

Novel Preparation of *cis,cis*-Trisubstituted Cyclopropane Nucleosides

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Abstract: Novel cyclopropane nucleosides, *cis*-2',*cis*-3'-bis(hydroxymethyl)cyclopropyl thymine **4a** and adenine **4b** were synthesized. The stereoselective ring contraction of cyclobutyl bromohydrin **8** afforded cyclopropyl aldehyde **9** with a *cis,cis* configuration. After oxidation, conversion to amide and Hofmann's rearrangement, methyl carbamate **12** was obtained. Its basic hydrolysis yielded amine **13**, then the target molecules were obtained by construction of bases. © 1999 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Over the past decade carbocyclic nucleosides have focused much attention in order to find new antitumor and antiviral agents. Several cyclopentane^{1,2} and cyclobutane³ analogues have shown promising biological activities.

More recently, cyclopropane nucleosides have also been found to be potential candidates, as this strained three-membered ring was known to be involved in many enzymatic processes.³ In this field, reported compounds could be divided in two families. The first ones have the base moiety directly linked to the ring.⁴⁻¹⁶ The other ones possess a spacer between the base and the ring, which could be either a methylene¹⁷⁻²⁰ or an unsaturated²¹⁻²³ group.

We have been particularly interested in the 1,2,3-trisubstituted compounds. Katagiri *et al.* have reported¹⁵ the synthesis of analogues **1** and **2** using a cyclopropanation reaction, but this methodology could only lead to *trans* derivatives (Figure 1).

To the best of our knowledge, the cyclopropylmethyl analogue **3** is the only one possessing a *cis,cis* configuration¹⁹ but this compound was found to be inactive. We found interesting to try to bring the base closer to the ring in order to test if these hindered molecules **4** were accessible and to evaluate their biological activities.

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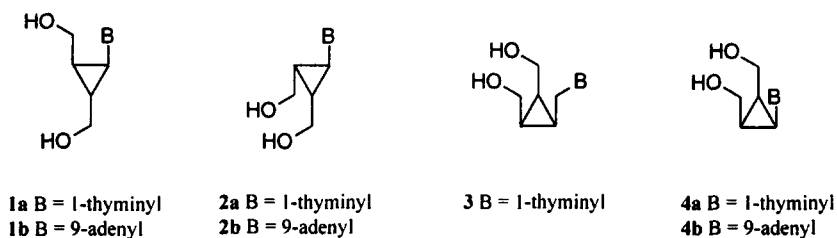
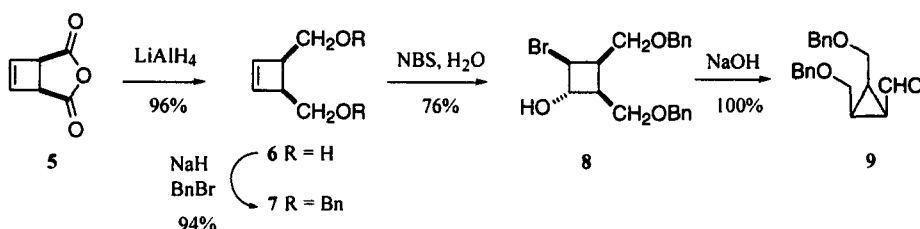


Figure 1

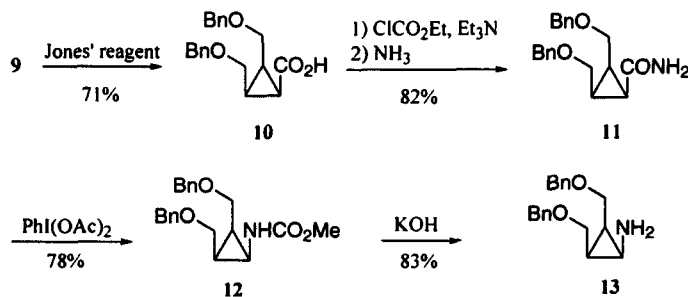
RESULTS AND DISCUSSION

The starting material was anhydride **5**. Reduction to diol **6** and benzyl protection afforded cyclobutene **7**, which could be selectively converted into bromohydrin **8**^{19,24} (Scheme 1). In basic medium, a totally stereoselective C₄-C₃ ring contraction gave aldehyde **9** exclusively, as already demonstrated elsewhere.¹⁹



