64. Synthesis of (5*R*)- and (5*S*)-5-Methyl-5,6-dihydrouridine Derivatives

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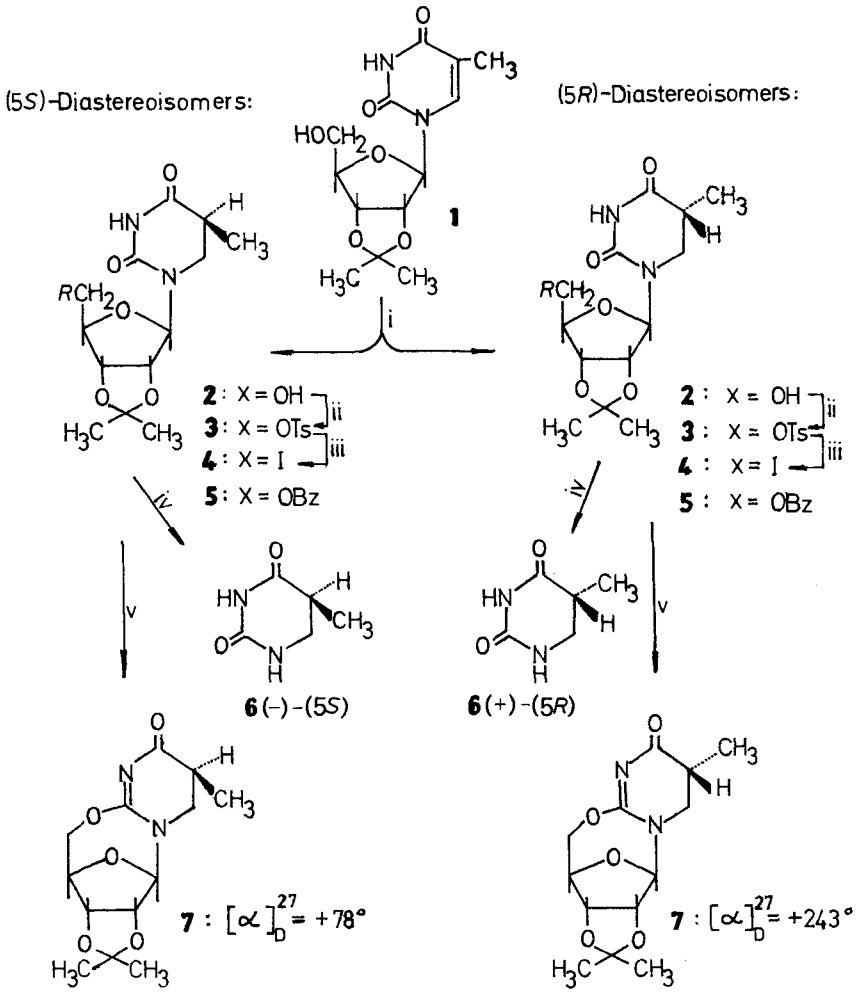
Summary

The hydrogenation of 2′,3′-*O*-isopropylidene-5-methyluridine (**1**) in water over 5% Rh/Al_2O_3 gave (5*R*)- and (5*S*)-5-methyl-5,6-dihydrouridine (**2**), separated as 5′-*O*-(*p*-tolylsulfonyl)- (**3**) and 5′-*O*-benzoyl- (**5**) derivatives by preparative TLC. on silica gel and ether/hexane developments. The diastereoisomeric differentiation at the C(5) chiral centre depends upon the reaction media and the nature of the protecting group attached to the ribosyl moiety.

The synthesis of iodo derivatives (5*R*)- and (5*S*)-**4** is also described. The diastereoisomers **4** were converted into (5*R*)- and (5*S*)-2′,3′-*O*-isopropylidene-5-methyl-2,5′-anhydro-5,6-dihydrouridine (**7**).

Many natural pyrimidine nucleosides as well as analogues of the nucleic acid constituents, functionalized or modified at the C(5),C(6)-double bond, manifest biological activities [1–4]. The saturation of the C(5),C(6)-double bond of DNA pyrimidine constituents represents also a major transformation induced by ionizing radiations *in vitro* models [5] and in living cells [6].

