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Synthesis of 9-Substituted Tetrahydrodiazepinopurines: Studies toward the Total Synthesis of Asmarines

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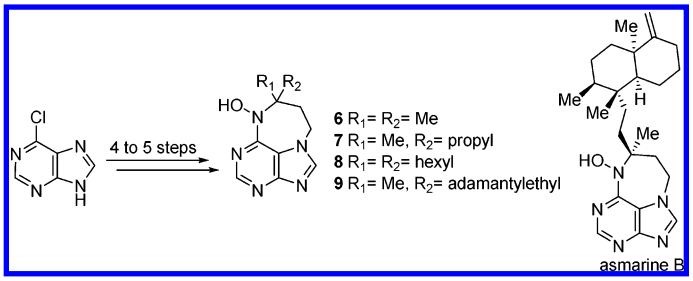

A methodology for the preparation of asmarine analogues has been developed. The asmarines are cytotoxic marine alkaloids with a unique tetrahydro[1,4]diazepino[1,2,3-*g*,*h*]purine (THDAP) structure. Three cyclization methods were applied for the preparation of the 9,9-disubstituted 10-hydroxy-THDAP system, namely, aminomercurization, iodocyclization, and acid-catalyzed cyclization. The DMPM group of the NOH functionality and cyanoethyl group of the N-9 atom were found to be the most suitable protecting groups. The structures of all compounds were mainly determined from NMR measurements including ^{15}N chemical shifts obtained from ^{15}NH HMBC spectra. The end products are at least about 1 order of magnitude less active than the natural product asmarine B.

Introduction

The unique structure of asmarines A and B,[1] and their selective cytotoxicity, encouraged us to develop a synthetic mode for the preparation of asmarine analogues. The asmarines[1,2] are structurally unusual compounds of mixed biogenesis. All embody a hydroxylaminopurine moiety attached to the diterpene skeleton of chelodane[3] (or closely related diterpenes), together comprising the 9,9-disubstituted 10-hydroxytetrahydrodiazepinopurine (10-hydroxy-THDAP) system.

The selective cytotoxicity among the asmarines, asmarine B (**1b**) (Figure 1) being the most active, indicates the importance of the lipophilic decalin portion for the activity. The bioactivity of the asmarines triggered the synthesis of asmarine analogues with a variety of substituents on C-9. It was also found that the *N*-OH group is essential for activity; i.e., asmarine H (**1c**) (Figure 1) is devoid of activity.

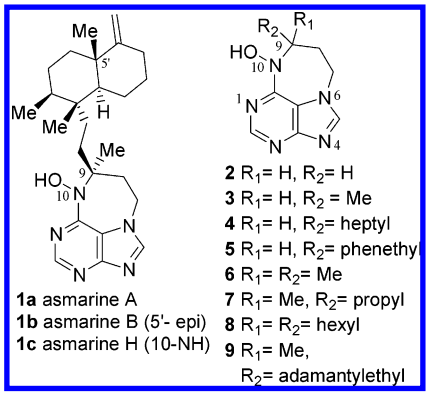

FIGURE 1. Asmarines **1a**−**c** and synthetic analogues **2**−**9**.

Results and Discussion

We reported the synthesis of 9-monosubstituted 10-hydroxy-THDAPs (compounds **2**−**4**)[4] in two previous papers.[5,6] In the same manner we also prepared com-

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(2) Rudi, A.; Shalom, H.; Schleyer, M.; Banayahu, Y.; Kashman, Y. *J. Nat. Prod.* **2004**, *67*, 106−109.

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(4) The atom numbers for the THDAP system are according to the IUPAC nomenclature and differ from the purine numbers.

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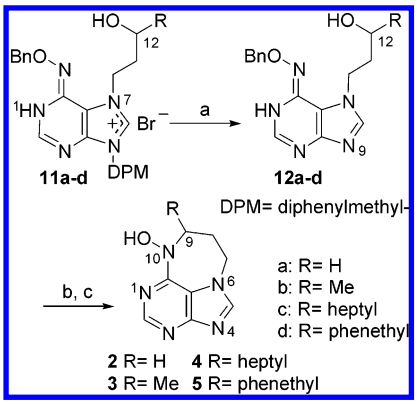
SCHEME 1. Synthesis of 9-Monosubstituted 10-Hydroxy-THDAP[a]



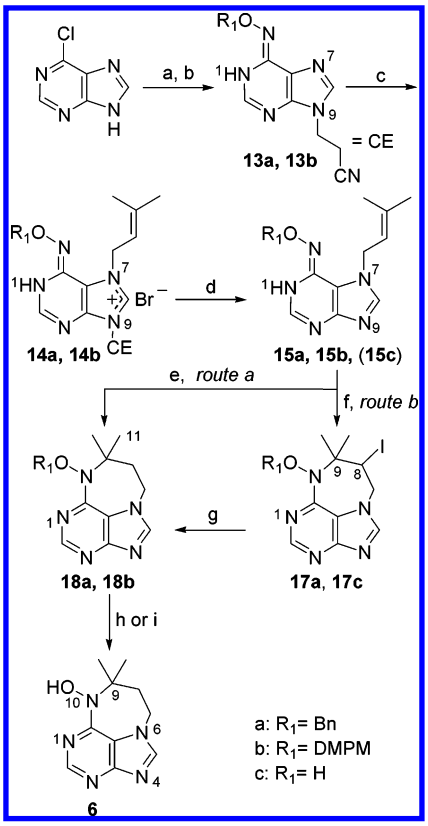
[a] Reagents and conditions: (a) TFA, CH_2Cl_2, rt, 24 h, 40−45%; (b) DIAD, PPh_3, dry THF, rt to 40 °C, 18 h, 68−95%; (c) 30% HBr in AcOH, 100 °C, 3.5 h (debenzylation), 66−93%.

pound **5** by appling the Mitsunobu reaction[7] for the cyclization of the (benzyloxy)imine alcohol **12d** (Scheme 1). Synthesis of 9,9-disubstituted 10-hydroxy-THDAPs, however, as in the asmarines, required a different cyclization mode, as the Mitsunobu reaction is limited for primary and secondary alcohols.

Three cyclization methods were applied for the preparation of 9,9-disubstituted 10-hydroxy-THDAPs (compounds **6**−**9**): (a) aminomercuration[8] of alkenylpurines **15a** and **15b** using mercury(II) acetate (route a), (b) iodocyclization[9] of the same alkenes **15a** and **15b** with iodine (route b, Scheme 2), and (c) acid-catalyzed cyclization[9,10] (30% HBr in AcOH) of acid-stable compounds applied on tertiary bromides **16d**−**e**, tertiary alcohols **20a,b**, or alkenes, e.g., compound **27** (Schemes 3−5).

Crucial to all three routes is the protecting group of the hydroxylamine and the N-9 atom of synthon **14**; i.e., following the alkylation of **13**, stable adeninium salts have to be obtained that can later be selectively deprotected under mild conditions. Several protecting groups were tried.[5] The 2-cyanoethyl (CE) group, previusly applied for protecting the imidazole NH group,[11] was found to be most suitable. Admitting the CE group to the N-9 position was achieved by the Michael addition of 6-chloropurine to acrylonitrile (Scheme 2).[12] Reacting the obtained adduct with *O*-benzyl- or *O*-(3,4-dimethoxybenzyl (DMPM))hydroxylamine[13] afforded compounds **13a** and **13b**, respectively. On the basis of Fujii's work,[14] further alkylation of the latter N-9-alkylated purines went to N-7, affording the adeninium salt **14** (or **11**,

SCHEME 2. Routes a and b Leading to 9,9-Dimethyl-10-hydroxy-THDAPs[a]



[a] Reagents and conditions: (a) acrylonitrile, DMSO, K_2CO_3, rt, 70 h, 78%; (b) *O*-benzylhydroxylamine for **13a** or *O*-(3,4-dimethoxybenzyl)hydroxylamine for **13b**, diisopropylethylamine, EtOH, reflux, 24 h, 80%, 59%; (c) $(CH_3)_2C{=}CHCH_2Br$, DMF, rt, 12 h, 75%, 61%; (d) 3% K_2CO_3 in MeOH, rt, 1 h, 72%, 73%; (e) (i) $Hg(OAc)_2$ in dry THF, 40 °C, 24 h; (ii) $NaBH_4$ in 2.5 N aq NaOH, 69%, 57%; (f) I_2, $NaHCO_3$ in 95% EtOH, rt, 48 h, 75%; (g) Bu_3SnH, dry THF, reflux, 3 h, 81%; (h) for **18a**, 30% HBr in AcOH, 100 °C, 3 h, 96%; (i) for **18b**, DDQ in $CH_2Cl_2-H_2O$ (18:1), rt, 4 h, 76%.

