Synthesis of Enantiomerically Pure Bis(hydroxymethyl)-Branched Cyclohexenyl and Cyclohexyl Purines as Potential Inhibitors of HIV

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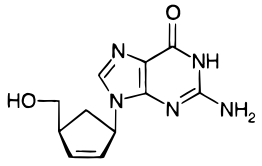
The synthesis of the enantiomerically pure bis(hydroxymethyl)-branched cyclohexenyl and cyclohexyl purines is described. Racemic *trans*-4,5-bis(methoxycarbonyl)cyclohexene [**(**±**)-6**] was reduced with lithium aluminum hydride to give the racemic diol **(**±**)-7**. Resolution of **(**±**)-7** via a transesterification process using lipase from *Pseudomonas* sp. (SAM-II) gave both diols in enantiomerically pure form. The enantiomerically pure diol (*S*,*S*)-**7** was benzoylated and epoxidized to give the epoxide **9**. Treatment of the epoxide **9** with trimethylsilyl trifluoromethanesulfonate and 1,5-diazabicyclo-[5.4.0]undec-5-ene followed by dilute hydrochloric acid gave (1*R*,4*S*,5*R*)-4,5-bis[(benzoyloxy)methyl]-1-hydroxycyclohex-2-ene (**10**). Acetylation of **10** gave (1*R*,4*S*,5*R*)-1-acetoxy-4,5-bis[(benzoyloxy)-methyl]cyclohex-2-ene (**11**). (1*R*,4*S*,5*R*)-1-Acetoxy-4,5-bis[(benzoyloxy)methyl]cyclohex-2-ene (**11**) was converted to the adenine derivative **12** and guanine derivative **13** via palladium(0)-catalyzed coupling with adenine and 2-amino-6-chloropurine, respectively. Hydrogenation of **12** and **13** gave the correspondning saturated adenine derivative **14** and guanine derivative **15**. (1*R*,4*S*,5*R*)-4,5-Bis[(benzoyloxy)methyl]-1-hydroxycyclohex-2-ene (**10**) was converted to the adenine derivative **16** and guanine derivative **17** via coupling with 6-chloropurine and 2-amino-6-chloropurine, respectively, using a modified Mitsunobu procedure. Hydrogenation of **16** and **17** gave the corresponding saturated adenine derivative **18** and guanine derivative **19**. Compounds **12**−**19** were evaluated for activity against human immunodeficiency virus (HIV), but were found to be inactive. Further biological testings are underway.

Introduction

During recent years nucleoside analogues have been extensively evaluated in the search for agents effective against the human immunodeficiency virus (HIV), the causative agent of acquired immune deficiency syndrome (AIDS).[1] More effective treatment has also been sought for other virus, in particular herpes simplex virus (HSV 1 and 2), varicella zoster virus (VZV), cytomegalo virus (CMV), and Epstein-Barr virus (EBV), which can prove lethal to AIDS patients and other immune-compromised individuals.[2] Carbocyclic nucleosides have emerged as a particularly interesting class of nucleosides and several derivatives with potent antiviral activity have been discovered.[3] Carbovir[4] (**1**) and carbocyclic oxetanocin G[2] (**2**) are two carbocyclic nucleoside analogues which were early reported to show *in vitro* activity against HIV. The carbocyclic oxetanocin G also shows activity against HSV 1 and 2. More recently a new carbocyclic nucleoside analogue, (1*R*,4*S*,5*R*)-9-[4,5-bis(hydroxymethyl)cyclopent-2-en-1-yl]-9*H*-adenine[5] (**3**), was reported to show potent anti-HIV activity *in vitro*. A special feature of the



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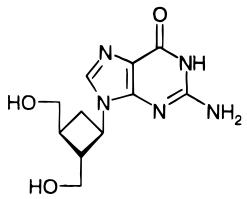

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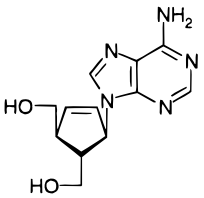

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carbocyclic nucleosides is the absence of a glycosidic linkage which increases the metabolic stability against phosphorylase and hydrolase enzymes, which cleave the glycosidic linkage in normal nucleosides.[6,7] The comparatively higher lipophilicity of the carbocyclic nucleo-

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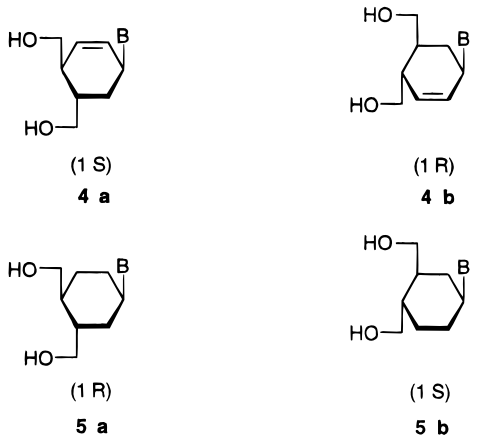
sides is potentially beneficial for increasing oral availability and cell wall penetration.

Despite the fact that the carbocyclic nucleosides have been extensively studied, few efforts have been directed toward the synthesis of six-membered carbocyclic nucleosides.[8] As a continuation of our work on the structure−activity relationship of different types of hydroxymethyl-branched nucleosides[9] we have synthesized (1*S*,4*S*,5*R*)- and (1*R*,4*S*,5*R*)-9-[4,5-bis(hydroxymethyl)cyclohex-2-en-1-yl]-9*H*-adenine and -guanine (**4a**,**b**). Compounds **4a** can be viewed as a ring expanded analogue of (1*R*,4*S*,5*R*)-9-[4,5-bis(hydroxymethyl)cyclopent-2-en-1-yl]-9*H*-adenine, while compounds **4b** can be viewed as analogues of carbovir. We have also synthesized the corresponding saturated compounds (1*R*,4*S*,5*R*)- and (1*S*,4*S*,5*R*)-9-[4,5-bis(hydroxymethyl)cyclohexyl]-9*H*-adenine and -guanine (**5a**,**b**). These structures can be viewed as ring expanded analogues of carbocyclic oxetanocin G.

