SYNTHESIS OF CARBA ANALOGUES OF 2′-DEOXY-4′-*C*-(HYDROXYMETHYL)NUCLEOSIDES

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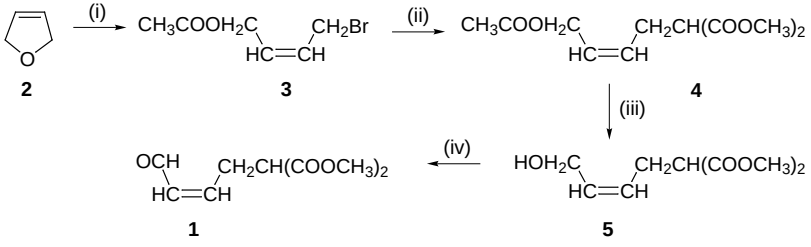
Racemic dimethyl 2-hydroxy-4-[5-methyl-2(1*H*),4(3*H*)-dioxopyrimidin-1-yl]- (**7a** and **8a**) and dimethyl 4-(6-aminopurin-9-yl)-2-hydroxycyclopentane-1,1-dicarboxylates (**7b** and **8b**) were prepared by addition of sodium salt of thymine and adenine, respectively, to dimethyl (*Z*)-(4-oxobut-2-en-1-yl)malonate (**1**). Reduction of the diesters with sodium borohydride in methanol in the presence of sulfuric acid gave corresponding racemic 2,2-bis(hydroxymethyl)-4-[5-methyl-2(1*H*),4(3*H*)-dioxopyrimidin-1-yl]- (**14a** and **15a**), 4-(6-aminopurin-9-yl)-2,2-bis(hydroxymethyl)cyclopentan-1-ol (**14b** and **15b**), methyl (±)-*cis*-2-hydroxy-1-hydroxymethyl-4-[5-methyl-2(1*H*),4(3*H*)-dioxopyrimidin-1-yl]- (**13a**), and methyl (±)-*cis*-4-(6-aminopurin-9-yl)-2-hydroxy-1-hydroxymethylcyclopentan-1-carboxylate (**13b**), respectively.

Key words: Carbanucleosides; Carbocyclic nucleosides; 4′-*C*-Branched nucleosides; Cyclopentanes; Nucleosides; Reductions; Additions.

This study is a part of our program aimed at the synthesis of 2′-deoxy-4′-*C*-substituted nucleosides and at the structure–antiviral activity relationship studies[1]. It deals with the synthesis of racemic carba analogues of 2′-deoxy-4′-*C*-(hydroxymethyl)nucleosides. Synthesis of racemates is advantageous for the screening of biological activity.

Carbocyclic nucleosides, where the ring oxygen of the sugar moiety is replaced by a methylene group, show enhanced biostability, since the molecule does not contain any acid-labile hemiacetal linkage. The discovery of the antibiotic and antitumor activity of the natural carbocyclic nucleosides aristeromycin and neplanocin A stimulated the search for other carbocyclic nucleoside analogues with biological activity. Later on, additional synthetic carbocyclic nucleosides with important therapeutic properties were discovered. Development in the area of synthetic approaches to carbocyclic nucleosides is the subject of several reviews[2–4].

For the synthesis of the target carba analogues, we have chosen dimethyl (*Z*)-(4-oxobut-2-en-1-yl)malonate (**1**) as a starting compound. The aldehyde **1** was obtained by described procedure[1g] from (*Z*)-but-2-ene-1,4-diol or by an alternative approach starting from 2,5-dihydrofuran (Scheme 1). Acetyl bromide easily cleaves cyclic ethers to the corresponding ω-bromoalkanol acetates[5]. Cleavage of 2,5-dihydrofuran (**2**) with acetyl bromide led to bromo acetate **3**. Alkylation of dimethyl malonate with the bromo derivative **3** gave compound **4** which was deacetylated with methanolic sodium methoxide. The obtained hydroxy derivative 5 was oxidized with pyridinium chlorochromate on alumina by described procedure[1g] to give aldehyde **1**.



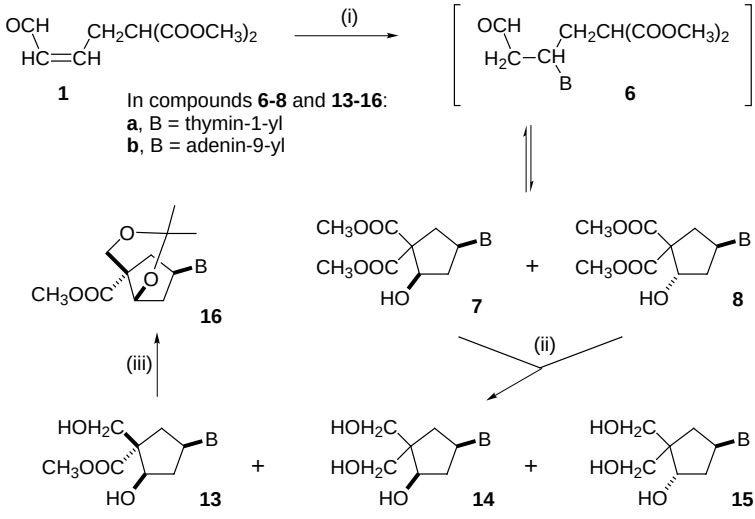
(i) CH_3COBr, 63%; (ii) $NaH/CH_2(COOMe)_2/DMF$, 71%; (iii) MeONa/MeOH, 97%, (iv) PCC (*cf.* ref.[1])

SCHEME 1

Addition of sodium salt of thymine or adenine to the activated double bond in the aldehyde **1** led to aldehyde **6** which spontaneously cyclized to give a mixture of (±)-*cis*- (**7a** or **7b**) and (±)-*trans*-isomers (**8a** or **8b**) in the ratio of 2 : 1 in both cases (Scheme 2). The isomers **7a** and **8a** were separated by chromatography on silica gel. The adenine derivatives **7b** and **8b** could not be separated by chromatography; nevertheless, the compound **7b** easily crystallized from methanol. Several days of crystallization of the mixture **7b** and **8b** afforded crystalline **7b** while the mother liquors contained a small amount of the mixture of **7b** and **8b** in the ratio 2 : 1 (by ^{1}H NMR). Because the cyclization reaction of aldehyde **1** to the cyclopentane derivatives **7a**, **7b** or **8a**, **8b** is reversible (*cf.* ref.[1g]), the separated isomers are unstable: in solution, both the *cis*-isomers and the *trans*-isomers undergo interconversion.

