

# CONFORMATIONALLY LOCKED NUCLEOSIDE ANALOGUES BASED ON THE BRIDGEHEAD SUBSTITUTED 7-OXONORBORNANE AND THEIR ANTIVIRAL PROPERTIES

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Dedicated to the 75th anniversary of Professor Antonín Holý's birthday and the 25th anniversary of the discovery of antiviral nucleoside phosphonates.

We report on the preparation of novel 1'-homonucleoside derivatives locked in a West conformation by 1',4'-bridge consisting of annulated benzene or naphthalene ring. The crucial step of the synthesis was Diels–Alder reaction of an appropriate aryne with a suitable furane derivative. Antiviral properties of novel compounds were studied and slight activity against HCV was detected in several compounds.

**Keywords:** 1'-Homonucleosides; Diels–Alder reaction; Cycloaddition; Antiviral agents.

For several decades, modified nucleoside analogues have been a synonym for extremely attractive topic in antiviral drug discovery<sup>1</sup>. In this context, conformationally locked nucleosides (CLNs) have attracted considerable attention of researchers especially due to the findings of Marquez and co-workers<sup>2</sup>, which were connected to the conformational preference studies of various enzymes involved in the metabolism and antiviral action of nucleoside derivatives. Their research resulted also in the discovery of N-MCT **1** that possesses significant activity against herpes viruses and provided solid base for further exploration of the CLNs<sup>3</sup>.

In parallel, the discovery of locked nucleic acids (LNA) **2** provided the second important stimulus for the exploration of bicyclic and tricyclic

nucleoside derivatives. The success of LNA has been based on the unique influence of certain CLN monomers incorporation into structure of oligonucleotides resulting in significant improvement of their hybridization properties<sup>4</sup>.

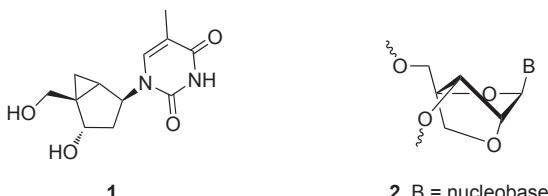


CHART 1

Both these impulses led to intensive studies of variously locked nucleosides. The research in this field was recently reviewed in detail<sup>5</sup>.

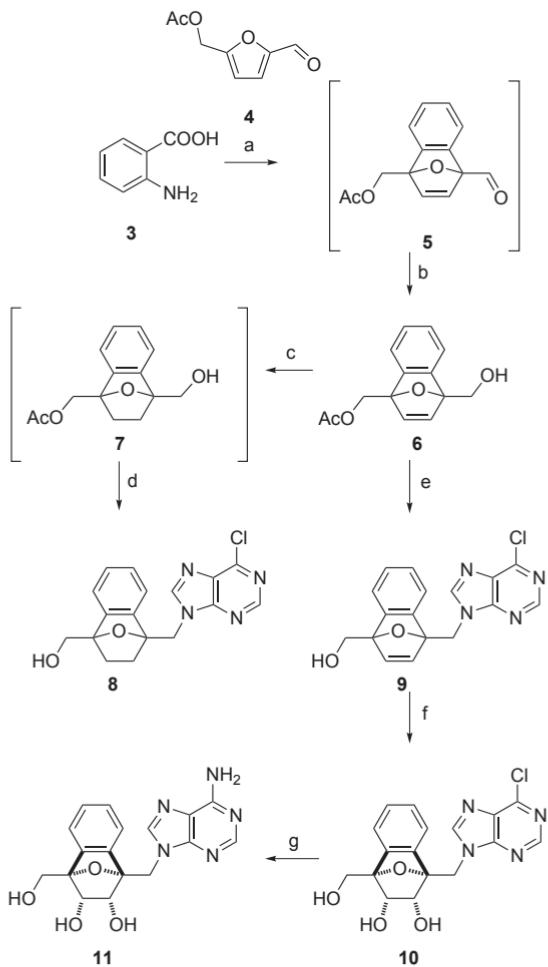
In our laboratory we have synthesized a broad library of locked nucleoside analogues containing compounds with significant activity against the Coxsackie B3 virus<sup>6</sup>. After a very recent discovery<sup>7</sup> that carbocyclic nucleoside analogues with an annulated benzene ring bear a remarkable activity against the Coxsackie B3 virus, we have decided to synthesize also non-carbocyclic nucleoside analogues with an annulated benzene ring in order to investigate their antiviral activity. Furthermore, our detailed SAR investigation revealed that 6-chloropurine derivatives possess the highest anti-Coxsackie activity<sup>8</sup>.

Goal of this project was to design and prepare a series of conformationally constrained nucleoside analogues with an aromatic ring employed as the locking bridge and to test these compounds for antiviral properties.

First of all, we prepared a dideoxyderivative **8** by five-step procedure starting with the Diels–Alder reaction of 5-acetoxymethyl-2-furanaldehyde (**4**) as a diene with *in situ* generated benzyne carried out by a slightly modified literature procedure<sup>9</sup>, which furnished compound **5**. This unstable adduct was immediately reduced to an unsaturated derivative **6**, which was obtained in 67% yield over two steps. Hydrogenation of this product provided saturated analogue **7**, which was used in the next step without purification. The nucleobase was introduced by means of Mitsunobu reaction (with 6-chloropurine, triphenylphosphine and diisopropylazodicarboxylate) and subsequently the hydroxymethyl group was deprotected with potassium hydrogencarbonate in the same pot (52% yield over three steps). The obtained chloropurine derivative **8** was subjected to antiviral screening. In addition, we obtained the unsaturated analogue **9** in good yield (59% over

two steps), by similar nucleobase introduction and deprotection, employing the intermediate **6** (Scheme 1).

Nucleoside **9** was further transformed to its *cis*-hydroxy derivative **10** utilizing osmium tetroxide. The chlorine atom at the C-6 position of the nucleobase was subsequently ammonolyzed to form an adenine derivative **11** (see Scheme 1). Although the reaction afforded product in good yields, pu-

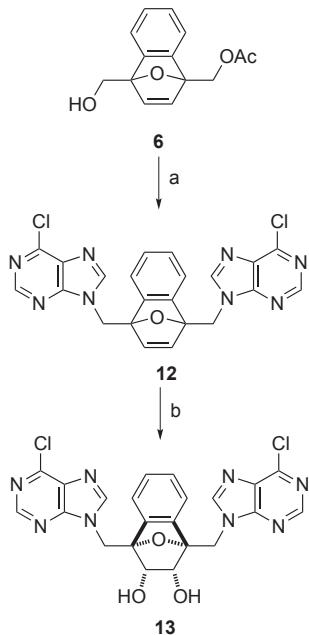


a) i. isoamyl nitrite,  $\text{Cl}_3\text{CCOOH}$ , dioxane; ii. **4**, toluene,  $60^\circ\text{C}$ ;  
 b)  $\text{NaBH}_4$ ,  $\text{MeOH}$ ,  $0^\circ\text{C}$ , 67% (two steps from **4**); c)  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2$ ,  $\text{MeOH}$ ;  
 d) i. 6-chloropurine,  $\text{Ph}_3\text{P}$ , DIAD, dioxane; ii.  $\text{KHCO}_3$ ,  $\text{MeOH}$ , 52% (three steps); e) i. 6-chloropurine,  $\text{Ph}_3\text{P}$ , DIAD, dioxane; ii.  $\text{KHCO}_3$ ,  $\text{MeOH}$ , 59% (two steps); f)  $\text{OsO}_4$ , NMMO, dioxane/ $\text{H}_2\text{O}$ , 79%; g)  $\text{NH}_3$ ,  $90^\circ\text{C}$ , 75%.

SCHEME 1

rification was somewhat tricky due to very low solubility of the compound. Satisfactorily pure product was obtained by precipitation from hot DMF solution with methanol.

Moreover, nucleoside analogues **12** and **13** with two 6-chloropurine nucleobases were prepared after deprotection of **6** by double Mitsunobu reaction and subsequent *cis*-hydroxylation, respectively (Scheme 2).



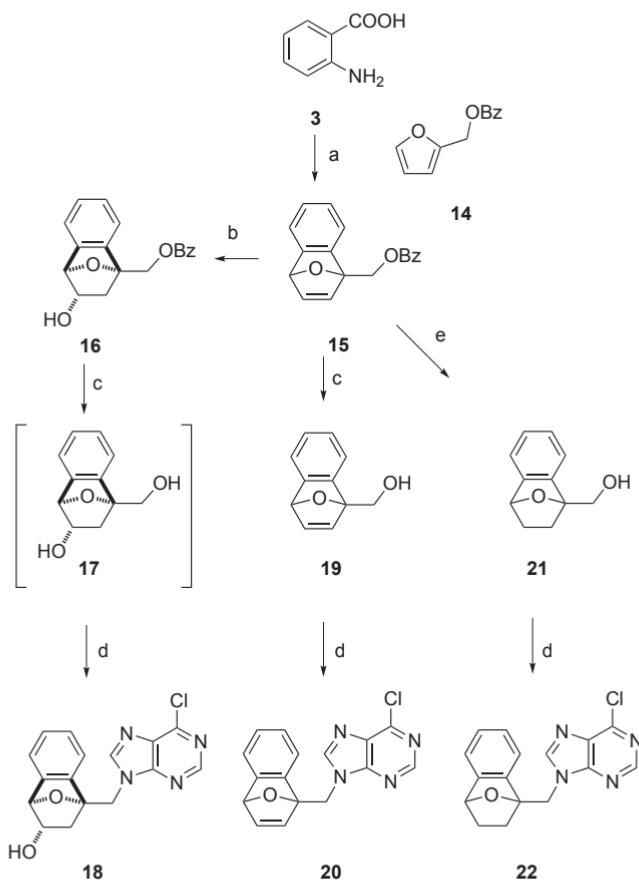
a) i.  $\text{K}_2\text{CO}_3$ ,  $\text{MeOH}$ ; ii. 6-chloropurine,  $\text{Ph}_3\text{P}$ ,  $\text{DIAD}$ ,  $\text{THF}$ , 57% (two steps); b)  $\text{OsO}_4$ ,  $\text{NMMO}$ , dioxane/ $\text{H}_2\text{O}$ , 59%.