Scheme 1). Thus, alkylation of compounds **13a** and **13b** with 4-bromo-2-methylbut-2-ene gave the stable adeninium salts **14a** and **14b**. Cleavage of the CE group (Hofmann-type elimination)[15] was successfully achieved with 3% K_2CO_3 in methanol, affording compounds **15a** and **15b** in good yields (72% and 73%).

Treatment of each of the latter two compounds with mercury(II) acetate in dry THF at 40 °C for 24 h, followed by reduction of the purinomercury intermediate with sodium borohydride in 2.5 N aq NaOH (route a, Scheme 2), afforded the 10-*O*-protected 9,9-dimethyl-THDAP products **18a** and **18b**, respectively, in 69% yield. Cleavage of the benzyl group of compound **18a** with 30% HBr in acetic acid at 100 °C for 3.5 h[5] and the DMPM group of compound **18b** with DDQ in $CH_2Cl_2-H_2O$ (18:1) at room temperature for 4 h afforded the desired compound **6** (Scheme 2).

Alternatively, reaction of **15a** with iodine in 95% ethanol in the presence of sodium bicarbonate at room temperature for 3 days (Scheme 2, route b) yielded the 9,9-disubstituted 10-(benzyloxy)-8-iodo-THDAP **17a** in

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(13) Drain, D. J.; W. R.Williams, H.; G. B. Howes, J. GB Patent 983664, 1965.
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TABLE 1. ^{15}N Chemical Shifts Deduced from Long-Range ^{1}H−^{15}N Heteronuclear Shift Correlations (40 MHz, d_6-DMSO, 60 °C)[a]

	N-1	N-3	N-4	N-6	N-10
1a	247.0	233.3	245.9	153.9	166.5
2	245.7	235.3	245.4	156.0	149.3
6	247.9	234.0	246.8	155.0	167.7
30	250.8	237.9	245.4	155.6	168.7
31	251.0	237.3	246.8	155.0	178.2
17a[b]	247.5	241.8	245.6	153.4	188.1
18a	253.2	240.0	246.8	155.0	188.8

[a] Chemical shifts in parts per million downfield from liquid NH_3. [b] The experiment was performed at 25 °C.

75% yield. Deiodination of the latter compound with tributyltin hydride, in boiling THF under light radiation, afforded compound **18a** (81% yield). Treatment of compound **15b** with iodine under the same conditions applied for **15a** (route b) cleaved, through oxidation, the DMPM protecting group, affording a 1:1 mixture of the free hydroxylamine **15c** and the desired 10-hydroxy-9,9-dimethyl-8-iodo-THDAP (**17c**). It is noteworthy that route a has steric limitations and is sluggish for larger 9-substituents. Also, route b requires protecting groups, which do not cleave under oxidative conditions.

The structures of all new compounds were established by MS experiments and from 1D and 2D NMR spectra including ^{15}NH HMBC measurements. Excellent agreement was found between the ^{13}C and the ^{15}N chemical shifts (deduced from the ^{15}NH HMBC) of compound **6** and asmarine A (Table 1). Compounds **6**, **18a**, and **18b**, the 9,9-disubstituted 10-hydroxy-THDAPs, exhibited broad peaks for the diazepino and benzyl protons in the NMR spectra. Steric hindrance around the C-9−N-10 bond most likely raises the activation energy for the N−OR inversion, resulting in the nonequivalency of the two methyl groups at room temperature. The broad signal of the two methyls (11-Me's, δ_H 1.43 ppm for compound **18a**) separated at −35 °C (δ_H 1.75 and 1.32 ppm), coalesced around 0 °C, and sharpened, as expected, at 50 °C. The calculated[16] free activation energy ($\Delta G^{\ddagger}$) of the exchange between the two enantiomeric conformers was found to be ca. 13.1 kcal mol^{-1}. Increasing the steric hindrance, by the 8-iodine atom as in compounds **17a** and **17c**, led to freezing of the conformational equilibrium, resulting in a single conformer, as seen by the appearance of two sharp singlets for the two diastereotopic methyl groups (δ_H 1.71 and 1.39 ppm for compound **17a**).

When the desired 9-substituents were larger, route a no longer worked and an alternative cyclization route was required. In both routes a and b, the $Hg(OAc)_2$ and I_2, respectively, create a C-9 carboniun ion intermediate which is attacked by the hydroxylamine nitrogen atom nucleophile to form the THDAP ring system. Applying the mercury(II) reagent introduces large atoms on C-8, severely hindering the nucleophilic attack on the vicinal C-9 atom. In the case of 9,9-disubstituted compounds, other than the dimethyl, the activation energy for the reaction became too large to overcome.

Two other approaches, both aimed at affording the C-9 carbocation, without large neighboring reagent groups at C-8, namely, removing a bromine atom from C-9 (e.g., from compound **16d**) with $AgClO_4$ and protonation of the C-8−C-9 double bond (e.g., compound **15a**), were considered. As the first approach failed, giving the E1 product **15a** instead of the S_N1 reaction, protonation conditions were explored.

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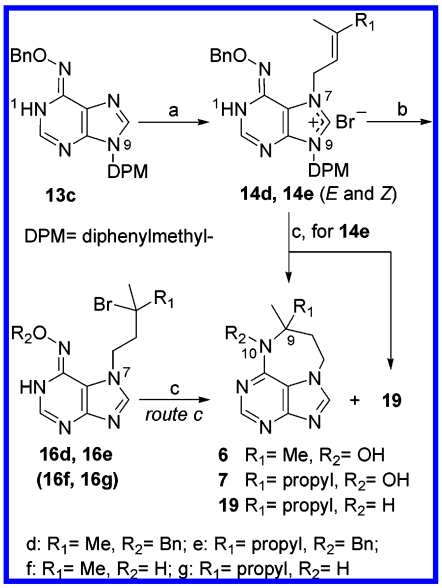
SCHEME 3. Route c Leading to 9,9-Disubstituted 10-Hydroxy-THDAP[a]



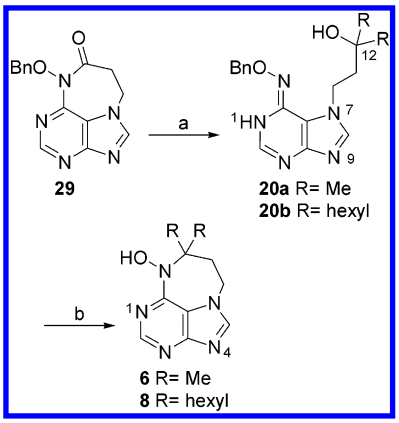
[a] Reagents and conditions: (a) for **14d**, $(CH_3)_2C{=}CHCH_2Br$, DMF, 70 °C,12 h, 81%; for **14e**, $C_3H_7C(CH_3){=}CHCH_2Br$, DMF, 70 °C, 72 h, 74%; (b) 15% HBr in AcOH, rt, 12 h, 72%, 68%; (c) 30% HBr in AcOH, 100 °C, 3 h, for **6**, 95%; for **7**, 48%.

