SYNTHESIS OF RACEMIC 2-HYDROXY-4- AND 2-HYDROXY-5-(HYDROXYMETHYL)CYCLOHEXANE NUCLEOSIDE ANALOGUES

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New racemic 2-hydroxy-4- and 2-hydroxy-5-(hydroxymethyl)cyclohexane analogues of adenine (**10b** and **16b**) and thymine nucleosides (**13b** and **19b**) were prepared by alkylation of 1,8-diazabicyclo[5.4.0]undec-7-ene salt of adenine and/or thymine with 3-vinyl-7-oxabicyclo[4.1.0]heptane followed by cis hydroxylation with osmium(VIII) oxide and sodium chlorate, oxidation with sodium periodate, and borohydride reduction.

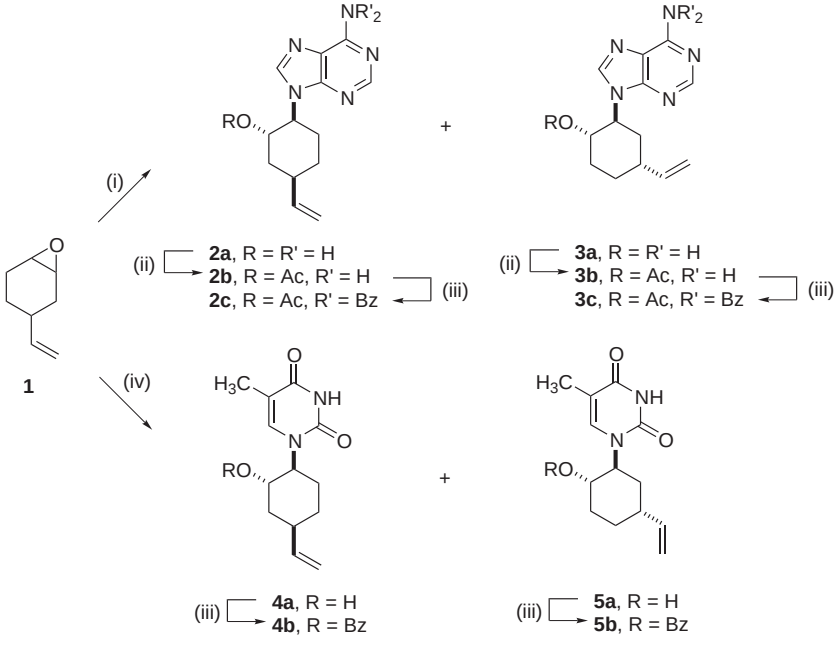
Keywords: Carbanucleosides; Carbocyclic nucleosides; Nucleosides; Cyclohexanes; Adenine; Thymine; Antivirals; Epoxides; NMR spectroscopy.

The search for new modified nucleosides as antivirals is still a promising field of research. As the hexitol nucleosides exhibit antiviral activity[1], a variety of their carbocyclic congeners and the cyclohexene analogues was prepared[2]. Recently, a potent antiviral activity of such compounds was found[2j,2k]. Nucleic acids containing cyclohexene nucleosides were also synthesized[3].

The present work is a part of the research programme[4] aimed at the synthesis and of structure–antiviral activity study of carbocyclic nucleosides. This paper deals with the synthesis of racemic cyclohexane nucleosides bearing a hydroxymethyl group in the 3′- and/or 4′-position.

3-Vinyl-7-oxabicyclo[4.1.0]heptane (**1**; mixture of isomers) was chosen as a starting material for synthesis of the target compounds. Cyclohexane nucleosides were prepared by direct alkylation of a nucleobase nitrogen with cyclohexene oxide as described in the literature[5,2e] for analogous compounds. Treatment of adenine or thymine with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) followed by 3-vinyl-7-oxabicyclo[4.1.0]heptane **1** in dimethylformamide at 125 °C afforded a mixture of racemic **2a** (27%) and **3a** (10%) or **4a** (21%) and **5a** (12%) as main UV-absorbing products (Scheme 1). The other possible isomers were not detected in the reaction mixtures. The mixture of **2a** and **3a** was *O*-acetylated with acetic anhydride

and acetic acid in acetonitrile using 4-(dimethylamino)pyridine as a catalyst. Crystallization of the mixture of acetates **2b** and **3b** gave crystalline **2b**. Acetate **3b** was obtained by chromatography of mother liquors. Thymine nucleosides were separated, after benzoylation, by crystallization from propan-2-ol (compound **4b**) and chromatography on a silica gel column (compound **5b**). The free nucleosides **2a** and **3a** were obtained by methanolysis of **2b** and **3b** with methanolic ammonia, compounds **4a** and **5a** were prepared by treatment of **4b** and **5b** with methanolic sodium methoxide.



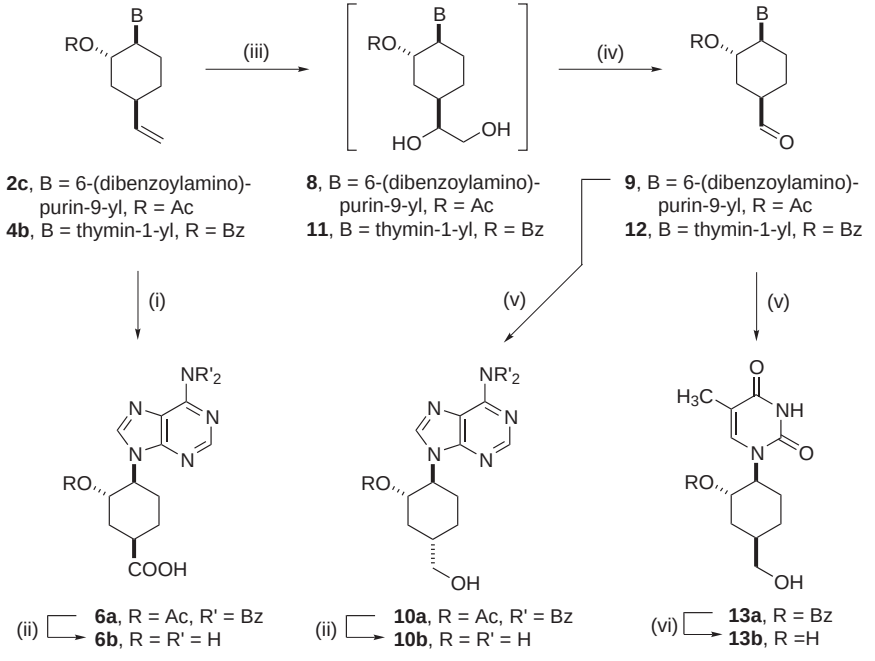
(i) adenine/DBU/DMF, 125 °C, 27% of **2a**, 10% of **3a**; (ii) Ac_2O/AcOH/DMAP/MeCN; (iii) BzCl/pyridine; (iv) thymine/DBU/DMF, 125 °C, 21% of **4a**, 12% of **5a**

SCHEME 1

Infrared spectra of thymine derivatives **4b** and **5b** exhibit NH bands at 3396 cm^{-1}, in agreement with the literature data[6] for N^1-substituted uracils. The positions of the absorption bands in UV spectra of these compounds remained virtually unchanged independently of pH whereas in alkaline medium, the absorption decreased: such pattern is characteristic of N^1-substituted uracil derivatives[7]. The linkage of the cyclohexane ring with adenine in position N-9 of compounds **2a** and **3a** was confirmed by their UV spec-

tra. The absorption maximum at 262 nm (water) and 260 nm (0.1 M HCl) in UV spectra of the adenine derivatives **2a** and **3a** corresponds to N^9-substituted adenine derivatives[8]. Also proton-coupled ^{13}C NMR spectra of compounds **2b**, **3b**, **4b** and **5b** confirmed the position of substitution on the nucleoside base. The long-range coupling constants ^3J(C-4′,H-2) = 3.9, ^3J(C-8′,H-2) = 4.9 (adenine derivatives **2b**, **3b**) and ^3J(C-2′,H-2) = 3.9, ^3J(C-6′,H-2) ≈ 3.0 (thymine derivatives **4b**, **5b**) were found in the spectra.