5,6-Dihydrouridine was the first natural reduced pyrimidine nucleoside to be discovered as an unusual component of the transfer-RNAs [7]. Later, 1-(β-D-ribofuranosyl)-5,6-dihydrothymine (5-methyl-5,6-dihydrouridine) was identified as a minor constituent in the chromosomal RNA of the rat ascites tumor [8]. The absolute configuration and optical purity of this dihydronucleoside has not yet been established. The syntheses [9–12], ^{1}H-NMR. studies [13–15], and X-ray analyses [16] [17] of the chemically sensitive 5,6-dihydropyrimidine nucleosides anticipated their discoveries in natural products. So far, however, information concerning the diastereoisomeric differentiation and possible epimerization of 5-methyl-5,6-dihydrouridine and its derivatives at the C(5) chiral centre have been scarce. Thus, from ^{1}H-NMR. studies, 2′,3′,5′-tri-*O*-acetyl-5-methyl-5,6-dihydrouridine [13] was considered as the uniform compound. In contrast to this finding our studies on the ^{13}C-NMR. spectral data of the same tri-*O*-acetyl compound revealed two distinguishable sets of resonances indicating a mixture of (5*R*)- and (5*S*)-diastereoisomers. The major diastereoisomer exhibited signals at δ 172.7, 153.5, 85.7, 42.8 and 12.4 ppm for C(4), C(2), C(1), C(6) and CH_3–C(5), respectively, the other diastereoisomer showing the corresponding signals at δ 172.5,



i: a) 5% Rh/Al_2O_3 in H_2O, b) 5% Rh/C in MeOH; ii: TsCl/py; iii: NaI/EtCOMe; iv: 2.3% HCl-solution at reflux, 1 h; v: AgOAc/MeOH.

153.0, 85.5, 43.2 and 12.8 ppm. The resonances for C(4'), C(2'), C(3'), C(5') and C(5) at δ 78.8, 70.9, 69.3, 63.7 and 35.2 ppm respectively, were superimposed in both diastereoisomers.

Hydrogenation of 2',3'-*O*-isopropylidene-5-methyluridine (**1**) in water over 5% Rh/Al_2O_3 catalyst has generated a mixture of diastereoisomeric 2',3'-*O*-isopropylidene-5-methyl-5,6-dihydrouridines (**2**), in a ratio of 3:2 (^{1}H-NMR.) [18]. As a continuation of this work, we investigated the influence of hydrogenation conditions on the diastereoisomer ratio. Thus, the hydrogenation of **1** in methanol over 5% Rh/C afforded a mixture of diastereoisomers **2** (approximately 1:1). However, the most significant diastereoisomeric differentiation was observed when the unprotected 5-methyluridine **1** was hydrogenated in water over 5% Rh/Al_2O_3 [18].

In order to determine the diastereoisomeric ratio, (5*R*, 5*S*)-5-methyl-5,6-dihydrouridine [18] was converted into the 2′,3′-*O*-isopropylidene derivative **2**. On the basis of ^{1}H-NMR. data the diastereoisomeric excess of the major component was estimated as 85%.

However, (5*R*)- and (5*S*)-diastereoisomers of 5-methyl-5,6-dihydrouridine and its derivatives have not yet been separated. In search for derivatives suited for chromatographic separations, (5*R*,5*S*)-2′,3′-*O*-isopropylidene-5-methyl-5,6-dihydrouridine (**2**) was converted into the corresponding 5′-*O*-tosyl- (**3**) and 5′-deoxy-5′-iodo- (**4**) compounds. In spite of careful column chromatography (silica gel, CH_2Cl_2/CH_3OH) and several recrystallizations, the diastereoisomers could not be separated. The ^{13}C-NMR. spectrum of the 5′-iodo compound **4**, obtained from chromatographed and recrystallized 5′-*O*-tosyl compound **3**, showed resonances for C(1′) at δ 91.9 and 93.3, for C(6) at δ 46.8 and 47.8, and for CH_3–C(5) at δ 13.1 and 12.3 ppm. The signals at δ 172.7 (C(4)), 152.6 (C(2)), 84.0 (C(4′)), 83.0 (C(2′)), 82.8 (C(3′)), 82.5 (C(5′)), and 35.5 (C(5)) were superimposed for both diastereoisomers.

