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Synthesis of enantiomeric 9-(2′,3′,4′-trihydroxybutyl)adenine derivatives from L-ascorbic and D-isoascorbic acids

Andrzej E. Wróblewski* and Wiesława Karolczak

Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Institute of Chemistry, Medical University of Łódź, 90-151 Łódź, Muszyñskiego 1, Poland

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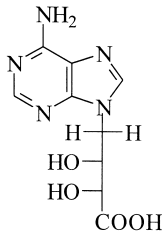
Abstract—L-Ascorbic and D-isoascorbic acids were employed in syntheses of 9-(2′,3′,4′-trihydroxybutyl)adenines protected at 3′ and 4′ oxygens (all four enantiomers) and at 2′ oxygen (2′*S*,3′*R* and 2′*S*,3′*S* enantiomers).

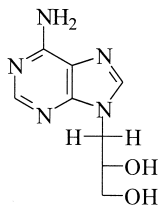
1. Introduction

Several purine acyclonucleosides have been known for their antiviral activity.[1] A natural product, 4-(6-amino-9*H*-purin-9-yl)-4-deoxy-D-erythronic acid (D-eritadenine) **1**, showed a marked hypocholesterolemic effect[2,3] and is extremely potent inhibitor of *S*-adenosyl-L-homocysteine hydrolase.[4] Discovery of antiviral activity of (2′*S*)-9-(2′,3′-dihydroxypropyl)adenine **2**[5] has prompted studies on the synthesis of other N(9)-substituted adenines and guanines possessing polyhydroxyalkyl chains. Among them, the stereoisomers of 9-(2′,3′,4′-trihydroxybutyl)adenine **3** have attracted a great deal of attention from both synthetic[6–11] and biological activity[12–14] points of views.

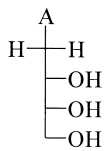
For the synthesis of the enantiomers of **3** several strategies have been developed. Initially, the terminal hydroxy group of a tetritol derivative was transformed into the amino group, which was next incorporated as N(9) of the adenine ring.[2,3,6] Reduction of esters of (2*R*,3*R*) and (2*S*,3*S*)-**1** afforded (2′*R*,3′*S*)[8] and (2′*S*,3′*R*)-**3**,[2,3,8,9] respectively. Alkylation of adenine with four-carbon chirons has also been successfully explored in synthesis of (2′*R*,3′*R*) and (2′*S*,3′*S*)-**3**, i.e. enantiomers having *threo* configuration. To this end, suitably protected 4-*O*-tosyl-D(or L)-threitols were obtained in multi-step procedures from D-(or L)-arabinitol,[7] D-mannitol[7] or diethyl L-tartrate.[8] Five and six-carbon chirons prepared from D-xylose, L-arabinose and D-mannose were also applied in synthesis of N(9) alkylated adenines.[7]



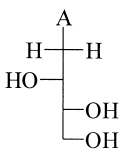
(2*R*,3*R*)-**1**



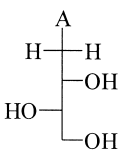
(2′*S*)-**2**



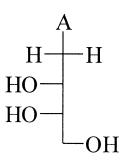
(2′*S*,3′*R*)-**3**



(2′*R*,3′*R*)-**3**



(2′*S*,3′*S*)-**3**



A = 9-adenyl

(2′*R*,3′*S*)-**3**

Keywords: purine acyclonucleosides; alkylation of adenine; stereoisomers.
* Corresponding author. Fax: +48-42-678-8398; e-mail: aewplld@ich.pharm.am.lodz.pl

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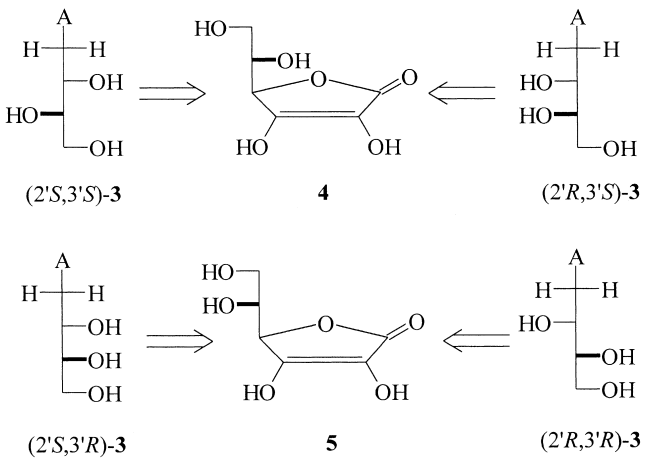
However, a two-step degradation sequence ($NaIO_4$ diol oxidation and $NaBH_4$ reduction) was required to shorten the alkyl chain. Finally DIBAL-H reduction of 2′,3′-*O*-isopropylidene adenosine[15] followed by degradation seems to be a method of choice for the synthesis of (2′*S*,3′*R*)-**3**.[9–11] When the intermediate aldehyde from the degradation step was subjected to a base-catalysed epimerisation, (2′*S*,3′*S*)-**3** was obtained.[11]

In this paper, we would like to present a new synthetic strategy for the synthesis of all of the suitably protected enantiomers of **3** based on alkylation of adenine with four-carbon chirons prepared from L-ascorbic **4** and D-isoascorbic acids **5**.

2. Results and discussion

In order to secure the *S* configuration at C(3′) of **3**, L-ascorbic acid **4** was employed as a starting material. Preserving the configurations at C(4) and C(5) of **4** would lead to (2′*S*,3′*S*)-**3**, while one inversion of configuration is required to obtain (2′*R*,3′*S*)-**3**. Similar approach was envisioned for the synthesis of (2′*S*,3′*R*)-**3** and (2′*R*,3′*S*)-**3** starting from D-isoascorbic acid **5** (Scheme 1).



