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Preparation of Carbocyclic *S*-Adenosylazamethionine Accompanied by a Practical Synthesis of (−)-Aristeromycin

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Abstract: For the preparation of a carbocyclic nitrogen analogue of *S*-adenosylmethionine (carba-AdoazaMet, **4**), a practical synthesis of (−)-aristeromycin (**7**) has been developed using variations of literature procedures. This approach called for a stereospecific synthesis of (3a*R*,6a*R*)-2,2-dimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one ((4*R*, 5*R*)-4,5-*O*-isopropylidene-2-cyclopentenone) (**8**), which was achieved by modifying reported procedures from D-(−)-ribose.

S-Adenosylmethionine (AdoMet, **1**, Figure 1) is the methyl donor cofactor for numerous biochemical methylation reactions.[1] Among the most significant of these methylase reactions are those responsible for the capping of mRNA at the N-7 of the terminal 5′-5′-guanosine triphosphate[2] and the O-2′ of the neighboring adenosines.[3] In searching for new antiviral agents whose mode of action is inhibition of viral mRNA methyltransferases,[4] analogues of AdoMet acting as cofactor-based inhibitors are being evaluated in our laboratory. In this direction, because of our work[5] and others[6] that have found carbocyclic nucleosides[7] to be potent inhibitors of AdoMet-mediated methylations, including those of viral mRNA, we became interested in carbocyclic AdoMet.

To simplify our initial undertaking in this area, however, we were attracted to the neutral AdoazaMet derivative **3**, whose analogues, because of their neutral nature, were seen as more stable than the sulfur parent to possible synthetic procedures to be used and to have many physicochemical properties in common with **1**.[8,9] In fact, compound **3** has displayed inhibitory effects on AdoMet-dependent processes.[8a] Coupling these observations with the aforementioned biological potential of carbocyclic nucleosides, this paper describes the first synthesis of carbocyclic AdoazaMet (**4**).

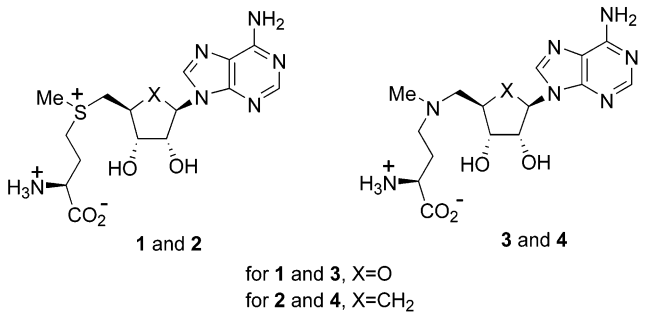

FIGURE 1. AdoMet, AdoazaMet, and Their Carbocyclic Derivatives.

A retrosynthetic analysis revealed that **4** could be assembled by coupling a protected 5′-methylamino-5′-deoxy derivative of (−)-aristeromycin (e.g., **5**) with a suitably equipped derivative of *S*-glutamic acid (**6**, Scheme 1).[8b,10] Since **5** was envisioned as being accessible from (−)-aristeromycin (**7**), an efficient and practical synthesis of **7** (or appropriate derivatives therefrom) became a central feature of the synthesis of **4**. However, a search of the literature for convenient syntheses of such compounds was not encouraging due to limitations ranging from the number of steps to nonstereospecificity to low yields.[11] The pathway to (−)-**7** reported by Borchardt and co-workers[12] starting from cyclopentenone **8** (shown in Scheme 2) and adapted by Chu's group[13] for preparing their L-like aristeromycin analogues showed promise. We found, however, use of the "hydroxymethylene" cuprate, as the source of the C-5′ side chain of **7** in the Borchardt/Chu approach, to be inconvenient and often leading to irreproducible yields. Furthermore, in this latter process, the reagent necessary for the ultimate removal of the hydroxymethylene *tert*-butyl protecting group also led to deprotection of the 2′,3′-hydroxyls, which was undesirable in our plan for achieving **4**. All of these difficulties