Our successful separation of the diastereoisomeric ethyl *N*-benzoylaminocyclohexanecarboxylates [19] [20] led us to prepare the *O*-benzoyl derivative **5** of compound **1**. Preparative TLC. on silica gel with ether/hexane 1:1 gave (5*S*)-**5** and (5*R*)-**5** in 68% and 32% yields, respectively. The ^{1}H-NMR. spectra of (5*S*)-**5** and (5*R*)-**5** have considerable diagnostic values, exhibiting different chemical shifts for H–N(3) (at 8.41 and 8.14 ppm) and H–C(1′) (at 5.76 and 5.60 ppm), as well as for the coupling of the C(6) geminal protons (see *Exper. Part*). The configurations of the diastereoisomers were assigned on the basis of their hydrolysis products *(vide infra)*.

The observation that the enantiomerically pure 5,6-dihydrothymine, obtained from the deaminated and hydrogenated 1-β-(5′-amino-5′-deoxy-D-allofuranuronosyl)-5-hydroxymethyluracil (polyoxin C) [21], can be stereochemically correlated with the synthetic product of (–)-(*S*)-absolute configuration [22], allowed us to inspect the absolute configurations at the C(5) centres of the 5′-*O*-benzoyl derivatives **5**. Compound **5** showed the expected susceptibility to *N*-glycosidic bond cleavages on treatment with hydrochloric acid. The (5*S*)-diastereoisomer **5** was cleaved to (–)-(*S*)-dihydrothymine (**6**). On the other hand the (5*R*)-diastereoisomer was cleaved into (+)-(*R*)-5,6-dihydrothymine (**6**) (compared with an authentic sample prepared from the optically active β-ureidoisobutyric acid [23]).

Finally, the diastereoisomers of the 5′-*O*-*p*-tolylsulfonate **3**, required for the iodination and intramolecular cyclizations to stereochemically defined products, were successfully separated adopting preparative TLC. on silica gel with ether/hexane, conveniently used for the separation of the 5′-*O*-benzoyl isomers **5**. The (5*S*)-diastereoisomer **3**, major component (76%), on treatment with hydrochloric acid, cleaved to 5,6-dihydrothymine, identical with the (–)-(*S*)-enantiomer **6**. The diastereoisomers **3** exhibited different chemical shifts in ^{1}H-NMR. for H–C(1′), H–C(2′), H–C(3′), H_2–C(6) and CH_3–C(5) (see *Exper. Part*).

The iodination of (5*S*)- and (5*R*)-**3** efficiently proceeded to the corresponding (5*S*)- and (5*R*)-iodo derivatives **4** by treatment with sodium iodide in 2-butanone. Epimerizations at C(5) was not observed by inspection of the ^{1}H-NMR. spectra.

However, when the (5*S*)- or (5*R*)-tosyl derivative **3** was treated with basic reagents (NaOH/EtOH or NaOMe/MeOH), epimerization at C(5) took place, giving from both diastereoisomers a mixture of (5*R*,5*S*)-2′,3′-*O*-isopropylidene-5-methyl-2,5′-anhydro-5,6-dihydrouridine (**7**). These isomerizations under basic conditions are explained by keto-enol tautomerization.

Attention was next directed to the stereochemically controlled synthesis of (5*S*)- and (5*R*)-2′,3′-*O*-isopropylidene-5-methyl-2,5′-anhydro-5,6-dihydrouridine (**7**). A (5*R*,5*S*)-mixture of **7** prepared from (5*R*,5*S*)-iodo compound **4** by reaction with silver acetate in methanol [24], could not be separated by standard chromatographic methods. The (5*S*)-isomer **7** and the (5*R*)-isomer were unambiguously prepared starting from (5*S*)- and (5*R*)-5′-iodo-derivatives **4**, according to *Brown et al.* [24]. The bicyclic (5*S*)- and (5*R*)-isomers **7** were also characterized by UV. spectra (253 nm), and ^{1}H-NMR. spectra with different chemical shifts for H–C(1′) at δ 5.09 and 5.17 ppm.