SCHEME 2

Since a number of C-4'-truncated nucleoside derivatives exerted significant anti-Coxsackievirus activities in our previous studies, we decided to prepare analogues missing hydroxymethyl group derived from this series as well.

The initial step of their synthesis was also Diels–Alder reaction of benzyne with furfuryl benzoate **14**. Double bond of **15** was hydroborated with borane-tetrahydrofuran complex to provide alcohol **16**, however yield of this reaction was low since complicated mixtures containing mainly compounds with disconnected oxygen bridge. Despite this unfortunate complication the derivative **18** was synthesized in two simple steps, alcohol

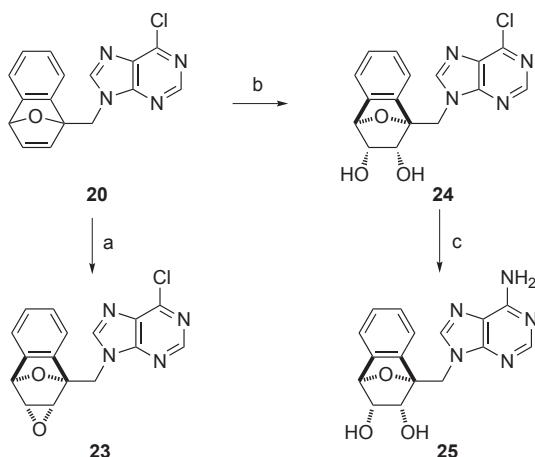
deprotection and introduction of the nucleobase by Mitsunobu reaction (Scheme 3).



a) i. isoamyl nitrite,  $\text{Cl}_3\text{CCOOH}$ , dioxane; ii. 14, toluene, 60 °C, 90%;  
 b) i.  $\text{BH}_3\text{-THF}$ , THF; ii.  $\text{NaBO}_3\text{-}4\text{H}_2\text{O}$ ,  $\text{H}_2\text{O}$ , 37%; c)  $\text{MeONa}$ ,  $\text{MeOH}$   
 80% for 17, 91% for 19; d) 6-chloropurine,  $\text{Ph}_3\text{P}$ , DIAD, THF, 79% for 18,  
 72% for 20, 76% for 22; e) i.  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2/\text{C}$ ,  $\text{MeOH}$ ; ii.  $\text{MeONa}$ ,  $\text{MeOH}$ ,  
 87% (two steps)

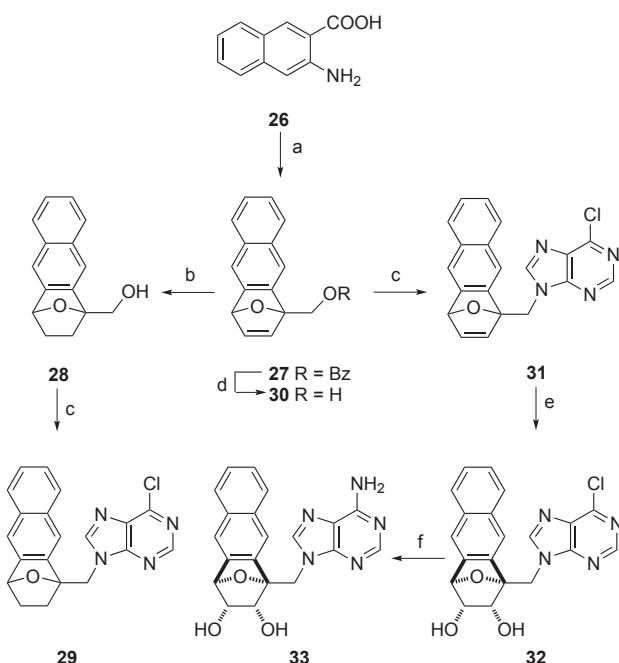
SCHEME 3

Analogue 20 and 22 were synthesized in a very similar manner as the hydroxymethyl-bearing analogues 8 and 9. After debenzoylation of the intermediate 15, the nucleobase was either directly introduced by Mitsunobu reaction to obtain analogue 20 or the double bond was hydrogenated first and the 6-chloropurine was put on afterwards to give the saturated counterpart 22 (see Scheme 3).



a) mCPBA, DCM, 64%; b)  $\text{OsO}_4$ , NMMO, acetone/ $\text{H}_2\text{O}$ , 62%;  
c)  $\text{NH}_3$ , 63%

SCHEME 4



SCHEME 5

Furthermore, reaction of **20** with *meta*-chloroperoxybenzoic acid afforded tetracyclic compound **23**. The unsaturated derivative **20** was also utilized in the synthesis of derivatives **24** and **25**, which were prepared by *cis*-hydroxylation of the double bond by osmium tetroxide. Compound **24** was transformed into **25** by heating the 6-chloropurine derivative with liquid ammonia in an autoclave (Scheme 4).

Compounds with an annulated napthalene were prepared similarly to the above described procedure – naphtyne generated *in situ* from 3-amino-2-naphtoic acid (**26**) was used as a dienophile in the Diels–Alder reaction and this procedure afforded compound **27**. Deprotection followed by Mitsunobu reaction resulted in the formation of **31**, which was further oxidized to **32**, and subsequently transformed into appropriate adenine derivative **33**. Also saturated derivative **29**, analogous to **22**, was prepared employing hydrogenation procedure into the reaction sequence (Scheme 5).

TABLE I  
Anti-HCV activities and cytotoxicity of the synthesized compounds

Entry	Compound	EC <sub>50</sub> , $\mu\text{M}$	CC <sub>50</sub> , $\mu\text{M}$
1	<b>8</b>	66.5	89.3
2	<b>9</b>	63.9	>100
3	<b>10</b>	45.1	>100
4	<b>11</b>	>100	>100
5	<b>12</b>	44.4	>100
6	<b>13</b>	>100	>100
7	<b>18</b>	68.7	95.2
8	<b>20</b>	16.1	72.4
9	<b>22</b>	21.9	72.6
10	<b>23</b>	21.4	73.8
11	<b>24</b>	>100	>100
12	<b>25</b>	>100	>100
13	<b>27</b>	11.0	13.6
14	<b>28</b>	8.01	11.1
15	<b>29</b>	6.31	11.6
16	<b>30</b>	85.3	>100

In conclusion, we prepared a series of novel 1'-homonucleoside analogues with conformation of the sugar ring locked in the West position by bridge consisting of either benzene or naphthalene ring. Our synthetic approach presents a concise and robust pathway towards these nucleoside derivatives.

The presented compounds underwent antiviral screening against a number of RNA viruses. Although none of the presented compounds exerted significant anti-Coxsackie virus activity (higher than 50  $\mu$ M), some of them possessed modest anti-HCV activity, which unfortunately largely correlated with cytotoxicity. The results of the anti-HCV screening are summarized in Table I. The highest selectivity index was observed for compound 20, which exerts  $EC_{50} = 16.1 \mu$ M and  $CC_{50} = 72.4 \mu$ M. Compound 29 significantly reduced the growth of CCRF-CEM cells with  $IC_{50} = 5.73 \mu$ M.

## EXPERIMENTAL

Melting points were determined on a Büchi B-540 apparatus. NMR spectra ( $\delta$ , ppm;  $J$ , Hz) were measured on a Bruker Avance II-600 and/or Bruker Avance II-500 instruments (600.1 or 500.0 MHz for  $^1H$  and 150.9 or 125.7 MHz for  $^{13}C$ ) in hexadeuterated dimethyl sulfoxide or  $CDCl_3$  and referenced to the solvent signal ( $DMSO-d_6$   $\delta$  2.50 and 39.70, respectively) or internal standard (TMS). Mass spectra were measured on a LTQ Orbitrap XL (Thermo Fisher Scientific) using electrospray ionization (ESI). Column chromatography was performed on Silica gel 60 (Fluka) and thin-layer chromatography (TLC) on Silica gel 60  $F_{254}$  foils (Merck). Solvents were evaporated at 2 kPa and bath temperature 30–60 °C; the compounds were dried at 13 Pa and 50 °C. The elemental analyses were obtained on a Perkin–Elmer CHN Analyzer 2400, Series II Sys (Perkin–Elmer). The elemental compositions for all compounds agreed to within  $\pm 0.4\%$  of the calculated values.