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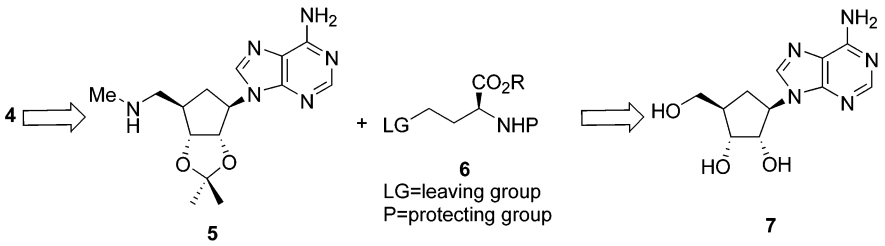
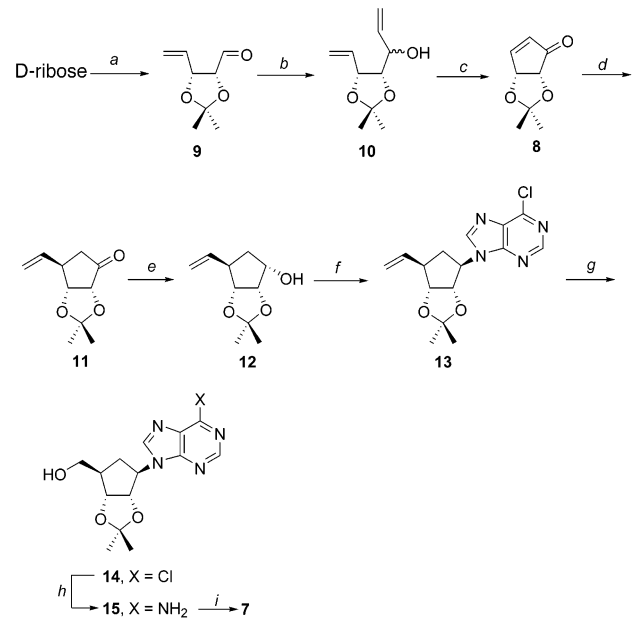
SCHEME 1

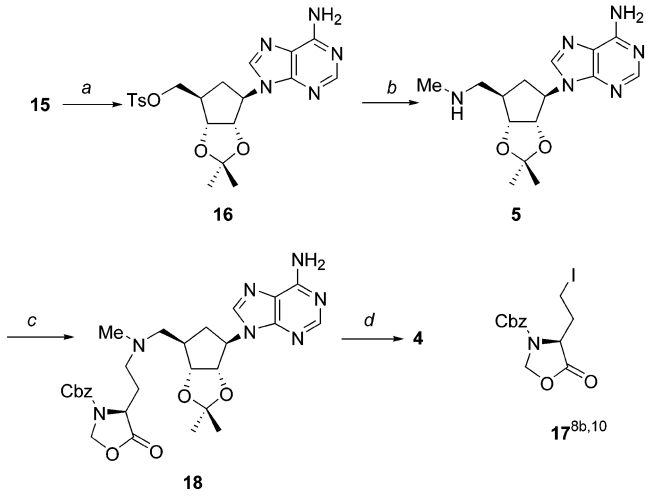


SCHEME 2[a]



[a] Reaction conditions: (a)[14a,19] (i) $(MeO)_2CMe_2$, MeOH; (ii) Ph_3P, I_2, imidazole; (iii) Zn, MeOH, 68%, three steps from ribose. (b) Vinylmagnesium bromide, CH_2Cl_2, 80% (procedure adapted from ref 14d). (c)[20] (i) Gurbbs catalyst, CH_2Cl_2; (ii) PCC, CH_2Cl_2, 90%, two steps from **10**. (d) Vinylmagnesium bromide, TMSCl, HMPA, CuBr·Me_2S, 80%. (e) $LiAlH_4$, THF, 98%. (f) 6-Chloropurine, DIAD, Ph_3P, THF. (g) (i) $NaIO_4$, OsO_4, MeOH/H_2O; (ii) $NaBH_4$, MeOH, 48%, three steps from **12**. (h) NH_3/MeOH, 91%. (i) HCl/MeOH, 95%.

SCHEME 3[a]



[a] Reaction conditions: (a) TsCl, pyridine; (b) $MeNH_2$, 75%, two steps. (c) **17**, DIPEA, MeCN/DMF. (d) BF_3·OEt_2, EtSH, CH_2Cl_2, 65%, two steps.

prompted us to seek an alternative, yet practical, synthesis of (−)-7 from 8. In this direction, a hybrid of the procedures reported (i) for achieving 8 from the inexpensive D-(−)-ribose with the requisite 2′,3′-dihydroxyl stereochemistry and (ii) for incorporating a ring closure metathesis (RCM) step was developed.[14] This is summarized by steps a−c in Scheme 2.