Applying acidic conditions to compounds of types **14d** and **14e** can potentially lead to four different reactions, i.e., removal of the DPM protecting group, debenzylation, undesired cleavage of the N−O hydroxylamine bond to give the free amine, and/or the desired cyclization (route c). The rates of the latter reactions change significantly under different conditions (Scheme 3), and many experiments were performed to find the right conditions.

Treating compound **14d** or **14e** with 15% HBr in AcOH at room temperature (Scheme 3, route c) deprotected the DPM group and added HBr to the double bond to give compounds **16d** and **16e**. The latter, under more severe conditions (30% HBr in AcOH at 100 °C for 3 h), unexpectedly gave the desired compounds **6** and **7** (in 93% and 48% yield, respectively). The sensitivity of the reaction to the conditions was well demonstrated when the reaction temperature was lowered from 100 to 85 °C, affording a mixture of the starting materials **16d** and **16e** (Scheme 3), the cyclic products **6** and **7**, and the free hydroxylamines **16f** and **16g**. From the absence of the protected tricyclic compound **18a** in the crude reaction mixture, it was concluded that the fastest reaction is the removal of the benzyl group, after which the cyclization takes place. Obtaining the cyclized compounds **6** and **7** from **16d** and **16e** is quite surprising as protonation of the purine system was expected to reduce the nucleophilicity of the exocyclic hydroxylamine nitrogen atom.

Applying the more severe cyclization conditions (30% in AcOH at 100 °C for 3 h) directly to **14e** afforded a mixture of compound **7** and the cyclic amino compound **19** in a ca. 1:2 ratio.

SCHEME 4. Alternative Approach for the Synthesis of 9,9-Disubstituted 10-Hydroxy-THDAP[a]



[a] Reagents and conditions: (a) methylmagnesium bromide or hexylmagnesium bromide (5 equiv), dry THF, 0 °C to rt, 1.5 h, 79%, 63%; (b) 30% HBr in AcOH, 100 °C, 3 h, 93%, 42%.

Route c could also be applied to the purine carbinols **20a** and **20b** (Scheme 4) prepared from benzyl hydroxamate **29**[5] with 5 equiv of the proper Grignard reagent.

Once the proper conditions of route c were established, they were applied to the synthesis of the 9-methyl-9-adamantylethyl derivative **9** starting from the appropriate allyl bromide **25** that was prepared from 1-(2-bromoethyl)adamantane (**21**)[17] in four steps (Scheme 5). Reaction of compound **25** with **13b** afforded compound **26** in 47% yield. Cleavaged of the CE protective group under basic conditions and subsequent acid-catalyzed cyclization yielded compound **9** in high yield (92%).

In a previous paper[5] we demonstrated the benefit of using ^{15}N NMR data[18] for the structure determination of various purine derivatives, namely, use of chemical shifts and $^{2}J_{NH}$ and $^{3}J_{NH}$ correlations. Thus, the main tautomeric form, and the hybridization of various nitrogen atoms in the molecules, could be established. Inter alia, comparison of the ^{15}N resonance of compounds **2**, **6**, **30**,[5] **31**,[5] and **18a**, shown in Table 1, clearly demonstrate

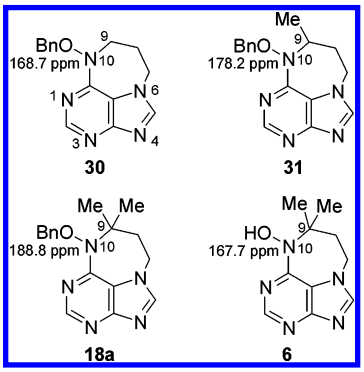


FIGURE 2. Examples of the β-effect in ^{15}N NMR on N-10 by the 9-substituents.

TABLE 2. Cytotoxicity for Compounds 1a, 1b, 2, 3, 4, 8, 9

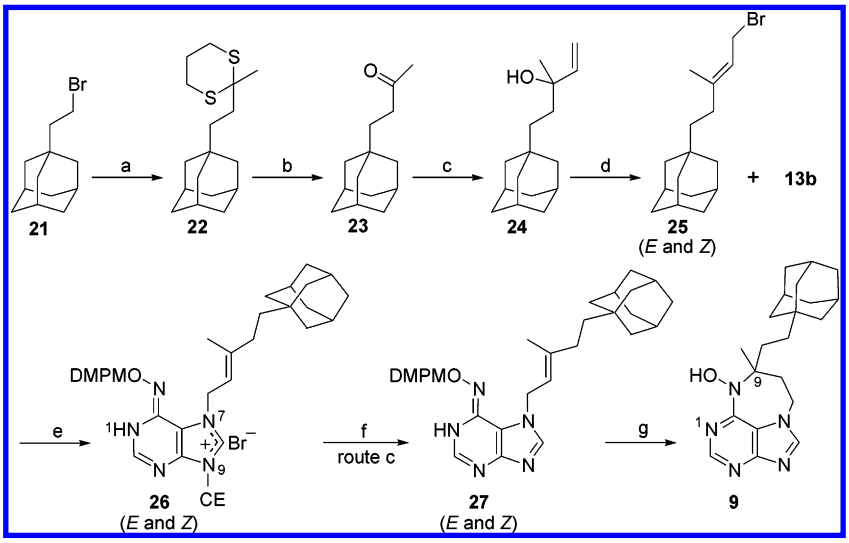
	GI50 (μg/mL)[a,19]						
	prostate	ovarian	melanoma	NSCL	pancreas	colon	
	DU-145	IGROV-ET	SK-MEL-28	A549	PANC1	HT29	LOVO
1a	2.7	0.7	2.7	4.1	1.1	0.4	1.0
1b	nt[b]	nt	0.5	0.4	nt	0.04	nt
2	9.3	5.2	la[c]	la	7.3	la	8.3
3	9.9	4.9	la	la	4.7	la	5.9
4	5.3	3.4	4.4	7.8	3.5	10	3.6
8	nt	nt	nt	4.0	nt	1.4	nt
9	nt	nt	nt	la	la	nt	nt

[a] Growth inhibition. [b] Not tested. [c] Low activity, higher than 10 μg/mL.

the ca. 10 ppm shift of N-10 by C-9 substituents (Figure 2) and the ca. 19 ppm shift due to the β-effect of the −OR substitutes on N-10 (**18a** vs **6**).

Compounds **2**−**9** were all found to be at least an order of magnitude less active than asmarine B (Table 2). The cyclization modes for 9-mono- and 9,9-disubstituted THDAPs can form the basis of SAR studies of asmarine analogues, as well as provide the way for the total synthesis of asmarine A starting from chelodane and the appropriate purine.

SCHEME 5. Synthesis of Compound 9 (route c)[a]



[a] Reagents and conditions: (a) 2-methyl-1,3-dithiane, butyllithium, dry THF, −45 °C to rt, followed by **21** in dry THF, 2 h, 56%; (b) DDQ, CH_3CN-H_2O (9:1), rt, 1.5 h, 95%; (c) vinylmagnesium chloride, dry THF, 0 °C, 20 min, 97%; (d) 48% HBr−hexanes, 0 °C, 1 h, 80%; (e) DMF, 45 °C, 3 days, 47%; (f) 3% K_2CO_3 in MeOH, rt, 1 h, 73%; (g) 30% HBr in AcOH, 90 °C, 3 h, 92%.

Experimental Section

General Methods. Starting materials, reagents, and solvents were purchased from commercial suppliers and used without further purification. Petroleum ether refers to the fractions with bp 64−68 °C. THF was freshly distilled from sodium metal and benzophenone under an atmosphere of argon before use. Vacuum liquid chromatography (VLC) was performed using silica gel 60 H prewashed with methanol. Chemical shifts (δ) are reported in parts per million, and the residual solvent peak used was as an internal standard. All NMR spectra were taken in d_6-DMSO unless otherwise reported. The $^1H-^{15}N$ HMBC experiments were optimized for a delay of 55 ms, and the ^{15}N chemical shifts are reported with respect to the peak for liquid NH_3 as a reference standard.