Infrared spectra of diesters **7a** and **8a** exhibit NH bands at 3 395 and/or 3 397 cm^{-1}, in agreement with the literature data[6] for N^1-substituted uracils. The absorption maximum at 262 nm (water) and 260 nm (0.1 M HCl) in UV spectra of the adenine derivative **7b** proved that the cyclopentane moiety is bound in the position N^9 of the adenine moiety[7]. The pairs of *cis*- and

trans-isomers were assigned on the basis of ^{1}H NMR spectral analysis similarly to the case of the pair *cis*- and *trans*-2-hydroxy-4-methoxycyclopentane-1,1-dicarboxylates[1g].



(i) thymine or adenine/NaH/DMF, 45% of **7a**, 22% of **8a**, 64% of **7b**; (ii) $NaBH_4/H_2SO_4$/MeOH, -12 °C, 25% of **13a**, 17% of **14a**, 15% of **15a**, 41% of **13b**, 10% of **14b** and 9% of **15b**; (iii) $Me_2CO/Me_2C(OMe)_2/H_2SO_4$

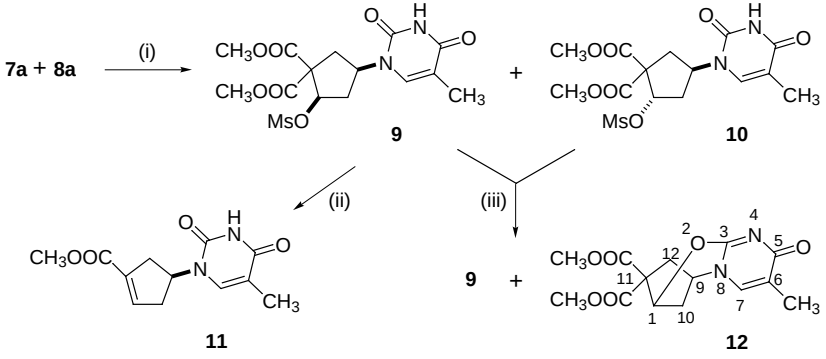
SCHEME 2

Mesylation of the mixture of **7a** and **8a** afforded a mixture of mesylates **9** and **10**. The pure *cis*-isomer **9** was separated from a mixture by crystallization from ethyl acetate. Reaction of the mesylate **9** with aqueous sodium hydroxide afforded the unsaturated ester **11**. Treatment of an acetonitrile solution of the mixture **9** and **10** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave a mixture of the unreacted **9** (60%) and the anhydro derivative **12** (21%) (Scheme 3). These results corresponded with the configuration assignment performed by ^{1}H NMR spectral analysis.

Reduction of the diesters **7** and **8** (**a** and/or **b**) with lithium aluminium hydride by the procedure described before[1g] led to a loss of UV absorption with the thymine analogues. The reduction of the adenine analogues was accompanied by cleavage of the pseudonucleoside bond.

Sodium borohydride is a powerful reducing agent for aldehydes and ketones. However, cases are reported in the literature in which reduction of carboxylic esters to primary alcohols has been observed[8]. Reduction of esters of simple heterocyclic, aromatic, and aliphatic acids was accomplished

with a large excess of sodium borohydride in methanol[9]. It was also found that the borohydride reduction of esters in dimethyl sulfoxide is accelerated in the presence of methanesulfonic acid[10].



(i) MsCl/pyridine, 82% of a mixture of **9** and **10**; (ii) aqueous NaOH, 69%; (iii) DBU/acetonitrile, 80 °C, 63% of **9**, 26% of **12**

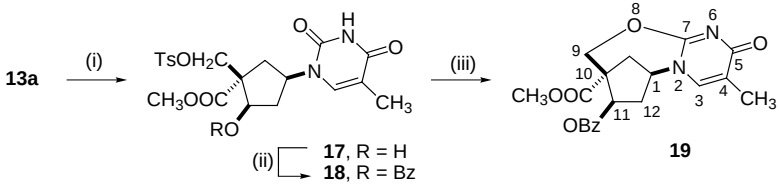
SCHEME 3

Reduction of a mixture of **7a** and **8a** with sodium borohydride in methanolic solution in the presence of sulfuric acid at –12 °C led to a mixture of compounds, which was separated by chromatography on silica gel giving **13a** (25%), **14a** (17%), and **15a** (15%). Reduction of **7b** under the same conditions afforded, after chromatography on silica gel, **13b** (41%) and a mixture of **14b** and **15b**. Extraction of the mixture with hot water and crystallization of the insoluble material from aqueous methanol gave **15b** (9%). The pure racemate **14b** was obtained in the yield of 10% by chromatography on a silica gel column.

The positions of the absorption bands in UV spectra of the esters **14a** and **15a** remained virtually unchanged independent of pH whereas in alkaline medium, the absorption decreased: such pattern is characteristic of N^1-substituted uracil derivatives[11]. Also the linkage of the cyclopentane ring with adenine in position N^9 of compounds **14b** and **15b** was confirmed by their UV spectra. The absorption maximum at 262 nm (water) and 261 nm (0.1 M HCl) in UV spectra of the adenine derivatives **14b** and **15b** corresponds to N^9-substituted adenine derivatives[7].

The structure proof for the ester **13a** was performed by transforming it to the isopropylidene derivative **16a** and to the anhydro derivative **19**. Ketalization of **13a** and **13b** led to the isopropylidene derivatives **16a** and **16b**, respectively. Tosylation and following benzoylation of **13a** gave the tosylate **18**. Treatment of the tosylate **18** in an acetonitrile solution with

DBU at 80 °C afforded the anhydro derivative **19** (Scheme 4). The ^{1}H NMR spectra of the thymine derivatives (**13a** and **16a**) and those of the corresponding adenine derivatives (**13b** and **16b**) were very similar, except for the signals of base protons.



(i) TsCl/pyridine, 82%, (ii) BzCl/pyridine, 81%; (iii) DBU/acetonitrile, 80 °C, 62%

SCHEME 4

In conclusion, new racemic carbocyclic 2′-deoxy-4′-*C*-(hydroxymethyl)nucleosides were synthesized by a simple and inexpensive procedure. This divergent approach provided two series of racemates with different configuration in the position C-3′. The synthesized compounds will be tested for antiviral activity.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. IR spectra were recorded on a Zeiss UR 20 spectrophotometer (wavenumbers in cm^{-1}) and UV spectra on a Unicam SP 8000 spectrometer. ^{1}H NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian XL-200 (200 MHz) instrument in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. Column chromatography was performed on 30–60 μm silica gel (Service Laboratories of the Institute) 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 prepared were dried at 13 Pa and 50 °C.