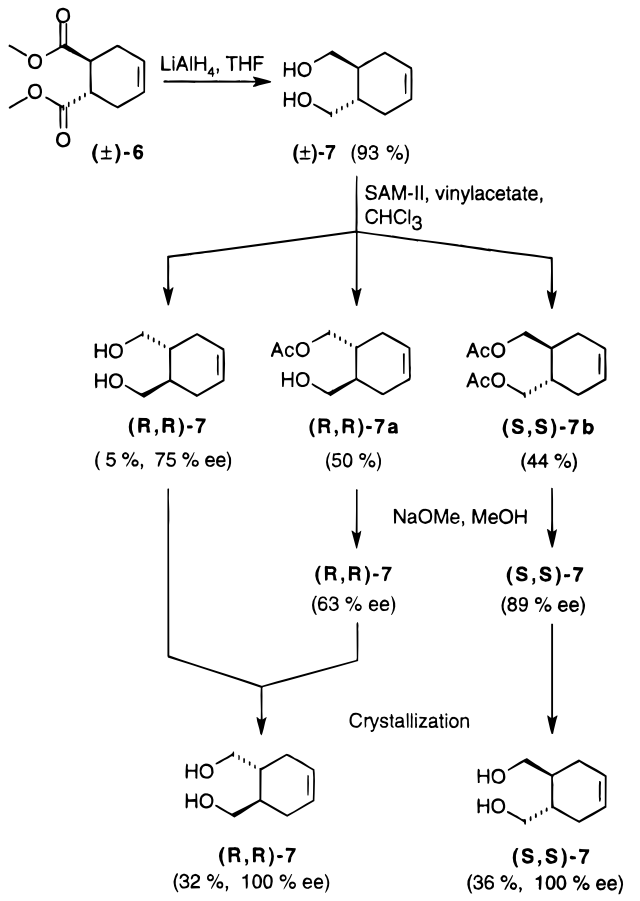


B=Adenine and Guanine

Results and Discussion

The synthesis starts from the racemic cyclohexene diester **(**±**)-6**, which was synthesized in a Diels−Alder reaction of 3-sulfolene and dimethyl fumarate (Scheme 1).[10] Reduction of the two ester groups in **(**±**)-6** with lithium aluminum hydride in tetrahydrofuran gave **(**±**)-7** in 93% yield. The racemic diol **(**±**)-7** was resolved via a lipase-catalyzed transesterification process. Ester hydrolases (lipases, esterases) are well known for their capability to differentiate between enantiotopic groups in meso substrates, as well as their capability to catalyze the hydrolysis of esters and their synthesis by esterification or transesterification.[11,12] The transesterification and hydrolysis of racemic *trans*-1,2-dihydroxy- and *trans*-1,2-diacetoxy-substituted cyclic substrates catalyzed by *Pseudomonas* lipases have been examined in detail.[13] In the transesterification reactions enantiomerically pure (≥98% ee) diacetates were obtained. High selectivity were also observed in the hydrolysis reactions resulting in monoacetates with excellent optical purity (≥95% ee). Similar results were observed when the transesterification and hydrolysis of *cis*-1,2-bis(hydroxymethyl)- and *cis*-1,2-bis(acetoxymethyl)-substituted cyclic substrates catalyzed by lipase from *Pseudomonas* sp. were examined.[14] Both the transesterification and the hydrolysis methodology produced the monoacetates in high optical purity (≥85% ee). In the literature only a few examples of *Pseudomonas* lipase-catalyzed transformations of racemic *trans*-1,2-bis(hydroxymethyl)- and *trans*-1,2-bis(acetoxymethyl)-substituted cyclic substrates have been pre-

Scheme 1



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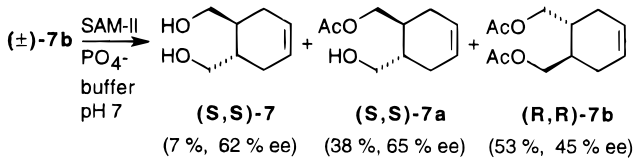
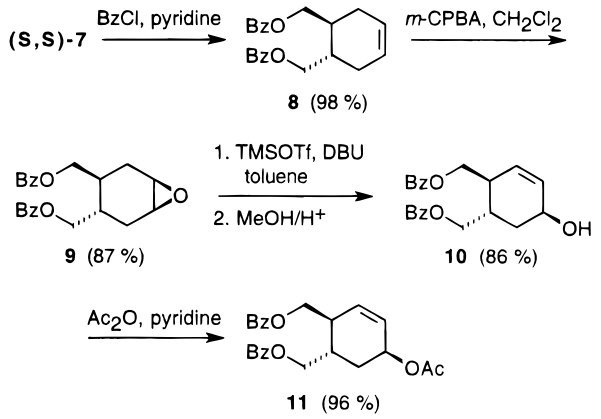
Scheme 2