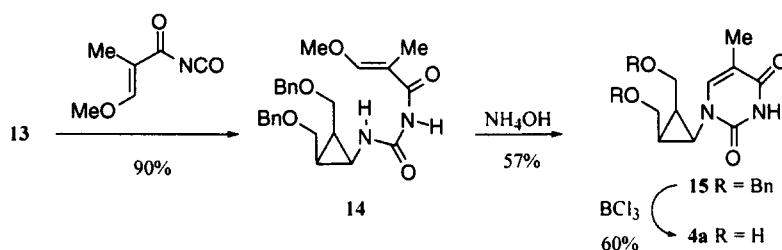
Scheme 1

Aldehyde **9** was then oxidized to acid **10** with Jones' reagent (Scheme 2). Reaction of **10** with ethyl chloroformate in the presence of triethylamine, followed by treatment with ammonia afforded amide **11**. Hofmann's rearrangement was achieved with bis(acetoxy)iodobenzene²⁵ leading to methyl carbamate **12** whereas attempts with other reagents such as lead tetraacetate or bis(trifluoroacetoxy)iodobenzene gave bad results. Finally, basic hydrolysis provided cyclopropylamine **13**, the key intermediate for the synthesis of pyrimidine and purine nucleosides.



Scheme 2

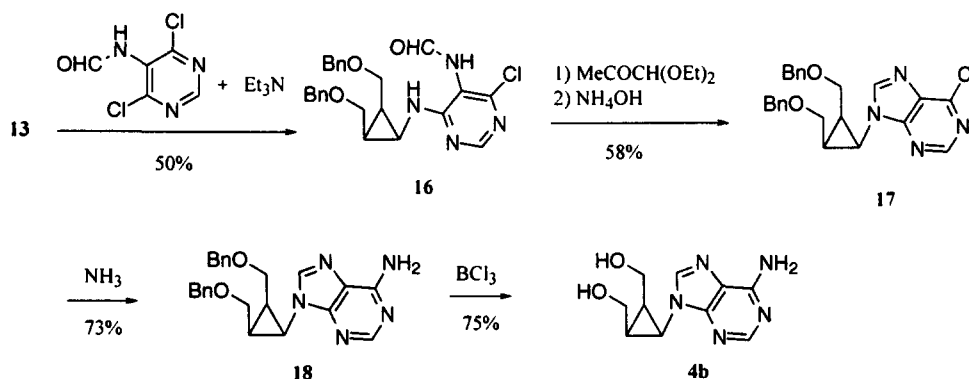
A pyrimidine nucleoside was prepared using the methodology initially developed by Shaw and Warren.²⁶ The reaction of amine **13** with β -methoxy- α -methylacryloyl isocyanate gave intermediate **14** (Scheme 3). The cyclization to thymine derivative **15** was carried out with aqueous ammonia in methanol under pressure. Subsequent debenzoylation with boron trichloride afforded thymine analogue **4a**.



Scheme 3

A purine nucleoside was synthesized by the modified procedure reported by Harnden et al.²⁷ Coupling of amine **13** with 4,6-dichloro-5-formamidopyrimidine in the presence of triethylamine yielded **16**, which was converted to 6-chloropurine derivative **17** after heating in diethoxymethylacetate (Scheme 4). In fact, initial attempts of coupling with 5-amino-4,6-dichloropyrimidine gave poor yields, and cyclization with triethylorthoformate in the presence of HCl resulted only in degradation products. Treatment of **17** with ammonia in methanol under pressure gave adenine derivative **18**, which provided adenine nucleoside **4b** after debenzoylation with boron trichloride.