***N*^{6}-(Benzyloxy)-9-(2-cyanoethyl)adenine (13a).** A mixture of 6-chloro-9-(2-cyanoethyl)purine[12] (150 mg, 0.7 mmol), *O*-benzylhydroxylamine (172 mg, 0.9 mmol), and diisopropylethylamine (186 mg, 1.4 mmol) in ethanol (10 mL) was heated under reflux for 24 h. The cooled mixture was filtered and the precipitate washed twice with cold water (2 mL), providing compound **13a** (170 mg, 80%) as a white solid. Recrystallization from ethanol gave colorless needles: mp 189 °C; IR (KBr) 3410, 3056, 1662, 1596 cm^{-1}; ^1H NMR (200 MHz), **13a** appears as two tautomeric forms, i.e., imino (i)/amino (a) in a ca. 5:1 ratio, δ 11.29 (i) and 11.02 (a) (br s, 1H), 8.35 (a) and 7.61 (i) (s, 1H), 7.89 (i) and 7.33 (a) (s, 1H), 7.27−7.35 (m, 5H), 5.02 (s, 2H), 4.49 (a) and 4.33 (i) (t, J = 6 Hz, 2H), 3.18 (a) and 3.07 (i) (t, J = 6 Hz, 2H); ^{13}C NMR (100 MHz) δ 144.3, 141.2 (2C), 138.7, 138.2, 128.8, 128.2, 127.7, 127.4, 118.2, 74.6, 38.8, 18.5; HRMS (ES) *m/z* calcd for $C_{15}H_{14}N_6ONa^+$ 317.1121, found 317.1120.

***N*^{6}-(3,4-Dimethoxybenzyloxy)-9-(2-cyanoethyl)adenine (13b).** Compound **13b** was prepared from 6-chloro-9-(2-cyanoethyl)purine[12] (2.28 g, 11.0 mmol), *O*-(3,4-dimethoxybenzyl)hydroxylamine[13] (3.11 g, 17.0 mmol), and diisopropylethylamine (1.4 g, 11.0 mmol) in ethanol (10 mL) under the same procedure described for the preparation of **13a**. The product **13b** (2.3 g, 59%) was obtained as a white solid. Recrystallization from ethanol gave colorless needles: mp 130 °C dec; ^1H NMR (200 MHz), **13b** appears as two tautomeric forms, i.e., imino (i)/amino (a) in a ca. 5:1 ratio, δ 11.29 (i) and 10.96 (a) (br s, 1H), 8.34 (a) and 7.61 (i) (s, 1H), 7.89 (i) and 7.34 (a) (s, 1H), 7.03 (s, 1H), 6.95 (d, J = 6 Hz, 1H), 6.91 (d, J = 6 Hz, 1H), 4.94 (s, 2H), 4.49 (a) and 4.34 (i) (br t, 2H), 3.19 (a) and 3.09 (i) (br t, 2H); ^{13}C NMR (100 MHz) δ 148.8, 148.6, 144.6, 141.6, 141.5, 138.5, 131.2, 120.6, 118.5, 112.2, 111.8, 111.5, 75.0, 55.8, 55.7, 39.0, 18.8; MS (FAB) *m/z* (rel intens) 301 (100, $M^+ - C_3H_4N$); HRMS (ES) *m/z* calcd for $C_{17}H_{19}N_6O_3$ 355.1513, found 355.1531.

***N*^{6}-(Benzyloxy)-9-(2-cyanoethyl)-7-(Δ^2-isopentenyl)adeninium Bromide (14a).** A mixture of compound **13a** (0.13 g, 0.45 mmol) and 4-bromo-2-methylbut-2-ene (0.13 g, 0.90 mmol) in DMF (3 mL) was stirred at room temperature, in the dark, under an argon atmosphere, for 12 h. The solvent was then evaporated and the residue purified by VLC (methanol/EtOAc, 1:6) affording compound **14a** (0.15 g, 75%) as a white solid: ^1H NMR (400 MHz) δ 12.15 (s, 1H), 9.54 (s, 1H), 7.89 (s, 1H), 7.30−7.40 (m, 5H), 5.35 (br t, J = 7 Hz, 1H), 5.10 (s, 2H), 4.95 (d, J = 7 Hz, 2H), 4.53 (t, J = 6.0 Hz, 2H), 3.22 (t, J = 6.0 Hz, 2H), 1.72 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (100 MHz) δ 148.8, 140.9, 140.6, 137.6, 137.2, 136.8, 128.2, 128.0, 127.7, 117.4, 116.4, 110.0, 75.5, 47.6, 40.9, 25.3, 18.0, 17.8; MS (FAB) *m/z* (rel intens) 363 (100, M^+); HRMS (FAB) *m/z* calcd for $C_{20}H_{23}N_6O$ (M^+) 363.1933, found 363.1943.

***N*^{6}-(3,4-Dimethoxybenzyloxy)-9-(2-cyanoethyl)-7-(Δ^2-isopentenyl)adeninium Bromide (14b).** Compound **14b** was prepared from compound **13b** (0.64 g, 1.8 mmol) and 4-bromo-2-methylbut-2-ene (0.61 g, 4.12 mmol) in DMF (3 mL) via the same procedure described for the preparation of **14a**. The residue was purified by VLC (methanol/EtOAc, 1:5), affording compound **14b** (0.55 g, 61%) as an amorphous solid: ^1H NMR (200 MHz) δ 9.06 (s, 1H), 7.60 (s, 1H), 6.98 (s, 1H), 6.87 (s, 2H), 5.33 (br t, 1H), 4.98 (d, J = 7.4 Hz, 2H), 4.80 (s, 2H), 4.37 (t, J = 6.0 Hz, 2H), 3.72 (s, 6H), 3.15 (t, J = 6.0 Hz, 2H), 1.73 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (100 MHz) δ 149.1, 148.6, 141.0, 140.9, 137.2, 137.0, 130.0, 120.9, 117.6, 116.5, 112.4, 111.5, 110.1, 75.6, 55.6, 55.5, 48.6, 47.6, 41.0, 25.5, 18.2, 18.0; MS (FAB) *m/z* (rel intens) 433 (100, M^+); HRMS (FAB) *m/z* calcd for $C_{22}H_{27}N_6O_3$ (M^+) 433.2145, found 433.2151.

***N*^{6}-(Benzyloxy)-9-(diphenylmethyl)-7-(Δ^2-isopentenyl)adeninium Bromide (14d).** Compound **14d** was prepared from compound **13c** (1.2 g, 2.95 mmol) and 4-bromo-2-methylbut-2-ene (660 mg, 4.4 mmol) in DMF (10 mL) at 70 °C for 12 h via the same procedure describe for the preparation of **14a**. The residue was purified by VLC (methanol/EtOAc, 1:10), affording compound **14d** (1.33 g, 81%) as a white solid: ^1H NMR (400 MHz) δ 12.25 (br s, 1H), 9.24 (s, 1H), 7.77 (s, 1H), 7.26−7.41 (m, 15H), 7.19 (s, 1H), 5.23 (t, 1H), 5.07 (s, 2H), 4.90 (d, J = 6 Hz, 2H), 1.63 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz) δ 149.0, 141.3, 139.0, 138.0, 137.2, 136.7, 136.5, 129.2, 129.0, 128.5, 128.4, 127.9, 117.8, 111.1, 75.6, 63.3, 48.1, 25.5, 18.4; MS (FAB) *m/z* (rel intens) 476 (75, M^+), 166 (100); HRMS (FAB) *m/z* calcd for $C_{30}H_{30}N_5O$ (M^+) 476.2450, found 476.2446.