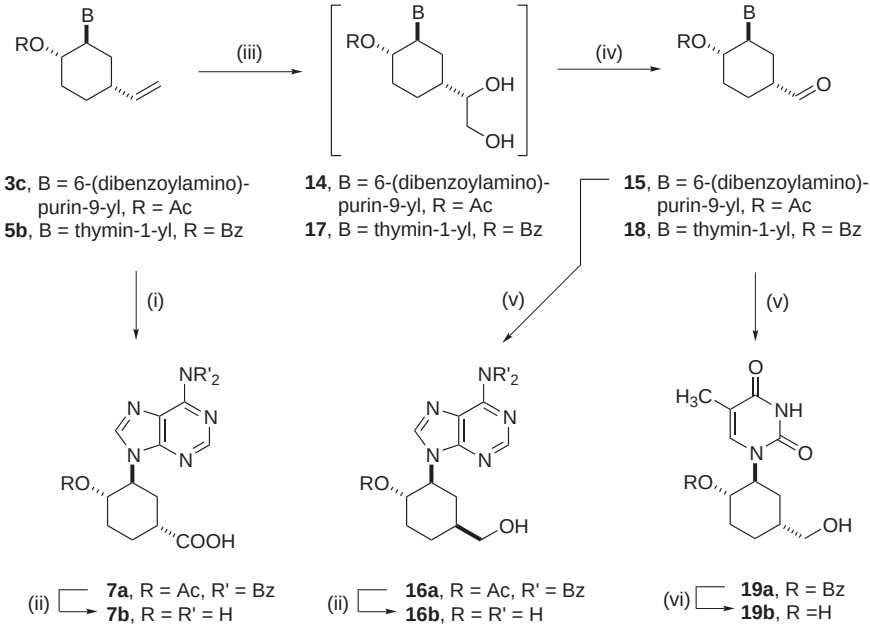
Oxidation of adenine vinyl derivatives **2c** and **3c** (obtained by benzoylation of **2b** and **3b**) with sodium periodate in aqueous 1,4-dioxane in the presence of catalytic amounts of ruthenium(IV) oxide (generated from ruthenium(III) chloride) led to carboxylic acids **6a** and **7a**, respectively (Schemes 2 and 3). Aldehydes **9** and **12** as intermediates of this oxidation and isomers with inverse configuration at α-carbon were not detected in the reaction mixture. Oxidation of vinyl derivatives **2c** and **3c** with ruthenium(IV) oxide under Sharpless' conditions[9] gave also the carboxylic acids



(i) $RuCl_3/NaIO_4$/aq. dioxane, 87%; (ii) NH_3/MeOH; (iii) $OsO_4/NaClO_3$/aq. dioxane; (iv) $NaIO_4$/aq. dioxane, **9** 64%, **12** 51%; (v) Amberlyst A-26 (BH_4^-)/aq. dioxane; **10a** 76%, **13a** 73%; (vi) MeONa/MeOH

SCHEME 2

without isomerisation. The reaction of thymine vinyl derivatives **4b** and **5b**, performed in the same manner, afforded an inseparable mixture of products. Deprotection of **6a** and **7a** with methanolic ammonia gave free carboxylic acids **6b** and **7b**, respectively.



(i) $RuCl_3/NaIO_4$/aq. dioxane, 85%; (ii) NH_3/MeOH; (iii) $OsO_4/NaClO_3$/aq. dioxane; (iv) $NaIO_4$/aq. dioxane, **15** 62%, **18** 49%; (v) Amberlyst A-26 (BH_4^-)/aq. dioxane; **16a** 78%, **19a** 77%; (vi) MeONa/MeOH

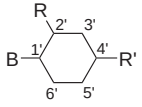
SCHEME 3

Transformation of the vinyl to the hydroxymethyl group was achieved by several simple steps. Treatment of vinyl compounds **2c**, **3c**, **4b**, and **5b** with osmium(VIII) oxide and sodium chlorate provided diols **8**, **11**, **14**, and **17**, respectively, as inseparable mixtures of stereoisomers. They were converted, by the reaction with potassium periodate, to the respective aldehydes **9**, **12**, **15**, and **18**. Reduction of these compounds with Amberlyst A-26 in the BH_4^- form in 1,4-dioxane afforded the hydroxymethyl derivatives **10a**, **13a**, **16a**, and **19a**, respectively. The reduction of the adenine derivatives **9** and **15** resulted in inversion of configuration on the carbon atom bearing the reduced aldehyde group. Free nucleosides were finally obtained by treatment with methanolic ammonia (**10b** and **16b**) and/or with methanolic sodium methoxide (**13b** and **19b**).

The structure of prepared compounds was determined by ^{1}H NMR spectra (see Tables I–IV). Values of coupling constants (J(1′,2′) = 10.0–11.0 Hz) correspond to a trans axial orientation of protons H-1′ and H-2′ and values of vicinal coupling constants (J(eq,ax) = 4.3–5.7 Hz, J(eq,eq) = 2.0–3.5 Hz) consist with an equatorial orientation of protons H-4′ (Table II) and H-5′ (Table III), respectively. The vicinal coupling constants of the protons H-4′

TABLE I

Chemical shifts (δ, ppm) of cyclohexane nucleosides



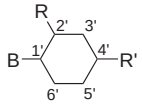
A, B = adenin-9-yl
T, B = thymin-1-yl

	2a	**6b**	**9**	**10a**	**4a**	**12**	**13b**
B	A	A	ABz_2	ABz_2	T	T	T
R	OH	OH	OAc	OAc	OH	OBz	OH
R′	$CH{=}CH_2$	COOH	CH=O	CH_2OH	$CH{=}CH_2$	CH=O	CH_2OH
H-1′	4.12	4.08	4.59	4.58	4.06	4.59	4.01
H-2′	4.22	4.16	5.14	5.25	3.84	5.32	3.76
H-3′eq	2.00	2.36	2.46	2.10	1.93	2.63	1.96
H-3′ax	1.62	1.50	1.78	1.25	1.54	n	1.36
H-4′	2.63	2.80	2.88	1.73	2.56	2.80	1.86
H-5′eq	1.72	2.12	2.05	1.85	1.65	2.30	1.70
H-5′ax	1.69	1.59	1.83	1.18	1.61	n	1.42
H-6′eq	1.78	1.83	2.34	2.12	1.54	n	1.48
H-6′ax	2.25	2.20	2.30	2.93	1.78	n	1.72
H-2,H-8	8.14	8.08	8.67	8.73	7.53	7.62	7.60
(H-6, CH_3)	8.10	8.05	8.66	8.68	1.78	1.68	1.77
NH_2 (NH)	7.12	7.11	–	–	11.10	11.16	11.08
H of R	4.84	4.95	1.50	1.50	4.83	arom	4.75
H of R′	6.12	12.4	9.74	3.35	6.12	9.73	3.50
	5.15	–	–	3.29	5.10	–	3.44
	5.12	–	–	4.61	5.06	–	4.47

n, cannot be determined (1.76–1.87 m, 4 H).

TABLE II

Coupling constants (*J*, Hz) of cyclohexane nucleosides



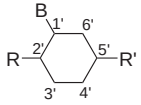
A, B = adenin-9-yl
T, B = thymin-1-yl

	2a	**6b**	**9**	**10a**	**4a**	**12**	**13b**
B	A	A	ABz_2	ABz_2	T	T	T
R	OH	OH	OAc	OAc	OH	OBz	OH
R′	$CH{=}CH_2$	COOH	CH=O	CH_2OH	$CH{=}CH_2$	CH=O	CH_2OH
1′,2′	10.0	10.0	10.4	10.4	10.4	11.0	10.0
2′,3′eq	4.3	4.3	4.8	4.5	4.9	5.0	4.6
2′,3′ax	11.0	10.8	11.6	11.5	11.0	11.0	11.3
3′eq,3′ax	13.2	13.2	13.0	12.6	12.8	12.8	13.2
3′eq,4′	2.4	2.4	2.5	2.7	2.2	2.1	2.4
3′ax,4′	4.8	5.1	5.6	12.2	4.9	n	5.1
4′,5′eq	2.8	2.5	2.5	2.5	2.3	2.0	2.4
4′,5′ax	4.8	4.9	5.3	12.0	4.3	n	4.8
5′eq,5′ax	13.2	13.7	13.2	13.6	13.4	12.8	13.4
5′eq,6′eq	3.5	2.8	3.4	3.5	n	2.0	3.0
5′eq,6′ax	4.8	3.7	3.7	3.6	3.8	2.0	n
5′ax,6′eq	3.5	4.0	4.4	3.7	4.3	n	3.8
5′ax,6′ax	13.0	13.6	13.6	13.0	13.2	n	13.4
6′eq,1′	4.0	3.9	4.0	4.3	4.0	4.0	3.8
6′ax,1′	12.0	12.2	12.6	12.6	12.0	11.0	11.0
6′eq,6′ax	13.0	13.2	13.2	13.0	13.2	n	12.8
3′eq,5′eq	2.0	2.0	2.2	2.0	2.0	2.2	2.0
2′,R	5.6	n	–	–	5.4	–	5.5
4′,R′	5.6	–	–	6.0	7.1	–	8.4
	–	–	–	6.4	–	–	7.3

n, cannot be determined.

(J(4′,3′ax) = 12.2 Hz, J(4′,5′ax) = 12.0 Hz) of compound **10a** and H-5′ (J(5′,4′ax) = 11.8 Hz, J(4′,6′ax) = 12.4 Hz) of compound **16b** correspond to an equatorial orientation of these protons. The structure of thymine analog **13b** was also proved by conversion to the oxabicyclooctane derivative **23**

TABLE III
Chemical shifts (δ, ppm) of cyclohexane nucleosides

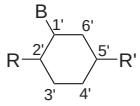


A, B = adenin-9-yl
T, B = thymin-1-yl

	3a	**7b**	**15**	**16b**	**5a**	**18**	**19b**
B	A	A	ABz_2	A	T	T	T
R	OH	OH	OAc	OH	OH	OBz	OH
R′	$CH{=}CH_2$	COOH	CH=O	CH_2OH	$CH{=}CH_2$	CH=O	CH_2OH
H-1′	4.32	4.34	4.57	4.14	4.31	4.59	4.20
H-2′	4.04	3.98	5.22	4.02	3.69	5.23	3.64
H-3′eq	1.82	1.88	1.96	2.01	1.76	2.11	1.70
H-3′ax	1.52	1.41	1.35	1.37	1.42	1.36	1.37
H-4′eq	1.78	2.09	2.31	1.74	1.69	2.26	1.70
H-4′ax	1.72	1.65	1.83	1.10	1.61	1.81	1.45
H-5′	2.61	2.81	2.95	1.59	2.55	2.87	1.85
H-6′eq	1.98	2.20	2.53	1.79	1.76	2.26	1.67
H-6′ax	2.32	2.33	2.66	1.94	1.84	2.20	1.74
H-2, H-8	8.17	8.17	8.77	8.13	7.59	7.81	7.58
(H-6, CH_3)	8.11	8.10	8.69	8.10	1.77	1.71	1.77
NH_2 (NH)	7.13	7.13	–	7.12	11.10	11.19	11.08
H of R	4.87	4.86	1.48	4.84	4.85	arom	4.82
H of R′	5.98	12.50	9.72	3.29	5.89	9.70	3.43 (2H)
	5.24	–	–	3.23	5.18	–	–
	5.20	–	–	5.52	5.15	–	4.55