(*Z*)-4-Brombut-2-en-1-yl Acetate (**3**)

Acetyl bromide (38.6 ml, 0.5 mol) was added dropwise under stirring to 2,5-dihydrofurane (39 ml, 0.5 mol), below 50 °C the exothermic reaction being controlled by the rate of acetyl bromide addition. After addition of acetyl bromide, the reaction mixture was heated to 90 °C for 1 h. Vacuum distillation of the reaction mixture afforded 61.1 g (63%) of bromo acetate **3**, b.p. 87 °C, 1.33 kPa. For $C_6H_9BrO_2$ (193.05) calculated: 37.33% C, 4.70% H, 41.39% Br; found: 37.07% C, 4.51% H, 41.53% Br. ^{1}H NMR: 2.09 s, 3 H (CH_3CO); 3.95 d, 2 H, *J*(CH_2,CH) = 6.7 (CH_2Br); 4.58 d, 1 H, *J*(CH_2,CH) = 5.8 (CH_2OAc); 5.78–6.06 m, 2 H (CH=CH).

Dimethyl (*Z*)-(4-Acetoxybut-2-en-1-yl)malonate (**4**)

A dispersion of sodium hydride in mineral oil (60%; 8.80 g, 0.22 mol) was slowly added under argon to a solution of dimethyl malonate (25 ml, 0.22 mol) in dimethylformamide

(600 ml), cooled to 0 °C. After 20 min stirring, bromo acetate **3** (38.6 g, 0.2 mol) was added. The reaction mixture was stirred at room temperature for 2 h, then neutralized with acetic acid and evaporated. The residue was partitioned between ethyl acetate (700 ml) and water (200 ml). The organic layer was separated and washed with water (200 ml), 10% aqueous sodium hydrogencarbonate (2 × 100 ml), and water (100 ml), dried over sodium sulfate. After evaporation of the solvent, column chromatography of the residue on silica gel (3 kg) in toluene–ethyl acetate (8 : 1) gave 34.9 g (71%) malonate **4**. The chromatography is not necessary for the next step, but the yields of the following steps are lower. For $C_{11}H_{16}O_6$ (244.3) calculated: 54.09% C, 6.60% H; found: 53.88% C, 6.71% H. ^{1}H NMR: 2.06 s, 3 H (CH_3CO); 2.66 dd, 2 H, J(CH_2,CH) = 7.6, J(CH_2,CH=) = 5.8 (CH_2); 3.4 t, 1 H (CH); 3.73 s, 3 H and 3.74 s, 3 H (2 × CH_3O); 4.49 d, 2 H, J(CH_2,CH=) = 4.57 (CH_2O); 5.70 m, 2 H (CH=CH).

Dimethyl (*Z*)-(4-Hydroxybut-2-en-1-yl)malonate (**5**)

A solution of acetate **4** (24.4 g, 0.1 mol) in 0.1 M methanolic sodium methoxide (250 ml) was allowed to stand at room temperature for 1 h and then neutralized with Dowex 50 (H^+). The ion exchanger was filtered off, washed with methanol and the combined filtrates were taken down to give 19.6 g (97%) of **5**, identical with that prepared earlier[1g].

Dimethyl (±)-*cis*- (**7a**) and (±)-*trans*-2-Hydroxy-4-[5-methyl-2(1*H*),4(3*H*)-dioxopyrimidin-1-yl]cyclopentane-1,1-dicarboxylate (**8a**)

A dispersion of sodium hydride in mineral oil (60%; 600 mg, 15 mmol) was added at room temperature under argon to a stirred suspension of thymine (2.65 g, 21 mmol) in dimethylformamide (40 ml) and the suspension was stirred for 30 min. Then a solution of aldehyde **1** (1.4 g, 7 mmol) in dimethylformamide (10 ml) was added, the mixture was stirred for 2 h and neutralized with acetic acid. The insoluble portion was filtered off and washed with ethyl acetate (30 ml). The combined filtrates were evaporated and the residue was dissolved in ethyl acetate. The separated thymine was filtered off, the clear solution was taken down and the residue was chromatographed on a silica gel column (150 g) in ethyl acetate giving 1.52 g (67% based on aldehyde **1**) of a mixture of racemates **7a** and **8a**. Both isomers were separated by flash chromatography of a small amount (300 mg) of the mixture on a silica gel column (100 g) in ethyl acetate–toluene (3 : 1) to give 185 mg of the racemate **7a** and 90 mg of the racemate **8a**.

Racemate **7a**: M.p. 170–172 °C. For $C_{14}H_{18}N_2O_7$ (326.3) calculated: 51.53% C, 5.56% H, 8.59% N; found: 51.79% C, 5.56% H, 8.41% N. UV (water): λ_{max} 273 nm (ε 11 000). IR (*c* = 2%, $CHCl_3$): 3 397 (NH); 3 588, 3 172 (OH); 1 727 (C=O, ester); 1 700, 1 685 (C=O, thymine); 1 280, 1 246 (C–O, ester); 1 37 (CH_3, ester). ^{1}H NMR: 1.72 ddd, 1 H, J(3a,2) = 2.1, J(3a,3b) = 14.6, J(3a,4) = 5.8 (H-3a); 1.79 s, 3 H (CH_3); 2.34–2.58 m, 3 H (H-5a, H-5b, H-3b); 3.67 s, 3 H (OCH_3); 3.69 s, 3 H (OCH_3); 4.56 td, 1 H, J(2,3b) = 5.5, J(2,OH) = 5.2 (H-2); 4.90 m, 1 H, J(4,3b) ≈ J(4,5a) ≈ J(4,5b) ≈ 9.5 (H-4); 5.89 d, 1 H (2-OH); 7.66 s, 1 H (H-6′); 11.27 s, 1 H (NH).