***E* And *Z* Isomers of *N*^{6}-(Benzyloxy)-9-(diphenylmethyl)-7-(3-methylhex-2-enyl)adeninium Bromide (14e).** Compound **14e** was prepared from **13c** (0.5 g, 1.2 mmol) and 1-bromo-3-methyl-2-hexene[20] (0.54 g, 3.0 mmol) in DMF (10 mL) at 70 °C for 72 h via the same procedure described for the preparation of **14a**. The residue was purified by VLC (methanol/EtOAc, 1:10), affording a mixture of the *E* and *Z* isomers of compound **14e** (0.45 g, 74%) as an amorphous solid: ^1H NMR (200 MHz), mixture of *trans* (*t*) and *cis* (*c*) isomers in a ca. 3:1 ratio, δ 12.21 (br s, 1H), 9.18 (*c*) and 9.15 (*t*) (s, 1H), 7.78 (s, 1H), 7.26−7.41 (m, 15H), 7.02 (s, 1H), 5.30 (t, J = 7.2 Hz, 1H), 5.07 (s, 2H), 4.92 (d, J = 6.4 Hz, 2H), 2.04 (*c*) and 1.87 (*t*) (br t, 2H), 1.62 (*t*) and 1.60 (*c*) (s, 3H), 1.26 (m, 2H), 0.73 (t, 3H); ^{13}C NMR (50 MHz) δ 149.4, 143.0, 142.6, 141.5, 138.3, 137.6, 136.8, 136.7, 129.4−128.2, 118.6 (*c*) and 117.8 (*t*), 111.3, 75.9, 63.5, 48.3, 47.9, 41.1 (*t*) and 33.7 (*c*), 23.3 (*c*), 20.8 (*c*), 20.4 (*t*), 16.7 (*t*), 13.9 (*c*), 13.8 (*t*); MS (FAB) *m/z* (rel intens) 504 (80, MH^+), 166 (100); HRMS (FAB) *m/z* calcd for $C_{32}H_{34}N_5O_1$ (MH^+) 504.2768, found 504.2763.

***N*^{6}-(Benzyloxy)-7-(Δ^2-isopentenyl)adenine (15a).** Compound **14a** (20 mg, 0.045 mmol) was stirred vigorously in methanol (2 mL) in the presence of K_2CO_3 (42 mg) at room temperature for 1 h. The solution was then poured into water (10 mL) and concentrated under vacuum to remove the methanol. The resulting syrup was extracted with ethyl acetate (2 × 20 mL) and the combined organic layer washed with brine, dried over Na_2SO_4, and evaporated, affording compound **15a** (10 mg, 72%) as a white solid: mp 195 °C; IR (CH_2Cl_2) 3403, 3053, 1658, 1597 cm^{-1}; ^1H NMR (200 MHz) δ 11.18 (s, 1H), 7.86 (s, 1H), 7.50 (s, 1H), 7.27−7.42 (m, 5H), 5.29 (br t, 1H), 5.01 (s, 2H), 4.77 (d, J = 7 Hz, 2H), 1.69 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.6, 143.3, 140.3, 139.7, 139.1, 138.1, 137.7, 128.6, 128.3, 127.9, 110.0, 76.0, 45.3, 25.6, 18.1; MS (CI) *m/z* (rel intens) 310 (100, MH^+), 204 (49, $MH^+ - C_7H_7O$); HRMS (CI) *m/z* calcd for $C_{17}H_{19}N_5O_1$ (MH^+) 310.1668, found 310.1667.

***N*^{6}-(3,4-Dimethoxybenzyloxy)-7-(Δ^2-isopentenyl)adenine (15b).** Compound **15b** was prepared from compound **14b** (200 mg, 0.39 mmol) and K_2CO_3 (210 mg) in methanol (10 mL) via the same procedure described for the preparation of **15a**. The product **15b** (105 mg, 73%) was obtained as an amorphous solid: ^1H NMR (400 MHz) δ 11.17 (br s, 1H), 7.86 (s, 1H), 7.53

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(s, 1H), 7.03 (s, 1H), 6.95 (d, $J = 8$ Hz, 1H), 6.91 (d, $J = 8$ Hz, 1H), 5.32 (br t, 1H), 4.99 (s, 2H), 4.81 (d, $J = 7$ Hz, 2H), 3.73 (s, 6H), 1.73 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz) δ 150.3, 148.8, 148.7, 143.3, 140.6, 140.2, 136.7, 130.9, 120.9, 120.4, 112.5, 111.7, 109.5, 75.2, 55.8, 55.7, 44.7, 25.5, 18.2; MS (FAB) *m/z* (rel intens) 370 (100, MH^+); HRMS (FAB) *m/z* calcd for $C_{19}H_{24}N_5O_3$ (MH^+) 370.1887, found 370.1879.

N^6-(Benzyloxy)-7-(3-bromo-3-methylbutyl)adenine (16d). Compound **14d** (150 mg, 0.32 mmol) in a solution of 15% HBr in AcOH (2 mL) was stirred for 12 h at room temperature, the solvent was then evaporated, and the residue was partitioned between ethyl acetate (20 mL) and 0.5 N aq $NaHCO_3$ (20 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by VLC (methanol/EtOAc, 1:20), affording compound **16d** (90 mg, 72%) as an amorphous solid: ^{1}H NMR (200 MHz) δ 11.28 (br s, 1H), 7.94 (s, 1H), 7.54 (s, 1H), 7.37−7.19 (m, 5H), 5.02 (s, 2H), 4.33 (br t, 2H), 2.17 (br t, 2H) 1.67 (s, 6H); ^{13}C NMR (50 MHz) δ 150.5, 143.6, 141.4, 140.1, 139.0, 128.5, 127.9, 109.8, 75.1, 66.6, 55.3, 47.9, 34.3; MS (CI) *m/z* (rel intens) 390 (7, MH^+), 310 (80), 204 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{20}BrN_5O$ (M^+) 389.0851, found 389.0850.

***N*^{6}-(Benzyloxy)-7-(3-bromo-3-methylhexyl)adenine (16e).** Compound **16e** was prepared from compound **14e** (350 mg, 0.69 mmol) via the same procedure described for the preparation of **16d**. The residue was purified by VLC (methanol/EtOAc, 1:20), affording compound **16e** (190 mg, 68%) as an amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.35−7.27 (m, 5H), 7.15 (s, 1H), 5.08 (s, 2H), 4.34 (t, $J = 8$ Hz, 2H), 2.15 (t, $J = 8$ Hz, 2H), 1.79 (t, 2H), 1.70 (s, 3H), 1.53 (m, 2H), 0.95 (t, $J = 7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 144.5, 139.6, 138.6, 137.6, 128.7, 128.6, 128.4, 128.1, 127.9, 110.4, 76.0, 69.4, 48.2, 46.1, 46.0, 31.1, 18.8, 14.0; MS (CI) *m/z* (rel intens) 418 (10, MH^+), 338 (30), 107 (100); HRMS (EI) *m/z* calcd for $C_{19}H_{24}BrN_5O$ (M^+) 417.1164, found 417.1167.