Scheme 3



sented, resulting in products with low optical purity (≤40% ee).[15,16] We have examined the *Pseudomonas* sp. lipase-catalyzed transformations of racemic *trans*-4,5-bis-(hydroxymethyl)cyclohexene **(**±**)-7**. Since the enantioselectivity of the enzyme can be greatly affected by the nature of the solvent, the effect of different organic cosolvents on the enantioselectivity of the enzyme in both the transesterification[17] and hydrolysis[18] reactions were studied. Transesterification of **(**±**)-7** using lipase from *Pseudomonas* sp. (SAM-II) and vinyl acetate in chloroform gave 44% of (*S*,*S*)-diacetate (*S*,*S*)-**7b**, 50% of (*R*,*R*)-monoacetate (*R*,*R*)-**7a**, and 5% of unesterified (*R*,*R*)-diol (*R*,*R*)-**7** (75% ee). Compounds (*S*,*S*)-**7b** and (*R*,*R*)-**7a** were deacetylated with methanolic sodium methoxide to give (*S*,*S*)-**7** (89% ee) and (*R*,*R*)-**7** (63% ee), respectively (Scheme 1). The enantiomeric purity and the absolute stereochemistry were determined by comparison with the optical rotation of compound (*S*,*S*)-**7** reported by Heathcook *et al.*[19] The enantiomeric purity was increased by recrystallization, which gave enantiomerically pure diols (*S*,*S*)-**7** and (*R*,*R*)-**7** with >99% ee, respectively. The total yield were 36% for (*S*,*S*)-**7** and 32% for (*R*,*R*)-**7** from racemic material. The addition of the cosolvent chloroform increased the enantioselectivity of the enzyme compared to using only vinyl acetate both as acylation agent and as solvent. Addition of other cosolvents such as dioxane, nitromethane, methyl *tert*-butyl ether, and toluene decreased the enantioselectivity. When dimethylformamide was used as cosolvent no reaction was observed. No correlation between enantioselectivity and solvent properties such as log *P* or dielectric constant (ϵ) were found. The hydrolysis of the racemic diacetate **(**±**)-7b** in phosphate buffer catalyzed by lipase from *Pseudomonas* sp. was also studied. The hydrolysis reaction was stereochemically complementary to the transesterification reaction resulting in the opposite pairs of enantiomers. The recovered (*R*,*R*)-diacetate (*R*,*R*)-**7b** was obtained in 45% ee (53% yield), the (*S*,*S*)-monacetate (*S*,*S*)-**7a** in 65% ee (38% yield), and the (*S*,*S*)-diol (*S*,*S*)-**7** in 62% ee (7% yield) (Scheme 2). Addition of the water-immiscible organic cosolvents diethyl ether or toluene gave only a minor improvement of the enantioselectivity. In both the enzymatic transformations the functional group with the *S*-configuration was preferentially reacted. These results are in agreement with the results obtained in the *Pseudomonas* lipase-catalyzed transformations of other racemic *trans*-1,2-bis(hydroxymethyl)- and *trans*-1,2-bis(acetoxymethyl)-substituted cyclic substrates.[15,16] However, compared to *Pseudomonas* lipase-catalyzed reactions of racemic *trans*-1,2-dihydroxy- and *trans*-1,2-diacetoxy-substituted cyclic substrates, in which the functional group with the *R*-configuration was preferentially reacted,[13] these results indicates a reversal of the enzyme enantioselectivity going from a *trans*-1,2-disubstituted cyclic substrate with primary alcohol or acetate groups to a *trans*-1,2-disubstituted cyclic substrate with secondary alcohol or acetate groups.

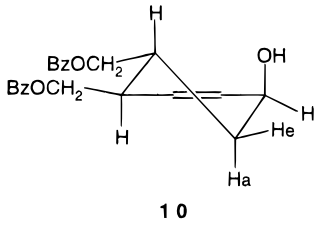


Figure 1.

The enantiomerically pure diol (*S*,*S*)-**7** was benzoylated with benzoyl chloride in pyridine at room temperature to give **8** in 98% yield (Scheme 3). Epoxidation of **8** with *m*-chloroperbenzoic acid in methylene chloride gave the epoxide **9** in 87% yield. The epoxide **9** was then converted to the allylic alcohol **10**. Treatment of **9** with trimethylsilyl trifluoromethanesulfonate and 1,5-diazabicyclo-[5.4.0]undec-5-ene in toluene at room temperature gave the corresponding allylic alcohol protected as a trimethylsilyl ether.[20] The trimethylsilyl group was removed by treatment with dilute hydrochloric acid in methanol to give exclusively the allylic alcohol **10**. The isolated yield of **10** from **9** was 86% after column chromatography. The configuration at C-1 in compound **10** was assigned by several ^{1}H NMR decoupling experiments. For H-6$_a$ two large coupling constants, 14.3 and 10.0 Hz with H-6$_e$ and H-5 respectively, were detected. The coupling constant between H-6$_a$ and H-1 is a small one of 2.5 Hz. All together these coupling constants indicates that the hydroxyl group on C-1 occupy a pseudoaxial position (Figure 1). Acetylation of the allylic alcohol **10** with acetic anhydride in pyridine at room temperature gave **11** in 96% yield (Scheme 3).

Compounds **12** and **13** were synthesized via palladium(0)-catalyzed coupling of the allylic acetate **11** with the anions of the purine bases.[21−23] Coupling under these

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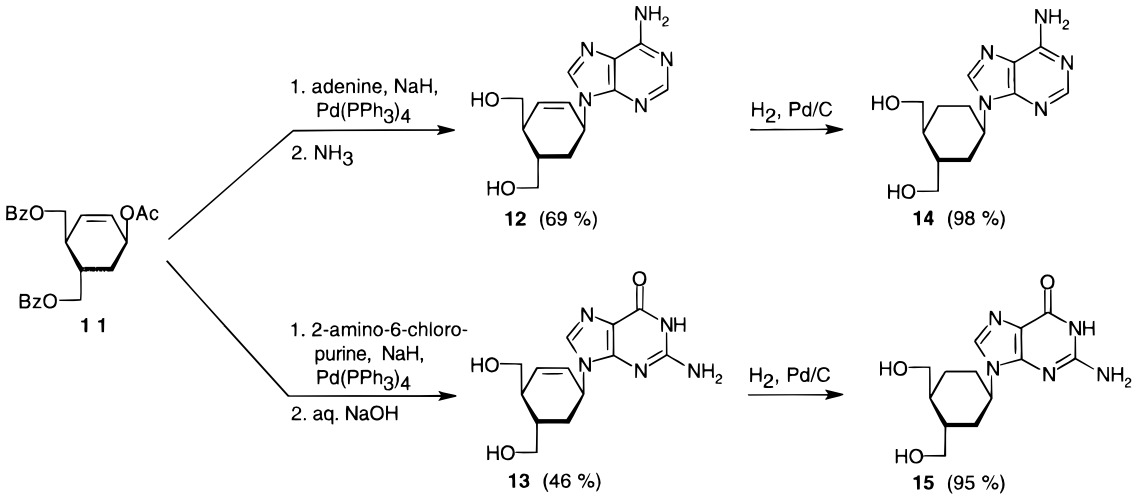
Scheme 4