Racemate **8a**: M.p. 164–166 °C. For $C_{14}H_{18}N_2O_7$ (326.3) calculated: 51.53% C, 5.56% H, 8.59% N; found: 51.69% C, 5.52% H, 8.51% N. UV (water): λ_{max} 273 nm (ε 11 700). IR (*c* = 2%, $CHCl_3$): 3 395 (NH); 3 583, 3 176 (OH); 1 725 (C=O, ester); 1 684 (C=O, thymine); 1 273, 1 235 (C–O, ester); 1 437 (CH_3, ester). ^{1}H NMR: 1.75 s, 1 H (CH_3); 1.91 m, 1 H (H-3a); 2.05 dd, 1 H, J(5a,4) = 8.8, J(5a,5b) = 13.7 (H-5a); 2.19 ddd, 1 H, J(3b,2) = 5.2, J(3b,3a) =

12.5, *J*(3b,4) = 10.7 (H-3b); 2.82 dd, 1 H, *J*(5b,4) = 9.2 (H-5b); 3.64 s, 3 H (OCH_3); 3.67 s, 3 H (OCH_3); 4.73 m, 1 H (H-2); 4.98 m, 1 H, *J*(4,3a) = 7.7 (H-4); 5.54 d, 1 H, *J*(OH,2) = 5.2 (2-OH); 7.50 s, 1 H (H-6′); 11.21 s, 1 H (NH).

The insoluble portions were suspended in water (20 ml), filtered off and washed with a small amount of ethanol and ether to recover 1.85 g of thymine.

Dimethyl (±)-*cis*- (**7b**) and
(±)-*trans*-4-(6-Purin-9-yl)-2-hydroxycyclopentane-1,1-dicarboxylate (**8b**)

A dispersion of sodium hydride in mineral oil (60%; 600 mg, 15 mmol) was added at room temperature under argon to a stirred suspension of adenine (2.84 g, 21 mmol) in dimethylformamide (60 ml) and the suspension was stirred for 30 min. Then a solution of aldehyde **1** (1.4 g, 7 mmol) in dimethylformamide (10 ml) was added and the mixture was stirred for 2 h and neutralized with acetic acid. The insoluble portion was filtered off and washed with ethyl acetate (30 ml). The combined filtrates were evaporated and the residue was dissolved in ethyl acetate. The separated adenine was filtered off and the clear solution was taken down. Column chromatography of the residue on silica gel (150 g) in ethyl acetate–acetone–ethanol–water (19 : 3 : 2 : 1) afforded 1.68 g (72% based on aldehyde **1**) of a 2 : 1 mixture of racemates **7b** and **8b**. Crystallization of the mixture from methanol (10 ml) gave 750 mg of the pure racemate **7b**, m.p. 167–169 °C. The mother liquors were concentrated to half of the original volume. After 6-days standing at room temperature, the solution deposited further 400 mg of crystalline compound **7b**. The procedure was repeated to obtain the isomer **7b** in the overall amount of 1.51 g (64%). For $C_{14}H_{17}N_5O_5$ (335.3) calculated: 50.15% C, 5.11% H, 20.89% N; found: 50.15% C, 5.20% H, 20.72% N. UV (water): λ_{max} 262 nm (ε 16 500); 0.1 M HCl: λ_{max} 260 nm (ε 16 100). ^{1}H NMR: 2.08 ddd, 1 H, *J*(3a,2) = 2.1, *J*(3a,3b) = 14.6, *J*(3a,4) = 5.2 (H-3a); 2.60–2.82 m, 2 H (H-3b, H-5a); 2.89 dd, 1 H, *J*(5b,4) = 9.5, *J*(5b,5a) = 13.7 (H-5b); 3.68 s, 3 H (OCH_3); 3.72 s, 3 H (OCH_3); 4.63 ddd, 1 H, *J*(2,3b) = 5.2, *J*(2,OH) = 7.3 (H-2); 4.99 m, 1 H, *J*(4,3b) ≈ *J*(4,5a) ≈ 9.1 (H-4); 6.44 d, 1 H (2-OH); 7.36 s, 2 H (NH_2); 8.14 s, 1 H (H-2′); 8.19 s, 1 H (H-8′).

Evaporation of the mother liquors gave 170 mg (8%) of a 2 : 1 mixture (by NMR) of racemates **7b** and **8b**.

Racemate **8b**: ^{1}H NMR (from the mixture of **7b** and **8b**): 2.19 m, 1 H (H-3a); 2.65 dd, 1 H, *J*(5a,4) = 8.0, *J*(5a,5b) = 14.0 (H-5a); 2.77 m, 1 H (H-3b); 3.12 dd, 1 H, *J*(5b,4) = 9.1 (H-5b); 3.67 s, 3 H and 3.69 s, 3 H (2 × OCH_3); 4.84 m, 1 H (H-2); 5.21 m, 1 H (H-4); 5.64 d, 1 H, *J*(OH,2) = 5.2 (2-OH); 7.21 s, 2 H (NH_2); 7.96 s, 1 H (H-2′); 8.11 s, 1 H (H-8′).

The insoluble portions were suspended in water (20 ml), filtered off and washed with a small amount of ethanol and ether to recover 1.91 g of adenine.

Methyl (±)-*cis*- (**9**) and (±)-*trans*-2-Mesyloxy-4-[5-methyl-2(1*H*),4(3*H*)-dioxopyrimidin-1-yl]cyclopentane-1,1-dicarboxylate (**10**)

Methanesulfonyl chloride (0.4 ml, 5.2 mmol) was added under ice cooling to a stirred solution of a mixture of racemates **7a** and **8a** (653 mg, 2 mmol) in pyridine (6 ml). After standing at room temperature for 5 h, the mixture was cooled to 0 °C, water (0.2 ml) was added and, after standing for 10 min, the solvent was evaporated. The residue was partitioned between water (4 ml) and ethyl acetate (20 ml), the organic layer was washed with water (2 × 5 ml), dried over anhydrous sodium sulfate and concentrated. The residue was triturated with ether. The solid product was filtered off to give 660 mg (82%) of a 2 : 1 mixture of

racemates **9** and **10**. Crystallization of the mixture (300 mg) from ethyl acetate afforded 132 mg of pure **9**, m.p. 169–171 °C. For $C_{15}H_{20}N_2O_9S$ (404.4) calculated: 44.55% C, 4.99% H, 6.93% N, 7.93% S; found: 44.77% C, 4.94% H, 6.86% N, 7.68% S. ^{1}H NMR: 1.79 s, 3 H (CH_3); 2.20 ddd, *J*(3a,2) = 3.8, *J*(3a,3b) = 14.8, *J*(3a,4) = 7.5 (H-3a); 2.56 m, 2 H (2 × H-5); 2.73 ddd, 1 H, *J*(3b,2) = 5.8, *J*(3b,4) = 9.2 (H-3b); 3.25 s, 3 H (CH_3SO_2); 3.74 s, 3 H and 3.76 s, 6 H (2 × $COOCH_3$); 4.89 m, 1 H (H-4); 5.48 dd, 1 H (H-2); 7.50 d, 1 H, *J* = 0.9 (H-6′); 11.31 s, 1 H (NH).