With 8 easily in hand, attention was turned to (−)-7 (Scheme 2) where the vinyl moiety was chosen as the source of its C-5′ hydroxymethylene. The incorporation of a vinyl group onto a cyclopentyl ring by 1,4-enone addition is known to be a high-yielding reaction,[15] but surprisingly to us, it has never been reported as a mask of the hydroxylmethyl group of carbocyclic nucleosides, particularly because the reagents leading to the same are commercially available and very inexpensive. Thus, employing a modified procedure[16] for the 1,4-addition of vinylmagnesium bromide to 8, the ketone **11** was cleanly afforded in 80% yield. Reduction of **11** with lithium aluminum hydride smoothly yielded alcohol **12** as the only isomer in 98% yield (reduction of **11** with sodium borohydride/cerium (III) chloride afforded a 4:1 product mixture containing **12** and its ostensibly alcoholic epimer). Mitsunobu reaction of **12** with 6-chloropurine gave the coupled product **13**, which was inseparable from an azadicarboxylate byproduct and used as same in the next step. Transformation of the ethylene of **13** to the hydroxymethyl group was accomplished in a two-step sequence: (i) oxidative cleavage of the double bond with osmium tetroxide/sodium periodate followed by (ii) sodium borohydride reduction to provide **14** in 47% yield (from **12**). Ammonolysis of **14** (to **15**) with subsequent hydrolysis proceeded smoothly to furnish (−)-aristeromycin (7) in 32% overall yield from 8.

With the completion of this synthesis of 7, consideration was given to its elaboration to **4**. The most immediate precursor to 7 (that is, **15**) offered the most likely candidate. In that regard, tosylation of **15** (Scheme 3) afforded **16** whose tosylate was displaced by methylamine to provide 5. Coupling of 5 with the *S*-glutamic acid

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derivative **17**[8b,10] in acetonitrile and *N*,*N*-dimethylformamide in the presence of diisopropylethylamine gave **18**. Attempts to purify this product by column chromatography resulted in a low yield due to its instability on silca gel. However, the NMR spectrum of the reaction mixture indicated a high-yield formation of **18**. Subjecting the reaction mixture directly, without purification, to boron trifluoride etherate and ethyl mercaptan in methylene chloride provided the desired compound **4**.

In conclusion, a practical synthesis of (−)-aristeromycin (**7**) has been developed. This served as the basis for the synthesis of a carbocyclic analogue of AdoazaMet, (that is, **4**). In achieving **4**, we synthesized cyclopentenone **8**, a well-established, useful chiral building block to carbocyclic nucleosides, from D-ribose by modifying several literature procedures. In view of the intensive interest in carbocyclic nucleosides[17] and the potent biological activity of (−)-aristeromycin,[18] the strategy described herein also offers an efficient synthesis of analogues of (−)-aristeromycin and carbocyclic AdoMet and AdoazaMet. The biological properties of **4** will be reported in due course.

Experimental Section

(4*R*,5*R*)-2,2-Dimethyl-5-vinyl-[1,3]dioxolane-4-carbaldehyde (9). Compound **9** was prepared from D-ribose according to refs 14a and 19 with a yield of 68% in three steps: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.55 (d, J = 3.0 Hz, 1H), 5.76 (m, 1H), 5.47 (dm, J = 15.8 Hz, 1H), 5.33 (dm, J = 12.8 Hz, 1H), 4.85 (t, J = 7.0 Hz, 1H), 4.22 (dd, J = 7.5, 3.0 Hz, 1H), 1.62 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 200.7, 131.4, 119.7, 111.3, 82.3, 79.1, 27.4, 25.4.