### [4-(Hydroxymethyl)-1,4-epoxynaphthalen-1(4H)-yl]methyl Acetate (6)

To a solution of anthranilic (1.02 g, 7.4 mmol) and trichloroacetic acids (10 mg, 0.06 mmol) in dry dioxane (15 ml) at 0 °C, isoamyl nitrite (1.4 g, 11.9 mmol) was added dropwise. This mixture was stirred at r.t. for 90 min, diazonium salt was filtered off and washed with dioxane (2  $\times$  5 ml, the salt was never allowed to dry entirely) and added to a solution of 5-acetoxymethyl-2-furaldehyde (1 g, 6 mmol) in dry dioxane (20 ml). Reaction mixture was heated to 60 °C for 2 h (evolution of  $N_2$  and  $CO_2$ ). Evaporation of volatiles afforded brown slurry of the crude aldehyde, which was without further purification dissolved in methanol (50 ml), cooled to 0 °C and to this solution solid  $NaBH_4$  (140 mg, 3.6 mmol) was added portionwise. After 1 h of stirring at 0 °C, the solvent was evaporated and chromatography of the residue on silica (hexanes/ethyl acetate 1:1) afforded 6 (990 mg, 67%) as a white solid. Analytical sample was crystallized from toluene/cyclohexane mixture (white needles). M.p. 84–85 °C. ESI MS  $m/z$  (%): 269.1 (100) [M + Na].  $^{13}C$  NMR (DMSO): 20.82 ( $CH_3$ ); 58.95 (8- $CH_2$ ); 61.10 (1- $CH_2$ ); 90.23 (C-1); 93.22 (C-8); 119.28 (C-3); 119.82 (C-6); 124.73 and 124.93 (C-4, C-5); 143.61 (C-10); 145.11 (C-9); 149.95 (C-2); 150.73 (C-7); 170.53 (COO).  $^1H$  NMR (DMSO): 2.06 s, 3 H ( $CH_3$ ); 4.10 dd, 1 H,  $J_{gem} = 12.4$ ,  $J(CH_2-OH) = 5.7$  and 4.24 dd,

1 H,  $J_{\text{gem}} = 12.5$ ,  $J(\text{CH}_2\text{-OH}) = 6.0$  (8-CH<sub>2</sub>O); 4.78 d, 1 H,  $J_{\text{gem}} = 12.7$  and 4.89 d, 1 H,  $J_{\text{gem}} = 12.7$  (1-CH<sub>2</sub>O); 5.23 t, 1 H,  $J(\text{OH-CH}_2) = 5.9$  (OH); 6.93 d, 1 H,  $J(10\text{-}9) = 5.4$  (H-10); 6.94–6.97 m, 2 H (H-4, H-5); 7.01 d, 1 H,  $J(9\text{-}10) = 5.4$  (H-9); 7.21 m, 1 H (H-3); 7.27 m, 1 H (H-6). For C<sub>14</sub>H<sub>14</sub>O<sub>4</sub> (246.26) calculated: 68.28% C, 5.73% H; found: 68.52% C, 5.46% H.

{(1S\*,4R\*)-4-[(6-Chloro-9H-purin-9-yl)methyl]-3,4-dihydro-1,4-epoxynaphthalen-1(2H)-yl}-methanol (8)

To a solution of **6** (200 mg, 0.8 mmol) in dry methanol (10 ml) was added Pd(OH)<sub>2</sub>/C (30 mg) and the mixture was hydrogenated (10 atm) overnight. Catalyst was filtered off on a cellulose pad and after evaporation of the solvent (200 mg of hydrogenated product), PPh<sub>3</sub> (430 g, 1.6 mmol), 6-chloropurine (190 mg, 1.2 mmol) and dry dioxane (20 ml) were added and a solution of DIAD (250  $\mu$ l, 1.2 mmol) in dry dioxane (5 ml) was introduced dropwise afterwards. Reaction mixture was stirred at r.t. overnight, volatiles were evaporated and chromatography on silica (hexanes/ethyl acetate 1:1) afforded crude acetylated compound, which was without further purification dissolved in methanol (50 ml) and stirred with solid KHCO<sub>3</sub> (400 mg, 4 mmol) for 2 h. After the solvent was evaporated, chromatography of the residue on silica (hexanes/ethyl acetate 1:3) afforded **8** (142 mg, 52%) as a white solid. Analytical sample was crystallized from toluene (white needles). M.p. 178 °C. ESI MS *m/z* (%): 343.1 (12) [M + H], 365.1 (100) [M + Na], 707.1 (3) [2M + Na]. <sup>13</sup>C NMR (DMSO): 29.95 (C-9'); 31.01 (C-10'); 43.68 (CH<sub>2</sub>N); 60.32 (CH<sub>2</sub>O); 86.59 (C-1'); 88.98 (C-8'); 118.01 (C-3'); 118.90 (C-6'); 126.52 (C-4'); 126.96 (C-5'); 130.27 (C-5); 144.63 (C-2'); 146.54 (C-7'); 148.38 (C-8); 149.30 (C-6); 151.96 (C-2); 152.48 (C-4). <sup>1</sup>H NMR (DMSO): 1.29 ddd, 1 H,  $J_{\text{gem}} = 11.5$ ,  $J(9'\text{en-}10'\text{en}) = 8.8$ ,  $J(9'\text{en-}10'\text{ex}) = 4.1$  (H-9'endo); 1.49 ddd, 1 H,  $J_{\text{gem}} = 11.6$ ,  $J(10'\text{en-}9'\text{en}) = 8.8$ ,  $J(10'\text{en-}9'\text{ex}) = 4.1$  (H-10'endo); 1.84 m, 1 H (H-10'exo); 1.99 td, 1 H,  $J_{\text{gem}} = J(9'\text{ex-}10'\text{ex}) = 11.0$ ,  $J(9'\text{ex-}10'\text{en}) = 3.9$  (H-9'exo); 4.06 dd, 1 H,  $J_{\text{gem}} = 12.4$ ,  $J(\text{CH}_2\text{-OH}) = 6.0$  and 4.10 dd, 1 H,  $J_{\text{gem}} = 12.4$ ,  $J(\text{CH}_2\text{-OH}) = 5.5$  (CH<sub>2</sub>O); 5.05 t, 1 H  $J(\text{OH-CH}_2) = 5.8$  (OH); 5.09 d, 1 H,  $J_{\text{gem}} = 15.2$  and 5.30 d, 1 H,  $J_{\text{gem}} = 15.2$  (CH<sub>2</sub>N); 7.09 td, 1 H,  $J(4'\text{-}5') = J(4'\text{-}3') = 7.4$ ,  $J(4'\text{-}6') = 1.0$  (H-4'); 7.14 td, 1 H,  $J(5'\text{-}4') = J(5'\text{-}6') = 7.4$ ,  $J(5'\text{-}3') = 1.0$  (H-5'); 7.26 td, 1 H,  $J(6'\text{-}5') = 7.2$ ,  $J(6'\text{-}3') = J(6'\text{-}4') = 1.0$  (H-6'); 7.30 td, 1 H,  $J(3'\text{-}4') = 7.3$ ,  $J(3'\text{-}5') = J(3'\text{-}6') = 1.0$  (H-3'); 8.54 s, 1 H (H-8); 8.89 s, 1 H (H-2). For C<sub>17</sub>H<sub>15</sub>ClN<sub>4</sub>O<sub>2</sub> (342.78) calculated: 59.57% C, 4.41% H, 16.34% N, 10.34% Cl; found: 59.62% C, 4.39% H, 16.09% N, 10.59% Cl.

{4-[(6-Chloro-9H-purin-9-yl)methyl]-1,4-epoxynaphthalen-1(4H)-yl}methanol (9)

To a mixture of **6** (645 mg, 2.6 mmol), PPh<sub>3</sub> (1.4 g, 5.2 mmol) and 6-chloropurine (605 mg, 4 mmol) in dry dioxane (50 ml), a solution of DIAD (800  $\mu$ l, 4 mmol) in dry dioxane (15 ml) was added dropwise. Reaction was refluxed 6 h, volatiles were evaporated and chromatography on silica (hexanes/ethyl acetate 2:1) afforded crude acetylated compound, which was without further purification dissolved in methanol and stirred with solid KHCO<sub>3</sub> (1.3 g, 13 mmol) for 30 min. After the solvent was evaporated, chromatography of the residue on silica (hexanes/ethyl acetate 1:4) afforded **9** (523 mg, 59%) as a white solid. Analytical sample was crystallized from toluene (white needles). M.p. 180 °C. ESI MS *m/z* (%): 341.1 (14) [M + H], 363.0 (100) [M + Na]. <sup>13</sup>C NMR (DMSO): 42.40 (CH<sub>2</sub>N); 58.78 (CH<sub>2</sub>OH); 90.91 (C-1'); 93.30 (C-8'); 119.10 (C-3'); 120.00 (C-6'); 124.88 (C-4'); 125.22 (C-5'); 130.49 (C-5); 143.25 (C-10'); 146.09 (C-9'); 148.26 (C-8); 149.36 (C-6); 149.46 (C-2'); 150.66 (C-7'); 151.99 (C-2); 152.39 (C-4). <sup>1</sup>H NMR (DMSO): 4.07 dd, 1 H,  $J_{\text{gem}} = 12.5$ ,  $J(\text{CH}_2\text{-OH}) = 5.6$  and

4.21 dd, 1 H,  $J_{\text{gem}} = 12.5$ ,  $J(\text{CH}_2\text{-OH}) = 5.8$  ( $\text{CH}_2\text{O}$ ); 5.18 t, 1 H  $J(\text{OH-CH}_2) = 5.7$  ( $\text{OH}$ ); 5.22 d, 1 H,  $J_{\text{gem}} = 15.3$  and 5.42 d, 1 H,  $J_{\text{gem}} = 15.3$  ( $\text{CH}_2\text{N}$ ); 6.93–7.00 m, 4 H ( $\text{H-4}', \text{H-5}, \text{H-9}', \text{H-10}'$ ); 7.26 m, 1 H ( $\text{H-6}'$ ); 7.37 m, 1 H ( $\text{H-3}'$ ); 8.66 s, 1 H ( $\text{H-8}$ ); 8.88 s, 1 H ( $\text{H-2}$ ). For  $\text{C}_{17}\text{H}_{13}\text{ClN}_4\text{O}_2$  (340.76) calculated: 59.92% C, 3.85% H, 16.44% N, 10.40% Cl; found: 59.80% C, 3.90% H, 16.15% N, 10.59% Cl.

