujii, G. C. Walker, N. J. Leonard, D. C. DeLong, K. Gerzon, *J. Med. Chem.*, **22**, 125 (1979); *c*) T. Fujii, T. Saito, I. Inoue, Y. Kumazawa, N. J. Leonard, *Chem. Pharm. Bull.*, **34**, 1821 (1986); *d*) N. J. Leonard, T. Fujii, T. Saito, *ibid.*, **34**, 2037 (1986); *e*) T. Fujii, T. Saito, I. Inoue, Y. Kumazawa, K. Tamura, *ibid.*, **36**, 107 (1988), and references cited therein.
12) *a*) A. V. El'tsov, Kh. L. Muravich-Aleksandr, I. Él'-Sakka, *J. Org. Chem. USSR* (*Engl. Transl.*), **9**, 1308 (1973); *Zh. Org. Khim.*, **9**, 1280 (1973) [*Chem. Abstr.*, **79**, 105193*z* (1973)]; *b*) T. Fujii, T. Saito, T. Muramoto, *Chem. Pharm. Bull.*, **31**, 4270 (1983).
13) T. Fujii, T. Saito, T. Nakasaka, *Chem. Pharm. Bull.*, **31**, 3521 (1983).
14) *a*) T. Fujii, T. Itaya, T. Saito, K. Mohri, M. Kawanishi, T. Nakasaka, *Chem. Pharm. Bull.*, **37**, 1504 (1989); *b*) T. Fujii, T. Saito, T. Nakasaka, *ibid.*, **37**, 3243 (1989).
15) A similar reduction of 3-benzyladenine (**3**: R = $PhCH_2$) has been published: Y. Maki, M. Suzuki, K. Ozeki, *Tetrahedron Lett.*, **1976**, 1199.
16) T. Itaya, K. Ogawa, H. Matsumoto, T. Watanabe, *Chem. Pharm. Bull.*, **28**, 2819 (1980).
17) See ref. 9*b* for details of the X-ray analysis and a parallel view of the molecular structure of the adduct **29b**.
18) T. Fujii, T. Saito, T. Fujisawa, *Chem. Pharm. Bull.*, **42**, 1231 (1994), and references cited therein.
19) T. Nakatsu, D. J. Faulkner, G. K. Matsumoto, J. Clardy, *Tetrahedron Lett.*, **25**, 935 (1984).
20) W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
21) The assignment is based on that[7] of the corresponding signal of agelasimine-A (**1a**).
22) A 2% NOE was observed for this signal on irradiation of the C(2)-protons signal at δ 4.34.