7,8,9,10-Tetrahydro-10-(benzyloxy)-8-iodo-9,9-dimethyl-[1,4]diazepino[1,2,3-*g*,*h*]purine (17a). To a stirred solution of compound **15a** (60 mg, 0.19 mmol) and $NaHCO_3$ (16 mg, 0.19 mmol) in 95% EtOH (4 mL) was added dropwise a solution of I_2 (144 mg, 0.57 mmol) in 95% EtOH (2 mL), and the mixture was stirred in the dark at room temperature for 48 h. The solvent was then evaporated and the residue purified by VLC (methanol/EtOAc, 1:9), affording compound **17a** (62 mg, 75%) as a yellow amorphous solid: ^{1}H NMR (400 MHz) δ 8.64 (s, 1H), 8.54 (s, 1H), 7.61 (m, 2H), 7.43 (m, 3H), 5.40 (d, $J = 10$ Hz, 1H), 5.25 (br t, 1H), 4.90 (d, $J = 10$ Hz, 1H), 4.63 (br m, 2H), 1.72 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz) δ 159.2, 151.6, 150.9, 144.0, 135.4, 128.5, 128.4, 127.8, 109.9, 77.4, 66.6, 51.1, 48.6, 29.1, 18.0; MS (CI) *m/z* (rel intens) 436 (15, MH^+), 310 (49), 202 (100). HRMS (CI) *m/z* calcd for $C_{17}H_{19}N_5O_1I$ (MH^+) 436.0635, found 436.0634.

7,8,9,10-Tetrahydro-10-(benzyloxy)-9,9-dimethyl[1,4]-diazepino[1,2,3-*g*,*h*]purine (18a). From Compound 15a. To a stirred solution of **15a** (130 mg, 0.42 mmol) in dry THF (5 mL) at 0 °C under an argon atmosphere was added mercury(II) acetate (400 mg, 1.25 mmol) in one portion. The solution was kept at 40 °C for 24 h. After the solution was cooled to room temperature, $NaBH_4$ (32 mg, 0.84 mmol) in 2.5 N aq NaOH (1 mL) was added and the solution stirred further for 20 min. The black precipitate was filtered off through Celite, the filtrate extracted with ethyl acetate (2 × 10 mL), and the combined organic layer washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by VLC (methanol/EtOAc, 1:6), affording **18a** (90 mg, 69%) as a colorless oil: ^{1}H NMR (400 MHz, 50 °C) δ 8.54 (s, 1H), 8.38 (s, 1H), 7.56 (m, 2H), 7.39 (m, 3H), 5.15 (br s, 2H), 4.31 (br t, 2H), 2.34 (br t, 2H), 1.42 (br s, 6H); ^{13}C NMR (100 MHz) δ 159.5, 151.8 (2C), 145.7, 135.8, 129.0, 128.4, 110.1, 77.7, 63.1, 42.1, 38.0, 22.9; MS (CI) *m/z* (rel intens) 310 (23, MH^+), 204 (100); HRMS (CI) *m/z* calcd for $C_{17}H_{20}N_5O_1$ (MH^+) 310.1667, found 310.1662.

From Compound 17a. A solution of compound **17a** (14 mg, 0.032 mmol) and Bu_3SnH (32 mg, 0.11 mmol) in dry THF (1 mL) under an argon atmosphere was refluxed for 3 h under light radiation. After cooling, the solvent was evaporated and the residue purified by VLC (EtOAc/methanol, 6:1), affording compound **18a** (8 mg, 81%) as an amorphous solid.

7,8,9,10-Tetrahydro-10-(3,4-dimethoxybenzyloxy)-9,9-dimethyl[1,4]diazepino[1,2,3-*g*,*h*]purine (18b). Compound **18b** was prepared from compound **15b** (140 mg, 0.38 mmol) and mercury(II) acetate (241 mg, 0.76 mmol) in dry THF (5 mL) followed by $NaBH_4$ (29 mg, 0.76 mmol) in 2.5 N aq NaOH (1 mL) via the same procedure described for the preparation of **18a**. The residue was purified by VLC (methanol/EtOAc, 1:5), affording compound **18b** (80 mg, 57%) as an amorphous solid: ^{1}H NMR (400 MHz, 96 °C), compound **18b** exhibited a complex spectum suggesting the existence of several conformers, δ 8.55 and 8.51 (2s, 1H), 8.38 (s, 1H), 6.82−7.25 (m, 3H), 5.13 and 5.09 (2s, 2H), 4.31 (br t, 2H), 3.66−3.82 (several s, 6H), 2.34 (br t, 2H), 1.44 and 1.42 (2s, 6H); ^{13}C NMR (100 MHz) δ 159.7, 151.7, 151.6, 149.6, 149.3, 147.6, 145.4, 145.3, 134.6, 133.7, 122.0, 120.8, 116.3, 115.2, 114.4, 114.0, 113.4, 112.9, 110.4, 108.5, 77.8, 75.4, 63.2, 56.2, 56.1, 42.1, 38.6, 24.6; MS (FAB) *m/z* (rel intens) 369 (90, MH^+), 204 (75), 175 (100); HRMS (ES) *m/z* calcd for $C_{19}H_{24}N_5O_3$ 370.1873, found 370.1851.

7,8,9,10-Tetrahydro-10-hydroxy-9,9-dimethyl[1,4]-diazepino[1,2,3-*g*,*h*]purine (6). From Compound 18a. Compound **18a** (73 mg, 0.24 mmol) was dissolved in cold 30% HBr in glacial acetic acid (3 mL) and heated to 100 °C for 3.5 h. The solvent was then evaporated and the residue triturated with ether (2 × 2 mL). The obtained residual hydrobromide salt was dissolved in methanol basified with K_2CO_3. The remaining gum after evaporation was purified by VLC (methanol/EtOAc, 1:6), affording compound **6** (50 mg, 96%) as an amorphous solid: ^{1}H NMR (400 MHz, 60 °C) δ 8.34 (s, 1H), 8.28 (s, 1H), 4.30 (br t, 2H), 2.28 (br t, 2H), 1.37 (s, 6H); ^{13}C NMR (125 MHz) δ 158.6, 151.5, 151.0, 144.6, 109.4, 62.0, 42.0, 38.1, 24.7; MS (EI) *m/z* (rel intens) 219 (28, M^+), 188 (100); HRMS (EI) *m/z* calcd for $C_{10}H_{13}N_5O$ (M^+) 219.1120, found 219.1121.

From Compound 18b. To a solution of compound **17c** (23 mg, 0.06 mmol) in a mixture of CH_2Cl_2−H_2O (18:1, 3.8 mL) was added DDQ (28 mg, 0. 12 mmol) in one portion. The reaction was stirred vigorously at room temperature for 4 h and the solvent then evaporated to dryness. The residue was dissolved in methanol basified with K_2CO_3 and then concentrated under vacuum. The remaining gum was purified by VLC (methanol/EtOAc, 1:6), affording compound **6** (10 mg, 76%) as an amorphous solid.

From Compound 16d. Compound **16d** (13 mg, 0.03 mmol) was dissolved in cold 30% HBr in AcOH (1 mL) and the solution stirred at 100 °C for 3 h. The solvent was then evaporated and the residue triturated with ether (2 × 2 mL). The hydrobromide salt was dissolved in methanol basified with K_2CO_3 and the solvent evaporated to dryness. The remaining gum was purified by VLC (methanol/EtOAc, 1:6), affording compound **6** (7 mg, 95%) as an amorphous solid.

Form Compound 20a. Compound **6** was prepared from compound **20a** (10 mg, 0.02 mmol) via the same procedure described for the acid-catalyzed cyclization of **16d**. The residue was purified by VLC (methanol/EtOAc, 1:6), affording compound **6** (5.2 mg, 93%) as an amorphous solid.

7,8,9,10-Tetrahydro-10-hydroxy-9-methyl-9-propyl[1,4]-diazepino[1,2,3-*g*,*h*]purine Hydrobromide (7). Compound **7** was prepared from compound **16e** (20 mg, 0.05 mmol) via the same procedure described for the acid-catalyzed cyclization of **16d**. The obtained solid from the reaction mixture was filtered and washed with ether to afford compound **7**·HBr (8 mg, 48%) as a white solid: ^{1}H NMR (500 MHz) δ 8.69 (s, 1H), 8.50 (s, 1H), 4.43 (br t, 2H), 2.54 (m, 1H), 2.42 (m, 1H), 1.97 (m, 1H), 1.76 (m, 1H), 1.49 (s, 3H), 1.36 (m, 2H), 0.89 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz) δ 155.2, 147.3, 146.2, 144.4, 108.3, 68.9, 42.5, 39.1, 35.0, 23.7, 16.9, 14.4; MS (EI) *m/z* (rel

intens) 247 (7, M^+), 231 (17), 188 (100); HRMS (CI) *m/z* calcd for $C_{12}H_{18}N_5O_1$ (MH^+) 248.1511, found 248.1507.