conditions have been reported to give both five-membered[21−23] and six-membered[8h] carbocyclic nucleosides with retention of the configuration at carbon one (C-1) of the allylic acetate. Thus, the allylic acetate **11** was coupled with adenine in the presence of sodium hydride and tetrakis(triphenylphosphine)palladium(0) followed by deprotection with methanolic ammonia under pressure to give the adenine derivative **12** in 69% yield (Scheme 4). Coupling of the allylic acetate **11** with 2-amino-6-chloropurine, a commonly used surrogate for the insoluble guanine base, following the same protocol as above gave the protected 2-amino-6-chloropurine derivative. Deprotection and hydrolytic cleavage of the 6-chloro moiety with aqueous sodium hydroxide gave the guanine derivative **13** in 46% overall yield. Both these coupling reactions resulted in exclusive formation of the desired N-9 alkylated isomers, which were assigned by NMR[24] and UV[25] spectroscopy. The stereoselectivity in these palladium(0)-catalyzed coupling reactions was confirmed from the ^{1}H NMR coupling constants of the adenine derivative **12** and the guanine derivative **13** obtained from selective decoupling experiments. For compound **12** the signal for H-6$_a$ appeared as a triplet of doublets with coupling constants of 11.2 Hz with H-6$_e$ and H-5 and 4.3 Hz with H-1. The signal for H-6$_e$ appears as doublet of triplets with coupling constants of 11.5 Hz with H-6$_a$ and 3.3 Hz with H-5 and H-1. A similar pattern for both protons was observed for compound **13**. Altogether these coupling constants confirm that the adenine and guanine bases, respectively, occupy a pseudoaxial position and that the palladium(0)-catalyzed coupling reactions thereby proceeds with retention of configuration at carbon one (C-1) of the allylic acetate. The adenine derivative **12** and the guanine derivative **13** were hydrogenated over palladium on carbon to give the corresponding saturated compounds **14** and **15** in 98 and 95% yield, respectively.

For the synthesis of compounds **16** and **17** a slightly modified Mitsunobu procedure was used.[9g,26,27] The triphenylphosphine−diisopropyl azodicarboxylate−purine complex was formed at 0 °C before it was cooled to −78 °C and the allylic alcohol was added. The mixture was then stirred at 0 °C for 48 h. Contrary to the palladium(0)-catalyzed reaction, coupling under Mitsunobu conditions have been shown to give both five-membered[27] and six-membered[8f] carbocyclic nucleosides with inversion of the configuration at carbon one (C-1) of the allylic alcohol. Thus, coupling of the allylic alcohol **10** with 6-chloropurine and 2-amino-6-chloropurine gave the protected 6-chloropurine and 2-amino-6-chloropurine derivatives, respectively (Scheme 5). Subsequent treatment of the 6-chloropurine derivative with methanolic ammonia under pressure gave the adenine derivative **16** in 52% overall yield. Deprotection and hydrolytic cleavage of the 6-chloro moiety in the protected 2-amino-6-chloropurine derivative with aqueous sodium hydroxide gave the guanine derivative **17** in 34% yield from **10**. The coupling of 2-amino-6-chloropurine gave exclusively the desired N-9 alkylated isomer, while the coupling of 6-chloropurine besides the desired N-9 alkylated isomer also gave traces (<5%) of the N-7 alkylated isomer. The regioselectivity of the alkylations were assigned by NMR[24] and UV[25] spectroscopy. Hydrogenation of compounds **16** and **17** over palladium on carbon gave the saturated adenine derivative **18** and guanine derivative **19** in 99 and 93% yield.

The guanine derivatives **13**, **15**, **17**, and **19** were purified by preparative high-pressure liquid chromatography. Comparisons of the retention times further indicate that the coupling reactions proceeded with complete retention and inversion, respectively.

Compounds **12**−**19** were tested for inhibition of HIV multiplication in an XTT assay on M4 cells,[28] and were found to be inactive in the assay. All compounds will be further screened for biological activity.

Experimental Section

Removal of solvents was performed under reduced pressure. ^{1}H and ^{13}C NMR were recorded using $CDCl_3$, MeOH-d_4, or DMSO-d_6 as solvents. TLC analyses were performed on Merck precoated 60 F-254 plates. The spots were visualized by UV light and/or charring with ethanol/sulfuric acid/acetic acid/*p*-anisaldehyde, 90:3:1:2. Column chromatography were performed using silica gel 60 (0.040−0.063 mm, Merck). High-

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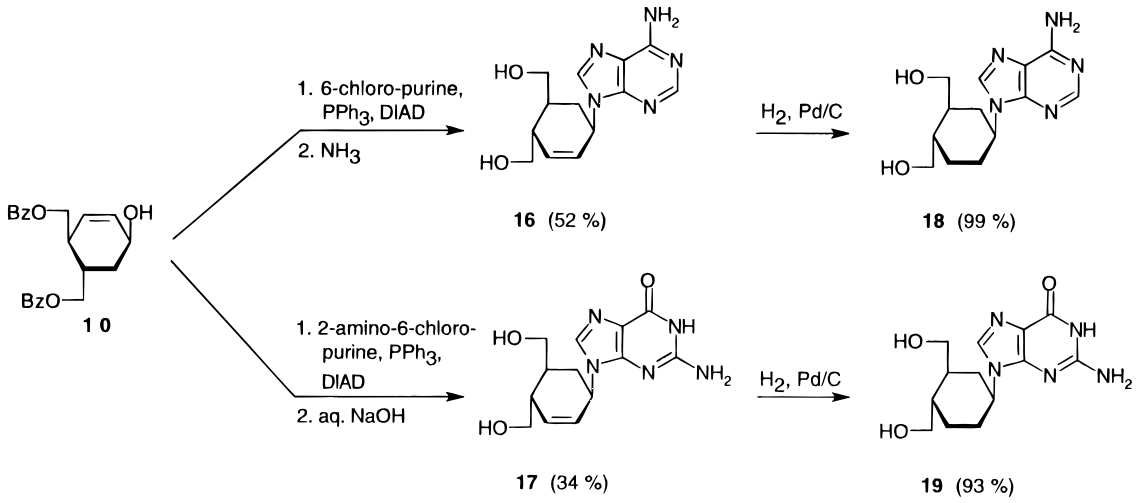
Scheme 5



pressure liquid chromatography were performed using a prepacked steel column (250 × 25 mm) using Polygosil 60-7, C-18 (Macherey-Nagel). Organic phases were dried over anhydrous magnesium sulfate. Optical rotations were measured in $CHCl_3$ or DMSO solutions at room temperature. Lipase from *Pseudomonas* sp. (SAM-II, 31.5 U/mg) was purchased from Fluka Biochemica.