(1*R*<sup>\*,2*R*<sup>\*,3*S*<sup>\*,4*S*<sup>\*</sup></sup></sup></sup>)-1-[(6-Chloro-9*H*-purin-9-yl)methyl]-4-(hydroxymethyl)-1,2,3,4-tetrahydro-1,4-epoxynaphthalene-2,3-diol (10)

To a solution of **9** (210 mg, 0.6 mmol) in dioxane/water mixture (4:1, 25 ml), NMNO (50% w/w solution in water, 1.5 ml), a 2% w/w solution of  $\text{OsO}_4$  in water (40  $\mu\text{l}$ ) was added and the reaction mixture was stirred at r.t. for 48 h. Volatiles were evaporated and chromatography on silica (ethyl acetate/ acetone/ethanol/water 20:3:1.2:0.8) and subsequent crystallization from methanol afforded **10** (185 mg, 79%) as a white powder. M.p. >230 °C (decomp.). ESI MS  $m/z$  (%): 373.1 (100) [M – H]. <sup>13</sup>C NMR (DMSO): 40.98 ( $\text{CH}_2\text{N}$ ); 58.01 ( $\text{CH}_2\text{O}$ ); 71.21 (C-9); 71.90 (C-10); 89.15 (C-1); 90.91 (C-8); 119.50 (C-3); 121.28 (C-6); 127.18 (C-4); 127.70 (C-5); 130.22 (C-5'); 142.62 (C-2); 145.10 (C-7); 148.19 (C-8'); 149.18 (C-6'); 151.87 (C-2'); 152.65 (C-4'). <sup>1</sup>H NMR (DMSO): 3.74 dd, 1 H,  $J(9\text{-OH}) = 6.5$ ,  $J(9\text{-10}) = 5.7$  ( $\text{H-9}$ ); 3.84 dd, 1 H,  $J(10\text{-OH}) = 6.5$ ,  $J(10\text{-9}) = 5.7$  ( $\text{H-10}$ ); 4.03 dd, 1 H,  $J_{\text{gem}} = 12.0$ ,  $J(\text{CH}_2\text{Ob-OH}) = 4.8$  ( $\text{CH}_2\text{Ob}$ ); 4.19 dd, 1 H,  $J_{\text{gem}} = 12.0$ ,  $J(\text{CH}_2\text{Oa-OH}) = 6.5$  ( $\text{CH}_2\text{Oa}$ ); 4.84 dd, 1 H,  $J(\text{OH-CH}_2) = 5.8$  and 4.8 ( $\text{CH}_2\text{O}$ ); 5.22 d, 1 H,  $J(\text{OH-9}) = 6.5$  ( $\text{9-OH}$ ); 5.24 d, 1 H,  $J(\text{OH-10}) = 6.6$  ( $\text{10-OH}$ ); 4.92 and 5.33 d, 2 H,  $J_{\text{gem}} = 15.4$  ( $\text{CH}_2\text{N}$ ); 7.03 td, 1 H,  $J(4\text{-5}) = J(4\text{-3}) = 7.5$ ,  $J(4\text{-6}) = 1.1$  ( $\text{H-4}$ ); 7.13 td, 1 H,  $J(5\text{-4}) = J(5\text{-6}) = 7.5$ ,  $J(5\text{-3}) = 1.1$  ( $\text{H-5}$ ); 7.18 dm, 1 H,  $J(3\text{-4}) = 7.4$  ( $\text{H-3}$ ); 7.35 dm, 1 H,  $J(6\text{-5}) = 7.3$  ( $\text{H-6}$ ); 8.50 s, 1 H ( $\text{H-8}'$ ); 8.89 s, 1 H ( $\text{H-2}'$ ). For  $\text{C}_{17}\text{H}_{15}\text{ClN}_4\text{O}_4$  (374.78) calculated: 54.48% C, 4.03% H, 14.95% N, 9.46% Cl; found: 54.42% C, 4.05% H, 15.15% N, 9.46% Cl.

(1*R*<sup>\*,2*R*<sup>\*,3*S*<sup>\*,4*S*<sup>\*</sup></sup></sup></sup>)-1-[(6-Amino-9*H*-purin-9-yl)methyl]-4-(hydroxymethyl)-1,2,3,4-tetrahydro-1,4-epoxynaphthalene-2,3-diol (11)

A solution of **10** (120 mg, 0.3 mmol) in liquid ammonia (20 ml) was heated in autoclave at 90 °C overnight. Ammonia was evaporated and the remaining solid was extracted with hot water (5 × 50 ml) to afford **11** (80 mg, 75%) as a brownish powder. M.p. 166 °C. ESI MS  $m/z$  (%): 356.1 (24) [M + H], 378.1 (100) [M + Na], 733.2 (5) [2M + Na]. <sup>13</sup>C NMR (DMSO): 39.95 ( $\text{CH}_2\text{N}$ ); 58.13 ( $\text{CH}_2\text{O}$ ); 71.16 (C-9); 72.01 (C-10); 89.45 (C-1); 90.75 (C-8); 118.03 (C-5'); 119.52 (C-3); 121.17 (C-6); 127.09 (C-4); 127.51 (C-5); 141.39 (C-8'); 143.06 (C-2); 145.17 (C-7); 150.21 (C-4'); 152.71 (C-2'); 156.11 (C-6'). <sup>1</sup>H NMR (DMSO): 3.74 dd, 1 H,  $J(9\text{-OH}) = 6.5$ ,  $J(9\text{-10}) = 5.7$  ( $\text{H-9}$ ); 3.81 dd, 1 H,  $J(10\text{-OH}) = 6.5$ ,  $J(10\text{-9}) = 5.7$  ( $\text{H-10}$ ); 4.04 dd, 1 H,  $J_{\text{gem}} = 11.9$ ,  $J(\text{CH}_2\text{Ob-OH}) = 4.9$  ( $\text{CH}_2\text{Ob}$ ); 4.20 dd, 1 H,  $J_{\text{gem}} = 11.9$ ,  $J(\text{CH}_2\text{Oa-OH}) = 6.2$  ( $\text{CH}_2\text{Oa}$ ); 4.87 dd, 1 H,  $J(\text{OH-CH}_2) = 6.2$  and 5.0 ( $\text{CH}_2\text{O}$ ); 4.71 and 5.14 d, 2 H,  $J_{\text{gem}} = 15.4$  ( $\text{CH}_2\text{N}$ ); 5.14 d, 1 H,  $J(\text{OH-9}) = 6.5$  ( $\text{9-OH}$ ); 5.32 d, 1 H,  $J(\text{OH-10}) = 6.5$  ( $\text{10-OH}$ ); 7.00 td, 1 H,  $J(4\text{-5}) = J(4\text{-3}) = 7.5$ ,  $J(4\text{-6}) = 1.1$  ( $\text{H-4}$ ); 7.09 dm, 1 H,  $J(3\text{-4}) = 7.4$  ( $\text{H-3}$ ); 7.11 td, 1 H,  $J(5\text{-4}) = J(5\text{-6}) = 7.4$ ,  $J(5\text{-3}) = 1.1$  ( $\text{H-5}$ ); 7.18 bs, 2 H ( $\text{NH}_2$ ); 7.35 dm, 1 H,  $J(6\text{-5}) = 7.3$  ( $\text{H-6}$ ); 7.94 s, 1 H ( $\text{H-8}'$ ); 8.25 s, 1 H ( $\text{H-2}'$ ). For  $\text{C}_{17}\text{H}_{17}\text{N}_5\text{O}_4 \cdot 1/2\text{H}_2\text{O}$  (364.36) calculated: 56.04% C, 4.98% H, 19.22% N; found: 55.83% C, 5.03% H, 18.89% N.

**9,9'-[*(1R\*,4S\*)-1,4-Epoxyphthalene-1,4-diyl*dimethanediyl]bis(6-chloro-9*H*-purine) (12)**

To a solution of **6** (250 mg, 1 mmol) in methanol (20 ml), potassium carbonate (300 mg, 2.2 mmol) was added and this suspension was stirred at r.t. for 15 min. The reaction mixture was diluted with water (50 ml), extracted with ethyl acetate (3 × 50 ml), combined organic extracts were dried over sodium sulfate and evaporated. To a solution of thus prepared diol,  $\text{PPh}_3$  (1.05 g, 4 mmol) and 6-chloropurine (462 mg, 3 mmol) in dry THF (30 ml), a solution of DIAD (600  $\mu\text{l}$ , 3 mmol) in dry THF (5 ml) was added dropwise. Reaction was stirred at r.t. overnight, volatiles were evaporated and chromatography on silica (ethyl acetate/hexanes/acetone 14:7:4) and subsequent crystallization from toluene afforded **12** (270 mg, 57%) as white crystals. M.p. 241 °C. ESI MS  $m/z$  (%): 477.1 (17) [M + H], 499.1 (100) [M + Na].  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 42.10 ( $\text{CH}_2\text{N}$ ); 91.69 (C-1', C-8'); 119.45 (C-3', C-6'); 126.09 (C-4', C-5'); 131.10 (C-5); 144.41 (C-9', C-10'); 145.91 (C-8); 147.40 (C-2', C-7'); 151.39 (C-6); 151.95 (C-4); 152.14 (C-2).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 5.16 d, 2 H,  $J_{\text{gem}} = 15.4$  and 5.26 d, 2 H,  $J_{\text{gem}} = 15.2$  ( $\text{CH}_2\text{N}$ ); 6.84 s, 2 H (H-9', H-10'); 6.97 m, 2 H (H-4', H-5'); 7.23 m, 2 H (H-3', H-6'); 8.28 s, 2 H (H-8); 8.83 s, 2 H (H-2). For  $\text{C}_{22}\text{H}_{14}\text{Cl}_2\text{N}_8\text{O}\cdot\text{C}_6\text{H}_{12}$  (561.47) calculated: 59.90% C, 4.67% H, 19.96% N, 12.63% Cl; found: 59.72% C, 4.51% H, 19.85% N, 12.35% Cl.