Evaporation of the mother liquors gave 163 mg of a 3 : 5 mixture (by NMR) of racemates **9** and **10**.

Racemate **10**: ^{1}H NMR (from the mixture of **9** and **10**): 1.75 s, 3 H (CH_3); 2.33 dd, 1 H, *J*(5a,4) = 8.2, *J*(5a,5b) = 13.8 (H-5a); 2.40 m, 1 H (H-3a); 2.50 m, 1 H (H-3b); 2.85 dd, 1 H, *J*(5b,4) = 9.2 (H-5b); 3.22 s, 3 H (CH_3SO_2); 3.71 s and 3.73 s, 6 H (2 × $COOCH_3$); 4.87 m, 1 H (H-4); 5.65 dd, 1 H, *J*(2,3a) = 2.9, *J*(2,3b) = 5.3 (H-2); 7.58 d, 1 H, *J* = 0.9 (H-6′); 11.27 s, 1 H (NH).

Methyl (±)-4-[5-Methyl-2(1*H*),4(3*H*)-dioxopyrimidin-1-yl]cyclopent-1-ene-1-carboxylate (**11**)

Aqueous sodium hydroxide (1 M solution, 1 ml) was added in five portions at 60 °C during 80 min to a solution of mesyl derivative **9** (202 mg, 0.5 mmol) in water (3 ml). The solution was heated at 60 °C for another 20 min and then extracted with ethyl acetate (3 × 10 ml). The extracts were combined, dried over sodium sulfate and the solvent was evaporated. Crystallization of the residue from ethyl acetate gave 86 mg (69%) of racemate **11**, m.p. 181–182.5 °C (ethyl acetate). For $C_{12}H_{14}N_2O_4$ (250.3) calculated: 57.59% C, 5.64% H, 11.19% N; found: 57.32% C, 5.61% H, 11.02% N. ^{1}H NMR: 1.75 d, 3 H, *J*(CH_3,6′) = 0.9 (CH_3); 2.64 m, 2 H (H-3a, H-5a); 2.95 m, 2 H (H-3b, H-5b); 3.96 s, 3 H (OCH_3); 5.17 m, 1 H, *J*(4,3a) = *J*(4,5a) = 5.4, *J*(4,3b) = *J*(4,5b) = 9.4 (H-4); 6.75 brs, 1 H (H-2); 7.38 d, 1 H (H-6′); 11.24 s, 1 H (NH).

Dimethyl (1*R**,9*S**)-6-Methyl-5-oxo-2-oxa-4,8-diazatricyclo[7.2.1.0^{3,8}]dodec-3,6-diene-11,11-dicarboxylate (**12**)

1,8-Diazabicyclo[5.4.0]undec-7-ene (0.23 ml, 1.5 mmol) was added to a solution of a mixture of racemates **9** and **10** (404 mg, 1 mmol) in acetonitrile (4 ml) and the solution was set aside at room temperature overnight. After neutralization with acetic acid and evaporation of the solvent to a small volume, the residue was chromatographed on a column of silica gel (40 g) eluting with ethyl acetate and then with ethyl acetate–acetone–ethanol–water (15 : 3 : 4 : 3). The first fraction afforded 255 mg (63%) of *cis*-racemate **9**. The other fraction gave 80 mg (26%) of anhydro derivative **12**, m.p. 204–205.5 °C. For $C_{14}H_{16}N_2O_6$ (308.3) calculated: 54.54% C, 5.23% H, 9.09% N; found: 54.57% C, 5.35% H, 8.89% N. UV (water): λ_{max} 232 and 255 nm (ε 8 000 and 7 700). ^{1}H NMR: 1.76 d, 3 H, *J*(CH_3,7) = 0.9 (CH_3); 2.28 dt, 1 H, *J*(10a,1) = *J*(10a,9) = 2.9, *J*(10a,10b) = 13.6 (H-10a); 2.41 dd, 1 H, *J*(12a,9) = 4.4, *J*(12a,12b) = 14.5 (H-12a); 2.44 brd, 1 H (H-10b); 2.94 dd, 1 H, *J*(12b,9) = 2.3 (H-12b); 3.70 s, 6 H (2 × OCH_3); 4.55 brs, 1 H (H-9); 5.35 brs, 1 H (H-1); 7.51 d, 1 H (H-7).

Methyl (1*R**,2*S**,4*S**)-2-Hydroxy-1-hydroxymethyl-4-[5-methyl-2(1*H*),4(3*H*)-dioxopyrimidin-1-yl]cyclopentane-1-carboxylate (**13a**), (±)-*cis*- (**14a**) and (±)-*trans*-2,2-Bis(hydroxymethyl)-4-[5-methyl-2(1*H*),4(3*H*)-dioxopyrimidin-1-yl]-cyclopentan-1-ol (**15a**)

A solution of the mixture of esters **7a** and **8a** (652 mg, 2 mmol) in methanol (7 ml) was added at –12 °C to a stirred solution of sodium borohydride (1.6 g) in methanol (16 ml), followed by a solution of sulfuric acid (1.2 ml) in ether (5 ml). After warming to room temperature, the insoluble portion was filtered off and washed with methanol. The combined filtrates were evaporated, the residue was dissolved in methanol (30 ml) and the solution was neutralized with dilute sulfuric acid and taken down. The residue was codistilled with methanol (2 × 30 ml) and chromatographed on a column of silica gel (100 g) in ethyl acetate–acetone–ethanol–water (100 : 15 : 6 : 4). Evaporation of the fraction with R_F 0.36 gave 150 mg (25%) of crystalline **13a**, m.p. 178–181 °C (ethanol). For $C_{13}H_{18}N_2O_6$ (298.3) calculated: 52.34% C, 6.08% H, 9.39% N; found: 52.12% C, 5.94% H, 9.35% N. ^{1}H NMR: 1.62–1.77 m, 1 H (H-3a); 1.69 dd, 1 H, *J*(5a,4) = 9.9, *J*(5a,5b) = 13.0 (H-5a); 1.77 d, 1 H, *J* = 0.8 (CH_3); 2.22 ddd, 1 H, *J*(3b,2) = 5.2, *J*(3b,3a) = 14.7, *J*(3b,4) = 9.9 (H-3b); 2.44 dd, 1 H, *J*(5b,4) = 8.2 (H-5b); 3.63 dd, 1 H, *J*(CH_2,OH) = 5.5 and 3.89 dd, 1 H, *J*(CH_2,OH) = 5.3, J_{gem} = 10.5 (CH_2O); 3.64 s, 3 H ($COOCH_3$); 4.26 m, 1 H, *J*(2,3a) = 3.6, *J*(2,OH) = 4.8 (H-2); 4.66 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 4.94 m, 1 H (H-4); 5.47 d, 1 H (2-OH); 7.69 d, 1 H, *J* = 0.8 (H-6′); 11.22 s, 1 H (NH).