***rac-trans*-4,5-Bis(hydroxymethyl)cyclohexene [(±)-7].** To a stirred suspension of lithium aluminum hydride (1.15 g, 30.2 mmol) in dry tetrahydrofuran (200 mL) *rac-trans*-4,5-bis-(methoxycarbonyl)cyclohexene[10] [(±)-**6**, 4.20 g, 21.4 mmol] in dry tetrahydrofuran (50 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 3 h before ethyl acetate (3 mL), water (2 mL), 10% aqueous sodium hydroxide (2 mL), and water (2 mL) again were added. After the mixture was stirred at room temperature for 3 h magnesium sulfate (23 g) was added and the stirring was prolonged for additional 2 h. The precipitate and magnesium sulfate were removed by filtration and washed several times with ethyl acetate. Concentration and purification by flash column chromatography (toluene−ethyl acetate; 2:1) gave compound (±)-7 (2.87 g, 93%) as a colorless syrup: ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 1.62−2.19 (m, 6 H), 2.97 (b, 2 H), 3.50−3.69 (dt, J = 11.0, 5.4 Hz, 2 H), 3.70−3.87 (dq, J = 11.3, 4.8, 2.6 Hz, 2 H), 5.66 (m, 2 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 28.54, 39.75, 66.24, 126.05.

Resolution of *rac-trans*-4,5-Bis(hydroxymetyl)cyclohexene [(±)-7] Using Lipase from *Pseudomonas* sp. (SAM-II) as Catalyst. A solution of compound (±)-**7** (5.60 g, 39.4 mmol), lipase from *Pseudomanas* sp. (SAM-II) (160 mg), vinyl acetate (15 mL), and chloroform (66 mL) was stirred at room temperature for 100 h until TLC indicated almost equal transesterification to diacetate and monoacetate, with only traces of unreacted diol. At this time the reaction mixture was centrifuged, and the clear supernatant was decanted and concentrated. Separation of the three products by column chromatography (toluene−ethyl acetate; 6:1 to 1:2) gave (*S*,*S*)-diacetate (*S*,*S*)-**7b** (3.89 g, 44%), (*R*,*R*)-monoacetate (*R*,*R*)-**7a** (3.62 g, 50%), and unesterified (*R*,*R*)-diol (*R*,*R*)-**7** (0.26 g, 5%; 75% ee). Compounds (*S*,*S*)-**7b** and (*S*,*S*)-**7a** were deacetylated, respectively, with methanolic sodium methoxide (12 mL, 0.2 M) in methanol (50 mL), neutralized with Dowex-(H^+), concentrated, and purified by column chromatography (toluene−ethyl acetate; 1:2) to give (*S*,*S*)-diol (*S*,*S*)-**7** (2.41 g, 98%, 89% ee) and (*R*,*R*)-diol (*R*,*R*)-**7** (2.74 g, 98%, 63% ee), respectively.

(4*S*,5*S*)-4,5-Bis(hydroxymethyl)cyclohexene [(*S*,*S*)-7]. The (*S*,*S*)-diol was crystallized from diethyl ether and hexane to give enantiomerically pure (*S*,*S*)-diol (*S*,*S*)-**7** (2.01 g, 36%): mp 62−63 °C; $[\alpha]^{22}_D$ 75.2° (*c* 0.80, $CHCl_3$) (lit. $[\alpha]^{22}_D$ 75.1°).[19] Anal. Calcd for $C_8H_{14}O_2$: C, 67.58; H, 9.92. Found: C, 67.38; H, 10.08.

(4*R*,5*R*)-4,5-Bis(hydroxymethyl)cyclohexene [(*R*,*R*)-7]. The (*R*,*R*)-diol was crystallized from diethyl ether and hexane to give enantiomerically pure (*R*,*R*)-diol (*R*,*R*)-**7** (1.79 g, 32%): mp 62−63 ° C; $[\alpha]^{22}_D$ −76.4° (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_8H_{14}O_2$: C, 67.58; H, 9.92. Found: C, 67.64; H, 10.02.

(4*S*,5*S*)-4,5-Bis[(benzoyloxy)methyl]cyclohexene (8). To a solution of compound (*S*,*S*)-**7** (1.81 g, 12.7 mmol) in pyridine (10.2 mL) was added benzoyl chloride (5.1 mL, 44.2 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 30 min and at 80 °C for 2 h before crushed ice was added. After 30 min of additional stirring at room temperature the reaction mixture was diluted with dichloromethane, washed with 5% aqueous sodium hydrogene carbonate, dried, and concentrated. Purification by flash column chromatography (toluene−ethyl acetate; 12:1) followed by crystallization from diethyl ether−hexane gave compound **8** (4.36 g, 98%) as white needles: mp 76 °C; $[\alpha]^{22}_D$ 80.4° (*c* 0.96, $CHCl_3$); ^{1}H NMR δ (250.13 MHz, $CDCl_3$) 2.04−2.38 (m, 6 H), 4.77 (m, 4 H), 5.72 (s, 2 H), 7.31−8.09 (m, 10 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 27.22, 34.61, 66.67, 125.37, 126.34, 129.53, 130.17, 132.91, 166.54. Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.62; H, 6.26.