**(1*R\*,2R\*,3S\*,4S\*)-1,4-Bis***[(6-chloro-9*H*-purin-9-yl)methyl]-1,2,3,4-tetrahydro-1,4-epoxynaphthalene-2,3-diol (13)

To a solution of **12** (150 mg, 0.3 mmol) in dioxane/water mixture (4:1, 20 ml), NMMO (50% w/w solution in water, 0.7 ml), a 2% w/w solution of  $\text{OsO}_4$  in water (30  $\mu\text{l}$ ) was added and the reaction mixture was stirred at r.t. for 48 h. Product, which gradually precipitated from the reaction mixture, was filtered off and crystallized from DMF/methanol mixture affording **13** (95 mg, 59%) as a grayish powder. M.p. >300 °C (decomp.). ESI MS  $m/z$  (%): 511.1 (12) [M + H], 533.1 (100) [M + Na].  $^{13}\text{C}$  NMR (DMSO): 40.85 ( $\text{CH}_2\text{N}$ ); 72.18 (C-9, C-10); 89.91 (C-1, C-8); 120.21 (C-4, C-5); 128.03 (C-3, C-6); 130.16 (C-5'); 142.18 (C-2, C-7); 148.11 (C-8'); 149.23 (C-6'); 151.82 (C-2'); 152.50 (C-4').  $^1\text{H}$  NMR (DMSO): 3.92 m, 2 H (H-9, H-10); 4.98 d, 2 H,  $J_{\text{gem}} = 15.5$  and 5.36 d, 2 H,  $J_{\text{gem}} = 15.5$  ( $\text{CH}_2\text{N}$ ); 5.55 m, 2 H (OH); 6.99 m, 2 H (H-3, H-6); 7.27 m, 2 H (H-4, H-5); 8.53 s, 2 H (H-8'); 8.86 s, 2 H (H-2'). For  $\text{C}_{22}\text{H}_{16}\text{Cl}_2\text{N}_8\text{O}_3$  (511.32) calculated: 51.68% C, 3.15% H, 21.91% N, 13.87% Cl; found: 51.57% C, 3.13% H, 21.49% N, 14.19% Cl.

**1,4-Epoxyphthalen-1(4*H*)-ylmethyl Benzoate (15)**

To a solution of anthranilic (1.82 g, 13.3 mmol) and trichloroacetic acids (16 mg, 0.1 mmol) in dry dioxane (30 ml) at 0 °C, isoamyl nitrite (1.82 g, 13.3 mmol) was added dropwise. This mixture was stirred at r.t. for 90 min, diazonium salt was filtered off and washed with dioxane (2 × 5 ml, the salt was never allowed to dry entirely) and added to a solution of furfuryl benzoate (2 g, 10.6 mmol) in dry dioxane (30 ml). Reaction mixture was heated to 60 °C for 1 h (evolution of  $\text{N}_2$  and  $\text{CO}_2$ ). Chromatography of the residue in toluene afforded product **15** (2.5 g, 90%) as a white solid. NMR spectrum was in agreement with the work of Chen and Chow.<sup>9</sup>

[(1*R*<sup>\*,3*S*<sup>\*,4*R*<sup>\*</sup></sup>)-3-Hydroxy-3,4-dihydro-1,4-epoxynaphthalen-1(2*H*)-yl]methyl Benzoate (16)</sup>

To 15 (2.57 g, 9.2 mmol) at 0 °C under Ar atmosphere, borane–THF complex (1 M solution, 5.5 ml) was added dropwise and the resulting solution was stirred at this temperature for 3 h. Excess borane was decomposed by careful addition of water and then NaBO<sub>3</sub>·4H<sub>2</sub>O (4.3 g, 27.7 mmol) in water (15 ml) was added and this suspension was stirred at r.t. overnight. Reaction mixture was then diluted with water (50 ml) and extracted with Et<sub>2</sub>O (3 × 50 ml). Chromatography (hexane/ethyl acetate 1:1) yielded product 16 (1 g, 37%) as a colorless oil, which solidifies on standing. M.p. 107 °C. ESI MS *m/z* (%): 295.2 (36) [M – H]. <sup>13</sup>C NMR (DMSO): 40.02 (C-10); 62.69 (CH<sub>2</sub>O); 72.87 (C-9); 85.55 (C-8); 86.59 (C-1); 118.67 (C-3); 120.61 (C-6); 126.89 and 127.09 (C-5, C-4); 129.07 (C-3'); 129.43 (C-2'); 129.60 (C-1'); 133.77 (C-4'); 143.66 (C-7); 145.90 (C-2); 165.69 (COO). <sup>1</sup>H NMR (DMSO): 1.67 dd, 1 H, *J*<sub>gem</sub> = 12.0, *J*(10ex-9) = 2.3 (H-10exo); 1.88 dd, 1 H, *J*<sub>gem</sub> = 12.0, *J*(10en-9) = 6.6 (H-10endo); 3.90 dddd, 1 H, *J*(9-10en) = 6.6, *J*(9-OH) = 5.0, *J*(9-10ex) = 2.3 (H-9); 5.00 d and 5.05 d, 2 H, *J*<sub>gem</sub> = 12.5 (CH<sub>2</sub>O); 5.09 s, 1 H (H-8); 5.28 d, 1 H, *J*(OH-9) = 5.0 (OH); 7.16–7.22 m, 2 H (H-4, H-5); 7.28 m, 1 H (H-3); 7.36 m, 1 H (H-6); 7.52 m, 2 H (H-3'); 7.66 m, 1 H (H-4'); 7.93 m, 2 H (H-2'). For C<sub>18</sub>H<sub>16</sub>O<sub>4</sub> (296.32) calculated: 72.96% C, 5.44% H; found: 72.82% C, 5.53% H.

(1*R*<sup>\*,2*S*<sup>\*,4*R*<sup>\*</sup></sup>)-4-[(6-Chloro-9*H*-purin-9-yl)methyl]-  
1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-ol (18)</sup>

To a solution of 16 (200 mg, 0.7 mmol) in absolute methanol (15 ml), sodium methoxide (75 mg, 1.4 mmol) was added and the reaction mixture was stirred at r.t. for 3 h. Volatiles were evaporated and column chromatography of the residue (toluene/ethyl acetate 1:2) afforded 17 as a white solid. To a mixture of the intermediate 17 (102 mg, 0.5 mmol), PPh<sub>3</sub> (262 mg, 1 mmol) and 6-chloropurine (116 mg, 0.75 mmol) in dry THF (10 ml) and a solution of DIAD (150 mg, 0.75 mmol) in dry THF (5 ml) were added dropwise. Reaction mixture was stirred at r.t. overnight, volatiles were evaporated and chromatography on silica (toluene/ethyl acetate 1:4) and subsequent crystallization from toluene afforded product 18 (136 mg, 79%) as white crystals. M.p. 191 °C. ESI MS *m/z* (%): 311.1 (79) [M + H], 333.0 (100) [M + Na]. <sup>13</sup>C NMR (DMSO): 40.50 (C-10'); 43.45 (CH<sub>2</sub>N); 73.20 (C-9'); 85.46 (C-8'); 87.06 (C-1'); 118.46 (C-3'); 120.66 (C-6'); 127.11 and 127.14 (C-4', C-5'); 130.38 (C-5); 143.63 (C-7'); 145.15 (C-2'); 148.45 (C-8); 149.32 (C-6); 151.97 (C-2); 152.56 (H-4). <sup>1</sup>H NMR (DMSO): 1.39 dd, 1 H, *J*<sub>gem</sub> = 12.1, *J*(10'a-9') = 2.3 (H-10'a); 1.92 dd, 1 H, *J*<sub>gem</sub> = 12.2, *J*(10'b-9') = 6.7 (H-10'b); 3.86 dddd, 1 H, *J*(9'-10'b) = 6.7, *J*(9'-OH) = 4.2, *J*(9'-10'a) = 2.3 (H-9'); 5.09 s, 1 H (H-8'); 5.21 bd, 1 H, *J*(OH-9') = 4.5 (OH); 5.15 d and 5.24 d, 2 H, *J*<sub>gem</sub> = 15.3 (CH<sub>2</sub>N); 7.09–7.14 m, 2 H (H-4', H-5'); 7.30–7.34 m, 2 H (H-3', H-6'); 8.61 s, 1 H (H-8); 8.88 s, 1 H (H-2). For C<sub>16</sub>H<sub>13</sub>ClN<sub>4</sub>O<sub>2</sub> (328.75) calculated: 58.45% C, 3.99% H, 17.04% N, 10.78% Cl; found: 58.05% C, 3.99% H, 17.14% N, 11.04% Cl.