7,8,9,10-Tetrahydro-9-methyl-9-propyl[1,4]diazepino-[1,2,3-*g*,*h*]purine (19) and Compound 7. Compounds **19** and **7** were prepared from compound **14e** (53 mg, 0.09 mmol) via the same procedure described for the acid-catalyzed cyclization of **16d**. Purification by VLC afforded compound **19** (11 mg, 53%) with methanol/EtOAc, 1:6, and then compound **7** (8 mg, 36%) with methanol/EtOAc, 1:5, both as amorphous solids. Data for compound **19**: ^{1}H NMR (500 MHz) δ 8.24 (s, 1H), 8.13 (s, 1H), 7.46 (br s, 1H), 4.33 (br t, 2H), 2.18 (m, 2H), 1.67 (m, 1H), 1.58 (m, 1H), 1.35 (m, 2H), 1.28 (s, 3H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz) δ 159.0, 152.0, 150.8, 144.3, 110.9, 55.0, 42.6, 42.5, 37.3, 26.2, 16.5, 14.3; MS (EI) *m/z* (rel intens) 231 (16, M^+), 188 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{17}N_5$ (M^+) 231.1484, found 231.1474.

***N*^{6}-(Benzyloxy)-7-(3-methyl-3-hydroxybutyl)adenine (20a).** To a solution of compound **29**[5] (100 mg, 0.34 mmol) in dry THF (5 mL) at 0 °C under an argon atmosphere was added methylmagnesium bromide (3 M solution in diethyl ether, 0.6 mL, 1.7 mmol). The mixture was stirred for 0.5 h at 0 °C, allowed to warm to room temperature, and then stirred further for 1.5 h. The reaction mixture was poured into a solution of saturated aq NH_4Cl (10 mL) and extracted with ethyl acetate (2 × 20 mL) and the combined organic layer washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by VLC (methanol/EtOAc, 1:20), affording compound **20a** (88 mg, 79%) as a yellow amorphous solid: ^{1}H NMR (200 MHz) δ 11.19 (br d, 1H), 7.87 (s, 1H), 7.53 (d, J = 4 Hz, 1H), 7.24−7.43 (m, 5H), 5.01 (s, 2H), 4.20 (t, J = 8 Hz, 2H), 1.74 (t, J = 8 Hz, 2H), 1.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 142.0 (2 × C), 140.2, 137.2, 128.4, 128.3, 128.1, 109.6, 75.9, 69.4, 44.7, 43.4, 29.4; MS (CI) *m/z* (rel intens) 328 (100, MH^+), 222 (25); HRMS (CI) *m/z* calcd for $C_{17}H_{22}N_5O_2$ (MH^+) 328.1773 found 328.1780.

***N*^{6}-(Benzyloxy)-7-(3-hexyl-3-hydroxynonyl)adenine (20b).** Compound **20b** was prepared from compound **29** (110 mg, 0.37 mmol) and hexylmagnesium bromide (2 M solution in diethyl ether, 1 mL, 1.85 mmol) via the same procedure described for the preparation of **20a**. The residue was purified by VLC (EtOAc), affording compound **20b** (110 mg, 63%) as a yellow amorphous solid: IR (CH_2Cl_2) 3400, 3053, 1657, 1596 cm^{-1}; ^{1}H NMR (400 MHz) δ 11.17 (s, 1H, NH), 7.84 (s, 1H), 7.52 (s, 1H), 7.25−7.40 (m, 5H), 5.02 (s, 2H), 4.20 (br t, 2H), 1.74 (br t, 2H), 1.20 (m, 20H), 0.82 (t, J = 6 Hz, 6H); ^{13}C NMR (100 MHz) δ 150.7, 143.2, 141.1, 140.2, 138.6, 128.4, 127.9, 127.7, 109.6, 75.1, 72.1, 43.2, 41.2, 39.1, 31.5, 29.7, 23.1, 22.4, 14.2; MS (CI) *m/z* (rel intens) 468 (20, MH^+), 199 (15), 107 (100); HRMS (CI) *m/z* calcd for $C_{27}H_{42}N_5O_2$ (MH^+) 468.3338, found 468.3340.

7,8,9,10-Tetrahydro-9,9-dihexyl-10-hydroxy[1,4]-diazepino[1,2,3-*g*,*h*]purine (8). Compound **8** was prepared from compound **20b** (70 mg, 0.15 mmol) via the same procedure described for the acid-catalyzed cyclization of **16d**. The residue was purified on a Sephadex LH-20 column (methanol), affording compound **8** (22.6 mg, 42%) as a pale brown amorphous solid: ^{1}H NMR (500 MHz) δ 9.54 (br s, 1H), 8.36 (s, 1H), 8.31 (s, 1H), 4.26 (br t, 2H), 2.33 (br t, 2H), 1.80 (br t, 2H), 1.67 (br t, 2H), 1.24 (br s, 16H), 0.84 (t, J = 6 Hz, 6H); ^{13}C NMR (100 MHz) δ 158.6, 151.5, 151.0, 144.6, 109.4, 66.6, 41.6, 36.2, 33.6, 31.2, 29.3, 23.1, 22.1, 20.6, 13.9; MS (CI) *m/z* (rel intens) 360 (40, MH^+), 344 (55); HRMS (CI) *m/z* calcd for $C_{20}H_{34}N_5O$ (MH^+) 360.2763, found 360.2765.

2-(2-Admantylethyl)-2-methyl-1,3-dithiane (22). To a stirred solution of 2-methyl-1,3-dithiane (1.23 g, 9.18 mmol) in dry THF (40 mL) under an argon atmosphere at −45 °C was added, dropwise, butyllithium (1.6 M in hexane, 5.7 mL). The solution was kept at this low temperature for 30 min and then allowed to warm to room temperature. 1-(2-Bromoethyl)-adamantane[17] (**21**; 1.91 g, 7.86 mmol) in dry THF (10 mL) was then added over a period of 20 min and the mixture stirred further for 1 h. The reaction mixture was poured into water (100 mL) and extracted with ether (2 × 100 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by VLC, affording with petroleum ether the starting bromide **21** (700 mg, 36%) as a white solid and with EtOAc/petroleum ether, 1:33, compound **22** (1.3 g, 56%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.85 (m, 4H), 1.65−1.97 (m, 13H), 1.59 (s, 3H), 1.50 (br d, 6H), 1.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.4, 42.4, 38.4, 37.2, 34.3, 32.0, 28.7, 27.5, 26.5, 25.4; MS (CI) *m/z* (rel intens) 297 (100, MH^+), 133 (64); HRMS (CI) *m/z* calcd for $C_{17}H_{29}S_2$ (MH^+) 297.1710, found 297.1714.

4-(1-Adamantyl)-2-butanone (23). Compound **23** was prepared according to a literature procedure.[21] To a stirred solution of compound **22** (700 mg, 2.36 mmol) in acetonitrile (16.8 mL) and water (2.5 mL), under an argon atmosphere, was added DDQ (700 mg, 3.08 mmol) dissolved in acetonitrile (1.5 mL). After the resulting solution was stirred at room temperature for 1.5 h, saturated aq $NaHCO_3$ (30 mL) was added and the solution extracted with ether (3 × 60 mL). The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by VLC (EtOAc/petroleum ether, 1:20), affording compound **23**[22] (602 mg, 95%) as a colorless oil: IR (CH_2Cl_2) 2931, 2881, 2840, 1722 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.37 (t, J = 8 Hz, 2H), 1.94 (s, 3H), 1.73 (br s, 3H), 1.65 (m, 6H), 1.44 (m, 6H), 1.33 (t, J = 8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210, 42.4, 37.7, 37.3, 32.0, 30.2, 28.8, 22.9; MS (CI) *m/z* (rel intens) 207 (MH^+, 100); HRMS (CI) *m/z* calcd for $C_{14}H_{23}O$ (MH^+) 207.1748, found 207.1749.