(4*S*,5*R*)-1-(2,2-Dimethyl-5-vinyl-[1,3]dioxolan-4-yl))-prop-2-en-1-ol (10). To a solution of **9** (8.50 g, 54.5 mmol) in anhydrous CH_2Cl_2 (150 mL) was added dropwise a solution of vinylmagnesium bromide (1 M in THF, 65 mL) at −40 °C. The reaction was allowed to warm to 0 °C over 1 h and then stirred at this temperature for 2 h. Saturated NH_4Cl (20 mL) was added to quench the reaction. The organic layer was separated, washed with brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (EtOAc/hexanes = 1:5) to afford **10**[14d] as a mixture of two isomers with the ratio of 4.5:1 (colorless oil, 8.03 g, 80%). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (m, 1H), 5.84 (m, 1H), 5.40−5.21 (m, 4H), 4.59 (t, J = 7.6 Hz, 1H), 4.13−4.10 (m, 1H), 4.09 (dd, J = 12.1, 5.7 Hz, 1H), 2.54 (m, 1H, OH), 1.53 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 134.2, 119.2, 117.0, 108.8, 80.7, 78.9, 70.6, 27.5, 25.1

(3a*R*,6a*R*)-2,2-Dimethyl-3a,6a-dihydrocyclopenta[1,3]-dioxol-4-one ((4*R*,5*R*)-4,5-*O*-Isopropylidene-2-cyclopentenone) (8). The cyclopentenone **8** was prepared from **10** according to ref 20 with a yield of 90% in two steps: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.59 (dd, J = 6.0, 2.3 Hz, 1H), 6.19 (d, J = 6.0 Hz, 1H), 5.25 (dd, J = 5.4, 2.3 Hz, 1H), 4.44 (d, J = 5.4 Hz, 1H), 1.39 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 203.2, 159.8, 134.4, 115.6, 78.7, 76.6, 27.5, 26.3

(3a*R*,6*R*,6a*R*)-2,2-Dimethyl-6-vinyltetrahydrocyclopenta-[1,3]dioxol-4-one (11). To a suspension of CuBr·Me_2S (0.35 g, 1.7 mmol) in THF (80 mL) at −78 °C was added dropwise vinylmagnesium bromide (25 mL, 25 mmol). The mixture was stirred for 10 min before a solution of **8** (3.08 g, 20 mmol), TMSCl (5.2 mL, 40.6 mmol), and HMPA (9 mL, 51.4 mmol) in THF (20 mL) was added in dropwise. After the reaction mixture was stirred at −78 °C for 3 h and warmed to 0 °C, saturated NH_4Cl (20 mL) was added and the resulting mixture stirred for 30 min. To this was added EtOAc (300 mL). The organic layer was separated, washed with H_2O (2 × 30 mL) and brine (40 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (EtOAc/hexanes = 1:3) to give **11** (reported as a racemate in ref 15) as a colorless liquid (2.91 g, 80%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.85 (ddd, J = 17.3, 10.6, 6.4 Hz, 1H), 5.17−5.07 (m, 2H), 4.65 (d, J = 5.3 Hz, 1H), 4.21 (d, J = 5.3 Hz, 1H), 3.11 (m, 1H), 2.85 (dd, J = 19.4, 8.6 Hz, 1H), 2.28 (dm, J = 19.4 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 213.1, 137.2, 116.4, 112.4, 81.4, 77.9, 39.8, 38.6, 26.9, 25.0.

(3a*S*,4*S*,6*R*,6a*R*)-2,2-Dimethyl-6-vinyltetrahydrocyclopenta[1,3]dioxol-4-ol (12). To a suspension of $LiAlH_4$ (1 g, 25.6 mmol) in dry THF (50 mL) at 0 °C was added dropwise a solution of **11** (2.7 g, 14.8 mmol) in THF (15 mL). The reaction mixture was then stirred at room temperature for 3 h before it was quenched sequentially with H_2O (1 mL), aqueous NaOH (15%, 1 mL), and H_2O (3 mL). The resulting solid was removed by filtration and the filtrate evaporated in vacuo to afford sufficiently pure **12** as a colorless liquid (2.68 g, 98%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.75 (ddd, J = 17.3, 10.6, 6.4 Hz, 1H), 5.08 (m, 2H), 4.48 (m, 1H), 4.06 (m, 1H), 2.75 (m, 1H), 2.48 (br, 1H), 1.90 (m, 2H), 1.52 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 138.2, 115.5, 111.8, 84.5, 79.2, 71.3, 44.5, 36.2, 26.3, 24.5. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.95; H, 8.77.