(4*R*,5*R*)-4,5-Bis[(benzoyloxy)methyl]-1,2-epoxycyclohexane (9). To a solution of compound **8** (3.74 g, 10.7 mmol) in dichloromethane (40 mL) was added *m*-chloroperoxybenzoic acid (3.2 g, 13.0 mmol) in portions at room temperature, and the reaction mixture was stirred for 4 h. The mixture was diluted with dichloromethane, washed with aqueous saturated sodium sulfite and aqueous sodium hydrogene carbonate, dried, and concentrated. Crystallization from diethyl ether and hexane gave compound **9** (3.42 g, 87%) as white needles: mp 118−119 °C; $[\alpha]^{22}_D$ 77.6° (*c* 0.88, $CHCl_3$); ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 1.69−2.42 (m, 6 H), 3.27 (m, 2 H), 4.34 (m, 4 H), 7.30−8.12 (m, 10 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 27.36, 28.76, 31.66, 34.40, 51.23, 52.46, 66.21, 66.44, 126.36, 129.51, 129.92, 132.99, 166.41. Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.11; H, 6.05. Found: C, 72.22; H, 6.08.

(1*R*,4*S*,5*R*)-4,5-Bis[(benzoyloxy)methyl]-1-hydroxycyclohex-2-ene (10). A 100-mL three-necked round-bottomed flask was connected to argon, flame dried, and charged with trimethylsilyl trifluoromethanesulfonate (1.64 mL, 9.0 mmol) and dry toluene (10 mL). To this mixture was added compound **9** (3.0 g, 8.2 mmol), 1,8-diazabicyclo[5.4.0]undec-7-en (1.52 mL, 10.2 mmol) in dry toluene (11 mL). The reaction mixture was stirred at room temperature for 20 h before trimethylsilyl trifluoromethanesulfonate (1.64 mL, 9.0 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.52 mL, 10.2 mmol) were added again. After 20 h of additional stirring the reaction mixture was diluted with toluene, washed with aqueous 0.1 M hydrochloric acid and aqueous sodium hydrogen carbonate, dried, and concentrated. The crude product was dissolved in methanol (70 mL) and aqueous hydrochloric acid (24 mL, 2 M), and the reaction mixture was stirred at room temperature for 5 h. The mixture was neutralized with sodium hydrogen carbonate, diluted with water, extracted with dichloromethane,

and dried. Concentration and purification by column chromatography (toluene−ethyl acetate, 1:4) gave compound **10** (2.59 g, 86%) as a colorless syrup: $[\alpha]^{22}_D$ 31.3° (c 0.67, $CHCl_3$); ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 1.72−1.82 (m, 1 H); 1.82−2.06 (m, 2 H), 2.39 (m, 1 H), 2.60 (m, 1 H), 4.32 (m, 1 H), 4.28−4.53 (m, 4 H), 5.85 (dd, J = 10.1, 2.3 Hz, 1 H), 5.94 (dq, J = 10.1, 3.7, 2.3 Hz, 1 H), 7.38−8.10 (m, 10 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 31.48, 33.26, 37.59, 63.44, 66.16, 66.66, 125.26, 126.40, 129.02, 129.56, 129.98, 130.43, 130.62, 133.04, 166.44. Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.11; H, 6.05. Found: C, 71.87; H, 6.08.

(1*R*,4*S*,5*R*)-1-Acetoxy-4,5-bis[(benzoyloxy)methyl]cyclohex-2-ene (11). Compound **10** (1.14 g, 3.1 mmol) was dissolved in pyridine (22 mL) and acetic anhydride (11 mL) was added. After stirring at room temperature for 3 h the reaction mixture was concentrated, codistilled with toluene, and purified by flash column chromatography (toluene−ethyl acetate, 6:1) to give compound **11** (1.22 g, 96%) as a colorless syrup: $[\alpha]^{22}_D$ −24.0° (c 0.85, $CHCl_3$); ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 1.84−2.11 (m, 2 H), 2.05 (s, 3 H), 2.38 (m, 1 H), 2.64 (m, 1 H), 4.38−4.56 (m, 4 H), 5.33 (m, 1 H), 6.00 (m, 2 H), 7.35−8.10 (m, 10 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 21.25, 30.34, 31.62, 37.54, 65.67, 66.10, 66.63, 126.40, 126.77, 129.57, 129.96, 132.72, 133.08, 166.38, 170.55. Anal. Calcd for $C_{24}H_{24}O_6$: C, 70.57; H, 5.92. Found: C, 70.47; H, 5.96.

(1*S*,4*S*,5*R*)-9-[4,5-Bis(hydroxymethyl)cyclohex-2-en-1-yl]-9*H*-adenine (12). To a stirred solution of adenine (0.18 g,1.3 mmol) in dry dimethylformamide (3.0 mL) was added sodium hydride (80% dispersion in oil, 0.037 g, 1.2 mmol), and the reaction mixture was stirred at room temperature under argon for 2 h. This frothy suspension was added dropwise to a suspension of **11** (0.42 g, 1.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.048 g, 0.04 mmol) in dry tetrahydrofuran (3.0 mL) under argon. The reaction mixture was immersed in a preheated oil bath (60 °C) and stirred for 20 h. After the mixture was cooled to room temperature, concentrated and purified by column chromatography (chloroform−methanol; 10:1), the protected adenine derivative was obtained. A solution of the protected adenine derivative in dry methanol (4.0 mL) was saturated with ammonia(g) and then heated in a bomb at 80 °C for 48 h. The ammonia was evaporated off under a stream of argon before the resulting solution was concentrated and purified by column chromatography (chloroform−methanol; 3:1) to give compound **12** (0.19 g, 69%): $[\alpha]^{22}_D$ −50.8° (*c* 0.66 DMSO); UV (H_2O) λ_{max} 262.2 nm; ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 1.72−2.10 (m, 4 H), 3.22−3.75 (m, 4 H), 4.54 (t, J = 5.3 Hz; 1 H), 4.81 (t, J = 5.3 Hz, 1 H), 5.15 (m, 1 H), 5.92 (dq, J = 9.9, 4.2, 2.0 Hz, 1 H), 6.18 (dq, J = 10.0, 2.5, 1.2 Hz, 1 H) 7.22 (b, 2H), 8.02 (s, 1 H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 30.45, 32.31, 40.87 (hidden in DMSO-d_6, detected in MeOH-d_4), 47.61, 62.40, 62.94, 119.22, 124.26, 136.33, 139.64, 149.10, 152.36, 156.07. Anal. Calcd for $C_{13}H_{17}O_2N_5$: C, 56.71; H, 6.22; N, 25.44. Found: C, 56.66; H, 6.19; N, 25.25 .