TABLE IV

Coupling constants (*J*, Hz) of cyclohexane nucleosides

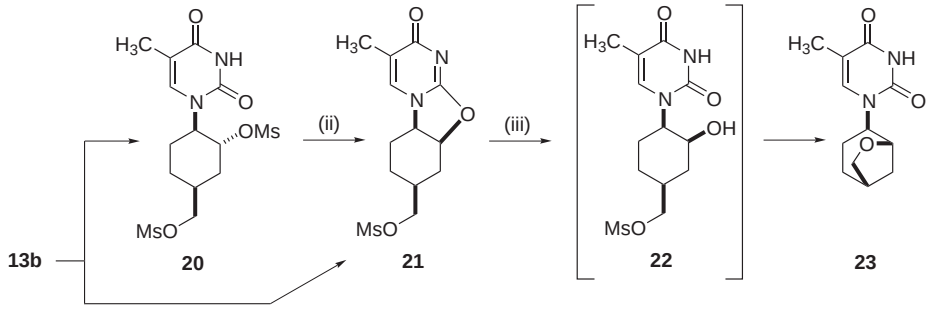


A, B = adenin-9-yl
T, B = thymin-1-yl

	3a	**7b**	**15**	**16b**	**5a**	**18**	**19b**
B	A	A	ABz_2	A	T	T	T
R	OH	OH	OAc	OH	OH	OBz	OH
R′	$CH{=}CH_2$	COOH	CH=O	CH_2OH	$CH{=}CH_2$	CH=O	CH_2OH
1′,2′	10.0	10.0	10.5	10.0	11.0	10.5	10.5
2′,3′eq	4.4	4.5	4.6	4.5	4.4	4.8	5.5
2′,3′ax	11.0	11.0	11.4	10.7	11.0	11.4	10.7
3′eq,3′ax	12.6	13.2	13.2	12.8	13.0	12.8	12.8
3′eq,4′eq	2.7	2.6	3.2	2.7	n	3.2	n
3′eq4′ax	3.8	3.7	3.9	3.4	4.4	4.0	4.0
3′ax,4′eq	4.1	3.8	4.0	3.4	3.7	3.9	4.2
3′ax,4′ax	13.4	13.6	13.4	13.6	13.6	13.8	13.8
4′eq,5′	2.7	2.6	2.2	3.4	n	2.5	n
4′ax,5′	4.6	5.0	5.6	11.8	4.4	5.7	5.4
4′eq,4′ax	13.2	13.8	13.4	13.6	13.6	13.8	13.8
6′eq,1′	4.0	4.4	4.6	4.1	4.0	4.0	4.2
6′ax,1′	12.6	12.6	12.8	12.4	12.0	12.0	12.0
6′eq,5′	2.5	2.2	2.2	3.5	n	2.5	2.2
6′ax,5′	5.0	5.0	5.4	12.4	4.6	4.8	4.4
6′eq,6′ax	13.0	13.2	13.2	12.6	13.0	13.0	12.8
4′eq,6′eq	2.2	2.2	2.2	2.1	n	n	2.2
2′,R	6.0	n	n	5.6	5.5	–	5.5
5′,R′	5.1	–	–	6.2	4.9	–	7.6
	–	–	–	6.2	–	–	–

n, cannot be determined.

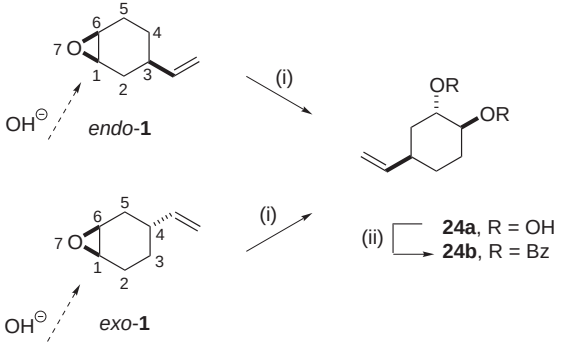
(Scheme 4). Mesylation of compound **13b** with methanesulfonyl chloride in pyridine afforded a mixture of dimesyl derivative **20** (80%) and anhydro derivative **21** (15%). Further treatment of dimesylate **20** with DBU in acetonitrile at room temperature gave **21** in the yield of 69%. Reaction of compound **21** with saturated methanolic lithium hydroxide gave hydroxy derivative **22** which was spontaneously converted to oxabicyclooctylthymine **23** (78%).



(i) MsCl/pyridine; **20** 80%, **21** 15%; (ii) DBU/MeCN, r.t., 69%; (iii) sat. methanolic LiOH, 60 °C, 78%

SCHEME 4

The obtained findings indicate that compounds **3a** and **5a** arose from the *endo*-epoxide (from a mixture of isomers of **1**), whereas the *exo*-epoxide afforded **2a** and **4a**. This assumption was verified by the reaction of a mixture of isomers of **1** with water and DBU which gave, after benzoylation, the racemic compound **24b** only (Scheme 5). The literature[10] data are consistent with this postulate.



(i) DBU/H_2O/DMF, 130 °C; (ii) BzCl/pyridine

SCHEME 5

In conclusion, new racemic 2-hydroxy-4- and 2-hydroxy-5-(hydroxymethyl)cyclohexyl analogues of adenine and thymine nucleosides were prepared from 3-vinyl-7-oxabicyclo[4.1.0]heptane. The obtained results demonstrate that inexpensive cyclohexane epoxides may be used in some cases as starting material for the synthesis of racemic carbocyclic nucleosides.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. IR spectra were recorded on a Bruker Equinox 55 spectrophotometer (wavenumbers in cm^{-1}) and UV spectra (λ_{max} in nm) on a Unicam SP 8000 spectrometer. NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian UNITY 500 instrument (500 MHz for ^1H and 125.7 MHz for ^{13}C) in hexadeuteriodimethyl sulfoxide and referenced to the solvent signal (δ 2.50 and 39.70, respectively). The spectra of the compounds **2a**, **3a**, **4a**, **5a**, **6b**, **7b**, **9**, **10a**, **12**, **13b**, **15**, **16b**, **18** and **19b** are given in Tables I–IV. Column chromatography was performed on Silica gel 60 (Fluka) and thin-layer chromatography (TLC) on Silufol UV 254 foils (Kavalier, Votice). Solvents were evaporated at 2 kPa and bath temperature 36–60 °C; the compounds were dried at 13 Pa and 50 °C. 3-Vinyl-7-oxabicyclo[4.1.0]heptane was a product of Aldrich.

(1*R**,2*R**,5*S**)-2-(6-Amino-9*H*-purin-9-yl)-5-vinylcyclohexyl Acetate (**2b**) and
(1*R**,2*R**,4*S**)-2-(6-Amino-9*H*-purin-9-yl)-4-vinylcyclohexyl Acetate (**3b**)

A solution of adenine (2.7 g, 20 mmol) in dimethylformamide (50 ml) and DBU (3.3 ml, 22 mmol) was stirred under argon at 125 °C (bath). 3-Vinyl-7-oxabicyclo[4.1.0]heptane (**1**; 2.6 ml, 20 mmol) was added to the solution and the mixture was heated to 125 °C for 2.5 h. After cooling, the reaction mixture was neutralized with acetic acid and evaporated. The residue was mixed with ethyl acetate (400 ml) and the insoluble material was filtered off and washed with the same solvent. The combined filtrates were washed with water (100 ml), the aqueous layer was extracted with ethyl acetate (2 × 200 ml) and the combined organic layers were dried over anhydrous sodium sulfate and evaporated. The residue was mixed with ether (20 ml), the crystalline mixture of **2a** and **3a** was filtered off and washed with ether. To a stirred suspension of **2a** and **3a** in acetonitrile (40 ml), acetic acid (1 ml), 4-(dimethylamino)pyridine (305 mg, 2.5 mmol) and acetic anhydride (2 ml, 21 mmol) were added. After 3 h stirring, methanol (1 ml) was added, the reaction mixture was set aside for 15 min and taken down. A solution of the residue in ethyl acetate (200 ml) was washed with water (50 ml), saturated aqueous $NaHCO_3$ (2 × 50 ml) and dried over anhydrous sodium sulfate. Crystallization of the residue from ethyl acetate afforded 1.27 g (21%) of compound **2b**. Chromatography of the mother liquors on a silica gel column (200 g) in ethyl acetate–acetone–ethanol–water (105:15:3:2) afforded 595 mg (10%) of compound **3b** and 380 mg (6%) of **2b**.