Experimental Part

General remarks. The techniques and apparatus have been described [25]. Optical rotations were measured in acetone, unless otherwise stated, using a *Zeiss-Winkel 179707* apparatus. ^{1}H- and ^{13}C-NMR. spectra were recorded in dimethyl sulfoxide, unless otherwise stated, on a *«Jeol JNM-FX 100»* FT-NNM spectrometer. Chemical shifts are given in δ (ppm) relative to tetramethylsilane as an internal standard.

*Preparation of (5*R*,5*S*)-2′,3′-*O*-isopropylidene-5-methyl-5,6-dihydrouridine* (**2**). *a)* To a solution of **1** [26] (100 mg, 0.34 mmol) in methanol (2.4 ml), 5% Rh/C (19 mg) was added. The mixture was stirred under 0.35 MPa of H_2 at RT. for 48 h. The catalyst was filtered off and the filtrate evaporated to dryness. Prep. TLC. (2 developments in CH_2Cl_2/CH_3OH 15:1) afforded a mixture of diastereoisomers **2** (46 mg, 46%), *ca.* 1:1 (^{1}H-NMR. $CDCl_3$) [18].

b) (5*R*,5*S*)-5-methyl-5,6-dihydrouridine [18] (110 mg, 0.42 mmol) was dissolved in anhydrous acetone (2.5 ml) and treated with desiccated cuprous sulfate (200 mg) and conc. sulfuric acid (0.0025 ml), according to [24]. Prep. TLC., as described under a), afforded a mixture of diastereoisomers **2** (100 mg, 79%), *ca.* 85:15 (^{1}H-NMR. $CDCl_3$) [18].

*Preparation of (5*R*,5*S*)-2′,3′-O-isopropylidene-5-methyl-5′-O-(p-tosyl)-5,6-dihydrouridine* (**3**). To a solution of (5*R*,5*S*)-**2** (474 mg, 1.58 mmol) in cooled (0°), dry pyridine (3.6 ml) was added recrystallized *p*-toluenesulfonyl chloride (415 mg, 2.18 mmol). After 24 h at RT., the solvent was removed azeotropically with methanol under reduced pressure. The residue was partitioned between water and CH_2Cl_2. The organic layer was washed with 10% acetic acid and water, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue subjected to prep. TLC. (2 developments in CH_2Cl_2/CH_3OH 15:1) giving a mixture of the (5*R*)- and (5*S*)-**3** as a foam (387 mg, 54%), Rf *ca.* 0.70 (CH_2Cl_2/CH_3OH 20:1), $[\alpha]_D^{23} = -9°$ ($c = 1$). – UV.: 223 (4.03), 263 (2.88), 274 (2.81). – IR.: 3420 br., 3235 br., 3080, 2982, 2935, 1720, 1703, 1685 sh, 1178, 763.

$C_{20}H_{26}N_2O_8S$ (454.49) Calc. C 52.85 H 5.77 N 6.17% Found C 52.73 H 5.68 N 6.22%

*Preparation of (5*R*,5*S*)-5′-deoxy-5′-iodo-2′,3′-O-isopropylidene-5-methyl-5,6-dihydrouridine* (**4**). To a solution of (5*R*,5*S*)-**3** (623 mg, 1.37 mmol) in 2-butanone (18 ml) was added NaI (604 mg, 4.03 mmol) and the mixture was heated under reflux for 3 h. A precipitate was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was partitioned between water and 5% solution of $Na_2S_2O_3$. The organic layer was dried (Na_2SO_4) and then removed under reduced pressure. The residue was chromatographed through a silica gel (20 g) column. CH_2Cl_2/CH_3OH 100:1 eluted a mixture of diastereoisomers **4** (518 mg, 95%), Rf *ca.* 0.74 (CH_2Cl_2/CH_3OH 20:1), m.p. 135–139° (CH_2Cl_2/hexane), $[\alpha]_D^{22} = -28.5°$ ($c = 1$). – IR.: 3330 br., 2980, 2948, 2930, 1724, 1699 *S*, 1691 *S*, 1685, 758, 698.