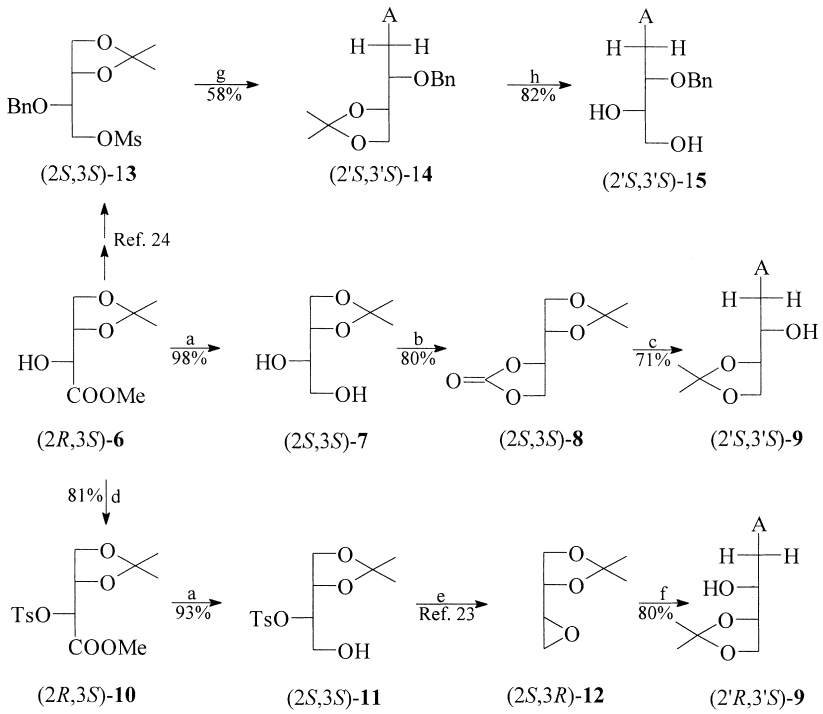
Scheme 1. Retrosynthesis of enantiomers of **3**.

For the alkylation of adenine three different pathways were applied: nucleophilic displacement of terminal mesylates[7,8] and openings of terminal epoxides[16] or carbonates[17] (Schemes 2–4).

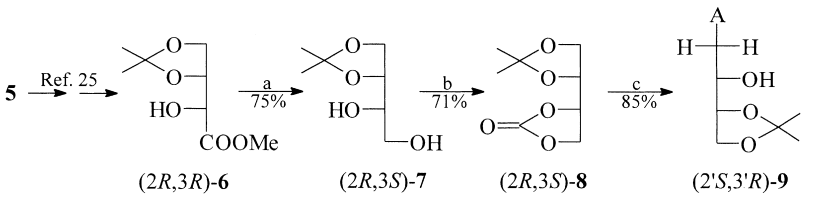
L-Ascorbic acid **4** was transformed into the protected α-hydroxyester (2*R*,3*S*)-**6** in 78% yield according to the literature procedure.[18] Reduction of (2*R*,3*S*)-**6** with a sodium borohydride–lithium chloride mixture[19] led quantitatively to the known diol (2*S*,3*S*)-**7**.[20,21] In the presence of carbonyldiimidazole[22] the crystalline cyclic carbonate (2*S*,3*S*)-**8** was formed from the diol in 80% yield. Alkylation of adenine with (2*S*,3*S*)-**8** in DMF at 120° for the 38 h led to (2′*S*,3′*S*)-**9** in 71% yield.

When the known epoxide (2*S*,3*R*)-**12**[20,23] was subjected to the reaction with adenine in the presence of cesium carbonate at 120°C for 68 h, (2′*R*,3′*S*)-**9** was obtained in 80% yield. For the synthesis of 2′-*O*-benzyl derivative (2′*S*,3′*S*)-**15** the recently reported[24] mesylate **13** was used as a starting material. Thus, alkylation of adenine with **13** in DMF at 140°C for 20 h in the presence of cesium carbonate afforded (2′*S*,3′*S*)-**14** in 58% yield. Standard deprotection of (2′*S*,3′*S*)-**14** led to crystalline (2′*S*,3′*S*)-**15** as a tetrahydrate.

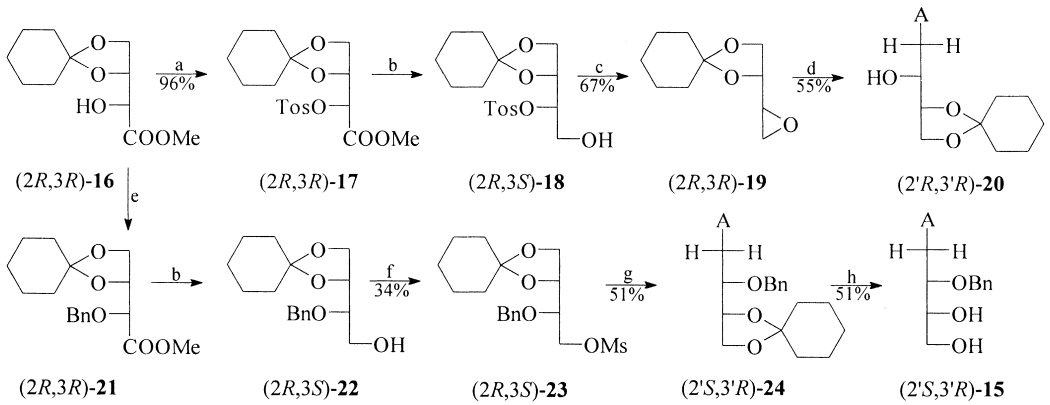
Starting from D-isoascorbic acid **5** the hydroxyester (2*R*,3*R*)-**6** was prepared in 55% overall yield.[25] Sodium borohydride–lithium chloride reduction[19] of (2*R*,3*R*)-**6** led to the diol (2*R*,3*S*)-**7**,[26,27] which was transformed into the



Scheme 2. *Reagents and conditions*: (a) $NaBH_4$–LiCl, THF–EtOH, 20°C, 16 h; (b) Im_2CO, CH_2Cl_2, 20°C, 16 h; (c) adenine, NaOH, DMF, 120°C, 38 h; (d) TsCl, pyridine, 0°C, 16 h; (e) K_2CO_3, methanol; (f) adenine, Cs_2CO_3, DMF, 120°C, 46 h; (g) adenine, DMF, 140°C, 20 h; (h) HCl, dioxane, 20°C, 24 h.



Scheme 3. *Reagents and conditions*: (a) $NaBH_4$–LiCl, THF–EtOH, 20°C, 16 h; (b) Im_2CO, CH_2Cl_2, 20°C, 16 h; (c) adenine, NaOH, DMF, 120°C, 38 h.