Compound **2b**: M.p. 179–182 °C. For $C_{15}H_{19}N_5O_2$ (301.3) calculated: 59.79% C, 6.36% H, 23.24% N; found: 59.70% C, 6.46% H, 23.02% N. ^1H NMR: 1.64 s, 3 H (CH_3COO); 1.75 ddd, 1 H, *J*(6ax,1) = 11.6, *J*(6ax,5) = 4.9, J_{gem} = 12.9 (H-6ax); 1.79 m, 2 H (2 x H-4); 1.86 brdq, 1 H, J_{gem} = 13.0 (H-3eq); 2.09 ddd, 1 H, *J*(6eq,1) = 4.5, *J*(6eq,5) = 2.6 (H-6eq); 2.47 tt, 1 H, *J*(3ax,4ax) = *J*(3ax,4eq) = 8.6 (H-3ax); 2.70 m, 1 H (H-5); 4.47 ddd, 1 H, *J*(2,1) = 10.4,

J(2,3ax) = 12.6, *J*(2,3eq) = 4.3 (H-2); 5.19 dt and 5.24 dt, 2 H, *J* = 1.7, 10.6 and 17.3 (CH_2=); 5.44 ddd, 1 H (H-1); 6.14 ddd, *J*(CH,5) = 6.2, *J*(CH,CH_2) = 10.6 and 17.3 (CH=); 7.17 brs, 2 H (NH_2); 8.11 s and 8.19 s, 2 H (H-2′, H-8′). ^{13}C NMR: 20.84 q, *J* = 128.9 (CH_3); 26.58 (C-4); 28.83 (C-3); 34.87 (C-6); 36.50 (C-5); 58.09 (C-2); 70.68 (C-1); 115.91 ddd, *J* = 153.3, 158.2 and 5.9 (CH_2=); 119.25 dt, *J*(C-5′,H-8′) = 11.7, *J*(C-5′,NH_2) = 4.9 (C-5′); 140.67 dd, *J* = 211.9, *J*(C-8′,H-2) = 4.9 (C-8′); 140.81 brdm, *J* = 153.3 (=CH-); 150.00 ddd, *J*(C-4′,H-2′) = 12.7, *J*(C-4′,H-8′) = 4.9, *J*(C-4′,H-2) = 3.9 (C-4′); 152.73 d, *J* = 198.2 (C-2′); 156.27 d, *J*(C-6′,H-2′) = 11.7 (C-6′); 169.93 qd, *J*(CO,CH_3) = 6.8, *J*(CO,H-1) = 3.9 (C=O).

Compound **3b**: M.p. 179–183 °C. For $C_{15}H_{19}N_5O_2$ (301.3) calculated: 59.79% C, 6.36% H, 23.24% N; found: 59.81% C, 6.49% H, 22.99% N. ^{1}H NMR: 1.62 m, 1 H (H-6ax); 1.63 s, 3 H (CH_3COO); 1.79 tdd, 1 H, *J*(5ax,4) = 4.5, *J*(5ax,6ax) = 13.9, *J*(5ax,6eq) = 3.7, J_{gem} = 13.9 (H-5ax); 1.83 m, 1 H (H-5eq); 1.91 brdq, 1 H, J_{gem} = 12.7 (H-6eq); 2.05 ddt, 1 H, *J*(3eq,2) = 4.4, *J*(3eq,4) = 2.2, J_{gem} = 13.2 (H-3eq); 2.59 td, 1 H, *J*(3ax,2) = 12.8, *J*(3ax,4) = 4.9 (H-3ax); 2.69 m, 1 H (H-4); 4.60 ddd, *J*(2,1) = 10.4 (H-2); 5.23 ddd and 5.24 ddd, 2 H, *J* = 1.5, 2.1, 10.9 and 17.3 (CH_2=); 5.31 td, 1 H, *J*(1ax,6ax) = 10.6, *J*(1ax,6eq) = 4.6 (H-1ax); 6.01 ddd, 1 H, *J*(CH,4) = 5.0, *J*(CH,CH_2) = 10.9 and 17.3 (CH=); 7.18 brs, 2 H (NH_2); 8.12 s and 8.24 s, 2 H (H-2′, H-8′). ^{13}C NMR: 20.52 q, *J* = 128.9 (CH_3); 26.60 and 27.10 (C-3, C-5); 33.73 (C-6); 35.27 (C-4); 53.15 (C-2); 73.65 (C-1); 115.78 ddd, *J* = 154.3, 157.2 and 5.9 (CH_2=); 118.97 dt, *J*(C-5′,H-8′) = 11.7, *J*(C-5′,NH_2) = 3.9 (C-5′); 139.93 dd, *J* = 211.9, *J*(C-8′,H-2) = 4.9 (C-8′); 140.16 brdm, *J* = 153.3 (=CH-); 149.77 ddd, *J*(C-4′,H-2′) = 12.7, *J*(C-4′,H-8′) = 4.9, *J*(C-4′,H-2) = 3.9 (C-4′); 152.40 d, *J* = 198.25 (C-2′); 156.13 d, *J*(C-6′,H-2′) = 11.7 (C-6′); 169.35 qd, *J*(CO,CH_3) = 6.8, *J*(CO,H-1) = 3.9 (C=O).

Deprotection of **2b** and **3b**

A solution of acetate **2b** or **3b** (301 mg, 1 mmol) in methanolic ammonia (saturated at 0 °C, 2.5 ml) was set aside at room temperature overnight. The crystalline product was filtered off, washed with methanol and ether, and dried. The mother liquors were evaporated and the residue was crystallized from methanol.

(1R,2R*,5S*)-2-(6-Amino-9H-purin-9-yl)-5-vinylcyclohexanol* (**2a**), yield 220 mg (85%). M.p. 197–199 °C. For $C_{13}H_{17}N_5O$ (259.3) calculated: 60.21% C, 6.61% H, 27.01% N; found: 59.97% C, 6.69% H, 26.89% N. UV, λ_{max} (ε) (water): 204 (23 540), 262 (14 110); (0.1 M HCl): 211 (23 210), 259 (14 730).

(1R,2R*,4S*)-2-(6-Amino-9H-purin-9-yl)-4-vinylcyclohexanol* (**3a**), yield 211 mg (81%). M.p. 178.5–180.5 °C. For $C_{13}H_{17}N_5O$ (259.3) calculated: 60.21% C, 6.61% H, 27.01% N; found: 59.92% C, 6.64% H, 26.79% N. UV, λ_{max} (ε) (water): 203 (26 380), 262 (14 700); (0.1 M HCl): 211 (24 490), 260 (15 060).

Benzoylation of **2b** and **3b**

Benzoyl chloride (2.9 ml, 25 mmol) was added to a solution of acetate **2b** or **3b** (3.01 g, 10 mmol) in pyridine (30 ml) and the mixture was set aside at room temperature for 5 days. Methanol (2 ml) was then added and, after 15 min, pyridine was evaporated. The residue was partitioned between ethyl acetate (300 ml) and water (50 ml). The organic layer was washed with water, 5% hydrochloric acid, water, saturated aqueous $NaHCO_3$ (50 ml each), and dried over anhydrous sodium sulfate, the solvent was taken down and the residue was crystallized from ethanol.

(1R,2R*,5S*)-2-[6-(Dibenzoylamino)-9H-purin-9-yl]-5-vinylcyclohexyl acetate* (**2c**), yield 4.19 g (87%). M.p. 143–144.5 °C. For $C_{29}H_{27}N_5O_4$ (509.6) calculated: 68.36% C, 5.34% H, 13.74% N; found: 68.12% C, 5.38% H, 13.54% N. ^{1}H NMR: 1.53 s, 3 H (CH_3COO); 1.80 ddd, 1 H, *J*(6ax,1) = 11.8, *J*(6ax,5) = 5.0, J_{gem} = 12.9 (H-6ax); 1.83 m, 2 H (H-4); 1.99 brdq, 1 H, *J* = 3.7, J_{gem} = 13.0 (H-3eq); 2.09 brddd, 1 H, *J*(6eq,1) = 4.8, *J*(6eq,5) = 2.0 (H-6eq); 2.56 m, 1 H, *J*(3ax,2) = 12.4, *J*(3ax,4) = 4.0 and 13.6 (H-3ax); 2.72 m, 1 H (H-5); 4.62 ddd, 1 H, *J*(2,1) = 10.5, *J*(2,3eq) = 4.3 (H-2); 5.21 dt and 5.24 dt, 2 H, *J* = 1.7, 10.6 and 17.3 (CH_2=); 5.37 ddd, 1 H (H-1); 6.14 ddd, *J*(CH,5) = 6.1, *J*(CH,CH_2) = 10.6 and 17.3 (CH=); 7.44 t, 4 H, 7.58 t, 2 H and 7.65 d, 4 H (H-arom.); 8.68 s and 8.72 s, 2 H (H-2′, H-8′).

(1R,2R*,4S*)-2-[6-(Dibenzoylamino)-9H-purin-9-yl]-4-vinylcyclohexyl acetate* (**3c**), yield 4.35 g (85%). M.p. 196–198 °C. For $C_{29}H_{27}N_5O_4$ (509.6) calculated: 68.36% C, 5.34% H, 13.74% N; found: 68.15% C, 5.33% H, 13.56% N. ^{1}H NMR: 1.50 s, 3 H (CH_3COO); 1.66 tdd, 1 H, *J*(H-6ax,1) = 11.2, *J*(6ax,5ax) = 13.0, *J*(6ax,5eq) = 4.4, J_{gem} = 12.6 (H-6ax); 1.82 tdd, 1 H, *J*(5ax,4) = 4.4, *J*(5ax,6ax) = 13.7, *J*(5ax,6eq) = 2.8 (H-5ax); 1.88 dm, 1H, J_{gem} 13.8 (H-5eq); 1.91 ddt, 1 H, *J*(6eq,1) = 4.6, *J*(6eq,5ax) = *J*(6eq,5eq) = 3.0 (H-6eq); 2.21 ddt, 1 H, *J*(3eq,2) = 4.3, *J*(3eq,4) = 2.2, J_{gem} = 13.2 (H-3eq); 2.68 td, 1 H, *J*(3ax,4) = 4.9 (H-3ax); 2.74 m, 1 H (H-4); 4.73 ddd, 1 H, *J*(2,1) = 10.4, *J*(2,3ax) = 12.8 (H-2); 5.24 dt and 5.26 dt, 2 H, *J* = 1.7, 10.7 and 17.6 (CH_2=); 5.25 m, 1 H (H-1); 6.01 ddd, *J*(CH,4) = 4.8, *J*(CH,CH_2) = 10.7 and 17.6 (CH=); 7.45 t, 4 H, 7.60 t, 2 H and 7.76 d, 4 H (H-arom.); 8.68 s and 8.77 s, 2 H (H-2′, H-8′).