1,4-Epoxynaphthalen-1(4*H*)-ylmethanol (19)

To a solution of 15 (300 mg, 1.1 mmol) in absolute methanol (20 ml), sodium methoxide (120 mg, 2.2 mmol) was added and the reaction mixture was stirred at r.t. for 3 h. Volatiles were evaporated and column chromatography of the residue (hexanes/ethyl acetate 4:1) afforded product 19 (173 mg, 91%) as a white solid. NMR spectrum corresponded with ref.<sup>10</sup>

### 6-Chloro-9-(1,4-epoxynaphthalen-1(4H)-ylmethyl)-9*H*-purine (20)

To a mixture of **19** (200 mg, 1.15 mmol),  $\text{PPh}_3$  (600 mg, 2.3 mmol) and 6-chloropurine (260 mg, 1.7 mmol) in dry THF (15 ml), a solution of DIAD (340 mg, 1.7 mmol) in dry THF (7 ml) was added dropwise. Reaction mixture was stirred at r.t. overnight, volatiles were evaporated and chromatography on silica (toluene/ethyl acetate 3:1) and subsequent crystallization from water/methanol mixture afforded product **20** (257 mg, 72%) as white crystals. M.p. 137 °C. ESI MS  $m/z$  (%): 311.1 (79) [M + H], 333.0 (100) [M + Na].  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 42.30 ( $\text{CH}_2\text{N}$ ); 82.87 (C-8'); 91.35 (C-1'); 118.98 (C-3'); 120.51 (C-6'); 125.27 (C-5'); 125.65 (C-4'); 131.01 (C-5); 141.19 (C-10'); 146.13 (C-9'); 146.54 (C-8); 146.62 (C-2'); 149.87 (C-7'); 151.06 (C-6); 151.98 (C-2); 152.01 (C-4).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 5.13 and 5.31 d, 1 H,  $J_{\text{gem}} = 15.2$  ( $\text{CH}_2\text{N}$ ); 5.75 d, 1 H,  $J(8'\text{-}9') = 1.9$  (H-8'); 6.75 d, 1 H,  $J(10'\text{-}9') = 5.5$  (H-10'); 6.93–7.00 m, 2 H (H-4', H-5'); 7.05 dd, 1 H,  $J(9'\text{-}10') = 5.5$ ,  $J(9'\text{-}8') = 1.9$  (H-9'); 7.20 m, 1 H (H-3'); 7.25 m, 1 H (H-6'); 8.36 s, 1 H (H-8); 8.83 s, 1 H (H-2). For  $\text{C}_{16}\text{H}_{11}\text{ClN}_4\text{O}$  (310.74) calculated: 61.84% C, 3.57% H, 18.03% N, 11.41% Cl; found: 61.69% C, 3.60% H, 17.79% N, 11.77% Cl.

### 3,4-Dihydro-1,4-epoxynaphthalen-1(4*H*)-ylmethanol (21)

To a solution of **1** (1 g, 3.6 mmol) in dry methanol (40 ml),  $\text{Pd}(\text{OH})_2/\text{C}$  (50 mg) was added and the mixture was hydrogenated (10 atm) overnight. Catalyst was filtered off on a cellulose pad, sodium methoxide (390 mg, 7.1 mmol) dry methanol (40 ml) was added and the reaction mixture was stirred at r.t. for 2 h. Volatiles were evaporated and column chromatography of the residue (hexanes/ethyl acetate 4:1) afforded product **21** (551 mg, 87%) as a white solid. NMR spectrum corresponded with ref.<sup>11</sup>

### 6-Chloro-9-(3,4-dihydro-1,4-epoxynaphthalen-1(4*H*)-ylmethyl)-9*H*-purine (22)

To a mixture of **21** (200 mg, 1.14 mmol),  $\text{PPh}_3$  (600 mg, 2.3 mmol) and 6-chloropurine (260 mg, 1.7 mmol) in dry THF (15 ml), a solution of DIAD (340 mg, 1.7 mmol) in dry THF (7 ml) was added dropwise. Reaction mixture was stirred at r.t. overnight, volatiles were evaporated and chromatography on silica (toluene/ethyl acetate 3:1) and subsequent crystallization from water/methanol mixture afforded product **22** (270 mg, 76%) as white crystals. M.p. 140 °C. ESI MS  $m/z$  (%): 313.1 (27) [M + H], 335.1 (100) [M + Na].  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 28.99 (C-9'); 29.30 (C-10'); 43.74 ( $\text{CH}_2\text{N}$ ); 78.87 (C-8'); 87.24 (C-1'); 117.55 (C-3'); 119.07 (C-6'); 126.79 (C-4'); 127.29 (C-5'); 130.84 (C-5); 142.75 (C-2'); 145.94 (C-7'); 146.73 (C-8); 150.93 (C-6); 151.92 (C-2); 152.16 (C-4).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.47–1.56 m, 2 H (H-9'endo, H-10'endo); 1.77 m, 1 H (H-10'exo); 2.21 m, 1 H (H-9'exo); 4.92 and 5.32 d, 1 H,  $J_{\text{gem}} = 15.1$  ( $\text{CH}_2\text{N}$ ); 5.45 d, 1 H,  $J(8'\text{-}9'\text{ex}) = 5.0$  (H-8'); 7.05 m, 1 H (H-4'); 7.11–7.16 m, 2 H (H-3', H-5'); 7.22 m, 1 H (H-6'); 8.34 s, 1 H (H-8); 8.84 s, 1 H (H-2). For  $\text{C}_{16}\text{H}_{13}\text{ClN}_4\text{O}\cdot 1/3\text{H}_2\text{O}$  (318.76) calculated: 60.29% C, 4.32% H, 17.58% N, 11.12% Cl; found: 60.17% C, 4.33% H, 17.19% N, 11.45% Cl.

### 6-Chloro-9-[(1*aR*<sup>\*,</sup>2*R*<sup>\*,</sup>7*R*<sup>\*,</sup>7*aR*<sup>\*)</sup>-7,7*a*-dihydro-2,7-epoxynaphtho[2,3-*b*]oxiren-2(1*aH*)-ylmethyl]-9*H*-purine (23)

To a solution of **20** (310 mg, 1 mmol) in DCM (45 ml), mCPBA (65%, 400 mg, 1.5 mmol) was added and the reaction mixture was stirred at r.t. overnight. Volatiles were evaporated and chromatography on silica (toluene/ethyl acetate 3:1) and subsequent crystallization

from water/methanol mixture afforded **23** (210 mg, 64%) as white crystals. M.p. >160 °C (decomp.). ESI MS *m/z* (%): 327.0 (34) [M + H], 349.9 (100) [M + Na]. <sup>13</sup>C NMR (CDCl<sub>3</sub>): 41.36 (CH<sub>2</sub>N); 54.83 (C-10'); 55.74 (C-9'); 77.14 (C-8'); 86.03 (C-1'); 120.06 (C-3'); 121.47 (C-6'); 127.37 (C-4'); 127.81 (C-5'); 131.05 (C-5); 143.14 (C-2'); 145.54 (C-7'); 146.56 (C-8); 151.13 (C-6); 151.94 (C-2); 152.03 (H-4). <sup>1</sup>H NMR (CDCl<sub>3</sub>): 3.50 d, 1 H, *J*(10'-9') = 3.6 (H-10'); 3.57 d, 1 H, *J*(9'-10') = 3.6 (H-9'); 5.11 d and 5.21 d, 2 H, *J*<sub>gem</sub> = 15.3 (CH<sub>2</sub>N); 5.27 s, 1 H (H-8'); 7.12 m, 1 H (H-4'); 7.18 m, 1 H (H-5'); 7.32–7.34 m, 2 H (H-3', H-6'); 8.36 s, 1 H (H-8); 8.83 s, 1 H (H-2'). For C<sub>16</sub>H<sub>11</sub>ClN<sub>4</sub>O<sub>2</sub> (326.74) calculated: 58.82% C, 3.39% H, 17.15% N, 10.85% Cl; found: 58.89% C, 3.39% H, 16.79% N, 10.67% Cl.

(1*R*<sup>\*,2*R*<sup>\*,3*S*<sup>\*,4*R*<sup>\*</sup></sup></sup>)-1-[(6-Chloro-9*H*-purin-9-yl)methyl]-  
1,2,3,4-tetrahydro-1,4-epoxynaphthalene-2,3-diol (**24**)</sup>

To a solution of **20** (800 mg, 2.6 mmol) in acetone/water mixture (1:1, 45 ml), NMNO (50% w/w solution in water, 6 ml), a 2% w/w solution of OsO<sub>4</sub> in water (150 µl) was added and the reaction mixture was stirred at r.t. for 48 h. Product, which gradually precipitated from the reaction mixture, was filtered off and crystallized from DMF/methanol mixture affording **24** (555 mg, 62%) as a white powder. M.p. >250 °C (decomp.). ESI MS *m/z* (%): 153.0 (100) [(M + 3K)<sup>3+</sup>/3], 345.1 (11) [M + H], 689.3 (36) [2 M + H]. <sup>13</sup>C NMR (DMSO): 41.00 (CH<sub>2</sub>N); 70.81 (C-10); 71.03 (C-9); 84.09 (C-8); 90.02 (C-1); 120.13 (C-3); 120.82 (C-6); 127.41 (C-4); 127.88 (C-5); 130.27 (C-5'); 141.84 (C-2); 143.64 (C-7); 148.14 (C-8'); 149.21 (C-6'); 151.87 (C-2'); 152.64 (H-4'). <sup>1</sup>H NMR (DMSO): 3.77–3.81 m, 2 H (H-9, H-10); 5.10 d, 1 H, *J*(OH-10) = 6.4 (10-OH); 5.11 s, 1 H (H-8); 5.00 d and 5.35 d, 2 H, *J*<sub>gem</sub> = 15.4 (CH<sub>2</sub>N); 5.49 d, 1 H, *J*(OH-10) = 5.5 (9-OH); 7.06 m, 1 H (H-4); 7.12 m, 1 H (H-5); 7.28 m, 1 H (H-6); 7.34 m, 1 H (H-3); 8.50 s, 1 H (H-8'); 8.87 s, 1 H (H-2'). For C<sub>16</sub>H<sub>13</sub>ClN<sub>4</sub>O<sub>3</sub> (344.75) calculated: 55.74% C, 3.80% H, 16.25% N, 10.28% Cl; found: 55.62% C, 3.86% H, 16.06% N, 10.19% Cl.