The relative configuration of all compounds was proved by ^1H NMR NOE experiments giving for **15**, 8.6% enhancement for H-2' and H-3' upon saturation of H-1', and for **18**, 9.0% enhancement for H-2' and H-3' upon saturation of H-1'. Another convincing confirmation of these configurations was through comparison between the vicinal coupling constants of the cyclopropane moiety for **4a** and **4b** with those¹⁵ for the other diastereomers **1a**, **2a**, **1b** and **2b**.^{28,29} Thus, the *cis,cis* configuration of aldehyde **9** was kept throughout the reaction sequences.



Scheme 4

CONCLUSION

Although the compounds described during all the synthetic route were rather strained, they were found to be thermally stable except in strong acidic medium. In this paper, we describe the novel preparation of *cis,cis*-trisubstituted cyclopropane nucleosides **4a** and **4b** obtained in fair overall yields (8% and 4%, respectively) considering the relative steric hindrance. Biological tests showed that these compounds did not have antitumor properties.

EXPERIMENTAL

General. All non-aqueous reactions were carried out under nitrogen atmosphere. All melting points are uncorrected. IR spectra were scanned on a FT infrared spectrophotometer. ^1H and ^{13}C NMR were recorded on a Bruker AC 400 instrument at 400 and 100.6 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS which was used as an internal standard. Elemental analyses were obtained from the service de microanalyse, CNRS ICSN, Gif-sur-Yvette. High resolution mass measurements were performed at the CRMPO, Rennes.

cis-2,cis-3-Bis(benzyloxymethyl)cyclopropanecarboxylic acid (10). Aldehyde **9** (2.50 g, 8.05 mmol) in acetone (25 mL) was cooled to -10°C . Jones' reagent³⁰ (10 mL) was added dropwise and the mixture was stirred at -5°C for 10 h. The suspension was filtered through celite and acetone was removed under reduced pressure. The resulting aqueous solution was extracted with ether (3×40 mL). The combined organic layers were extracted with 1M NaOH (2×40 mL). The basic phase was reacidified with concentrated H_2SO_4 to pH=2 and extracted with ether (3×50 mL). The ethereal phases were dried over MgSO_4 , evaporated to dryness, and purification by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 3:1; $R_f = 0.50$ ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 1:1)) afforded acid **10** (1.87 g, 71%) as a white solid: mp $57-58^\circ\text{C}$ (petroleum ether); IR (KBr) 3446, 1687, 1452, 1230, 1076 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.34–7.25 (m, 10H, $2 \times \text{C}_6\text{H}_5$), 4.49 (m, 4H, $2 \times$ benzylic (AB system), $J = 11.8$ Hz), 3.86 (dd, 2H, CH_2 , $J = 10.3, 6.2$ Hz), 3.79 (dd, 2H, CH_2 , $J = 10.3, 7.4$ Hz), 1.94 (dd, 1H, H-1, $J = 9.3, 7.9$ Hz), 1.86 (m, 2H, H-2 and H-3); ^{13}C NMR (CDCl_3) δ 177.3, 138.1, 128.3, 127.7, 127.6, 72.9, 64.1, 24.3, 20.0; Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{O}_4$: C, 73.60; H, 6.79. Found: C, 73.91; H, 6.74.