The fraction with R_F 0.14 afforded a mixture of **14a** and **15a**. Repeated chromatography on the same column afforded 92 mg (17%) of **14a** (R_F 0.15) and 81 mg (15%) of **15a** (R_F 0.13).

Racemate **14a**: For $C_{12}H_{18}N_2O_5$ (270.3) calculated: 53.32% C, 6.71% H, 10.36% N; found: 53.06% C, 6.89% H, 10.11% N. UV (water): λ_{max} 275 nm (ε 10 800); 0.1 M NaOH: λ_{max} 273 nm (ε 8 500). ^{1}H NMR: 1.53 dd, 1 H, *J*(3a,4) = 9.5, *J*(3a,3b) = 13.1 (H-3a); 1.72 ddd, 1 H, *J*(5a,1) = 5.5, *J*(5a,5b) = 13.8, *J*(5a,4) = 7.8 (H-5a); 1.88 dd, 1 H, *J*(3b,4) = 8.5 (H-3b); 2.27 ddd, 1 H, *J*(5b,1) = 5.6, *J*(5b,4) = 8.4 (H-5b); 3.29 m, 2 H (CH_2O); 3.51 d, 2 H, *J*(CH_2,OH) = 5.5 (CH_2O); 3.93 ddd, 1 H (H-1); 4.29 t, 1 H, *J*(OH,CH_2) = 5.5 (CH_2O**H**); 4.61 t, 1 H, *J*(OH,CH_2) = 5.3 (CH_2O**H**); 4.88 m, 1 H (H-4); 4.93 d, 1 H, *J*(OH,1) = 4.9 (1-OH); 7.70 d, 1 H (H-6′); 11.16 s, 1 H (NH).

Racemate **15a**: For $C_{12}H_{18}N_2O_5$ (270.3) calculated: 53.32% C, 6.71% H, 10.36% N; found: 53.02% C, 6.90% H, 10.08% N. UV (water): λ_{max} 275 nm (ε 11 200); 0.1 M NaOH: λ_{max} 273 nm (ε 8 900). ^{1}H NMR: 1.41 dd, 1 H, *J*(3a,4) = 9.8, *J*(3a,3b) = 13.1 (H-3a); 1.79 d, 3 H, *J*(CH_3,6′) = 0.9 (CH_3); 1.88 dd, 1 H, *J*(3b,4) = 8.8 (H-3b); 1.77–1.90 m, 1 H (H-5a); 2.04 ddd, 1 H, *J*(5b,1) = 6.1, *J*(5b,5a) = 13.0, *J*(5b,4) = 9.6 (H-5b); 3.26–3.53 m, 4 H (2 × CH_2O); 4.09 m, 1 H (H-1); 4.29 t, 1 H, *J*(OH,CH_2) = 5.3 (CH_2O**H**); 4.66 t, 1 H, *J*(OH,CH_2) = 5.2 (CH_2O**H**); 4.70 d, 1 H, *J*(OH,1) = 4,3 (1-OH); 5.04 p, 1 H (H-4); 7.53 d, 1 H (H-6′); 11.18 s, 1 H (NH).

Methyl (1*R**,2*S**,4*S**)-4-(6-Aminopurin-9-yl)-2-hydroxy-1-hydroxymethylcyclopentane-1-carboxylate (**13b**), (±)-*cis*- (**14b**) and (±)-*trans*-4-(6-Aminopurin-9-yl)-2,2-bis(hydroxymethyl)cyclopentan-1-ol (**15b**)

A solution of the ester **7b** (671 mg, 2 mmol) in 2-methoxyethanol (7 ml) was added at –12 °C to a stirred solution of sodium borohydride (1.6 g) in methanol (16 ml), followed by a solution of sulfuric acid (1.2 ml) in ether (5 ml). After warming to room temperature, the insoluble portion was filtered off and washed with methanol. The combined filtrates were

evaporated, the residue was dissolved in methanol (30 ml) and the solution was neutralized with diluted sulfuric acid and taken down. The residue was codistilled with methanol (2 × 30 ml) and chromatographed on a column of silica gel (100 g) eluting with ethyl acetate–acetone–ethanol–water (15 : 3 : 4 : 3). The first fraction was rechromatographed eluting with ethyl acetate–acetone–ethanol–water (36 : 6 : 5 : 3) to give 125 mg (41%) of **13b**. For $C_{13}H_{17}N_5O_4$ (307.3) calculated: 50.81% C, 5.58% H, 22.79% N; found: 50.52% C, 5.72% H, 22.51% N. ^{1}H NMR: 1.99–2.14 m, 1 H (H-3a); 2.08 dd, 1 H, *J*(5a,4) = 9.5, *J*(5b,5a) = 13.1 (H-5a); 2.47 ddd, 1 H, *J*(3b,2) = 5.5, *J*(3b,4) = 9.2, *J*(3b,3a) = 14.6 (H-3b); 2.72 dd, 1 H, *J*(5b,4) = 8.2 (H-5b); 3.69 dd, 1 H, *J*(CH_2,OH) = 5.5 and 3.98 dd, 1 H, *J*(CH_2,OH) = 5.2, J_{gem}= 10.7 (CH_2O); 3.67 s, 3 H ($COOCH_3$); 4.32 m, 1 H, *J*(2,3a) = 3.4 (H-2); 4.68 t, 1 H (CH_2O**H**); 4.98 m, 1 H (H-4); 5.90 d, 1 H, *J*(OH,2) = 5.8 (2-OH); 7.29 s, 2 H (NH_2); 8.14 s, 1 H (H-2′); 8.23 s, 1 H (H-8′).