(1*R*<sup>\*,2*R*<sup>\*,3*S*<sup>\*,4*R*<sup>\*</sup></sup></sup>)-1-[(6-amino-9*H*-purin-9-yl)methyl]-  
1,2,3,4-tetrahydro-1,4-epoxynaphthalene-2,3-diol (**25**)</sup>

A solution of **24** (170 mg, 0.5 mmol) in liquid ammonia (20 ml) was heated in autoclave at 90 °C overnight. Ammonia was evaporated and the remaining solid was extracted on a filter with methanol (100 ml) and crystallized from water/methanol mixture to afford **25** (102 mg, 63%) as a brownish powder. M.p. >270 °C (decomp.). ESI MS *m/z* (%): 326.1 (100) [M + H], 348.1 (83) [M + Na], 673.2 (32) [2 M + Na]. <sup>13</sup>C NMR (DMSO): 39.93 (CH<sub>2</sub>N); 70.96 and 71.01 (C-9 and C-10); 84.11 (C-8); 90.32 (C-1); 118.07 (C-5'); 120.05 (C-3); 120.69 (C-6); 127.30 (C-4); 127.68 (C-5); 141.39 (C-8'); 142.22 (C-2); 143.65 (C-7); 150.21 (C-4'); 152.72 (C-2'); 156.11 (C-6'). <sup>1</sup>H NMR (DMSO): 3.76–3.79 m, 2 H (H-9, H-10); 4.77 and 5.17 d, 2 H, *J*<sub>gem</sub> = 15.4 (CH<sub>2</sub>N); 5.12 s, 1 H (H-8); 5.17 m, 1 H (10-OH); 5.40 m, 1 H (9-OH); 7.02 td, 1 H, *J*(4-5) = *J*(4-3) = 7.5, *J*(4-6) = 1.1 (H-4); 7.10 td, 1 H, *J*(5-4) = *J*(5-6) = 7.4, *J*(5-3) = 1.0 (H-5); 7.18 bs, 2 H (NH<sub>2</sub>); 7.21 dm, 1 H, *J*(3-4) = 7.4 (H-3); 7.28 dm, 1 H, *J*(6-5) = 7.3 (H-6); 7.92 s, 1 H (H-8'); 8.24 s, 1 H (H-2'). For C<sub>16</sub>H<sub>15</sub>N<sub>5</sub>O<sub>3</sub> (325.32) calculated: 59.07% C, 4.65% H, 21.53% N; found: 58.70% C, 4.67% H, 21.30% N.

## 1,4-Epoxyanthracen-1(4H)-ylmethyl Benzoate (27)

To a refluxing solution of furfuryl benzoate (2.5 g, 13.3 mmol) in dioxane (15 ml), solutions of 3-amino-2-naphthoic acid (80%, 2.5 g, 10.7 mmol) in dioxane (20 ml) and isoamylnitrite (2.5 g, 21 mmol) in dioxane (10 ml) were simultaneously, but from separate syringes, added. Reaction mixture was further refluxed for another 90 min, after which volatiles were evaporated and the chromatography on silica (hexanes/ethyl acetate 10:1) afforded **27** as a white solid. Crystallization from benzene/hexane mixture yielded pure product (1.1 g, 31%) in the form of white crystals. M.p. 159 °C. ESI MS *m/z* (%): 351.3 (100) [M + Na]. <sup>13</sup>C NMR (CDCl<sub>3</sub>): 61.86 (CH<sub>2</sub>O); 81.84 (C-12); 90.50 (C-1); 188.05 (C-3); 118.71 (C-10); 126.29 and 126.41 (C-6, C-7); 128.07 and 128.26 (C-5 and C-8); 128.43 (C-3'); 129.55 (C-1'); 129.86 (C-2'); 131.68 and 131.80 (C-4 and C-9); 133.26 (C-4'); 140.88 (C-14); 143.34 (C-2); 143.43 (C-13); 144.98 (C-11); 166.47 (COO). <sup>1</sup>H NMR (CDCl<sub>3</sub>): 5.13 dd, 1 H, *J*<sub>gem</sub> = 12.7, *J*(CH<sub>2</sub>a-13) = 0.7; 5.36 d, 1 H, *J*<sub>gem</sub> = 12.7 (CH<sub>2</sub>O); 5.86 d, 1 H, *J*(12-13) = 2.0 (H-12); 6.90 d, 1 H, *J*(14-13) = 5.6 (H-14); 7.09 ddd, 1 H, *J*(13-14) = 5.6, *J*(13-12) = 1.9, *J*(13-CH<sub>2</sub>a) = 0.6 (H-13); 7.42–7.46 m, 4 H (H-3', H-6, H-7); 7.57 m, 1 H (H-4'); 7.59 s, 1 H (H-3); 7.60 s, 1 H (H-10); 7.71–7.74 m, 2 H (H-5, H-8); 8.10 s, 1 H (H-2'). For C<sub>22</sub>H<sub>16</sub>O<sub>3</sub> (328.26) calculated: 80.47% C, 4.91% H; found: 80.46% C, 4.83% H.

## 3,4-Dihydro-1,4-epoxyanthracen-1(2H)-ylmethanol (28)

To a solution of **27** (350 mg, 1.06 mmol) in methanol/dioxane mixture (20 ml, 1:1), Pd(OH)<sub>2</sub>/C (50 mg) was added and the reaction mixture was subjected to hydrogenation (10 atm) overnight. Catalyst was filtered off on a cellulose pad and sodium methoxide (108 mg, 2.2 mmol) was added to the solution. After stirring at r.t. for 1 h, volatiles were evaporated and chromatography on silica (hexanes/ethyl acetate 1:4) and subsequent crystallization from toluene/cyclohexane mixture afforded product **28** (202 mg, 84%) as white crystals. M.p. 136 °C. ESI MS *m/z* (%): 249.1 (100) [M + Na]. <sup>13</sup>C NMR (DMSO): 28.49 (C-14); 29.16 (C-13); 60.71 (CH<sub>2</sub>O); 77.61 (C-12); 88.63 (C-1); 116.49 and 116.62 (C-3 and C-10); 125.70 and 125.71 (C-6 and C-7); 128.16 and 128.25 (C-5, C-8); 132.41 and 132.42 (C-4 and C-9); 144.69 (C-2); 145.26 (C-11). <sup>1</sup>H NMR (DMSO): 1.36 ddd, 1 H, *J*<sub>gem</sub> = 11.4, *J*(14en-13en) = 8.9, *J*(14en-13ex) = 4.0 (H-14endo); 1.46 ddd, 1 H, *J*<sub>gem</sub> = 11.5, *J*(13en-14en) = 9.0, *J*(13en-14ex) = 4.0 (H-13endo); 1.99 td, 1 H, *J*<sub>gem</sub> = *J*(14ex-13ex) = 11.2, *J*(14ex-13en) = 4.0 (H-14exo); 2.13 tdd, 1 H, *J*<sub>gem</sub> = *J*(13ex-14ex) = 11.2, *J*(13ex-12) = 5.3, *J*(13ex-14en) = 4.1 (H-13exo); 4.15 dd, 1 H, *J*<sub>gem</sub> = 12.2, *J*(CH<sub>2</sub>-OH) = 5.8 and 4.21 dd, 1 H, *J*<sub>gem</sub> = 12.2, *J*(CH<sub>2</sub>-OH) = 5.8 (CH<sub>2</sub>); 5.13 t, 1 H, *J*(OH-CH<sub>2</sub>) = 5.8 (OH); 5.48 d, 1 H, *J*(12-13ex) = 5.2 (H-12); 7.45–7.47 m, 2 H (H-6, H-7); 7.699 s, 1 H and 7.703 s, 1 H (H-3 and H-10); 7.85–7.88 m, 2 H (H-5, H-8). For C<sub>15</sub>H<sub>14</sub>O<sub>2</sub> (226.27) calculated: 79.62% C, 6.24% H; found: 79.28% C, 6.24% H.

6-Chloro-9-(3,4-dihydro-1,4-epoxyanthracen-1(2H)-ylmethyl)-9*H*-purine (29)

To a mixture of **28** (152 mg, 0.67 mmol), PPh<sub>3</sub> (350 mg, 1.4 mmol) and 6-chloropurine (154 mg, 1 mmol) in dry dioxane (15 ml), a solution of DIAD (202 mg, 1 mmol) in dry dioxane (5 ml) was added dropwise. Reaction mixture was stirred at r.t. overnight, volatiles were evaporated and chromatography on silica (toluene/ethyl acetate 4:1) and subsequent crystallization from methanol afforded product **29** (184 mg, 76%) as white crystals. M.p. >200 °C (decomp.). ESI MS *m/z* (%): 363.0 (100) [M + H], 385.0 (52) [M + Na]. <sup>13</sup>C NMR