cis-2,cis-3-Bis(benzyloxymethyl)cyclopropanecarboxamide (11). A solution of acid **10** (1.80 g, 5.51 mmol) and Et_3N (0.92 mL, 6.62 mmol) in dry THF (45 mL) was stirred at -5°C . To this cooling mixture, ethyl chloroformate (0.63 mL, 6.62 mmol) was added dropwise and stirring was continued for 1 h at -5°C . A saturated solution of NH_3 in THF (60 mL) was then carefully added at -5°C and stirring was pursued for 1 h at 0°C . The reaction mixture was allowed to warm to room temperature, stirred for 2 h and filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 2:1; $R_f = 0.20$) to give **11** (1.47 g, 82%) as a white solid: mp $89-91^\circ\text{C}$ (hexane/EtOAc); IR (KBr) 3401, 1662, 1452, 1110, 1066 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.38–7.28 (m, 10H, $2 \times \text{C}_6\text{H}_5$), 6.38 (br s, 1H, NH), 5.37 (br s, 1H, NH), 4.51 (m, 4H, $2 \times$ benzylic (AB system), $J = 11.9$ Hz), 3.86–3.76 (m, 4H, $2 \times \text{CH}_2$), 1.80 (t, 1H, H-1, $J = 8.7$ Hz),

1.66 (m, 2H, H-2 and H-3); ^{13}C NMR (CDCl_3) δ 171.8, 138.1, 128.4, 127.8, 127.7, 73.0, 65.8, 22.8, 21.4; HRMS Calcd for $\text{C}_{12}\text{H}_{14}\text{NO}_2$ ($\text{M}^+ - \text{CH}_2\text{OBn}$): 204.1025. Found: 204.1030.

Methyl N-[cis-2,cis-3-bis(benzyloxymethyl)cyclopropyl]carbamate (12). Carboxamide **11** (1.30 g, 3.99 mmol) was added to a stirred solution of KOH (0.56 g, 9.98 mmol) in MeOH (30 mL). The mixture was cooled to 5°C and bis(acetoxy)iodobenzene (1.31 g, 4.00 mmol) was added in one portion. The solution was stirred at ice-bath temperature for 15 min followed by warming to room temperature for an additional 2 h. MeOH was then removed in vacuo and the yellow residue was partitioned between H_2O (70 mL) and CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic extracts were washed with H_2O (30 mL) and brine (30 mL), dried over MgSO_4 , and evaporated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, cyclohexane/EtOAc 2:1; $R_f = 0.20$) to yield **12** (1.11 g, 78%) as a colorless oil: IR (neat) 3413, 2863, 1733, 1498, 1454, 1232, 1091 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.38–7.27 (m, 10H, $2 \times \text{C}_6\text{H}_5$), 5.29 (br s, 1H, NH), 4.47 (m, 4H, $2 \times$ benzylic (AB system), $J = 12.8$ Hz), 3.70–3.60 (m, 7H, $2 \times \text{CH}_2$ and CH_3), 2.83 (t, 1H, H-1, $J = 7.0$ Hz), 1.55–1.42 (m, 2H, H-2 and H-3); ^{13}C NMR (CDCl_3) δ 158.1, 138.0, 128.4, 127.7, 72.9, 65.7, 52.2, 30.5, 19.7; Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_4$, 0.2 H_2O : C, 70.25; H, 7.13; N, 3.90. Found: C, 70.28; H, 6.97; N, 3.65.

cis-2,cis-3-Bis(benzyloxymethyl)cyclopropylamine (13). Methyl carbamate **12** (1.52 g, 4.27 mmol) and KOH (4.50 g, 80.00 mmol) in MeOH (30 mL) were stirred under reflux for 48 h. MeOH was then removed under reduced pressure and H_2O (30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (5×30 mL). The combined organic phases were washed with brine (30 mL), dried over MgSO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, cyclohexane/EtOAc 1:1; $R_f = 0.40$) to afford **13** (1.06 g, 83%) as a pale yellow oil: IR (neat) 3500–3400, 1454, 1089, 1074 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.34–7.25 (m, 10H, $2 \times \text{C}_6\text{H}_5$), 4.50 (m, 4H, $2 \times$ benzylic (AB system), $J = 11.8$ Hz), 3.74–3.66 (m, 4H, $2 \times \text{CH}_2$), 2.66 (t, 1H, H-1, $J = 6.9$ Hz), 1.44 (br s, 2H, NH_2), 1.25–1.19 (m, 2H, H-2 and H-3); ^{13}C NMR (CDCl_3) δ 138.5, 128.3, 127.8, 127.6, 72.9, 65.4, 30.4, 20.1; HRMS Calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_2$ [$\text{M} - \text{CH}_2\text{C}_6\text{H}_5$] $^+$: 206.1181. Found: 206.1183.