Scheme 4. *Reagents and conditions*: (a) TsCl, pyridine, 0°C, 16 h; (b) $NaBH_4$–LiCl, THF–EtOH, 20°C, 16 h; (c) K_2CO_3–methanol, 20°C, 30 h; (d) adenine, Cs_2CO_3, 120°C, 46 h; (e) BnBr, Ag_2O, 20°C, 23 h; (f) MsCl, pyridine, 20°C, 23 h; (g) adenine, Cs_2CO_3, DMF, 140°C, 20 h; (h) HCl, dioxane, 20°C, 24 h.

cyclic carbonate (2*R*,3*S*)-**8** (Scheme 3). Alkylation of adenine with the carbonate was accomplished in the same way as described for (2′*S*,3′*S*)-**9** providing the epimeric (2′*S*,3′*R*)-**9** in 85% yield.

Methyl (2*R*,3*R*)-3,4-*O*-cyclohexylidene-1-hydroxybutanoate (2*R*,3*R*)-**16**[25] was used as a key intermediate in the synthesis of (2′*R*,3′*R*)-**20** and (2′*S*,3′*R*)-**15** (Scheme 4). Under standard conditions the hydroxyester was transformed into the tosylate (2*R*,3*R*)-**17**. The ester group in (2*R*,3*R*)-**17** was reduced with a sodium borohydride–lithium chloride mixture[19] to give the hydroxytosylate (2*R*,3*S*)-**18**, which was treated with potassium carbonate in methanol to produce the epoxide (2*R*,3*R*)-**19**. Alkylation of adenine with the epoxide led to (2′*R*,3′*R*)-**20** in 55% yield.

To synthesise (2′*S*,3′*R*)-**15** the hydroxy group in (2*R*,3*R*)-**16** was benzylated, the ester function in (2*R*,3*R*)-**21** was reduced with a sodium borohydride–lithium chloride mixture[19] and the hydroxymethyl group in (2*R*,3*S*)-**22** was subjected to mesylation. The mesylate (2*R*,3*S*)-**23** was reacted with adenine in the presence of cesium carbonate at 140°C to give (2′*S*,3′*R*)-**24** in 51% yield. Hydrolysis of the cyclohexylidene group led to amorphous (2′*S*,3′*R*)-**15** as the tetrahydrate.

3. Conclusions

The elaborated strategies incorporate several synthetic shortcuts and improvements over existing procedures. A sodium borohydride–lithium chloride mixture was used instead of lithium aluminum hydride[21,28] to efficiently reduce α-hydroxyesters to terminal diols with a non-aqueous workup. Transformation of terminal diols into carbonates results simultaneously in activation of C(1) for nucleophilic substitution and protection of C(2) hydroxyls and leads to retention of configuration at C(2). As an alternative to aluminum hydride[23] the same reducing mixture ($NaBH_4$–LiCl) was found effective in reduction of esters in the presence of a tosyl group, thus allowing conversion of an α-hydroxyester subunit into a terminal epoxide with inversion of configuration in three steps. Due to poor nucleophilicity of adenine its alkylation was performed as the last step of the reaction sequence.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were taken in $CDCl_3$ on the Varian Mercury-300 spectrometer at 300 and 75.5 MHz, respectively. IR spectral data were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analysis were performed by the Microanalytical Laboratory of this Faculty on a Perkin–Elmer PE 2400 CHNS analyzer. Polarimetric measurements were conducted on a Perkin–Elmer 241 MC apparatus.

The following adsorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets silica gel 60 F_{254}. TLC plates were developed in various chloroform: methanol solvent systems. Visualisation of spots was effected with iodine vapours.

4.1.1. (2*S*,3*S*)-1,2-*O*-Isopropylidenebutane-1,2,3,4-tetrol, (2*S*,3*S*)-7. A solution of (2*R*,3*S*)-**6**[18] (0.513 g, 2.70 mmol) in THF–ethanol (1:2, 12 mL) containing anhydrous LiCl (0.34 g, 8.1 mmol) was cooled to 0°C and, while stirred,

$NaBH_4$ (0.30 g, 8.1 mmol) was added portionwise. The reaction mixture was stirred overnight at room temperature and quenched with acetone (1.5 mL). After 30 min the suspension was diluted with chloroform (50 mL), anhydrous $MgSO_4$ (3 g) was added and filtered through a layer of Celite 535. The clear solution was evaporated to leave pure (2*S*,3*S*)-**7** (0.430 g, 98%) as a colourless oil. $[\alpha]_D^{20}=+5.2$ (c=2.0, methanol). IR (film): ν=3399 (br), 2988, 2927, 1372, 1155 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.37 and 1.45 (6H, 2s), 2.44 (2H, brs), 3.61–3.73 (3H, m), 3.86 (1H, dAB, J_{AB}=8.1 Hz, J=6.6 Hz), 4.05 (1H, dAB, J_{AB}=8.1 Hz, J=6.6 Hz), 4.15–4.21 (1H, m). ^{13}C NMR ($CDCl_3$): δ=25.56, 26.72, 64.09, 65.99, 72.30, 76.73, 109.68. Anal. calcd for $C_7H_{14}O_4$ (162.18): C, 51.83; H, 8.70. Found: C, 51.66; H, 9.01.

4.1.2. (2*R*,3*S*)-1,2-*O*-Isopropylidenebutane-1,2,3,4-tetrol, (2*R*,3*S*)-7. In a similar manner as described for (2*S*,3*S*)-**7**, from (2*R*,3*R*)-**6**[25] (0.62 g, 3.2 mmol), pure (2*R*,3*S*)-**7** (0.397 g, 75%) was obtained as a colourless oil. $[\alpha]_D^{20}=+7.4$ (c=3.5, methanol). IR (film): ν=3381, 2984, 2879, 1372, 1067 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.36 and 1.43 (6H, 2s), 2.12 (1H, t, J=5.8 Hz), 2.49 (1H, d, J=4.7 Hz), 3.60–3.70 (1H, m), 3.70–3.85 (2H, m), 3.91–4.00 (1H, m), 4.04–4.13 (2H, m). ^{13}C NMR ($CDCl_3$): δ=25.36, 26.85, 63.84, 66.58, 72.63, 76.22, 109.51. Anal. calcd for $C_7H_{14}O_4$ (162.18): C, 51.83; H, 8.70. Found: C, 51.59; H, 8.74.