(3a*S*,4*R*,6*R*,6a*R*)-[6-(6-Chloropurin-9-yl)-2,2-dimethyltetrahydrocyclo-penta[1,3]dioxol-4-yl]methanol (14). A solution of DIAD (5.65 mL, 27.3 mmol) was added dropwise to a suspension of 6-chloropurine (3 g, 19.2 mmol), Ph_3P (7.14 g, 27.3 mmol), and **12** (2.50 g, 13.6 mmol) in dry THF (80 mL) at 0 °C. The mixture was stirred at the same temperature for 30 min and allowed to warm to room temperature. After the reaction was stirred at room temperature for 12 h, it was brought to 50 °C and stirred for another 8 h. The solvent was removed under the reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexanes = 1:3) to afford **13** contaminated with the azadicarboxylate byproduct.

The above mixture was dissolved in MeOH (35 mL) and H_2O (18 mL), and $NaIO_4$ (4.33 g, 20.2 mmol) was added. After the mixture was cooled to 0 °C, OsO_4 (30 mg) was added. The reaction was stirred at the same temperature for 1 h and then at room temperature for 2 h. The white solid that resulted was removed by filtration and the filtrate removed at ambient temperature. Methylene chloride (200 mL) was added to the residue and the organic solution washed with H_2O (30 mL) and brine (30 mL) and dried ($MgSO_4$).

The CH_2Cl_2 was removed under reduced pressure at ambient temperature and the residue dissolved in MeOH (40 mL). This solution was cooled to 0 °C, and $NaBH_4$ (1.2 g, 30.8 mmol) was added portionwise. After the reaction was stirred at the same temperature for 1 h, the solvent was removed and CH_2Cl_2 (150 mL) and water (30 mL) were added. The organic layer was separated and washed with brine and dried ($MgSO_4$). After removing the solvent under reduced pressure, the product was purified by a short silica gel column chromatography (beginning with EtOAc/hexanes = 1:2 and then just EtOAc) to give **14** as a white solid[21] (2.09 g, 48% from **12**): mp 169−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.26 (s, 1H), 5.03 (dd, J = 6.5, 6.0 Hz, 1H), 4.88 (m, 1H), 4.75 (dd, J = 6.9, 3.9 Hz, 1H), 3.87 (dq, J = 21.5, 10.6, 4.3 Hz, 2H), 2.57 (br, 1H), 2.54 (m, 3H), 1.60 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 151.6, 151.3, 144.6, 132.3, 113.9, 84.0, 81.8, 63.5, 63.0, 45.4, 33.0, 27.6, 25.1

(3a*S*,4*R*,6*R*,6a*R*)-[6-(6-Aminopurin-9-yl)-2,2-dimethyltetrahydrocyclo-penta[1,3]dioxol-4-yl]methanol (15). A solu-

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tion of **14** (2 g, 6.12 mmol) in MeOH (150 mL) was saturated with NH_3 at 0 °C and heated at 100 °C for 24 h in a Parr stainless steel, sealed reaction vessel. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/methanol = 5:1) to afford **15** as a white solid (1.72 g, 91%): mp 205−206 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.26 (s, 1H), 8.13 (s, 1H), 7.24 (s, 2H), 5.00 (t, J = 6.7 Hz, 1H), 4.79 (m, 2H), 4.55 (m, 1H), 3.50 (bs, 2H), 2.23 (m, 3H), 1.47 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 156.1, 152.3, 149.4, 139.8, 119.2, 112.5, 83.0, 80.7, 62.0, 60.5, 45.4, 33.7, 27.5, 25.1. Anal. Calcd for $C_{14}H_{19}N_5O_3$: C, 55.07; H, 6.27; N, 22.94. Found: C, 55.31; H, 6.31; N, 22.84.

(−)-(1*R*,2*S*,3*R*,5*R*)-3-(6-Aminopurin-9-yl)-5-hydroxymethylcyclopentane-1,2-diol ((−)-Aristeromycin) (7). Compound **15** (400 mg, 1.31 mmol) was dissolved in a mixture of 1 N HCl (10 ML) and MeOH (10 mL). This reaction mixture was stirred at room temperature for 3 h and neuturalized with basic ion-exchange resin (Amberlite IRA-67). Filtration and evaporation of this mixture afforded **7** as a white solid (330 mg, 95%), whose spectroscopic data was consistent with that reported.[11a]

(3′a*S*,4′*R*,6′*R*,6a′*R*)-9-(2′,2′-Dimethyl-6′-methylaminomethyltetrahydro-cyclopenta[1′,3′]dioxol-4′-yl)-9*H*-purin-6-ylamine (5). Compound **15** (1.6 g, 5.25 mmol) was dissolved in anhydrous pyridine (24 mL). This solution was cooled to −20 °C, and *p*-toluenesulfonyl chloride (1.12 g, 5.92 mmol) was added. The reaction flask was moved to a freezer ($t \approx -20$ °C) and kept there for 3 days. The resultant mixture was diluted with CH_2Cl_2 (300 mL) and the organic solution washed with cold H_2SO_4 (2 M, 3 × 25 mL) and brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded a white foam (assumed to be **16**), which was used in the next step without further purification.