$C_{13}H_{19}IN_2O_5$ (410.22) Calc. C 38.06 H 4.67 N 6.83% Found C 38.43 H 4.97 N 7.08%

Preparation of (5R,5S)-5'-O-benzoyl-2',3'-O-isopropylidene-5-methyl-5,6-dihydrouridine (**5**). To a solution of (5*R*,5*S*)-**2** (132 mg, 0.44 mmol) in dry pyridine (1 ml) was added benzoyl chloride (0.079 ml, 0.68 mmol). The mixture was stirred and heated at 60° for 3 h and the solvent removed azeotropically with methanol under reduced pressure. The residue was then partitioned between $CHCl_3$ and a saturated solution of $NaHCO_3$. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to dryness. Prep. TLC. (5 developments in CH_2Cl_2/CH_3OH 30:1) afforded a mixture of diastereoisomers **5** (130 mg, 73%). Rechromatography by prep. TLC. (8 developments in ether/hexane 1:1) separated (5*S*)-**5** (73 mg, 68% based on the total amount of the isolated diastereoisomers). The analytical sample had Rf *ca.* 0.42 (4 developments in ether/hexane 1:1), m.p. 67–68° (ether/hexane), $[\alpha]_D^{25} = -37°$ ($c = 1$). – UV.: 227 (4.10), 273 (3.12), 281 *S* (3.04). – IR.: 3420 br., 3248 br., 3088 br., 2985, 2935, 1725 br., 1705, 1697, 1603, 1587, 718, 691. – ^{1}H-NMR. ($CDCl_3$): 8.41 (*s*, 1H, H–N(3)); 8.09–7.35 (*m*, 5H, ArH); 5.76 (*d*, $J = 2.2$, 1H, H–C(1')); 4.94–4.77 (*m*, 2H, H–C(2') and H–C(3')); 4.66 (*d*×*d*, $J = 3.5$ and 11.6, 1H, H_a–C(5')); 4.54–4.27 (*m*, 2H, H–C(4') and Hb–C(5')); 3.36 (*d*×*d*, $J = 6.1$ and 12.4, 1H, Ha–C(6)); 3.12 (*d*×*d*, $J = 9.3$ and 12.4, 1H, Hb–C(6)); 2.81–2.42 (*m*, 1H, H–C(5)); 1.58 and 1.37 (2*s*, each 3H, $(H_3C)_2$–C)); 1.10 (*d*, $J = 7.1$, 3H, H_3C–C(5)).

$C_{20}H_{24}N_2O_7$ (404.41) Calc. C 59.40 H 5.98 N 6.93% Found C 59.67 H 6.27 N 6.97%

(5*R*)-**5** was obtained in 32% (35 mg) yield, based on the total amount of the isolated diastereoisomers, Rf *ca.* 0.51, m.p. 47–54° (ether/hexane), $[\alpha]_D^{25} = -20°$ ($c = 1$). – UV.: 231 (4.11), 275 (2.88), 282 (2.83). – IR.: 3415 br., 3240 br., 3080 br., 2988, 2937, 1723 br., 1705, 1695 *S*, 716, 691. – ^{1}H-NMR. ($CDCl_3$): 8.14 (*s*, 1H, H–N(3)); 8.10–7.35 (*m*, 5H, ArH); 5.60 (*d*, $J = 2.4$, 1H, H–C(1')); 4.98 (*d*×*d*, $J = 2.4$ and 6.5, 1H, H–C(2')); 4.85 (*d*×*d*, $J = 3.7$ and 6.5, 1H, H–C(3')); 4.66–4.28 (*m*, 3H, H–C(4') and 2H–C(5')); 3.53–3.12 (*m*, 2H, 2H–C(6)); 2.84–2.45 (*m*, 1H, H–C(5)); 1.58 and 1.37 (2*s*, each 3H, $(H_3C)_2$–C)); 1.13 (*d*, $J = 6.8$, 3H, H_3C–C(5)).