(1*R**,2*R**,5*S**)-2-[5-Methyl-2,4-dioxo-3,4-dihydroxypyrimidin-1(2*H*)-yl]-5-vinylcyclohexyl Benzoate (**4b**) and (1*R**,2*R**,4*S**)-2-[5-Methyl-2,4-dioxo-3,4-dihydroxypyrimidin-1(2*H*)-yl]-4-vinylcyclohexyl Benzoate (**5b**)

A solution of thymine (5.10 g, 40 mmol) and DBU (6.6 ml, 44 mmol) in dimethylformamide (80 ml) was heated at 130 °C under argon. 3-Vinyl-7-oxabicyclo[4.1.0]heptane (5.20 ml, 40 mmol) was added in 5 portions to the stirred solution during 3 h and the mixture was heated to 130 °C for additional 1.5 h. After cooling, the reaction mixture was neutralized with acetic acid and evaporated. The residue was partitioned between ethyl acetate (700 ml) and water (140 ml), the aqueous layer was extracted with ethyl acetate (200 ml) and the combined organic layers were dried over anhydrous sodium sulfate and evaporated. Benzoyl chloride (4.3 ml, 37 mmol) was added dropwise to an ice-cool solution of the residue in pyridine (60 ml) and the mixture was set aside at room temperature overnight. Methanol (2 ml) was then added and, after 15 min, pyridine was evaporated. The residue was partitioned between ethyl acetate (300 ml) and water (50 ml). The organic layer was washed with water, 5% hydrochloric acid, water, saturated aqueous $NaHCO_3$ (50 ml each), dried over anhydrous sodium sulfate, and the solvent was taken down. Crystallization of the residue from propan-2-ol afforded 2.40 g (17%) of compound **4b**. Chromatography of the mother liquors on a silica gel column (250 g) in ethyl acetate–toluene (1:1) and crystallization from propan-2-ol afforded 1.70 g (12%) of isomer **5b** and 600 mg (4%) of compound **4b**.

Compound **4b**: M.p. 227–229 °C. For $C_{20}H_{22}N_2O_4$ (354.4) calculated: 67.78% C, 6.26% H, 7.90% N; found: 67.65% C, 6.35% H, 7.91% N. IR (*c* 2%, $CHCl_3$): 3396 (NH); 1710, 1688 (C=O); 1655 (C=C); 1603, 1585, 1492, 1452, 1317, 1179, 1114, 1071, 1028 and 687 (arom.); 1273 (C–O); 924 (=CH_2). ^{1}H NMR: 1.71 d, 3 H, *J* = 1.2 (CH_3); 1.73 dq, 1 H, J_{gem} = 12.8 (H-3eq); 1.78 m, 2 H (H-4); 1.81 ddd, 1 H, *J*(6ax,1) = 11.5, *J*(6ax,5) = 5.0, J_{gem} = 12.8 (H-6ax); 2.10 qd, 1 H, *J*(3ax,2) = *J*(3ax,4ax) = 12.3, *J*(3ax,4eq) = 5.0 (H-3ax); 2.21 ddt, 1 H, *J* = 2.1 (H-6eq); 2.68 m, 1 H (H-5); 4.63 brtd, 1 H, *J*(2,1) = 11.0, *J*(2,3eq) = 4.0 (H-2); 5.18 dt and

5.25 dt, 2 H, *J* = 1.7, 10.5 and 17.2 (CH_2=); 5.31 td, 1 H, *J*(1,6eq) = 4.5 (H-1); 6.21 ddd, *J*(CH,5) = 6.7, *J*(CH,CH_2) = 10.5 and 17.2 (CH=); 7.49 t, 2 H, 7.64 t, 1 H and 7.84 d, 2 H (H-arom.); 7.70 brs, 1 H (H-6′); 11.19 s, 1 H (NH). ^{13}C NMR: 12.03 qd, *J* = 127.9, *J*(CH_3,H-6′) = 4.9 (CH_3); 25.09 (C-4); 28.93 (C-3); 35.00 (C-6); 36.65 (C-5); 57.90 (C-2); 70.64 (C-1); 109.24 brq, *J*(C-5′,CH_3) = 6.8, *J*(C-5′,H-6′) = 1.0 (C-5′); 115.45 ddd, *J* = 153.3, 158.2 and 5.9 (CH_2=); 128.91 dd, *J* = 164.1 and 7.8, 129.22 ddd, *J* = 163.1, 5.9 and 7.8, 129.53 m and 133.66 dt, *J* = 164.1 and 6.8 (C-arom.); 138.11 brdm, *J* = 180.7, *J*(C-6′,CH_3) ≈ *J*(C-6′,H-2) ≈ 3.9 (C-6′); 140.60 brdm, *J* = 152.3 (=CH-); 151.43 dd, *J*(C-2′,H-2) = 3.9, *J*(C-2′,H-6′) = 8.8 (H-2′); 163.71 dq, *J*(C-4′,CH_3) = 3.9, *J*(C-4′,H-6′) = 9.8 (C-4′); 165.08 brq, *J* = 3.9 (C=O).

Compound **5b**: M.p. 165–168 °C. For $C_{20}H_{22}N_2O_4$ (354.4) calculated: 67.78% C, 6.26% H, 7.90% N; found: 67.49% C, 6.28% H, 7.73% N. IR (*c* 2%, $CHCl_3$): 3396 (NH); 1711, 1688 (C=O); 1655 (C=C); 1603, 1585, 1492, 1471, 1317, 1178, 1113, 1071, 1028 and 687 (arom.); 1273 (C–O); 991(trans CH=CH); 924 (=CH_2). ^{1}H NMR: 1.71 d, 3 H, *J* = 1.1 (CH_3); 1.66 tdd, 1 H, *J*(6ax,1) = 11.5, *J*(6ax,5ax) = 13.6, *J*(6ax,5eq) = 6.0, J_{gem} = 13.6 (H-6ax); 1.80 tdd, 1 H, *J*(5ax,4) = 4.1, *J*(5ax,6eq) = 3.9, J_{gem} = 13.6 (H-5ax); 1.83 m, 1 H (H-5eq); 1.99 ddt, 1 H, *J*(3eq,2) = 4.0, *J*(3eq,4) = 2.1, J_{gem} = 13.2 (H-3eq); 2.04 m, 1 H (H-6eq); 2.24 td, 1 H, *J*(3ax,4) = 5.0 (H-3ax); 2.68 m, 1 H (H-4); 4.82 brddd, 1 H, *J*(2,1) = 10.5, *J*(2,3ax) = 12.5 (H-2); 5.22 ddd and 5.23 ddd, 2 H, *J* = 1.6, 2.0, 10.9 and 17.3 (CH_2=); 5.26 brtd, 1 H, *J*(1,6eq) = 4.9 (H-1); 5.97 ddd, *J*(CH,4) = 4.8, *J*(CH,CH_2) = 10.9 and 17.3 (CH=); 7.48 t, 2 H, 7.63 t, 1 H and 7.83 d, 2 H (H-arom.); 7.81 brq, 1 H, *J* = 1.0 (H-6′); 11.18 s, 1 H (NH). ^{13}C NMR: 12.22 qd, *J* = 128.9, *J*(CH_3,H-6′) = 4.9 (CH_3); 26.78 and 26.86 (C-3, C-5); 32.37 (C-6); 35.26 (C-4); 52.40 (C-2); 73.67 (C-1); 109.24 brq, *J*(C-5′,CH_3) = 6.8, *J*(C-5′,H-6′) = 1.0 (C-5′); 115.74 ddd, *J* = 153.3, 158.2 and 5.9 (CH_2=); 137.83 brdm, *J* = 180.2, *J*(C-6′,CH_3) ≈ *J*(C-6′,H-2) ≈ 3.9 (C-6′); 140.21 brdm, *J* = 153.3 (=CH-); 151.51 dd, *J*(C-2′,H-2) = 3.9, *J*(C-2′,H-6′) = 8.8 (H-2′); 163.67 dq, *J*(C-4′,CH_3) = 3.9, *J*(C-4′,H-6′) = 9.8 (C-4′);

Deprotection of Compounds **4b** and **5b**

A solution of benzoate **4b** or **5b** (354 mg, 1 mmol) in 0.1 M methanolic sodium methoxide (6 ml) was set aside at room temperature overnight and then neutralized with Dowex 50 (H^+). The resin was filtered off, washed with methanol and the combined filtrates were evaporated. The residue was triturated with ether, the crystalline solid was filtered off and washed with ether.