Crystallization of the other fraction from methanol afforded 130 mg (23%) of a mixture of **14b** and **15b**. The product was extracted with hot water (7 ml, 60 °C) the insoluble portion was filtered off and recrystallized from aqueous methanol to give 50 mg (9%) of **15b**, m.p. 247–248 °C. For $C_{12}H_{17}N_5O_3$ (279.3) calculated: 51.60% C, 6.14% H, 25.07% N; found: 51.55% C, 6.22% H, 24.96% N. UV (water): λ_{max} 262 nm (ε 16 100); 0.1 M HCl: λ_{max} 261 nm (ε 15 000). ^{1}H NMR: 1.75 dd, 1 H, *J*(3a,4) = 9.0, *J*(3a,3b) = 13.3 (H-3a); 2.04–2.18 m, 1 H (H-5a); 2.16 dd, 1 H, *J*(3b,4) = 9.3 (H-3b); 2.38 ddd, 1 H, *J*(5b,1) = 5.8, *J*(5b,5a) = 12.8, *J*(5b,4) = 9.4 (H-5b); 3.40–3.58 m, 4 H (2 × CH_2O); 4.21 m, 1 H (H-1); 4.33 t, 1 H, *J*(OH,CH_2) = 5.3 (CH_2O**H**); 4.70 t, 1 H, *J*(OH,CH_2) = 5.3 (CH_2O**H**); 4.79 d, 1 H, *J*(OH,1) = 4.3 (1-OH); 5.08 brp, 1 H (H-4); 7.19 s, 2 H (NH_2); 8.12 s, 1 H (H-2′); 8.23 s, 1 H (H-8′).

Chromatography of the aqueous extract on a column of silica gel (20 g) elutig with ethyl acetate–acetone–ethanol–water (15 : 3 : 4 : 3) gave 55 mg (10%) of **14b**, 199–201 °C. For $C_{12}H_{17}N_5O_3$ (279.3) calculated: 51.60% C, 6.14% H, 25.07% N; found: 51.53% C, 6.18% H, 24.92% N. UV (water): λ_{max} 262 nm (ε 16 400); 0.1 M HCl: λ_{max} 261 nm (ε 15 900). ^{1}H NMR: 1.91 dd, 1 H, *J*(3a,4) = 9.2, *J*(3a,3b) = 13.4 (H-3a); 2.02–2.22 m, 2 H (H-3b, H-5a); 2.45–2.58 m, 1 H (H-5b); 3.37 m, 2 H and 3.56 m, 2 H (2 × CH_2O); 4.04 q, 1 H, *J*(1,5a) = *J*(1,5b) = 5.8 (H-1); 4.31 t, 1 H, *J*(OH,CH_2) = 5.3 (CH_2O**H**); 4.68 t, 1 H, *J*(OH,CH_2) = 5.0 (CH_2O**H**); 4.86 brp, 1 H (H-4); 5.19 d, 1 H, *J*(OH,1) = 5.2 (1-OH); 7.32 s, 2 H (NH_2); 8.12 s, 1 H (H-2′); 8.23 s, 1 H (H-8′).

Methyl (1*R**,6*S**,8*R**)-3,3-Dimethyl-8-[5-methyl-2(1*H*),4(3*H*)-dioxopyrimidin-1-yl]-2,4-dioxabicyclo[4.3.0]nonane-6-carboxylate (**16a**)

A stirred mixture of **13a** (60 mg, 0.2 mmol), acetone (1 ml), 2,2-dimethoxypropane (0.5 ml), and one drop of sulfuric acid was stirred at room temperature for 1 h. The mixture was then neutralized with solid sodium hydrogencarbonate, the insoluble portion was filtered off and washed with acetone. The combined filtrates were taken down. Crystallization of the residue from methanol afforded 45 mg (66%) of isopropylidene derivative **16a**, m.p. 203–205 °C. For $C_{16}H_{22}N_2O_6$ (338.4) calculated: 56.80% C, 6.55% H, 8.28% N; found: 56.69% C, 6.52% H, 8.21% N. ^{1}H NMR: 1.41 s, 3 H and 1.46 s, 3 H ($C(CH_3)_2$); 1.62 dd, 1 H, *J*(9a,8) = 3.6, *J*(9a,9b) = 15.6 (H-9a); 1.77 d, 1 H, *J* = 0.8 (CH_3); 2.09 dd, 1 H, *J*(7a,8) = 9.0, *J*(7a,7b) = 13.6 (H-7a); 2.40 dd, 1 H, *J*(7b,8) = 8.5 (H-7b); 2.48 m, 1 H (H-9b); 3.69 s, 3 H ($COOCH_3$); 3.70 d, 1 H and 4.17 d, 1 H, J_{gem} = 12.0 (CH_2O); 4.45 d, 1 H, *J*(1,9b) = 4.5 (H-1); 5.20 m, 1 H, *J*(8,9b) = 11.0 (H-8); 7.77 d, 1 H, *J* = 0.8 (H-6′); 11.24 s, 1 H (NH).

Methyl (1*R**,6*S**,8*R**)- 8-(6-Aminopurin-9-yl)-3,3-dimethyl-2,4-dioxabicyclo[4.3.0]nonane-6-carboxylate (**16b**)

A stirred mixture of **13b** (61 mg 0.2 mmol), acetone (1 ml), 2,2-dimethoxypropane (0.5 ml), dimethylformamide (0.5 ml), and two drops of sulfuric acid was stirred at room temperature for 1 h. The mixture was then neutralized with solid sodium hydrogencarbonate, the insoluble portion was filtered off and washed with acetone. The combined filtrates were taken down. Crystallization of the residue from methanol afforded 42 mg (61%) of isopropylidene derivative **16b**, m.p. 242–244 °C. For $C_{16}H_{21}N_5O_4$ (347.4) calculated: 55.32% C, 6.09% H, 20.16% N; found: 55.45% C, 6.25% H, 20.18% N. ^{1}H NMR: 1.38 s, 3 H and 1.45 s, 3 H ($C(CH_3)_2$); 1.98 dd, 1 H, *J*(9a,9b) = 14.8, *J*(9a,8) = 4.3 (H-9a); 2.39 dd, 1 H, *J*(7a,8) = 8.6, *J*(7a,7b) = 13.4 (H-7a); 2.58–2.73 m, 2 H (H-9b, H-7b); 3.72 d, 1 H and 4.19 d, 1 H, J_{gem} = 11.9 (CH_2O); 3.73 s, 3 H ($COOCH_3$); 4.56 d, 1 H, *J*(1,9b) = 4.0 (H-1); 5.14 m, 1 H (H-8); 7.22 brs, 2 H (NH_2); 8.13 s, 1 H (H-2′); 8.21 s, 1 H (H-8′).