$C_{20}H_{24}N_2O_7$ (404.41) Calc. C 59.40 H 5.98 N 6.93% Found C 59.29 H 6.23 N 6.93%

Separation of (5R)- and (5S)-2',3'-O-isopropylidene-5-methyl-5'-O-(p-tosyl)-5,6-dihydrouridine (**3**). A mixture of (5*R*)- and (5*S*)-**3** (387 mg) was subjected to prep. TLC. (6 developments in ether/hexane 1.5:1). The diastereoisomer with lower mobility (294 mg, 76% based on the total amount of the isolated diastereoisomers) was identified as (5*S*)-**3** *(vide infra)*. The analytical sample had Rf *ca.* 0.10 (4 developments in ether/hexane 1:1), $[\alpha]_D^{25} = -9.5°$ ($c = 1$). – ^{1}H-NMR. ($CDCl_3$): 7.78 and 7.36 (2*d*, $J = 8.1$, 4H, ArH); 5.71 (*d*, $J = 2.7$, 1H, H–C(1')); 4.83 (*d*×*d*, $J = 2.7$ and 6.6, 1H, H–C(2')); 4.71 (*d*, $J = 6.6$, 1H, H–C(3')); 4.37–4.0 (*m*, 3H, H–C(4') and 2H–C(5')); 3.46 (*d*×*d*, $J = 5.6$ and 12.6, 1H, Ha–C(6)); 3.17 (*d*×*d*, $J = 9.3$ and 12.6, 1H, Hb–C(6)); 2.90–2.49 (*d*, $J = 6.8$, 1H, H–C(5)); 2.45 (*s*, 3H, H_3C–Ts); 1.54 and 1.33 (2*s*, each 3H, $(H_3C)_2$–C); 1.26 (*d*, $J = 6.8$, 3H, H_3C–C(5)).

The minor isomer was (5*R*)-**3** (93 mg, 24% based on the total amount of isolated diastereoisomers), Rf *ca.* 0.14, $[\alpha]_D^{25} = -1°$ ($c = 1$). – ^{1}H-NMR. ($CDCl_3$): 7.58 (*s*, 1H, H–N(3)); 7.79 and 7.35 (2*d*, $J = 8.3$, 4H, ArH); 5.58 (*s*, $J = 2.4$, 1H, H–C(1')); 4.88 (*d*×*d*, $J = 2.4$ and 6.4, 1H, H–C(2')); 4.79 (*d*, $J = 6.4$, 1H, H–C(3')); 4.2 (*m*, 3H, H–C(4') and 2H–C(5')); 3.48 (*d*×*d*, $J = 6.2$ and 11.8, 1H, Ha–C(6)); 3.22 (*d*×*d*, $J = 11.2$ and 11.8, 1H, Hb–C(6)); 2.81–2.56 (*m*, 1H, H–C(5)); 2.45 (*s*, 3H, H_3C–Ts); 1.53 and 1.32 (2*s*, each 3H, $(H_3C)_2$–C); 1.26 (*d*, $J = 6.8$, 3H, H_3C–C(5)).

Preparation of (–)-(S)-5,6-dihydrothymine (**6**). *a)* To a suspension of (5*S*)-**5** (123 mg, 0.30 mmol) in water (7 ml) was added conc. HCl-solution (0.49 ml). The mixture was heated at 100° for 1 h, then diluted with water (15 ml) and neutralized with Ag_2CO_3. A precipitate was filtered off and the excess silver ion removed from the filtrate by precipitation with hydrogen sulfide and filtration through a short *Celite* column. The filtrate was then evaporated to dryness under reduced pressure and the residue crystallized from methanol, affording product (–)-(*S*)-**6** (24 mg, 62%), m.p. 259–260°, $[\alpha]_D^{23} = -11.0°$ ($c = 0.5$, pyridine), [[22]: m.p. 261–262°, $[\alpha]_D^{23} = -11.3°$ ($c = 0.49$, pyridine)].

b) Compound (5*S*)-**3** (180 mg, 0.40 mmol) was suspended in water (10.5 ml), treated with conc. HCl-solution (0.71 ml). The workup was as described under *a*. The residue was recrystallized several times from methanol affording product (–)-(*S*)-**6** (28 mg, 55%), $[\alpha]_D^{28} = -12°$ ($c = 0.5$, pyridine).