5-(1-Adamantyl)-3-methyl-1-penten-3-ol (24). To a solution of compound **23** (540 mg, 2.6 mmol) in dry THF (20 mL) under an argon atmosphere at 0 °C was added dropwise vinylmagnesium chloride (16.5% in THF, 6 mL). The solution was stirred for 20 min, poured slowly into saturated aq NH_4Cl (50 mL), and then extracted with ether (2 × 30 mL). The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo to give compound **24** (590 mg, 97%) as a colorless oil: IR (CH_2Cl_2) 3050, 2890, 1452, 1271 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.81 (dd, J = 16, 10 Hz, 1H), 5.11 (d, J = 16 Hz, 1H,), 4.96 (d, J = 10 Hz, 1H), 1.37−1.86 (m, 17H), 1.19 (s, 3H), 0.96 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.6, 111.9, 73.6, 42.7, 38.4, 37.5, 35.2, 32.1, 29.0, 27.9; MS (CI) *m/z* (rel intens) 233 (7, MH^+), 217 (50), 135 (100); HRMS (CI) *m/z* calcd for $C_{16}H_{26}O$ (MH^+) 234.1983, found 234.1983.

***E* And *Z* Isomers of 5-(1-Adamantyl)-1-bromo-3-methylpent-2-ene (25).** To a solution of compound **24** (210 mg, 0.9 mmol) in petroleum ether (4 mL) at 0 °C was added 48% aq HBr (4 mL). The mixture was stirred vigorously at 0 °C for 1 h, then poured into water (20 mL), and extracted with petroleum ether (2 × 30 mL). The combined organic layer was washed with 0.5 N aq $NaHCO_3$ (20 mL) and brine, dried over Na_2SO_4, and then concentrated in vacuo, affording compound **25** as a colorless oil (215 mg, 80%), an *E*/*Z* mixture (used readily without further purification): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.50 (m, 1H), 4.02 and 4.00 (d, J = 8 Hz, 2H), 1.14−1.95 (m, 22H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.0, 120.3 and 119.7, 42.6, 42.3, 37.1, 32.6, 29.9, 28.7, 24.8, 23.6.

***E* And *Z* Isomers of *N*^{6}-(3,4-Dimethoxybenzyloxy)-9-(2-cyanoethyl)-7-(5-(1-adamantyl)-3-methylpent-2-enyl)-adeninium Bromide (26)**. Compound **26** was prepared by reacting compound **13b** (166 mg, 0.47 mmol) and compound **25** (130 mg, 4.4 mmol) in DMF (3 mL) at 45 °C for 72 h, via the same procedure described for the preparation of **14a**. The residue was purified by VLC (methanol/EtOAc, 1:6), affording compound **26** as an amorphous solid (143 mg, 47%), an *E*/*Z* mixture: ^{1}H NMR (200 MHz) δ 9.60 (s, 1H), 7.84 and 7.83 (2s, 1H), 6.60−7.01 (m, 3H), 5.36 (br t, 1H), 4.99 (br m, 4H),

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4.58 (t, J = 6 Hz, 2H), 3.66−3.71 (several s, 6H), 3.22 (t, J = 6 Hz, 2H), 2.02−1.37 (m, 17H), 1.73 and 1.70 (2s, 3H), 1.03 (br t, 2H); ^{13}C NMR (125 MHz) δ 149.4, 149.0, 147.5, 145.4, 141.3, 137.7, 137.3, 133.8, 133.0, 130.4, 127.7, 121.3, 120.7, 117.9, 116.6, 116.5, 116.1, 114.9, 114.5, 113.2, 112.9, 112.3, 112.0, 110.5, 76.0, 74.1, 56.1, 56.0, 48.1, 47.7, 42.6, 42.2, 42.1, 42.0, 41.4, 40.3, 37.0, 33.7,33.8, 32.1, 28.5, 25.6, 23.6, 18.3, 17.2; MS (FAB) *m/z* (rel intens) 571 (30, MH^+); HRMS (ES) *m/z* calcd for $C_{33}H_{43}N_6O_3$ 571.3391, found 571.3402.

***E* And *Z* Isomers of N^6-(3,4-Dimethoxybenzyloxy)-7-(5-(1-adamantyl)-3-methylpent-2-enyl)adenine (27).** Compound **27** was prepared by reacting compound **26** (130 mg, 0.2 mmol) with K_2CO_3 (42 mg) in methanol (2 mL), via the same procedure described for the preparation of **15a**. Compound **27** was obtained as a colorless oil, an *E*/*Z* mixture (76 mg, 73%): ^{1}H NMR (200 MHz) δ 11.12 (br s, 1H), 7.85 (s, 1H), 7.51 (s, 1H), 6.99−6.59 (m, 3H), 5.31 (br t, 1H), 4.94 and 4.91 (2s, 2H), 4.81 (br d, 2H), 3.95−3.59 (5s, 6H), 2.02−1.32 (m, 17H), 1.73 and 1.70 (2s, 3H), 1.03 (br t, 2H); ^{13}C NMR (100 MHz) δ 150.1, 148.9, 148.8, 148.7, 147.3, 147.0, 141.7, 143.4, 140.1, 133.7, 132.7, 130.9, 128.0−111.6 (multiplet belonging to the DMPM protecting group), 109.5, 75.2, 73.2, 55.6 (5C), 44.7, 42.5, 41.9, 41.8, 36.8, 32.3, 28.3, 28.3, 25.1, 23.3, 16.6; MS (FAB) *m/z* (rel intens) 518 (100, MH^+); HRMS (ES) *m/z* calcd for $C_{30}H_{40}N_5O_3$ 518.3125, found 518.3169.

7,8,9,10-Tetrahydro-9-(2-(1-adamantyl)ethyl)-10-hydroxy-9-methyl[1,4]diazepino[1,2,3-*g*,*h*]purine (9). Compound **9** was prepared from compound **27** (7 mg, 0.01 mmol) at 90 °C via the same procedure described for the acid-catalyzed cyclization of **16d**. The solvent was then evaporated to dryness and the residue partitioned between 0.05 N aq NaOH (3 mL) and ethyl acetate (2 × 5 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by VLC (methanol/EtOAc, 1:10), affording compound **9** (4.6 mg, 92%) as an amorphous solid: ^{1}H NMR (200 MHz) δ 9.52 (br s, 1H), 8.36 (s, 1H), 8.32 (s, 1H), 4.27 (br t, 2H), 2.34 (m, 1H), 2.20 (m, 1H), 1.89 (s, 3H), 1.66−1.55 (m, 8H), 1.44 (s, 6H), 1.33 (s, 3H), 1.11 (t, 2H); ^{13}C NMR (100 MHz) δ 158.5, 151.5 (2C), 144.4, 109.3, 64.3, 48.6, 40.1, 37.1, 36.7, 35.5, 31.7, 31.2, 28.0, 22.6; MS (CI) *m/z* (rel intens) 368 (6, MH^+), 352 (100); HRMS (FAB) *m/z* calcd for $C_{21}H_{30}N_5O_1$ (MH^+) 368.2450, found 368.2458.

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Supporting Information Available: Experimental procedure and characterization of compounds **11d**, **12d**, and **5** and ^{1}H, ^{13}C, and ^{15}N HMBC NMR spectra for selected compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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