4.1.3. (2*S*,3*S*)-1,2-*O*-Isopropylidenebutane-1,2,3,4-tetrol 3,4-cyclic carbonate, (2*S*,3*S*)-8. To a solution of (2*S*,3*S*)-**7** (0.43 g, 2.6 mmol) in CH_2Cl_2 (8 mL) freshly calcinated molecular sieves A4 (2 g) were added and the suspension was stirred at room temperature for 30 min. Carbonyldiimidazole (0.45 g, 2.8 mmol) was then added portionwise and the reaction mixture was stirred overnight. Sieves were filtered off, and the residue was partitioned between CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$ and concentrated. The crude product was recrystallised from chloroform: hexanes to give the cyclic carbonate (2*S*,3*S*)-**8** (0.40 g, 80%) as colourless needles. Mp 134.5–135°C. $[\alpha]_D^{20}=+29.9$ (c=1.3, methanol). IR (KBr): ν=2990, 2935, 2904, 1786, 1160, 1073, 1052 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.37 and 1.44 (6H, 2s), 3.99 (1H, dAB, J_{AB}=8.7 Hz, J=6.3 Hz), 4.14 (1H, dAB, J_{AB}=8.7 Hz, J=6.6 Hz), 4.26 (1H, ddd, J=6.6, 6.3, 2.4 Hz), 4.48 (1H, dAB, J_{AB}=8.4 Hz, J=6.0 Hz), 4.51 (1H, dAB, J_{AB}=8.4 Hz, J=8.1 Hz), 4.72 (1H, ddd, J=8.1, 6.0, 2.4 Hz). ^{13}C NMR ($CDCl_3$): δ=25.40, 26.04, 64.95, 66.42, 74.78, 75.17, 110.62, 153.83. Anal. calcd for $C_8H_{12}O_5$ (188.18): C, 51.06; H, 6.42. Found: C, 51.00; H, 6.48.

4.1.4. (2*R*,3*S*)-1,2-*O*-Isopropylidenebutane-1,2,3,4-tetrol 3,4-cyclic carbonate, (2*R*,3*S*)-8. In a similar way as described for (2*S*,3*S*)-**8**, from (2*R*,3*S*)-**7** (0.54 g, 3.4 mmol) and carbonyldiimidazole (0.60 g, 3.7 mmol), the cyclic carbonate (2*R*,3*S*)-**8** (0.444 g, 71%) was obtained as a colourless very viscous oil. $[\alpha]_D^{20}=-11.9$ (c=1.8, methanol). IR (film): ν=2990, 2935, 2891, 1787, 1161, 1074, 1053 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.36 and 1.43 (6H, 2s), 3.92 (1H, dAB, J_{AB}=9.0 Hz, J=3.6 Hz,), 4.16 (1H, dAB, J_{AB}=9.0 Hz, J=6.3 Hz), 4.20–4.28 (1H, m), 4.40–4.59 (3H, m). ^{13}C NMR ($CDCl_3$): δ=24.85, 26.72, 66.20, 66.80, 74.98, 75.96, 110.55, 154.55. Anal. calcd for $C_8H_{12}O_5$ (188.18): C, 51.06; H, 6.42. Found: C, 51.35; H, 6.46.

4.1.5. (2′*S*,3′*S*)-9-(3′,4′-*O*-Isopropylidene-2′,3′,4′-trihydroxybutyl)adenine, (2′*S*,3′*S*)-9. To a solution of (2*S*,3*S*)-**8** (0.475 g, 2.53 mmol) in DMF (5 mL), adenine (0.31 g, 2.3 mmol) was added followed by solid NaOH (15 mg, 0.38 mmol). The reaction mixture was kept at 120°C for 38 h. The solvent was removed in vacuo, and the residue was coevaporated with toluene (3×15 mL). The crude product was extracted with methanol (10 mL), the solution was concentrated and subjected to chromatography on a silica gel column with chloroform–methanol (4:1, v/v). Appropriate fractions were collected to give (2′*S*,3′*S*)-**9** (0.454 g, 71%) as a white powder, which was recrystallised from methanol–petroleum ether (colourless plates). Mp 180–181°C. $[\alpha]_D^{20}=-40.8$ (c=1.0, methanol). IR (KBr): ν=3215, 3167, 2978, 2471, 1706, 1658, 1569, 1371, 1065, 862 cm^{-1}. ^1H NMR (CD_3OD): δ=1.35 and 1.44 (6H, 2s), 3.94 (1H, dAB, J_{AB}=7.8 Hz, J=6.6 Hz), 3.96 (1H, ddd, J=9.3, 3.6, 3.3 Hz), 4.08 (1H, dAB, J_{AB}=7.8 Hz, J=6.9 Hz), 4.15 (1H, ddd, J=6.9, 6.6, 3.6 Hz), 4.24 (1H, dAB, J_{AB}=14.1 Hz, J=9.3 Hz), 4.38 (1H, dAB, J_{AB}=14.1 Hz, J=3.3 Hz), 8.11 (1H, s), 8.20 (1H, s). ^{13}C NMR (CD_3OD): δ=25.64, 26.73, 48.14, 66.51, 70.27, 78.04, 110.79, 119.88, 143.64, 150.68, 153.54, 157.16. Anal. calcd for $C_{12}H_{17}N_5O_3$ (279.29): C, 51.60; H, 6.14; N, 25.08. Found: C, 51.91; H, 5.93; N, 25.06.

4.1.6. (2′*S*,3′*R*)-9-(3′,4′-*O*-Isopropylidene-2′,3′,4′-trihydroxybutyl)adenine, (2′*S*,3′*R*)-9. In a similar way as described for (2′*S*,3′*S*)-**9**, from (2*R*,3*S*)-**8** (0.357 g, 1.90 mmol), and adenine (0.257 g, 1.90 mmol), the adenine derivative (2′*S*,3′*R*)-**9** (0.450 g, 85%) was obtained as a white powder. Mp 194–195°C. $[\alpha]_D^{20}=-20.5$ (c=1.2, methanol). IR (KBr): ν=3473, 3363, 3241, 2986, 2933, 1689, 1638, 1305, 1070 cm^{-1}. ^1H NMR (CD_3OD): δ=1.33 and 1.42 (6H, 2s), 3.81–4.20 (5H, m), 4.54 (1H, dd, J=14.3, 2.9 Hz), 8.11 (1H, s), 8.19 (1H, s). ^{13}C NMR (CD_3OD): δ=25.60, 27.16, 48.37, 67.99, 72.01, 78.39, 111.01, 119.79, 143.69, 150.85, 153.52, 157.07. Anal. calcd for $C_{12}H_{17}N_5O_3$ (279.29): C, 51.60; H, 6.14; N, 25.08. Found: C, 51.53; H, 6.21; N, 24.87.