The above obtained white foam was dissolved in methylamine (∼20 mL) in a Parr stainless steel, sealed reaction vessel and set aside for 60 h. The reaction vessel was opened after it was cooled to 0 °C, and the excess methylamine allowed to evaporate. The residue was purified by silica gel column chromatography (EtOAc/MeOH/NH_4OH = 10:1:1) to afford **5** as a white solid (1.25 g, 75% from **15**): mp 179−181 °C; $[\alpha]^{25.4}_D$ − 15.882° (*c* 0.255, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.88 (s, 1H), 6.62 (s, 2H), 5.10 (dd, J = 7.1, 5.6 Hz, 1H), 4.76 (m, 1H), 4.61 (m, 1H), 2.79 (m, 2H), 2.50 (s, 3H), 2.39 (m, 3H), 2.08 (br, 1H), 1.57 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.1, 152.8, 150.0, 139.8, 120.5, 113.9, 83.7, 83.4, 62.0, 54.9, 44.2, 36.8, 35.2, 27.6, 25.2. Anal. Calcd for $C_{15}H_{22}N_6O_2 \cdot 0.2\ H_2O$: C, 55.91; H, 6.95; N, 26.09. Found: C, 55.72; H, 6.94, N, 25.73.

(1′*R*,2*R*,2′*R*,3′*S*,4′*R*)-2-Amino-4-{[4′-(6-aminopurin-9-yl)-2′,3′-dihydroxycyclo-pent-1′-ylmethyl]methylamino}butyric Acid (Carba-AdoazaMet) (4). To a solution of **5** (0.48 g, 1.5 mmol), diisopropylethylamine (0.30 mL, 1.71 mmol) in MeCN (35 mL), and DMF (10 mL) was added a solution of **17**[8b,10] (0.58 g, 1.55 mmol) in MeCN (10 mL). This reaction mixture was brought to 60 °C and kept at this temperature for 36 h. Removal of the solvent under vacuum afforded a sticky residue whose NMR spectra indicated a high-yield formation of **18**, which was used without further purification since attempts at its silica gel chromatographic purification led to product decomposition.

A solution of the above residue in CH_2Cl_2 (10 mL) was added to a stirred mixture of $BF_3 \cdot OEt_2$ (3.2 mL, 25.8 mmol) and EtSH (6 mL, 77.5 mmol) at 0 °C. This reaction mixture was allowed to warm to room temperature and stirred at this temperature for 24 h. The solvent was removed, and the residue was first purified with ion-exchange resin (eluted first with H_2O (300 mL), and then 0.6 M ammonium bicarbonate) followed by column chromatography (silica gel 230−400 mesh, CH_2Cl_2/MeOH/NH_4OH = 2:1:1) to yield **4** as white solid (372 mg, 65%): mp >160 °C (dec); $[\alpha]^{25.3}_D$ −7.647° (*c* 0.238, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 7.98 (s, 1H), 7.81 (s, 1H), 4.56 (m, 1H), 4.31 (m, 1H), 3.87 (bs, 1H), 3.64 (bs, 1H), 2.71−2.60 (m, 4H), 2.31 (s, 3H), 2.26 (m, 2H), 2.01 (m, 1H), 1.90 (m, 1H), 1.57 (q, J = 11.0 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 175.8, 155.2, 152.2, 149.0, 140.8, 118.6, 74.9, 73.4, 60.8, 59.8, 54.6, 54.5, 40.9, 40.3, 31.3, 26.8. Anal. Calcd for $C_{16}H_{25}N_7O_4 \cdot 1.5\ H_2O$: C, 47.28; H, 6.94; N, 24.12. Found: C, 47.55; H, 6.92; N, 23.81.

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