1-[(1R,2R*,4S*)-2-Hydroxy-4-vinylcyclohexyl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**4a**), yield 230 mg (92%). M.p. 143–145.5 °C. For $C_{13}H_{18}N_2O_3 \cdot 0.5H_2O$ (518.6) calculated: 60.22% C, 7.39% H, 10.80% N; found: 60.51% C, 7.34% H, 10.67% N. UV, λ_{max} (ε) (water): 273 (11 440); (0.1 M NaOH): 272 (5920).

1-[(1R,2R*,5S*)-2-Hydroxy-5-vinylcyclohexyl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**5a**), yield 234 mg (93%). M.p. 203.5–204.5 °C. For $C_{13}H_{18}N_2O_3$ (250.3) calculated: 62.38% C, 7.25% H, 11.19% N; found: 62.09% C, 7.41% H, 11.30% N. UV, λ_{max} (ε) (water): 273 (9090); (0.1 M NaOH): 272 (7350).

Preparation of Carboxylic Acids **6a** and **7a**. General Procedure

Ruthenium(III) chloride hydrate (7 mg) was added to a solution of the vinyl derivative **2c** or **3c** (459 mg, 0.9 mmol) in 1,4-dioxane (12 ml). Then a saturated solution of sodium periodate was added dropwise with stirring which was continued until the starting vinyl derivative disappeared. The reaction was monitored by TLC in ethyl acetate–toluene (1:1).

The mixture was filtered, the solid was washed with 1,4-dioxane and the combined filtrates were evaporated. A solution of the residue in ethyl acetate (70 ml) was washed with water (10 ml), 15% aqueous sodium thiosulfate (10 ml), dried over anhydrous sodium sulfate, the solvent was taken down and the residue was crystallized from ethyl acetate.

(1R,3S*,4S*)-3-Acetoxy-4-[6-(dibenzoylamino)-9H-purin-9-yl]cyclohexanecarboxylic acid* (**6a**), yield 413 mg (87%). M.p. 143–145 °C. For $C_{28}H_{25}N_5O_6$ (527.5) calculated: 63.75% C, 4.78% H, 13.28% N; found: 63.47% C, 4.99% H, 12.99% N. ^{1}H NMR: 1.53 s, 3 H (CH_3COO); 1.72 ddd, 1 H, *J*(2ax,1) = 5.3, *J*(2ax,3) = 11.4, J_{gem} = 12.8 (H-2ax); 1.74 tdd, 1 H, *J*(6ax,1) = 4.9, *J*(6ax,5ax) = 13.6, *J*(6ax,5eq) = 4.0, J_{gem} = 13.6 (H-6ax); 2.05 dq, 1 H, *J*(5eq,6ax) = *J*(5eq,6eq) = 4.0, J_{gem} = 13.0 (H-5eq); 2.21 dpent, 1 H, *J* = 2.2 (H-6eq); 2.36 ddt, 1 H, *J*(2eq,1) = 2.6, *J*(2eq,3) = 4.6, *J*(2eq,6eq) = 2.0 (H-2eq); 2.53 qd, 1 H, *J*(5ax,6ax) = 13.2, *J*(5ax,6eq) = 4.0 (H-5ax); 4.58 ddd, 1 H, *J*(4,3) = 10.4, *J*(4,5ax) = 12.7, *J*(4,5eq) = 4.1 (H-4); 5.36 ddd, 1 H (H-3); 7.44 t, 4 H, 7.58 t, 2 H and 7.74 d, 4 H (H-arom.); 8.63 s and 8.65 s, 2 H (H-2′, H-8′); 12.75 brs, 1 H (COOH).

(1R,3S*,4S*)-4-Acetoxy-3-[6-(dibenzoylamino)-9H-purin-9-yl]cyclohexanecarboxylic acid* (**7a**), yield 405 mg (85%). M.p. 128–131 °C. For $C_{28}H_{25}N_5O_6$ (527.5) calculated: 63.75% C, 4.78% H, 13.28% N; found: 63.46% C, 5.02% H, 13.00% N. ^{1}H NMR: 1.48 s, 3 H (CH_3COO); 1.54 tdd, 1 H, *J*(5ax,4) = 11.5, *J*(5ax,6ax) = 13.6, *J*(5ax,6eq) = 3.5, J_{gem} 13.6 (H-5ax); 1.79 tdd, 1 H, *J*(6ax,1) = 5.1, J_{gem} = 13.9 (H-6ax); 1.99 brddt, 1 H (H-5eq); 2.16 dpent, 1 H, *J* = 2.5 (H-6eq); 2.37 ddt, 1 H, *J*(2eq,1) = 2.2, *J*(2eq,3) = 4.4, J_{gem} = 13.2 (H-2eq); 2.60 td, 1 H, *J*(2ax,1) = 5.1 (H-2ax); 2.96 m, 1 H (H-1); 4.84 ddd, 1 H, *J*(3,2ax) = 12.8, *J*(3,4) = 10.4 (H-3); 5.22 td, 1 H, *J*(4,5eq) = 4.6 (H-4); 7.44 t, 4 H, 7.60 t, 2 H and 7.76 d, 4 H (H-arom.); 8.68 s and 8.81 s, 2 H (H-2′, H-8′); 12.65 brs, 1 H (COOH).

Deprotection of **6a** and **7a**

Compound **6a** or **7a** (264 mg, 0.5 mmol) was dissolved under stirring in methanolic ammonia (saturated at 0 °C, 4.5 ml) and then set aside at room temperature for 3 days. The solvent was evaporated and the residue was crystallized from propan-2-ol (**6b**) or ethanol (**7b**).

(1R,3S*,4S*)-4-(6-Amino-9H-purin-9-yl)-3-hydroxycyclohexanecarboxylic acid* (**6b**), yield 108 mg (78%). M.p. > 265 °C. For $C_{12}H_{15}N_5O_3$ (277.3) calculated: 51.98% C, 5.45% H, 25.26% N; found: 51.90% C, 5.52% H, 25.14% N.

(1R,3S*,4S*)-3-(6-Amino-9H-purin-9-yl)-4-hydroxycyclohexanecarboxylic acid* (**7b**), yield 106 mg (76%). M.p. > 265 °C. For $C_{12}H_{15}N_5O_3$ (277.3) calculated: 51.98% C, 5.45% H, 25.26% N; found: 51.69% C, 5.63% H, 24.98% N.

Preparation of Aldehydes **9**, **12**, **15**, and **18**

Osmium tetroxide (10 mg, 0.04 mmol), followed by pulverized sodium chlorate (3 g, 28 mmol) and water (3 ml), was added to a stirred solution of vinyl derivative **2c**, **3c**, **4b** or **5b** (3 mmol) in 1,4-dioxane (25 ml). The mixture was stirred at room temperature for 3 days. The solids were removed by filtration, washed with 1,4-dioxane and the solvent was evaporated. The residue was partitioned between ethyl acetate (100 ml) and water (15 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the combined organic extracts were dried over anhydrous sodium sulfate and taken down. A saturated aqueous sodium periodate was added dropwise to a stirred solution of the residue in 1,4-dioxane (25 ml) and the stirring was continued until the starting vinyl derivative disappeared. The reaction was monitored by TLC in ethyl acetate. The insoluble material was filtered off and

washed with 1,4-dioxane and the combined filtrates were evaporated. The residue was partitioned between ethyl acetate (100 ml) and water (20 ml), the organic layer was separated, washed with 10% aqueous sodium thiosulfate (20 ml), dried over sodium sulfate and evaporated. The residue was chromatographed on a silica gel column (180 g) in ethyl acetate.

(1R,2R*,5S*)-2-[6-(Dibenzoylamino)-9H-purin-9-yl]-5-formylcyclohexyl acetate* (**9**), yield 980 mg (64%) after crystallization from propan-2-ol. M.p. 173–175 °C. For $C_{28}H_{25}N_5O_5$ (511.5) calculated: 65.74% C, 4.93% H, 13.69% N; found: 65.35% C, 5.11% H, 13.41% N.

(1R,2R*,5S*)-5-Formyl-2-[5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl]cyclohexyl benzoate* (**12**), yield 545 mg (51%) of a solid foam. For $C_{19}H_{20}N_2O_5$ (356.4) calculated: 64.03% C, 5.66% H, 7.86% N; found: 63.77% C, 5.90% H, 7.59% N.

(1R,2R*,4S*)-2-[6-(Dibenzoylamino)-9H-purin-9-yl]-4-formylcyclohexyl acetate* (**15**), yield 955 mg (62%) after crystallization from propan-2-ol. M.p. 164.5–166.5 °C. For $C_{28}H_{25}N_5O_5$ (511.5) calculated: 65.74% C, 4.93% H, 13.69% N; found: 65.35% C, 5.11% H, 13.41% N.

(1R,2R*,4S*)-4-Formyl-2-[5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl]cyclohexyl benzoate* (**18**), yield 524 mg (49%) of a solid foam. For $C_{19}H_{20}N_2O_5$ (356.4) calculated: 64.03% C, 5.66% H, 7.86% N; found: 63.76% C, 5.84% H, 7.57% N.

Reduction of Aldehydes **9**, **12**, **15** and **18**. General Procedure

Amberlyst A-26 (BH_4^- form, 3 g) was added to a solution of aldehyde **9**, **12**, **15** or **18** (1 mmol) in 1,4-dioxane (20 ml) and the mixture was stirred until the starting compound disappeared. The reaction was monitored by TLC in ethyl acetate. The resin was then filtered off, washed with 1,4-dioxane and the filtrates were evaporated. The residue was chromatographed on a silica gel column (50 g) in ethyl acetate–acetone–ethanol–water (200:30:12:8, compounds **10a** and **16a**) and/or ethyl acetate (**13a** and **19a**).