4.1.7. Methyl (2*R*,3*S*)-3,4-*O*-isopropylidene-2,3,4-trihydroxy-3-*O*-(*p*-toluenesulfonyl)butanoate, (2*R*,3*S*)-10. To a cooled (−5°C) solution of (2*R*,3*S*)-**6** (2.76 g, 14.5 mmol) in dry pyridine (10 mL), tosyl chloride (2.76 g, 14.5 mmol) was added portionwise and the reaction mixture was left at 0°C overnight. The solution was poured into ice–water. The solid was filtered off, thoroughly washed with water and air-dried to give a crude product (4.027 g, 81%), which was recrystallised from chloroform–hexanes (colourless needles). Mp 62–63°C. $[\alpha]_D^{20}=+28.9$ (c=2.7, methanol). IR (KBr): ν=2999, 2937, 1762, 1367, 1178 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.29 and 1.30 (6H, 2s), 2.45 (3H, s), 3.70 (3H, s), 3.74 (1H, dd, J=9.3, 5.1 Hz), 4.03 (1H, dd, J=9.3, 6.3 Hz), 4.57 (1H, ddd, J=9.3, 6.3, 5.1 Hz), 4.83 (1H, d, J=5.1 Hz), 7.35 (2H, d, J=8.7 Hz), 7.84 (2H, d, J=8.7 Hz). ^{13}C NMR ($CDCl_3$): δ=21.98, 25.39, 26.18, 53.05, 65.30, 74.82, 76.96, 110.73, 128.29, 129.83, 132.97, 145.34, 166.93. Anal. calcd for $C_{15}H_{20}O_7S$ (344.31): C, 52.31; H, 5.97. Found: C, 52.43; H, 6.09.

4.1.8. Methyl (2*R*,3*S*)-3,4-*O*-cyclohexylidene-2,3,4-trihydroxy-3-*O*-(*p*-toluenesulfonyl)butanoate, (2*R*,3*R*)-17. In a similar manner as described for (2*R*,3*S*)-**10**, from (2*R*,3*R*)-**16** (0.657 g, 2.81 mmol) and tosyl chloride (0.570 g, 3.00 mmol), (2*R*,3*R*)-**17** (1.05 g, 96%) was obtained as a colourless oil. $[\alpha]_D^{20}=+6.4$ (c=1.6, methanol). IR (film): ν=2936, 2862, 1757, 1371, 1096 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.25–1.42 (2H, m), 1.45–1.57 (8H, m), 2.45 (3H, s), 3.64 (3H, s), 3.93 (1H, dAB, J_{AB}=9.0 Hz, J=4.6 Hz), 4.00 (1H, dAB, J_{AB}=9.0 Hz, J=6.0 Hz), 4.35 (1H, ddd, J=6.1, 6.0, 4.6 Hz), 4.79 (1H, d, J=6.1 Hz), 7.35 (2H, d, J=8.3 Hz), 7.80 (2H, d, J=8.3 Hz). ^{13}C NMR ($CDCl_3$): δ=21.98, 23.92, 24.10, 25.23, 34.78, 36.27, 52.84, 65.39, 74.48, 77.01, 111.37, 128.29, 129.88, 132.79, 145.45, 167.15. Anal. calcd for $C_{18}H_{24}O_7S$ (384.37): C, 56.24; H, 6.29. Found: C, 56.56; H, 6.57.

4.1.9. (2*S*,3*S*)-1,2-*O*-Isopropylidene-3-*O*-(*p*-toluenesulphonyl)butane-1,2,3,4-tetrol, (2*S*,3*S*)-11. A solution of (2*R*,3*S*)-**10** (1.376 g, 4.000 mmol) in THF–EtOH (1:2, 18 mL) containing anhydrous LiCl (0.504 g, 12.0 mmol) was cooled to −5°C and $NaBH_4$ (0.444 g, 12.0 mmol) was added at this temperature portionwise. The reaction mixture was stirred at room temperature overnight, treated with acetone (8 mL) and after 30 min diluted with chloroform. Anhydrous $MgSO_4$ (3 g) was added and the suspension was vigorously stirred for 1 h and filtered through a layer of Celite 535. Solvents were evaporated and the crude product was chromatographed on a silica gel column with chloroform–methanol (50:1) to give (2*S*,3*S*)-**11** (1.165 g, 93%) as a colourless oil. $[\alpha]_D^{20}=+9.9$ (c=1.1, methanol). IR (film): ν=3452, 2993, 2931, 1355, 1178 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.27 and 1.28 (6H, 2s), 2.17 (1H, brs), 2.45 (3H, s), 3.80 and 3.82 (2H, AB part of ABX, J_{AB}=12.9 Hz, J=5.1, 4.3 Hz), 3.88 (1H, dAB, J_{AB}=9.0 Hz, J=5.7 Hz), 4.01 (1H, dAB, J_{AB}=9.0 Hz, J=6.9 Hz), 4.31 (1H, ddd, J=6.9, 5.7, 4.8 Hz), 4.57 (1H, ddd, J=5.1, 4.8, 4.3 Hz), 7.33–7.37 and 7.82–7.86 (4H, m). ^{13}C NMR ($CDCl_3$): δ=21.72, 25.28, 26.09, 62.08, 65.35, 74.49, 81.68, 110.04, 128.08, 129.80, 133.29, 145.10. Anal. calcd for $C_{14}H_{20}O_6S$ (316.30): C, 53.07; H, 6.50. Found: C, 52.89; H, 6.49.