Methyl (1*R**,2*S**,4*S**)-2-Hydroxy-4-[5-methyl-2(1*H*),4(3*H*)-dioxopyrimidin-1-yl]-1-(tosyloxymethyl)cyclopentane-1-carboxylate (**17**)

Tosyl chloride (286 mg, 1.5 mmol) was added to a solution of **13a** (298 mg, 1 mmol) in pyridine (4 ml). After standing at room temperature for 5 h, water (0.2 ml) was added and the solution was set aside for 10 min. The solvent was evaporated and the residue was partitioned between chloroform (20 ml) and water (5 ml). The organic layer was separated, washed with water (2 × 5 ml) and evaporated. Crystallization of the residue from ethyl acetate afforded 370 mg (82%) of the tosyl derivative **17**, m.p. 209–212 °C. For $C_{20}H_{24}N_2O_8S$ (452.5) calculated: 53.09% C, 5.35% H, 6.19% N, 7.09% S; found: 53.00% C, 5.34% H, 6.14% N, 7.09% S. ^{1}H NMR: 1.64–1.83 m, 2 H (H-3a, H-5a); 1.77 s, 3 H (5′-CH_3); 2.27 ddd, 1 H, *J*(3b,2) = 5.5, *J*(3b,3a) = 14.0, *J*(3b,4) = 8.5 (H-3b); 2.37 dd, 1 H, *J*(5b,4) = 8.2, *J*(5b,5a) = 13.1 (H-5b); 2.42 s, 3 H (CH_3); 3.53 s, 3 H (OCH_3); 4.19 m, 1 H (H-2); 4.22 d, 1 H and 4.38 d, 1 H, J_{gem} = 9.2 (CH_2O); 4.92 p, 1 H (H-4); 5.81 d, 1 H, *J*(OH,2) = 5.2 (2-OH); 7.50 d, 2 H, *J*(*m*,*o*) = 8.3 (*m*-H tosyl); 7.63 s, 1 H (H-6′); 7.77 d, 2 H (*o*-H tosyl); 11.23 s, 1 H (H-3′).

Methyl (1*R**,2*S**,4*S**)-2-Benzoyloxy-4-[5-methyl-2(1*H*),4(3*H*)-dioxopyrimidin-1-yl]-1-(tosyloxymethyl)cyclopentane-1-carboxylate (**18**)

A solution of benzoyl chloride (0.13 ml, 1.125 mmol) in pyridine (2 ml) was added dropwise during 2 h to a stirred solution of tosyl derivative **17** (339 mg, 0.75 mmol) in pyridine (4 ml) and the mixture was set aside for another 2 h. Then water (0.2 ml) was added and, after standing at room temperature for 15 min, the solvent was evaporated. The residue was partitioned between ethyl acetate (15 ml) and water (5 ml). The organic layer was separated, washed with water (2 × 5 ml), dried over anhydrous sodium sulfate and evaporated. Column chromatography of the residue (40 g of silica gel, ethyl acetate–toluene 4 : 1) and crystallization from ethanol afforded 340 mg (81%) of compound **18**, m.p. 200–202 °C. For $C_{27}H_{28}N_2O_9S$ (556.6) calculated: 58.26% C, 5.07% H, 5.03% N, 5.76% S; found: 58.15% C, 5.20% H, 4.98% N, 5.75% S. ^{1}H NMR: 1.61 s, 3 H (5-CH_3); 2.04 ddd, 1 H, *J*(3a,2) = 4.3, *J*(3a,3b) = 14.6, *J*(3a,4) = 8.8 (H-3a); 2.22 dd, 1 H, *J*(5a,4) = 10.4, *J*(5a,5b) = 13.4 (H-5a); 2.31 s, 3 H (CH_3); 2.44 dd, 1 H, *J*(5b,4) = 8.2 (H-5b); 2.61 ddd, 1 H, *J*(3b,2) = 5.8, *J*(3b,4) = 8.8 (H-3b); 3.62 s, 3 H (OCH_3); 4.38 d, 1 H and 4.45 d, 1 H, J_{gem} = 9.6 (CH_2); 4.98 brp, 1 H

(H-4); 5.62 dd, 1 H (H-2); 7.31 d, 2 H, *J*(*m*,*o*) = 8.3 (*m*-H tosyl); 7.44 d, 1 H, *J* = 0.8 (H-6′); 11.27 s, 1 H (H-3′).

Methyl (1*R**,10*S**,11*R**)-11-Benzoyloxy-4-methyl-5oxo-8-oxa-2,6-diazatricyclo[8.2.1.$0^{2,7}$]trideca-3,6-diene-10-carboxylate (**19**)

A solution of tosylate **18** (166 mg, 0.3 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (90 µl, 0.6 mmol) in acetonitrile (3 ml) was heated under reflux for 7 h and then concentrated to a third of the original volume. The residue was diluted with ethyl acetate (30 ml), washed with water (2 × 4 ml), dried over sodium sulfate and evaporated to a small volume. The crystalline compound was filtered off, washed with ethyl acetate and dried. It was obtained 71 mg (62%) of the anhydro derivative **19**, m.p. 259–261°C. For $C_{20}H_{20}N_2O_6$ (384.4) calculated: 62.49% C, 5.24% H, 7.29% N; found: 62.22% C, 5.28% H, 7.18% N. ^{1}H NMR: 1.79 s, 3 H (CH_3); 2.06 brdd, 1 H (H-12a); 2.30 dd, 1 H, *J* = 1.5, *J*(13a,13b) = 14.1 (H-13a); 2.54 brdd, 1 H (H-13b); 3.06 ddd, 1 H, *J*(12b,12a) = 15.4, *J*(18b,1) = 8.7 (H-12b); 3.66 s, 3 H (CH_3O); 4.38 d, 1 H and 4.82 dd, 1 H, *J* = 1.5, J_{gem} = 12.2 (CH_2O); 4.56 brt, 1 H (H-1); 5.63 dd, 1 H, *J*(11,12a) = 6.1, *J*(11,12b) = 10.7 (H-11); 7.52–7.74 m and 7.98–8.03 m, 6 H (H-3, H-arom.).

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