[cis-2',cis-3'-Bis(benzyloxymethyl)cyclopropyl]-3-(3''-methoxy-2''-methylacryloyl)urea (14). A solution of 3-methoxy-2-methylacryloyl chloride²⁶ (0.27 g, 2.00 mmol) and silver cyanate (0.53 g, 3.50 mmol) in dry benzene (3.5 mL) was heated under reflux for 30 min. The mixture was then cooled to 0°C and the supernatant liquor was added to amine **13** (0.30 g, 1.00 mmol). The solution was stirred for 20 h at room temperature and concentrated. The residue was purified by column chromatography (silica gel, cyclohexane/EtOAc 1:1; $R_f = 0.25$) to yield **14** (0.40 g, 90%) as a white solid: mp 101°C (Et_2O); IR (KBr) 3262, 1685, 1673, 1610, 1455, 1253, 1128, 1097 cm^{-1} ; ^1H NMR (CDCl_3) δ 9.11 (br s, 1H, NH), 8.33 (br s, 1H, NH), 7.38–7.25 (m, 11H, $2 \times \text{C}_6\text{H}_5$ and $\text{CH}=\text{C}$), 4.58 (d, 2H, benzylic (AB system), $J = 11.3$ Hz), 4.46 (d, 2H, benzylic (AB system), $J = 11.8$ Hz), 3.85 (s, 3H, OCH_3), 3.71–3.61 (m, 4H, $2 \times \text{CH}_2$), 3.02 (td, 1H, H-1', $J = 7.4, 2.9$ Hz), 1.78 (s, 3H, CH_3), 1.56–1.51 (m, 2H, H-2' and H-3'); ^{13}C NMR (CDCl_3) δ 196.0, 158.5, 155.9, 138.2, 128.3, 127.9, 127.6, 107.1, 73.0, 65.7, 61.4, 29.6, 19.4, 8.8; Anal. Calcd for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_5$: C, 68.47; H, 6.89; N, 6.38. Found: C, 68.18; H, 6.78; N, 6.01.

1-[cis-2',cis-3'-Bis(benzyloxymethyl)cyclopropyl]thymine (15). A mixture of urea **14** (0.37 g, 0.84 mmol), 25% NH_4OH (7 mL) and MeOH (7 mL) was heated at 85°C for 24 h in a sealed tube. After removal of the solvents, the residue was purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 3:1; R_f = 0.20 (cyclohexane/EtOAc 1:1)) to afford **15** (0.20 g, 57 %) as a white solid: mp 139–141°C (petroleum ether/EtOAc); IR (KBr) 3438, 1708, 1662, 1450, 1305, 1099, 1072 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.99 (br s, 1H, NH), 7.67 (q, 1H, $\text{CH}=\text{C}$, J = 1.0 Hz), 7.37–7.26 (m, 10H, $2\times\text{C}_6\text{H}_5$), 4.42 (m, 4H, $2\times\text{benzylic}$ (AB system), J = 11.3 Hz), 3.60 (m, 4H, $2\times\text{CH}_2$), 3.13 (t, 1H, H-1', J = 7.4 Hz), 1.81 (d, 3H, CH_3 , J = 1.0 Hz), 1.80–1.74 (m, 2H, H-2' and H-3'); ^{13}C NMR (CDCl_3) δ 164.1, 152.3, 142.8, 137.6, 128.5, 127.9, 127.7, 110.3, 73.2, 65.9, 37.7, 20.5, 12.2; Anal. Calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.52; H, 6.41; N, 6.62.