Preparation of (+)-(R)-5,6-dihydrothymine (**6**). A suspension of (5*R*)-**5** (138 mg, 0.34 mmol) in water (8.5 ml) was treated with conc. HCl-solution (0.55 ml). The workup, as described for the cleavage of the (5*S*)-isomer **5** into (5*S*)-**6**, afforded the (+)-(*R*)-enantiomer **6** (32 mg, 73%), m.p.

260–261° (MeOH), $[\alpha]_D^{23} = +11.0°$ ($c = 0.5$, pyridine), [[23]: m.p. 264–265°, $[\alpha]_D^{21} = +17°$ ($c = 0.55$, pyridine)].

Preparation of (5S)-5'-deoxy-5'-iodo-2',3'-O-isopropylidene-5-methyl-5,6-dihydrouridine (**4**). A solution of (5*S*)-**3** (268 mg, 0.59 mmol) in 2-butanone (8 ml), treated with NaI (260 mg, 1.73 mmol) as described for the iodination of (5*R*,5*S*)-**3**, afforded the (5*S*)-isomer **4** (210 mg, 87%) by prep. TLC. (3 developments in CH_2Cl_2/CH_3OH 50:1). The analytical sample had Rf *ca.* 0.32 (4 developments in ether/hexane 1:1), m.p. 141–143° (acetone/hexane), $[\alpha]_D^{23} = -35°$ ($c = 1$). – ^{1}H-NMR. ($CDCl_3$): 7.88 (br. *s*, 1 H, H–N(3)); 5.71 (*d*, $J = 3.2$, 1 H, H–C(1')); 4.89 (*d*×*d*, $J = 3.2$ and 3.8, 1 H, H–C(2')); 4.63 (*d*×*d*, $J = 3.9$ and 6.8, 1 H, H–C(3')); 3.96 (*d*×*d*, $J = 3.9$ and 5, 1 H, H–C(4')); 3.66–3.21 (*m*, 4 H, 2 H–C(5') and 2 H–C(6)); 2.96–2.54 (*m*, $J = 7.1$, 1 H, H–C(5)); 1.56 and 1.36 (2 *s*, each 3 H, $(H_3C)_2$–C); 1.30 (*d*, $J = 7.1$, 3 H, H_3C–C(5)).

Preparation of (5R)-5'-deoxy-5'-iodo-2',3'-O-isopropylidene-5-methyl-5,6-dihydrouridine (**4**). A solution of (5*R*)-**3** (87 mg, 0.19 mmol) in 2-butanone (2.5 ml), treated with NaI (84 mg, 0.56 mmol) as described for the iodination of (5*R*,5*S*)-**3**, afforded (5*R*)-**4** (64 mg, 81%), Rf *ca.* 0.44 (4 developments in ether/hexane 1:1), m.p. 133–134° (acetone/hexane), $[\alpha]_D^{25} = -14°$ ($c = 1$). – ^{1}H-NMR. ($CDCl_3$): 7.79 (*s*, 1 H, H–N(3)); 5.58 (*d*, $J = 2.8$, 1 H, H–C(1')); 4.96 (*d*×*d*, $J = 2.8$ and 6.6, 1 H, H–C(2')); 4.68 (*d*×*d*, $J = 3.7$ and 6.6, 1 H, H–C(3')); 4.02 (*d*×*d*, $J = 3.7$ and 5.3, 1 H, H–C(4')); 3.70–3.21 (*m*, 4 H, 2 H–C(5') and 2 H–C(6)); 2.93–2.60 (*m*, $J = 6.8$, 1 H, H–C(5)); 1.56 and 1.36 (2 *s*, each 3 H, $(H_3C)_2$–C); 1.27 (*d*, $J = 6.8$, 3 H, H_3C–C(5)).