4.1.10. (2*R*,3*R*)-1,2-*O*-Cyclohexylidene-3,4-epoxybutane-1,2-diol, (2*R*,3*R*)-19. A solution of (2*R*,3*R*)-**17** (0.836 g, 2.18 mmol) in THF–EtOH (1:2, 12 mL) containing anhydrous LiCl (0.273 g, 6.51 mmol) was cooled to 0°C and $NaBH_4$ (0.240 g, 6.51 mmol) was added at this temperature portionwise. The reaction mixture was stirred at room temperature overnight, treated with acetone (2 mL) and after 30 min diluted with chloroform (30 mL). Anhydrous $MgSO_4$ (2 g) was added and the suspension was vigorously stirred for 1 h and filtered through a layer of Celite 535. Solvents were evaporated to give crude (2*R*,3*S*)-**18** (0.700 g) as a colourless very viscous oil of sufficient purity to be used in the next step. IR (film): ν=3412, 2926, 2854, 1365, 1097 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.30–1.40 (2H, m), 1.50–1.65 (8H, m), 2.10–2.30 (1H, brs), 2.46 (3H, s), 3.68–3.83 (2H, m), 3.90 (1H, dAB, J_{AB}=12.7 Hz, J=3.6 Hz), 3.99 (1H, dd, J=8.5, 6.3 Hz), 4.21 (1H, ddd, J=7.3, 6.3, 5.1 Hz), 4.52 (1H, ddd, J=7.3, 4.4, 3.6 Hz), 7.26–7.38 and 7.79–7.84 (4H, m). ^{13}C NMR ($CDCl_3$): δ=21.97, 23.93, 24.17, 25.27, 34.73, 36.36, 62.37, 66.21, 73.75, 82.39, 110.73, 127.94, 130.03, 133.43, 145.34.

A solution of (2*R*,3*S*)-**18** (0.700 g) in methanol (3 mL) was stirred with anhydrous K_2CO_3 (0.291 g, 2.11 mmol) at room temperature for 30 h. After addition of saturated NH_4Cl, the solution was concentrated in vacuo. Water (5 mL) was added to the residue, the aqueous phase was then extracted with CH_2Cl_2 (3×10 mL) and the organic extracts were dried over $MgSO_4$ and concentrated. The crude product was chromatographed on a silica gel column with chloroform–methanol (200:1, v/v) to give (2*R*,3*R*)-**19** (0.240 g, 67%) as a colourless oil. $[\alpha]_D^{20}=-23.6$ (c=0.7, methanol). IR (film): ν=2935, 2860, 1449, 1368, 1163, 1102 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.30–1.45 (2H, m), 1.45–1.70 (8H, m), 2.68 (1H, dd, J=5.1, 2.7 Hz), 2.79 (1H, dd, J=5.1, 4.2 Hz), 3.03 (1H, ddd, J=5.1, 4.2, 2.7 Hz), 3.84 (1H, dd, J=8.0, 6.2 Hz), 3.98 (1H, ddd, J=6.5, 6.2, 5.1 Hz), 4.09 (1H, dd, J=8.0, 6.5 Hz). ^{13}C NMR ($CDCl_3$): δ=24.07, 24.22, 25.36, 35.28, 36.25, 44.12, 52.37, 65.77, 76.01, 110.69. Anal. calcd for $C_{10}H_{16}O_3$ (184.23): C, 65.19; H, 8.76. Found: C, 64.96; H, 8.80.

4.1.11. 9-[(2′*R*,3′*S*)-2′,3′,4′-Trihydroxy-3′,4′-*O*-isopropylidenebutyl]adenine, (2′*R*,3′*S*)-9. A mixture of the epoxide (2*S*,3*R*)-**12** (0.144 g, 1.00 mmol), adenine (0.135 g, 1.00 mmol), DMF (3 mL) and cesium carbonate (0.40 g, 1.2 mmol) was stirred at 120°C for 46 h. After cooling the suspension was filtered and the subsequent solution was concentrated in vacuo (0.1 mm Hg) and the residue was coevaporated with toluene (3×3 mL). The crude product was purified on a silica gel column with chloroform–methanol (4:1, v/v) to give (2′*R*,3′*S*)-**9** (0.223 g, 80%), which was recrystallised from methanol–petroleum ether (colourless needles). Mp 176–178°C. $[\alpha]_D^{20}=+8.8$ (c=3.6, methanol). IR (KBr): ν=3291, 2926, 1701, 1652, 1072, 669 cm^{-1}. ^{1}H NMR (CD_3OD): δ=1.33 and 1.42 (6H, 2s), 3.86 (1H, dt, J=8.4, 3.0 Hz), 3.9–4.1 (3H, ABC system), 4.15 (1H, dd, J_{AB}=14.4 Hz, J=8.4 Hz), 4.54 (1H, dd, J_{AB}=14.4 Hz, J=3.0 Hz), 8.11 (1H, s), 8.19 (1H, s). ^{13}C NMR (CD_3OD): δ=26.34, 27.92, 49.13, 68.73, 72.74, 79.15, 111.71, 120.54, 144.44, 151.60, 154.26, 157.82. Anal. calcd for $C_{12}H_{17}O_3N_5$ (279.29): C, 51.60; H, 6.14; N, 25.08. Found: C, 51.25; H, 6.38; N, 24.92.

4.1.12. 9-[(2′*R*,3′*R*)-3′,4′-*O*-Cyclohexylidene-2′,3′,4′-trihydroxybutyl]adenine, (2′*R*,3′*R*)-20. In a similar manner as described for (2′*R*,3′*S*)-**9**, from (2*R*,3*R*)-**19** (0.25 g, 1.3 mmol), adenine (0.20 g, 1.5 mmol), DMF (5 mL) and Cs_2CO_3 (0.65 g, 2.0 mmol), (2′*R*,3*R*′)-**20** (0.246 g, 55%) was obtained as a white powder. Mp 185–186°C. $[\alpha]_D^{20}=+25.9$ (c=0.7, methanol). IR (KBr): ν=3338, 3199, 2931, 2544, 1619, 1574, 1479, 1340, 1232, 1094 cm^{-1}. ^{1}H NMR (CD_3OD): δ=1.38–1.41 (2H, m), 1.43–1.70 (8H, m), 3.91 (1H, dAB, J_{AB}=7.8 Hz, J=6.9 Hz), 3.96 (1H, ddd, J=8.4, 3.9, 3.6 Hz), 4.05 (1H, dAB, J_{AB}=7.8 Hz, J=6.6 Hz), 4.14 (1H, ddd, J=6.9, 6.6, 3.9 Hz), 4.26 (1H, dAB, J_{AB}=14.1 Hz, J=8.4 Hz), 4.37 (1H, dAB, J_{AB}=14.1 Hz, J=3.6 Hz), 8.11 (1H, s), 8.19 (1H, s). ^{13}C NMR (CD_3OD): δ=25.03, 25.19, 26.47, 35.84, 37.02, 48.23, 66.25, 70.25, 77.67, 111.28, 119.90, 143.66, 150.77, 153.54, 157.18. Anal. calcd for $C_{15}H_{21}O_3N_5$ (319.36): C, 56.41; H, 6.62; N, 21.93. Found: C, 56.56; H, 6.44; N, 21.78.