1-[cis-2',cis-3'-Bis(hydroxymethyl)cyclopropyl]thymine (4a). A solution of compound **15** (0.15 g, 0.37 mmol) in dry CH_2Cl_2 (10 mL) was cooled to -78°C. A 1M solution of BCl_3 in CH_2Cl_2 (8.0 mL) was added dropwise and the mixture was stirred for 6 h at -78°C. MeOH (10 mL) was carefully added, and the mixture was then allowed to warm to room temperature and concentrated. The residue was coevaporated three times with MeOH (10 mL). MeOH (10 mL) was added, and the resulting solution was neutralized by a saturated solution of NH_3 in MeOH. The suspension thus obtained was evaporated to dryness. The residue was purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1; R_f = 0.40) to afford, after recrystallization from MeOH, compound **4a** (50 mg, 60%) as a white solid: mp 205°C dec.; IR (KBr) 3400–3300, 1698, 1668, 1455, 1292, 1045, 1029, 1014 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 11.28 (br s, 1H, NH), 7.56 (s, 1H, $\text{CH}=\text{C}$), 4.62 (t, 2H, $2\times\text{OH}$, J = 5.0 Hz), 3.46 (m, 4H, $2\times\text{CH}_2$), 3.06 (t, 1H, H-1', J = 7.4 Hz), 1.73 (s, 3H, CH_3), 1.46 (m, 2H, H-2' and H-3'); ^{13}C NMR ($\text{DMSO}-d_6$) δ 164.1, 152.7, 143.1, 108.8, 56.1, 37.2, 22.2, 12.1; HRMS Calcd for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_4$: 226.0953. Found: 226.0952.

6-[[cis-2',cis-3'-Bis(benzyloxymethyl)cyclopropyl]amino]-4-chloro-5-formamidopyrimidine (16). A mixture of amine **13** (0.30 g, 1.00 mmol), 5-formamido-4,6-dichloropyrimidine (0.38 g, 2.00 mmol) and Et_3N (0.8 mL) in dioxane (6 mL) was heated under reflux for 8 h. The mixture was then concentrated to dryness and purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 3:1; R_f = 0.20 ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 2:1)) to afford **16** (0.22 g, 50 %) as a white solid: mp 93–94°C; IR (KBr) 3394, 3131, 1693, 1577, 1506, 1400, 1272, 1091 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.33 (s, 1H, H-2), 7.85 (s, 1H, CHO), 7.36–7.26 (m, 10H, $2\times\text{C}_6\text{H}_5$), 6.25 (br s, 1H, NHCHO), 4.47 (m, 4H, $2\times\text{benzylic}$ (AB system), J = 11.8 Hz), 3.78–3.68 (m, 4H, $2\times\text{CH}_2$), 3.09 (td, 1H, H-1', J = 7.4, 2.9 Hz), 1.70–1.63 (m, 3H, NH, H-2' and H-3'); ^{13}C NMR (CDCl_3) δ 159.6, 159.1, 156.1, 138.0, 128.4, 127.7, 127.6, 111.6, 72.8, 65.9, 31.6, 19.9; HRMS Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_2\text{Cl}$ [$\text{M} - \text{CH}_2\text{OBn}$] $^+$: 331.0962. Found: 331.0962.