(DMSO): 29.37 (C-13'); 29.70 (C-14'); 43.64 (CH<sub>2</sub>N); 77.96 (C-12'); 86.99 (C-1'); 116.51 (C-3'); 117.02 (C-10'); 125.92 and 126.08 (C-6' and C-7'); 128.12 and 128.20 (C-5', C-8'); 130.30 (C-5); 132.10 and 132.47 (C-4' and C-9'); 142.29 (C-2'); 144.32 (C-11'); 148.24 (C-8); 149.26 (C-6); 151.84 (C-2); 152.51 (C-4). <sup>1</sup>H NMR (DMSO): 1.47 ddd, 1 H, *J*<sub>gem</sub> = 11.7, *J*(13'en-14'en) = 8.9, *J*(13'en-14'ex) = 4.1 (H-13'endo); 1.58 ddd, 1 H, *J*<sub>gem</sub> = 11.7, *J*(14'en-13'en) = 8.8, *J*(14'en-13'ex) = 4.1 (H-14'endo); 1.80 ddd, 1 H, *J*<sub>gem</sub> = 11.7, *J*(14'ex-13'ex) = 11.0, *J*(14'ex-13'en) = 4.1 (H-14'exo); 2.14 dddd, 1 H, *J*<sub>gem</sub> = 11.7, *J*(13'ex-14'ex) = 11.0, *J*(13'ex-12') = 5.3, *J*(13'ex-14'en) = 4.0 (H-13'exo); 5.25 d, 1 H and 5.39 d, 1 H *J*<sub>gem</sub> = 15.3 (CH<sub>2</sub>N); 5.58 d, 1 H, *J*(12'-13'ex) = 5.1 (H-12'); 7.45-7.49 m, 2 H (H-6', H-7'); 7.71 s, 1 H (H-10'); 7.81 m, 1 H (H-5'); 7.85 m, 1 H (H-8'); 7.89 s, 1 H (H-3'); 8.61 s, 1 H (H-8); 8.91 s, 1 H (H-2). For C<sub>20</sub>H<sub>15</sub>ClN<sub>4</sub>O (362.81) calculated: 66.21% C, 4.17% H, 15.44% N, 9.77% Cl; found: 66.16% C, 4.26% H, 15.03% N, 9.47% Cl.

### 1,4-Epoxyanthracen-1(4*H*)-ylmethanol (30)

To a solution of **27** (150 mg, 0.46 mmol) in absolute methanol (15 ml), sodium methoxide (54 mg, 1 mmol) was added and the reaction mixture was stirred at r.t. for 1 h. Volatiles were evaporated and column chromatography of the residue (hexanes/ethyl acetate 1:2) afforded product **30** (95 mg, 92%) as a white solid. Crystallization of analytical sample was accomplished from toluene/cyclohexane mixture. NMR spectrum was in agreement with the work of Chen and Chow<sup>9</sup>.

### 6-Chloro-9-(1,4-epoxyanthracen-1(4*H*)-ylmethyl)-9*H*-purine (31)

To a mixture of **30** (375 mg, 1.7 mmol), PPh<sub>3</sub> (880 mg, 3.3 mmol) and 6-chloropurine (386 mg, 2.5 mmol) in dry dioxane (35 ml), a solution of DIAD (500 mg, 2.5 mmol) in dry dioxane (10 ml) was added dropwise. Reaction mixture was stirred at r.t. overnight, volatiles were evaporated and chromatography on silica (toluene/ethyl acetate 4:1) and subsequent crystallization from methanol afforded product **31** (405 mg, 66%) as white crystals. M.p. 232.5 °C. ESI MS *m/z* (%): 361.6 (59) [M + H], 383.6 (100) [M + Na]. <sup>13</sup>C NMR (DMSO): 42.41 (CH<sub>2</sub>N); 81.08 (C-12'); 90.90 (C-1'); 117.98 (C-3'); 118.64 (C-10'); 126.54 and 126.65 (C-6' and C-7'); 128.21 and 128.29 (C-5' and C-8'); 130.56 (C-5); 131.28 and 131.47 (C-4' and C-9'); 140.84 (C-14'); 143.61 (C-2'); 144.77 (C-13'); 145.62 (C-11'); 148.23 (C-8); 149.38 (C-6); 152.01 (C-2); 152.47 (C-4). <sup>1</sup>H NMR (DMSO): 5.61 dd, 1 H, *J*<sub>gem</sub> = 15.3, *J*(CH<sub>2</sub>b-13') = 0.9 (CH<sub>2</sub>b); 5.55 d, 1 H, *J*<sub>gem</sub> = 15.3 (CH<sub>2</sub>a); 5.89 d, 1 H, *J*(12'-13') = 2.0 (H-12'); 6.95 d, 1 H, *J*(14'-13') = 5.5 (H-14'); 7.04 ddd, 1 H, *J*(13'-14') = 5.5, *J*(13'-12') = 2.0, *J*(13'-CH<sub>2</sub>b) = 0.8 (H-13'); 7.46-7.49 m, 2 H (H-6', H-7'); 7.67 s, 1 H (H-10'); 7.76-7.80 m, 2 H (H-5', H-8'); 7.87 s, 1 H (H-3'); 8.73 s, 1 H (H-8); 8.89 s, 1 H (H-2). For C<sub>20</sub>H<sub>13</sub>ClN<sub>4</sub>O (360.80) calculated: 66.58% C, 3.63% H, 15.53% N, 9.83% Cl; found: 66.45% C, 3.58% H, 14.99% N, 9.50% Cl.

### (1*R*<sup>\*,</sup>2*R*<sup>\*,</sup>3*S*<sup>\*,</sup>4*R*<sup>\*)</sup>-1-[(6-Chloro-9*H*-purin-9-yl)methyl]-1,2,3,4-tetrahydro-1,4-epoxyanthracene-2,3-diol (32)

To a solution of **29** (250 mg, 0.7 mmol) in dioxane/water mixture (4:1, 25 ml), NMNO (50% w/w solution in water, 1.5 ml), a 2% w/w solution of OsO<sub>4</sub> in water (40 µl) was added and the reaction mixture was stirred at r.t. overnight. Volatiles were evaporated and chromatography on silica (toluene/ethyl acetate 1:4) and subsequent crystallization from methanol afforded **30** (225 mg, 81%) as a white powder. M.p. >230 °C (decomp.). ESI MS *m/z* (%):

393.1 (30) [M – H], 787.2 (100) [2 M – H].  $^{13}\text{C}$  NMR (DMSO): 41.13 ( $\text{CH}_2\text{N}$ ); 71.78 (C-14'); 72.00 (C-13'); 84.11 (C-12'); 89.95 (C-1'); 119.02 and 119.04 (C-3' and C-10'); 126.41 and 126.59 (C-6' and C-7'); 128.25 and 128.37 (C-5' and C-8'); 130.28 (C-5); 132.38 (C-4'); 132.77 (C-9'); 139.64 (C-2'); 140.91 (C-11'); 148.25 (C-8); 149.21 (C-6); 151.84 (C-2); 152.71 (C-4).  $^1\text{H}$  NMR (DMSO): 3.90–3.95 m, 2 H (H-13', H-14'); 5.19 d, 1 H,  $J(\text{OH}-14') = 6.6$  (14'-OH); 5.25 s, 1 H (H-12'); 5.11 and 5.45 d, 2 H,  $J_{\text{gem}} = 15.5$  ( $\text{CH}_2\text{N}$ ); 5.57 d, 1 H,  $J(\text{OH}-13') = 5.6$  (13'-OH); 7.43–7.47 m, 2 H (H-6', H-7'); 7.72–7.74 m, 2 H (H-8', H-10'); 7.82 m, 1 H (H-5'); 7.88 bs 1 H (H-3'); 8.57 s, 1 H (H-8); 8.92 s, 1 H (H-2). For  $\text{C}_{20}\text{H}_{15}\text{ClN}_4\text{O}_3$  (394.81) calculated: 60.84% C, 3.83% H, 14.19% N, 8.98% Cl; found: 60.48% C, 3.76% H, 13.99% N, 9.09% Cl.

(1*R*<sup>4</sup>,2*R*<sup>5</sup>,3*S*<sup>6</sup>,4*R*<sup>7</sup>)-1-[(6-Amino-9*H*-purin-9-yl)methyl]-  
1,2,3,4-tetrahydro-1,4-epoxyanthracene-2,3-diol (33)

A solution of 32 (150 mg, 0.4 mmol) in liquid ammonia (20 ml) was heated in an autoclave at 90 °C overnight. Ammonia was evaporated and the remaining solid was extracted with hot water (5 × 50 ml) to afford 33 (110 mg, 73%) as a brownish powder. M.p. >300°C (decomp.). ESI MS *m/z* (%): 376.2 (41) [M + H], 398.2 (100) [M + Na].  $^{13}\text{C}$  NMR (DMSO): 40.04 ( $\text{CH}_2\text{N}$ ); 71.89 and 71.99 (C-13' and C-14'); 81.12 (C-12'); 90.28 (C-1'); 118.09 (C-5); 118.85 and 118.95 (C-3' and C-10'); 126.32 and 126.44 (C-6' and C-7'); 128.23 (C-5' and C-8'); 132.37 (C-4'); 132.71 (C-9'); 139.95 (C-2'); 141.03 (C-11'); 141.39 (C-8); 150.28 (C-4); 152.65 (C-2); 156.08 (C-6).  $^1\text{H}$  NMR (DMSO): 3.89–3.92 m, 2 H (H-13', H-14'); 5.25 m, 1 H (14'-OH); 5.26 s, 1 H (H-12'); 4.87 and 5.27 d, 2 H,  $J_{\text{gem}} = 15.5$  ( $\text{CH}_2\text{N}$ ); 5.49 m, 1 H (13'-OH); 7.14 bs, 2 H ( $\text{NH}_2$ ); 7.40–7.44 m, 2 H (H-6', H-7'); 7.63 m, 1 H (H-8'); 7.74 s, 1 H (H-10'); 7.78 s, 1 H (H-3'); 7.82 m, 1 H (H-5'); 7.96 s, 1 H (H-8); 8.31 s, 1 H (H-2). For  $\text{C}_{20}\text{H}_{17}\text{N}_5\text{O}_3 \cdot 1/2\text{H}_2\text{O}$  (384.39) calculated: 62.49% C, 4.72% H, 18.22% N; found: 62.62% C, 4.77% H, 17.72% N.

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