(1R,2R*,5R*)-2-[6-(Dibenzoylamino)-9H-purin-9-yl]-5-(hydroxymethyl)cyclohexyl acetate* (**10a**), yield 390 mg (76%) of a solid foam. For $C_{28}H_{27}N_5O_5$ (513.6) calculated: 65.49% C, 5.30% H, 13.64% N; found: 65.18% C, 5.53% H, 13.35% N.

(1R,2R*,5S*)-5-(Hydroxymethyl)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclohexyl benzoate* (**13a**), yield 262 mg (73%) of a solid foam. For $C_{19}H_{22}N_2O_5$ (358.4) calculated: 63.67% C, 6.19% H, 7.82% N; found: 63.38% C, 6.40% H, 7.61% N. ^{1}H NMR: 1.60 m, 1 H (H-3eq); 1.60 tt, 1 H, J(4ax,3ax) = 13.6, J(4ax,3eq) = J(4ax,5) = 4.4, J_{gem} = 13.6 (H-4ax); 1.65 ddd, 1 H, J(6ax,1) = 11.2, J(6ax,5) = 5.4, J_{gem} = 12.6 (H-6ax); 1.70 d, 3 H, J = 1.1 (CH_3); 1.84 dm, 1 H (H-4eq); 1.98 m, 1 H (H-5); 2.05 qd, 1 H, J(3ax,4ax) = 13.0, J(3ax,4eq) = 3.8, J_{gem} = 13.0 (H-3ax); 2.20 ddt, 1 H, J(6eq,1) = 4.8, J(6eq,4eq) = J(6eq,5) = 2.1, J_{gem} = 12.9 (H-6eq); 3.58 ddd, 1 H, J(CH^a,5) = 8.2, J_{gem} = 10.6 (CH^aH-O); 3.64 ddd, 1 H, J(CH^b,5) = 7.4 (CH^bH-OH); 4.57 brtd, 1 H, J(2,1) = J(2,3ax) = 11.5, J(2,3eq) = 4.3 (H-2); 4.60 t, 1 H, J(CH_2,OH) = 5.3 (CH_2O**H**); 5.27 td, 1 H (H-1); 7.48 t, 2 H, 7.63 t, 1 H and 7.83 d, 2 H (H-arom.); 7.80 brq, 1 H (H-6′); 11.15 s, 1 H (NH).

(1R,2R*,4R*)-2-[6-(Dibenzoylamino)-9H-purin-9-yl]-4-(hydroxymethyl)cyclohexyl acetate* (**16a**), yield 400 mg (78%) of a solid foam. For $C_{28}H_{27}N_5O_5$ (513.6) calculated: 65.49% C, 5.30% H, 13.64% N; found: 65.25% C, 5.41% H, 13.49% N. ^{1}H NMR: 1.21 td, 1 H, J(5ax,4) = 13.4, J(5ax,6ax) = 13.8, J(5ax,6eq) = 3.8, J_{gem} =13.4 (H-5ax); 1.51 s, 3 H (CH_3COO); 1.56 tdd, 1 H, J(6ax,1) = 11.0, J(6ax,5eq) = 3.4, J_{gem} = 13.8 (H-6ax); 1.72 m, 1 H (H-4); 1.83 dq, 1 H (H-5eq); 2.06 ddt, 1 H, J(6eq,1) = 4.8, J(6eq,5eq) = 2.8 (H-6eq); 2.12 m and 2.14 m, 2 H (2 × H-3); 3.30 brdt, 1 H, J(CH^a,4) = 6.0, J_{gem} = 11.6 (CH^aH-O); 3.34 brdt, 1 H, J(CH^b,4) = 6.4 (CH^bH-OH); 4.66 m, 1 H (H-2); 4.62 t, 1 H, J(CH_2,OH) = 6.4 (CH_2O**H**); 5.21 td, J(1,2) =

J(1,6ax) = 11.0, *J*(1,6eq) = 4.8 (H-1); 7.44 t, 4 H, 7.58 t, 2 H and 7.75 d, 4 H (H-arom.); 8.68 s and 8.71 s, 2 H (H-2′, H-8′).

(1R,2R*,4S*)-4-(Hydroxymethyl)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclohexyl benzoate* (**19a**), yield 276 mg (77%) of a solid foam. For $C_{19}H_{22}N_2O_5$ (358.4) calculated: 63.67% C, 6.19% H, 7.82% N; found: 63.46% C, 6.36% H, 7.63% N. ^{1}H NMR: 1.65 m, 1 H (H-6ax); 1.65 m, 1 H (H-5ax); 1.71 d, 3 H, *J* = 1.1 (CH_3); 1.80 m, 1 H (H-5eq); 1.85 ddt, 1 H, *J*(3eq,2) = 4.6, *J*(3eq,4) = 2.2, J_{gem} = 12.8 (H-3eq); 1.97 m, 1 H (H-4); 2.00 m, 1 H (H-6eq); 2.11 td, *J*(3ax,4) = 5.3, J_{gem} = 13.0 (H-3ax); 3.53 dd, 2 H, *J*(CH_2,4) = 7.6, *J*(CH_2,OH) = 5.1 (CH_2); 4.68 t, 1 H (CH_2O**H**); 4.76 ddd, 1 H, *J*(2,1) = 10.1, *J*(2,3ax) = 13.3, *J*(2,3eq) = 4.6 (H-2); 5.20 td, 1 H, *J*(1,6ax) = 10.5, *J*(1,6eq) = 5.0 (H-1); 7.48 t, 2 H, 7.63 t, 1 H and 7.84 d, 2 H (H-arom.); 7.80 brq, 1 H (H-6′); 11.17 s, 1 H (NH).

Deprotection of Compounds **10a** and **16a**

A solution of dibenzoate **10a** or **16a** (207 mg, 0.5 mmol) in methanolic ammonia (3 ml) was set aside at room temperature for 3 days. The crystalline compound was filtered off and washed with methanol and ether.

(1R,2R*,5R*)-2-(6-Amino-9H-purin-9-yl)-5-(hydroxymethyl)cyclohexanol* (**10b**), yield 105 mg (80%). M.p. 215–217 °C. For $C_{12}H_{17}N_5O_2$ (263.3) calculated: 54.74% C, 6.51% H, 26.60% N; found: 54.74% C, 6.64% H, 26.44% N. ^{1}H NMR: 1.00–1.10 m, 2 H (H-3ax, H-6ax); 1.61 m, 1 H, Σ*J* ≈ 43 (H-5); 1.78 dpent, 1 H, *J* ≈ 2.7, J_{gem} = 12.8 (H-4eq); 1.91 dq, 1 H, *J* = 3.5, J_{gem} = 13.0 (H-3eq); 2.03 dm, 1 H, J_{gem} = 13.0 (H-6eq); 2.06 qd, 1 H, *J*(3ax,4eq) = 3.8, *J*(3ax,4ax) ≈ 13.3 (H-3ax); 3.27 brdt, 1 H and 3.30 brdt, 1 H, *J* = 6.0, J_{gem} = 11.0 (CH_2O); 4.04 tt, 1 H, *J*(1,6eq) = 4.6, *J*(1,2) = *J*(1,6ax) = 10.0 (H-1); 4.07 td, 1 H, *J*(2,3eq) = 4.2, *J*(2,3ax) = 12.0 (H-2); 4.52 t, 1 H, *J* = 5.4 (CH_2O**H**); 4.84 d, 1 H, *J*(OH,1) = 5.4 (1-OH); 7.11 brs, 2 H (NH_2); 8.10 s, 1 H and 8.14 s, 1 H (H-2′, H-8′).

(1R,2R*,4R*)-2-(6-Amino-9H-purin-9-yl)-4-(hydroxymethyl)cyclohexanol* (**16b**), yield 101 mg (77%). M.p. 157–158.5 °C. For $C_{19}H_{22}N_2O_5$ (358.4) calculated: 63.67% C, 6.19% H, 7.82% N; found: 63.39% C, 6.40% H, 7.59% N.

Deprotection of Compounds **13a** and **19a**

Compound **13a** or **19a** (179 mg, 0.5 mmol) was treated with methanolic sodium methoxide using the same conditions as for compounds **4b** and **5b**.

1-[(1R,2R*,4S*)-2-Hydroxy-4-(hydroxymethyl)cyclohexyl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**13b**), yield 121 mg (89%). M.p. 197–199 °C. For $C_{12}H_{18}N_2O_4 \cdot H_2O$ (272.3) calculated: 52.93% C, 7.40% H, 10.29% N; found: 52.96% C, 7.61% H, 10.17% N.

1-[(1R,2R*,5S*)-2-Hydroxy-5-(hydroxymethyl)cyclohexyl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**19b**), yield 116 mg (85%). M.p. 220–223 °C. For $C_{12}H_{18}N_2O_4 \cdot H_2O$ (272.3) calculated: 52.93% C, 7.40% H, 10.29% N; found: 53.22% C, 7.47% H, 10.36% N.