9-[cis-2',cis-3'-Bis(benzyloxymethyl)cyclopropyl]-6-chloropurine (17). A solution of pyrimidine **16** (185 mg, 0.41 mmol) in diethoxymethyl acetate (3 mL) was heated at 120°C for 22 h. After removal of the solvent, the residue was dissolved in MeOH (3 mL) and concentrated NH_4OH (0.3 mL). The mixture was stirred at room temperature for 1 h and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 4:1; R_f = 0.60 ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 2:1))

to yield **17** (103 mg, 58%) as a white solid: mp 144–146°C; IR (KBr) 2898, 1589, 1552, 1330, 1060 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.74 (s, 1H, H-2 or H-8), 8.64 (s, 1H, H-8 or H-2), 7.36–7.26 (m, 10H, $2\times\text{C}_6\text{H}_5$), 4.47 (d, 2H, benzylic (AB system), $J = 11.3$ Hz), 4.39 (d, 2H, benzylic (AB system), $J = 11.3$ Hz), 3.61–3.46 (m, 5H, $2\times\text{CH}_2$ and H-1'), 2.08–1.99 (m, 2H, H-2' and H-3'); ^{13}C NMR (CDCl_3) δ 153.4, 152.0, 150.9, 147.8, 137.3, 131.6, 128.5, 127.9, 127.8, 73.3, 65.4, 32.4, 20.3; HRMS Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_2\text{Cl}$ [$\text{M} - \text{CH}_2\text{C}_6\text{H}_5$] $^+$: 343.0961. Found: 343.0958.

9-[cis-2',cis-3'-Bis(benzyloxymethyl)cyclopropyl]adenine (18). A mixture of chloropurine **17** (0.14 g, 0.32 mmol) and a solution of NH_3 in MeOH (1:1 (v/v) prepared at -78°C , 15 mL) was heated at 80°C for 24 h in a stainless steel bomb. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95:5; $R_f = 0.40$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1)) to yield **18** (98 mg, 73%) as a white solid: mp 152–153°C; IR (KBr) 3426, 3313, 1648, 1602, 1307, 1093 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.36 (s, 1H, H-2 or H-8), 8.30 (s, 1H, H-8 or H-2), 7.37–7.26 (m, 10H, $2\times\text{C}_6\text{H}_5$), 5.67 (br s, 2H, NH_2), 4.49 (d, 2H, benzylic (AB system), $J = 11.3$ Hz), 4.40 (d, 2H, benzylic (AB system), $J = 11.3$ Hz), 3.69–3.64 (m, 2H, CH_2), 3.51–3.46 (m, 3H, CH_2 and H-1'), 2.04–1.94 (m, 2H, H-2' and H-3'); ^{13}C NMR (CDCl_3) δ 155.5, 153.1, 151.5, 142.8, 137.6, 128.4, 127.8, 127.7, 119.5, 73.2, 65.7, 32.0, 20.2; Anal. Calcd for $\text{C}_{24}\text{H}_{25}\text{N}_5\text{O}_2$, 0.5 H_2O : C, 67.91; H, 6.17; N, 16.49. Found: C, 67.97; H, 6.03; N, 16.33.

9-[cis-2',cis-3'-Bis(hydroxymethyl)cyclopropyl]adenine (4b). The same experimental procedure as for **4a** starting from **18** (80 mg, 0.19 mmol) led to the crude product. Purification by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 85:15; $R_f = 0.20$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1)) afforded, after recrystallization from MeOH, compound **4b** (34 mg, 75%) as a white solid: mp 207°C dec.; IR (KBr) 3361, 3270, 3118, 1679, 1614, 1573, 1299, 1016 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 8.16 (s, 1H, H-2 or H-8), 8.15 (s, 1H, H-8 or H-2), 7.37 (br s, 2H, NH_2), 5.08 (t, 2H, $2\times\text{OH}$, $J = 5.4$ Hz), 3.53–3.46 (m, 2H, CH_2), 3.39 (t, 1H, H-1', $J = 7.4$ Hz), 3.37–3.27 (m, 2H, CH_2), 1.68 (m, 2H, H-2' and H-3'); ^{13}C NMR ($\text{DMSO}-d_6$) δ 156.1, 152.4, 150.6, 142.8, 118.7, 55.8, 31.1, 22.3; HRMS Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_5\text{O}_2$: 235.1069. Found: 235.1072.

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