(1*S*,4*S*,5*R*)-9-[4,5-Bis(hydroxymethyl)cyclohex-2-en-1-yl]-9*H*-guanine (13). To a stirred solution of 2-amino-6-chloropurine (0.24 g, 1.4 mmol) in dry dimethylformamide (3.0 mL) was added sodium hydride (80% dispersion in oil, 0.038 g, 1.3 mmol), and the reaction mixture was stirred at room temperature under argon for 2 h. This frothy suspension was added dropwise to a suspension of **11** (0.44 g, 1.1 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.049 g, 0.04 mmol) in dry tetrahydrofuran (3.0 mL) under agron. The reaction mixture was immersed in a preheated oil bath (60 °C) and stirred for 20 h. After the mixture was cooled to room temperature, concentrated, and purified by column chromatography (toluene−ethyl acetate; 1:1), the protected 2-amino-6-chloropurine derivative was obtained. A solution of the protected 2-amino-6-chloropurine derivative in aqueous sodium hydroxide (8.0 mL, 1.0 M) was refluxed for 4 h. The reaction mixture was neutralized with aqueous hydrochloric acid (2 M). Concentration, filtration through a column of Sephadex LH-20 (water), and purification by preparative high-pressure liquid chromatography (water−methanol, 80:20, v/v) gave compound **13** (0.14 g, 46%): $[\alpha]^{22}_D$ 10.3° (*c* 0.98, DMSO); UV (H_2O) λ_{max} 252.8 nm; ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 1.61−2.09 (m, 4 H), 3.22−3.75 (m, 4 H), 4.54 (b, 1 H), 4.79 (b, 1 H), 4.93 (m, 1 H), 5.82 (dq, J = 10.0, 4.4, 2.0 Hz, 1 H), 6.05 (dq, J = 10.0, 2.7, 1.0 Hz, 1 H), 6.65 (s, 2 H), 7.68 (s, 1 H), 9.90 (b, 1 H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 30.60, 32.09, 40.81 (hidden in DMSO-d_6, detected in MeOH-d_4), 47.17, 62.36, 63.00, 116.94, 124.29, 136.16, 136.24, 150.72, 153.61, 157.09. Anal. Calcd for $C_{13}H_{17}O_3N_5 1.0H_2O$: C, 50.48; H, 6.19; N, 22.64. Found: C, 50.62; H, 5.93; N, 22.31.

(1*R*,4*S*,5*R*)-9-[4,5-Bis(hydroxymethyl)cyclohexan-1-yl]-9*H*-adenine (14). A suspension of compound **12** (0.028 g, 0.10 mmol) and 10% palladium on carbon (25 mg) in methanol (3.0 mL) was hydrogenated at atmospheric pressure for 24 h. The reaction mixture was filtered through celite and concentrated. Purification by column chromatography (chloroform−methanol; 3:1) gave compound **14** (0.028 g, 98%): $[\alpha]^{22}_D$ −2.3° (*c* 0.87, DMSO); ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 1.61−2.32 (m, 8 H), 3.47−3.71 (m, 4 H), 4.39−4.76 (m, 3 H), 7.15 (b, 2 H), 8.11 (s, 1 H), 8.23 (s, 1 H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 22.26, 27.66, 29.12, 36.31, 37.04, 50.01, 62.47, 62.77, 119.07, 139.35, 149.27, 152.10, 156.03. Anal. Calcd for $C_{13}H_{19}O_2N_5 \cdot 1.0H_2O \cdot 0.2$MeOH: C, 52.54; H, 7.28; N, 23.21. Found: C, 52.40; H, 7.24; N, 22.91.

(1*R*,4*S*,5*R*)-9-[4,5-Bis(hydroxymethyl)cyclohexan-1-yl]-9*H*-guanine (15). Compound **13** (0.045 g, 0.15 mmol) was hydrogenated as described for preparation of compound **14.** Purification by preparative high-pressure liquid chromatography (water−methanol, 80:20, v/v) gave compound **15** (0.043 g, 95%): $[\alpha]^{22}_D$ 3.2° (*c* 1.16 DMSO); ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 1.57−2.20 (m, 8 H), 3.47−3.65 (m, 4 H), 4.35 (m, 1 H), 4.58 (b, 2 H), 6.75 (b, 1 H), 7.77 (s, 1 H), 9.92 (b, 1 H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 22.30, 28.20, 29.14, 36.33, 37.04, 49.09, 62.47, 62.84, 116.64, 135.58, 150.77, 153.30, 156.95. Anal. Calcd for $C_{13}H_{19}O_3N_5 \cdot 1.1H_2O \cdot 0.4$MeOH: C, 49.65; H, 6.30; N, 21.67. Found: C, 49.61; H, 6.68; N, 21.91.