4.1.13. (2*R*,3*S*)-3-*O*-Benzyl-1,2-*O*-cyclohexylidene-4-*O*-(methanesulphonyl)butane-1,2,3,4-tetrol, (2*R*,3*S*)-23. To

a solution of (2*R*,3*R*)-**16** (1.40 g, 6.08 mmol) in CH_2Cl_2 (30 mL) freshly calcinated molecular sieves 4A (6 g) were added followed by Ag_2O (2.25 g, 9.73 mmol). This suspension was treated with benzyl bromide (2.08 g, 12.2 mmol) in several portions and vigorously stirred at room temperature for 23 h. The reaction mixture was filtered through a layer of Celite 535, and the solution was concentrated in vacuo (0.1 mm Hg) to leave crude (2*R*,3*R*)-**21** (2.11 g) as an yellowish oil, which was used in the next step without purification. IR (film): ν=3030, 2924, 2854, 1745 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.30–1.50 (2H, m), 1.50–1.70 (8H, m), 3.76 (3H, s), 3.95–4.06 (3H, m), 4.32 (1H, ddd, *J*=6.5, 6.0, 5.0 Hz), 4.49 and 4.66 (2H, AB system, J_{AB}=11.7 Hz), 7.25–7.40 (5H, m).

To a solution of (2*R*,3*R*)-**21** (2.11 g) in a mixture of THF–ethanol (1:2, 50 mL) anhydrous LiCl (0.590 g, 14.0 mmol) was added. The reaction mixture was cooled to 0°C and $NaBH_4$ (1.08 g, 28.5 mmol) was added portionwise. After stirring at room temperature for 21 h acetone (8 mL) was injected. The crude product was diluted with CH_2Cl_2 (50 mL), vigorously stirred with powdered $MgSO_4$ (4 g) and filtered through a layer of Celite 535. The solution was concentrated in vacuo to give crude (2*R*,3*S*)-**22** (1.55 g) as an almost colourless oil sufficiently pure to be used in the next step. IR (film): ν=3342, 2926, 2854, 744, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.30–1.50 (2H, m), 1.50–1.70 (8H, m), 2.13 (1H, brs), 3.45–3.55 (1H, m), 3.60–3.77 (1H, m), 3.77–3.95 (2H, m), 4.02–4.12 (2H, m), 4.6–4.7 (2H, m), 7.25–7.40 (5H, m).

To a cooled −5°C solution of (2*R*,3*S*)-**22** (1.55 g) in CH_2Cl_2 (10 mL) containing dry pyridine (1.3 mL), mesyl chloride (0.79 g, 6.9 mmol) was added dropwise. After 23 h of stirring at room temperature the reaction mixture was diluted with CH_2Cl_2 (13 mL) and washed with water. Aqueous layer was extracted with CH_2Cl_2 (2×10 mL) and combined organic extracts were washed with brine and dried over $MgSO_4$. Solvents were evaporated and the residual pyridine was removed by coevaporation with toluene. The crude product was purified on a silica gel column with methylene chloride–methanol (100:1, v/v) to give (2*R*,3*S*)-**23** (0.759 g, 34%) as a colourless oil. $[\alpha]_D^{20}$=+16.1 (*c*=0.9, methanol). IR (film): ν=3030, 2937, 2862, 1176, 744, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.30–1.50 (2H, m), 1.50–1.70 (8H, m), 3.01 (3H, s), 3.61 (1H, ddd, *J*=7.3, 4.6, 2.4 Hz), 3.86 (1H, m), 4.05–4.15 (2H, m), 4.32 (1H, dd, *J*=11.1, 4.6 Hz), 4.61 (1H, dd, *J*=11.1, 2.4 Hz), 4.58 and 4.76 (2H, AB system, J_{AB}=11.5 Hz), 7.25–7.30 (5H, m). ^{13}C NMR ($CDCl_3$): δ=23.96, 24.24, 25.28, 34.77, 36.70, 37.67, 66.77, 69.01, 73.02, 73.90, 78.19, 110.39, 128.14, 128.16, 128.59, 137.32. Anal. calcd for $C_{18}H_{26}O_6S$ (370.45): C, 58.37; H, 7.07. Found: C, 58.24; H, 7.05.

4.1.14. 9-[(2′*S*,3′*S*)-2′-*O*-Benzyl-3′,4′-*O*-isopropylidene-2′,3′,4′-trihydroxybutyl]adenine, (2′*S*,3′*S*)-14. To a solution of (2*S*,3*S*)-**13** (0.716 g, 2.17 mmol) in DMF (10 mL) adenine (0.290 g, 2.17 mmol) and Cs_2CO_3 (1.40 g, 4.34 mmol) were added and the reaction mixture was stirred at 140°C for 20 h. Solids were filtered off and solvents were removed in vacuo followed by coevaporation of toluene (3×3 mL). The crude product was purified on a silica gel column with chloroform–methanol (50:1 to 4:1, v/v) to give (2′*S*,3′*S*)-**14** (0.465 g, 58%) as a white powder which was recrystallised from methanol–hexanes (colourless plates). Mp 172–174°C. $[\alpha]_D^{20}$=−45.4 (*c*=1.6, methanol). IR (KBr): ν=3295, 3126, 2981, 1674, 1606, 1309, 1078, 698 cm^{-1}. ^1H NMR (CD_3OD): δ=1.37 and 1.46 (6H, 2s), 3.92 (1H, ddd, *J*=9.0, 5.7, 3.9 Hz), 4.00 (1H, dAB, J_{AB}=8.4 Hz, *J*=6.9 Hz), 4.13 (1H, dAB, J_{AB}=8.4 Hz, *J*=6.6 Hz), 4.16–4.33 (3H, m), 4.30 (1H, d, *J*=11.7 Hz), 4.55 (1H, d, *J*=11.7 Hz), 6.90–6.97 (2H, m), 7.05–7.13 (3H, m), 8.01 (1H, s), 8.11 (1H, s). ^{13}C NMR (CD_3OD): δ=25.70, 26.87, 45.82, 66.48, 74.36, 77.43, 77.87, 110.81, 119.92, 128.71, 129.01, 129.18, 138.56, 143.52, 150.49, 153.40, 157.08. Anal. calcd for $C_{19}H_{23}N_5O_3{\cdot}0.25H_2O$ (369.23): C, 61.03; H, 6.33; N, 18.73. Found: C, 61.06; H, 6.22; N, 18.82.