[(1*R**,3*S**,4*S**)-3-(Mesyloxy)-4-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)cyclohexyl]methyl Mesylate (**20**)

A solution of **13b** (204 mg, 0.75 mmol) in pyridine (4 ml) was evaporated and the solution of the residue in pyridine (3 ml) was treated with methanesulfonyl chloride (0.4 ml, 4 mmol) at 0 °C. The mixture was set aside at room temperature for 3 h. Water (0.2 ml) was then added and, after 15 min, pyridine was evaporated. The residue was partitioned between

ethyl acetate (200 ml) and water (10 ml). The insoluble portion was filtered off and crystallized from ethanol; yield 35 mg (15%) of **21**. The organic phase was separated, washed with 5% hydrochloric acid, water and 10% aqueous sodium hydrogencarbonate (10 ml each), then dried over anhydrous sodium sulfate, and the solvent was evaporated. Crystallization of the residue from acetone–ether afforded 247 mg (80%) of dimesylate **20**, m.p. 138–141 °C. For $C_{14}H_{22}N_2O_8S_2$ (410.5) calculated: 40.97% C, 5.40% H, 6.82% N, 15.62% S; found: 40.72% C, 5.51% H, 6.60% N, 15.43% S. ^{1}H NMR: 1.68 tt, 1 H, *J*(6ax,1) = *J*(6ax,5eq) = 4.5, *J*(6ax,5ax) = J_{gem} = 13.4 (H-6ax); 1.76 m, 3 H (2 × H-5, H-6eq); 1.78 s, 3 H (CH_3); 1.87 ddd, 1 H, *J*(2ax,1) = 5.4, *J*(2ax,3) = 11.0, J_{gem} = 13.2 (H-2ax); 2.27 ddt, 1 H, *J*(2eq,1) = *J*(2eq,6eq) = 2.1, *J*(2eq,3) = 4.8 (H-2eq); 2.29 m, 1 H (H-1); 3.04 s, 3 H and 3.24 s, 3 H (2 × CH_3SO_2); 4.36 dd, 1 H, *J*(CH^a,1) = 7.2, J_{gem} = 10.2 (CH^aH-O); 4.42 dd, 1 H, *J*(CH^b,1) = 8.7 (CH^bH-O); 4.46 brtd, 1 H, *J*(4,3) = *J*(4,5ax) = 10.8, *J*(4,5eq) = 4.4 (H-4); 4.93 brtd, 1 H (H-3); 7.81 s, 1 H (H-6′); 11.24 s, 1 H (NH).

[(5a*R**,8*S**,9a*S**)-3-Methyl-2-oxo-5a,6,7,8,9,9a-hexahydro-2*H*-pyrimido[2,1-*b*]-[1,3]benzoxazol-8-yl]methyl mesylate (**21**)

DBU (0.2 ml, 1.3 mmol) was added to a solution of dimesylate **20** (205 mg, 0.5 mmol) in acetonitrile and the solution was set aside at room temperature for 1 h. The mixture was then concentrated and adsorbed on silica gel. Chromatography on a silica gel column (20 g) in ethyl acetate–acetone–ethanol–water (15:3:4:3) gave 108 mg (69%) of compound **21**, m.p. 155–156 °C. For $C_{13}H_{18}N_2O_5S$ (314.4) calculated: 49.67% C, 5.77% H, 8.91% N, 10.20% S; found: 49.51% C, 5.80% H, 8.82% N, 10.08% S. ^{1}H NMR: 1.04 dddd, 1 H, *J*(7ax,6ax) = 12.6, *J*(7ax,6eq) = 3.8, *J*(7ax,8) = 10.2, J_{gem} = 13.6 (H-7ax); 1.31 ddd, 1 H, *J*(9ax,8) = 10.9, *J*(9ax,9a) = 9.2, J_{gem} = 13.4 (H-9ax); 1.60 brdq, 1 H, *J*(7eq,6eq) = *J*(7eq,8) = 4.4, *J*(7eq,9eq) = 1.5 (H-7eq); 1.80 d, 3 H, *J* = 1.2 (CH_3); 1.87 ddt, 1 H, *J*(6ax,7eq) = 4.6, J_{gem} = 15.4 (H-6ax); 1.90 m, 1 H (H-8); 2.12 dddd, 1 H, *J*(9eq,8) = 4.0, *J*(9eq,9a) = 6.3 (H-9eq); 2.29 dq, 1 H, *J*(6eq,7eq) = 4.0 (H-6eq); 3.17 s, 3 H (CH_3SO_2); 4.05 d, 2 H, *J*(CH_2,8) = 6.7 (CH_2O); 4.48 brdt, 1 H, *J*(5a,6eq) = 4.0, *J*(5a,6ax) = 4.2, *J*(5a,9a) = 7.0 (H-5a); 5.08 brdt, 1 H (H-9a); 7.74 brq, 1 H (H-4).

5-Methyl-1-[(1*R**,4*S**,5*R**)-6-oxabicyclo[3.2.1]oct-4-yl]pyrimidine-2,4(1*H*,3*H*)-dione (**23**)

A solution of compound **21** (94 mg, 0.3 mmol) in saturated methanolic lithium hydroxide (1.5 ml) was heated at 60 °C for 2 h and, after cooling, neutralized with Dowex 50 (H^+). The resin was filtered off, washed with methanol and the combined filtrates were evaporated. Crystallization of the residue from water afforded 55 mg (78%) of oxabicyclooctylthymine **23**, m.p. 239–242 °C. For $C_{12}H_{16}N_2O_3$ (236.3) calculated: 61.00% C, 6.83% H, 11.86% N; found: 60.83% C, 6.98% H, 11.77% N. ^{1}H NMR: 1.58 tddd, 1 H, *J*(2′ax,1′) = 2.2, *J*(2′ax,3′ax) = 12.6, *J*(2′ax,3′eq) = 5.4, *J*(2′ax,7′exo) = 1.5, J_{gem} = 12.6 (H-2′ax); 1.63 brddt, 1 H, *J*(2′eq,1′) = 3.2, *J*(2′eq,3′ax) = 6.2, *J*(2′eq,3′eq) = 1.8 (H-2′eq); 1.71 brdt, 1 H, *J*(3′eq,5′) = 1.7, J_{gem} 12.6 (H-3′eq); 1.76 d, 3 H, *J* = 1.2 (CH_3); 1.76 brdt, 1 H, *J*(8′eq,1′) = *J*(8′eq,5′) = 1.5, J_{gem} = 11.6 (H-8′eq); 1.81 brtd, 1 H, *J*(3′ax,4′) = 11.7 (H-3′ax); 1.89 dddd, 1 H, *J*(8′ax,1′) = 4.6, *J*(8′ax,2′ax) = 2.3, *J*(8′ax,5′) = 6.6 (H-8′ax); 2.40 m, 1 H (H-1′); 3.74 ddd, 1 H, *J*(7′exo,1′) = 4.4, J_{gem} = 7.8 (H-7′exo); 3.87 brd, 1 H, *J*(7′endo,1′) = 1.0 (H-7′endo); 4.20 dt, 1 H (H-5′); 4.34 brdd, 1 H, *J*(4′,3′eq) = 5.6, *J*(4′,5′) = 0.5 (H-4′); 7.55 brq, 1 H (H-6); 11.21 s, 1 H (NH).

(1*R**,2*R**,4*S**)-4-Vinylcyclohexane-1,2-diyl Dibenzoate (**24b**)

A solution of epoxide **1** (1.3 ml, 10 mmol), DBU (1.6 ml, 10 mmol) and water (0.8 ml) in dimethylformamide (15 ml) was heated at 130 °C for 6 h. After cooling, the mixture was neutralized with hydrochloric acid and the solvent was evaporated. A solution of the residue in water (5 ml) was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (5 × 15 ml). The combined extracts were evaporated, the residue was codistilled with pyridine, dissolved in pyridine (15 ml) and the solution was cooled to 0 °C. Benzoyl chloride (2.3 ml, 20 mmol) was added to the solution and the mixture was set aside at room temperature for 4 h. Water (0.5 ml) was then added and, after 15 min, pyridine was evaporated. The residue was partitioned between ethyl acetate (40 ml) and water (20 ml). The organic layer was separated, washed with water, 5% hydrochloric acid, water, aqueous 10% sodium $NaHCO_3$ (3×) and water (20 ml each), dried over anhydrous sodium sulfate, and the solvent was evaporated. Chromatography of the residue on a silica gel column (100 g) with toluene–ethyl acetate (98:2) gave 1.40 g (40%) of dibenzoate **24b**. For $C_{22}H_{22}O_4$ (350.4) calculated: 75.41% C, 6.33% H; found: 75,36% C, 6.39% H. ^{1}H NMR: 1.63 dddd, 1 H, *J*(5ax,4) = 3.8, *J*(5ax,6a) = 9.5, *J*(5ax,6b) = 8.2, J_{gem} = 13.6 (H-5ax); 1.75 ddt, 1 H, *J*(5eq,4) = 7.0, *J*(5eq,6a) = 4.2, *J*(5eq,6b) = 3.8 (H-5eq); 1.88 brdtd, 1 H, *J*(6b,1) = 6.5, J_{gem} = 13.8 (H-6b); 1.96 m, 2 H (2 x H-3); 2.03 ddt, 1 H, *J*(6a,1) = 3.5 (H-6a); 2.56 m, 1 H (H-4); 5.08 dt, 1 H, *J*(CH,4) = J_{gem} = 1.7, *J*(CH,CH_{cis}) = 10.6 and 5.16 dt, 1 H, *J*(CH,4) = J_{gem} = 1.7, *J*(CH,CH_{trans}) = 17.3 (CH_2=); 5.19 td, 1 H, *J*(1,2) = 6.0 (H-1); 5.29 td, 1 H, *J*(2,3a) = 3.9, *J*(2,3b) = 6.0 (H-2); 5.92 ddd, 1 H, *J*(CH,4) = 5.7 (CH=); 7.52 m, 4 H, 7.65 m, 2 H and 7.97 m, 4 H (H-arom.).

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