(1*R*,4*S*,5*R*)-9-[4,5-Bis(hydroxymethyl)cyclohex-2-en-1-yl]-9*H*-adenine (16). A 100-mL three-necked round-bottomed flask was connected to argon, flame dried, and charged with 6-chloropurine (0.29 g, 3.1 mmol), triphenylphosphine (0.49 g, 1.9 mmol) and dry tetrahydrofuran (11 mL). To the mixture was added dropwise diisopropyl azocarboxylate (0.37 mL, 1.9 mmol), and the resulting mixture was stirred at 0 °C for 30 min under argon. The reaction mixture was cooled to −78 °C before a suspension of **10** (0.46 g, 1.25 mmol) in dry tetrahydrofuran (5.5 mL) was added, and the mixture was stirred at 0 °C for 24 h. The solvent was evaporated and the residue was purified by column chromatograpy (toluene−ethyl acetate; 1:1) to give the protected 6-chloropurine derivative. A solution of the protected 6-chloropurine derivative in dry methanol (3.0 mL) was saturated with ammonia(g) and then heated in a bomb at 80 °C for 48 h. The ammonia was evaporated off under a stream of argon before the resulting solution was concentrated and purified by column chromatography (chloroform−methanol; 3:1) to give compound **16** (0.18 g, 52%): $[\alpha]^{22}_D$ 122.0° (*c* 1.00 DMSO); UV (H_2O) λ_{max} 261.6 nm; ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 1.59−2.28 (m, 4 H), 3.16−3.71 (m, 4 H), 4.64 (t, J = 5.2 Hz, 1 H), 4.74 (t, J = 5.2 Hz, 1 H), 5.08 (m, 1 H), 5.85 (d, J = 10.1 Hz, 1 H), 6.02 (dt, J = 10.2, 2.3 Hz), 7.22 (b, 2 H), 8.07 (s, 1 H), 8.12 (s, 1 H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 33.36, 37.55, 40.06 (hidden in DMSO-d_6, detected in MeOH-d_4), 51.33, 63.03, 63.27, 119.00, 127.09, 133.89, 138.92, 149.26, 152.35, 156.04. Anal. Calcd for $C_{13}H_{17}O_2N_5$: C, 56.71; H, 6.22; N, 25.44. Found: C, 56.46; H, 6.37; N, 25.32.

(1*R*,4*S*,5*R*)-9-[4,5-Bis(hydroxymethyl)cyclohex-2-en-1-yl]-9*H*-guanine (17). A 100-mL, three-necked, round-bottomed flask was connected to argon, flame dried, and charged with 2-amino-6-chloropurine (0.31 g, 1.8 mmol), triphenylphosphine (0.47 g, 1.8 mmol), and dry tetrahydrofuran (10 mL). To the mixture was added dropwise diisopropyl azocarboxylate (0.36 mL, 1.8 mmol), and the resulting mixture was stirred at 0 °C for 30 min. The reaction mixture was cooled to −78 °C before a suspension of **10** (0.44 g, 1.2 mmol) in dry tetrahydrofuran (5.0 mL) was added, and the mixture was stirred at 0 °C for 24 h. The solvent was evaporated and the residue was purified by column chromatography (toluene−ethyl acetate; 1:1) to give the protected 2-amino-6-chloropurine deriva-

tive. A solution of the protected 2-amino-6-chloropurine derivative in aqueous sodium hydroxide (6.5 mL, 0.5 M) was refluxed for 4 h. After the mixture was cooled to room temperature the pH was adjusted to 7 with 2 M aqueous hydrochloric acid. Concentration, filtration through a column of Sephadex LH-20 (water), and purification by preparative high-pressure chromatography (water−methanol, 80:20, v/v) gave compound **17** (0.12 g, 34%): $[\alpha]^{22}_D$ 25.1° (*c* 0.84, DMSO); UV (H_2O) λ_{max} 253.0 nm; ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 1.54−2.12 (m, 4 H), 3.18−3.71 (m, 4 H), 4.42−5.90 (b, 2 H), 4.98 (m, 1 H), 5.83 (d, J = 10.2 Hz, 1 H), 5.99 (dt, J = 10.0, 2.0 Hz, 1 H), 6.71 (b, 2H), 7.78 (s, 1 H), 9.89 (b, 1 H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 33.59, 37.56, 40.07 (hidden in DMSO-d_6, detected in MeOH-d_4), 50.65, 62.97, 63.26, 116.67, 127.11, 133.95, 134.93, 150.93, 153.63, 157.01. Anal. Calcd for $C_{13}H_{17}O_3N_5 \cdot 2.0H_2O$: C, 47.69; H, 6.47; N, 21.39. Found: C, 47.39; H, 5.68; N, 20.75. This was the best result obtained after repeated purification and duplicated elemental analysis.

(1*S*,4*S*,5*R*)-9-[4,5-Bis(hydroxymethyl)cyclohexan-1-yl]-9*H*-adenine (18). A suspension of compound **16** (0.058 g, 0.21 mmol) and 10% palladium on carbon (40 mg) in methanol (4.0 mL) was hydrogenated at atmospheric pressure for 24 h. The reaction mixture was filtered through celite and concentrated. Purification by column chromatography (chloroform−methanol; 3:1) gave compound **18** (0.058 g, 99%): $[\alpha]^{22}_D$ 3.5° (c 1.3, DMSO); ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 1.18−2.09 (m, 8 H), 3.32−3.60 (m, 4 H), 4.10 (b, 1 H), 4.25 (b, 1 H), 4.57 (m, 1 H), 7.18 (b, 2 H), 8.09 (s, 1 H), 8.14 (s, 1 H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 28.52, 31.61, 35.71, 40.32, 40.72, 53.70, 63.15, 119.07, 139.01, 149.13, 152.15, 156.02. Anal. Calcd for $C_{13}H_{19}O_2N_5 \cdot 0.75$MeOH: C, 54.80; H, 7.35; N, 23.24. Found: C, 54.77; H, 7.05; N, 23.04.

(1*S*,4*S*,5*R*)-9-[4,5-Bis(hydroxymethyl)cyclohexan-1-yl]-9*H*-guanine (19). Compound **17** (0.036 g, 0.12 mmol) was hydrogenated as described for preparation of compound **18.** Purification by HPLC (water−methanol, 80:20, v/v) gave compound **19** (0.034 g, 93%): $[\alpha]^{22}_D$ −12.2° (*c* 1.08, DMSO); ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 1.15−2.02 (m, 8 H), 3.18−3.63 (m, 4 H), 4.08 (m, 1 H), 4.47−4.59 (dt, J = 5.2, 5.1 Hz, 2 H), 6.48 (b, 2 H), 7.72 (s, 1 H), 9.95 (b, 1 H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 28.58, 31.68, 35.94, 40.58, 40.79, 52.91, 63.13, 116.69, 135.18, 150.66, 153.42, 156.95. Anal. Calcd for $C_{13}H_{19}O_3N_5 \cdot 0.8H_2O \cdot 0.2$MeOH: C, 50.46; H, 6.86; N, 22.29. Found: C, 50.69; H, 6.53; N, 22.09.

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