4.1.15. 9-[(2′*S*,3′*R*)-2′-*O*-Benzyl-3′,4′-*O*-cyclohexylidene-2′,3′,4′-trihydroxybutyl]adenine, (2′*S*,3′*R*)-24. In a similar manner as described for (2′*S*,3′*S*)-**14**, from (2*R*,3*S*)-**23** (0.759 g, 2.05 mmol), adenine (0.280 g, 2.05 mmol) and Cs_2CO_3 (1.3 g, 4.0 mmol), (2′*S*,3′*R*)-**24** (0.427 g, 51%) was obtained as an yellowish oil. $[\alpha]_D^{20}$=−32.4 (*c*=1.3, methanol). IR (film): ν=3325, 2937, 2862, 1614, 1576, 1481, 748, 700 cm^{-1}. ^1H NMR (CD_3OD): δ=1.35–1.48 (2H, m), 1.51–1.69 (8H, m), 3.88 (1H, dd, *J*=8.4, 6.0 Hz), 3.92 (1H, ddd, *J*=6.6, 5.4, 3.3 Hz), 4.16 (1H, ddd, *J*=6.6, 6.0, 5.4 Hz), 4.26 (1H, dd, *J*=14.4, 7.5 Hz), 4.43 (1H, AB, J_{AB}=11.4 Hz), 4.46 (1H, dd, *J*=14.4, 3.6 Hz), 4.55 (1H, AB, J_{AB}=11.4 Hz), 7.00–7.08 (2H, m), 7.10–7.18 (3H, m), 8.04 (1H, s), 8.14 (1H, s). ^{13}C NMR (CD_3OD): δ=25.01, 25.22, 26.40, 35.66, 37.30, 45.60, 66.89, 73.94, 76.81, 78.08, 111.22, 119.85, 128.79, 129.12, 129.20, 138.60, 143.39, 150.79, 153.48, 157.07. Anal. calcd for $C_{22}H_{27}N_5O_3$ (409.47): C, 64.52; H, 6.64; N, 17.10. Found: C, 64.21; H, 6.44; N, 17.01.

4.1.16. 9-[(2′*S*,3′*S*)-2′-*O*-Benzyl-2′,3′,4′-trihydroxybutyl]-adenine, (2′*S*,3′*S*)-15. A mixture of (2′*S*,3′*S*)-**14** (0.667 g, 1.81 mmol), dioxane (15 mL) and aqueous HCl (1 M/L, 19.3 mL) was stirred at room temperature for 24 h, evaporated in vacuo and coevaporated with dioxane (3×5 mL). The residue was recrystallised from methanol–petroleum ether to give (2′*S*,3′*S*)-**15** (0.487 g, 82%) as colourless crystals. Mp 165–166°C. $[\alpha]_D^{20}$=−65.3 (*c*=1.5, methanol). IR (KBr): ν=3259, 3100, 2923, 1691, 1423, 1225, 1056, 703 cm^{-1}. ^1H NMR (CD_3OD): δ=3.68–3.85 (3H, m), 4.07 (1H, ddd, *J*=8.4, 4.8, 3.0 Hz), 4.27 (1H, d, *J*=12.0 Hz), 4.39 (1H, dAB, J_{AB}=14.4 Hz, *J*=8.4 Hz), 4.45 (1H, dAB, J_{AB}=14.4 Hz, *J*=4.8 Hz), 4.60 (1H, d, *J*=12.0 Hz), 6.96–7.03 (2H, m), 7.04–7.11 (3H, m), 8.19 (1H, s), 8.25 (1H, s). ^{13}C NMR (CD_3OD): δ=47.05, 63.52, 73.13, 74.45, 77.37, 119.57, 128.62, 128.95, 129.59, 138.64, 144.59, 146.31, 150.04, 151.36. Anal. calcd for $C_{16}H_{19}N_5O_3{\cdot}4H_2O$ (401.41): C, 47.87; H, 5.79; N, 17.45. Found: C, 47.96; H, 6.01; N, 17.50.

4.1.17. 9-[(2′*S*,3′*R*)-2′-*O*-Benzyl-2′,3′,4′-trihydroxybutyl] adenine, (2′*S*,3′*R*)-15. In a similar manner as described for (2′*S*,3′*S*)-**15**, from (2′*S*,3′*R*)-**24** (0.167 g, 0.450 mmol), (2′*S*,3′*R*)-**15** (0.076 g, 51%) was obtained as an amorphous solid after crystallisation from methanol. Mp 109–111°C. $[\alpha]_D^{20}$=−39.3 (*c*=2.1, methanol). IR (KBr): ν=3253, 3065,

2879, 1705, 1452, 1219, 1052, 748 cm^{-1}. ^1H NMR (CD_3OD): δ=3.66–3.80 (3H, m), 3.90–3.96 (1H, m), 4.37 (1H, AB, J=11.7 Hz), 4.41 (1H, dd, J=14,7, 8.1 Hz), 4.57 (1H, AB, J=11.7 Hz), 4.58 (1H, dd, J=14.7, 3.3 Hz), 7.00–7.04 (2H, m), 7.05–7.18 (3H, m), 8.23 (1H, s), 8.25 (1H, s). ^{13}C NMR (CD_3OD): δ=46.13, 64.01, 72.92, 73.28, 77.62, 119.47, 128.65, 129.01, 129.51, 138.65, 144.61, 146.46, 150.27, 151.36. Anal. calcd for $C_{16}H_{19}N_5O_3 \cdot 4H_2O$ (401.41): C, 47.87; H, 5.79; N, 17.45. Found: C, 47.97; H, 5.80; N, 17.12.

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