Preparation of (5R,5S)-2',3'-O-isopropylidene-5-methyl-2,5'-anhydro-5,6-dihydrouridine (**7**). To a solution of (5*R*,5*S*)-**4** (205 mg, 0.50 mmol, $[\alpha]_D^{22} = -28.5°$) in CH_3OH abs. (80 ml) was added CH_3COOAg (375 mg, 2.25 mmol). The mixture was heated under reflux for 15 min. The precipitate was filtered off and the excess of silver ion was removed from the filtrate by precipitation with hydrogen sulfide and filtration through a short *Celite* column. The filtrate was then evaporated under reduced pressure to a solid residue which, on trituration with acetone, afforded crystalline **7** (54 mg, 38%), Rf *ca.* 0.31 (CH_2Cl_2/CH_3OH 20:1), m.p. 215–230° (dry CH_3OH), $[\alpha]_D^{21} = +160°$ ($c = 0.5$, DMSO). – UV.: 253 (3.99). – IR.: 3434 br., 2999, 2985, 2967, 2934, 1685, 1561, 1554, 1545.

$C_{13}H_{18}N_2O_5$ (282.29) Calc. C 55.31 H 6.43 N 9.93% Found C 55.47 H 6.72 N 10.16%

Preparation of (5S)-2',3'-O-isopropylidene-5-methyl-2,5'-anhydro-5,6-dihydrouridine (**7**). A solution of (5*S*)-**4** (250 mg, 0.61 mmol) in anhydrous methanol (98 ml), treated with CH_3COOAg (457 mg, 2.74 mmol) as described for the preparation of (5*R*,5*S*)-**7**, afforded the (5*S*)-**7** (68 mg, 40%), m.p. 205–211° (CH_3OH), $[\alpha]_D^{27} = +78°$ ($c = 0.5$, DMSO). – ^{1}H-NMR.: 5.09 (*s*, 1 H, H–C(1')); 4.90 (*d*, $J = 5.5$, 1 H, H–C(2')); 4.79 (*d*, $J = 5.5$, 1 H, H–C(3')); 4.54 (br. *s*, 1 H, H–C(4')); 4.08 (*d*, $J = 12.7$, 1 H, H_b–C(5')); 3.84 (*d*×*d*, $J = 6.5$ and 12.7, 1 H, H_a–C(6)); 3.43 (*d*×*d*, $J = 9.9$ and 12.7, 1 H, H_b–C(6)); 1.39 and 1.28 (2 *s*, each 3 H, $(H_3C)_2$–C); 1.0 (*d*, $J = 6.8$, 3 H, H_3C–C(5)).

Preparation of (5R)-2',3'-O-isopropylidene-5-methyl-2,5'-anhydro-5,6-dihydrouridine (**7**). A solution of (5*R*)-**4** (190 mg, 0.46 mmol) in dry CH_3OH (74 ml), treated with CH_3COOAg (128 mg, 0.77 mmol) as described for (5*R*,5*S*)-**7**, afforded (5*R*)-**7** (70 mg, 53%), m.p. 229–234° (CH_3OH), $[\alpha]_D^{27} = +243°$ ($c = 0.5$, DMSO). – ^{1}H-NMR.: 5.17 (*s*, 1 H, H–C(1')); 4.86 (br. *s*, 2 H, H–C(2') and H–C(3')); 3.99 (*d*, $J = 12.3$, 1 H, H_b–C(5')); 3.83 (*d*×*d*, $J = 6.8$ and 12.7, 1 H, H_a–C(6)); 3.38 (*d*×*d*, $J = 12.7$ and 12.7, 1 H, H_b–C(6)); 1.40 and 1.28 (2 *s*, each 3 H, $(H_3C)_2$–C); 0.98 (*d*, $J = 6.5$, 3 H, H_3C–C(5)).

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