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Stereoselective Transformations in the Thymidine Series

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The stereoselective 5% Rh/Al_2O_3 hydrogenations of thymidine, 3′,5′-anhydro- X and 3′-deoxy- XII thymidines to the corresponding (5S)-5,6-dihydrothymidine derivatives I, IX, and XIII were evidenced by ^1H- and ^{13}C-NMR analyses and N-glycosidic bond cleavages to (-)-S-5,6-dihydrothymine. The regioselective syntheses of the configurationally defined (5S)-5′-O-tosyl- (III) and (5S)-5′-deoxy-5′-iodo- (IV) 5,6-dihydrothymidines are described.

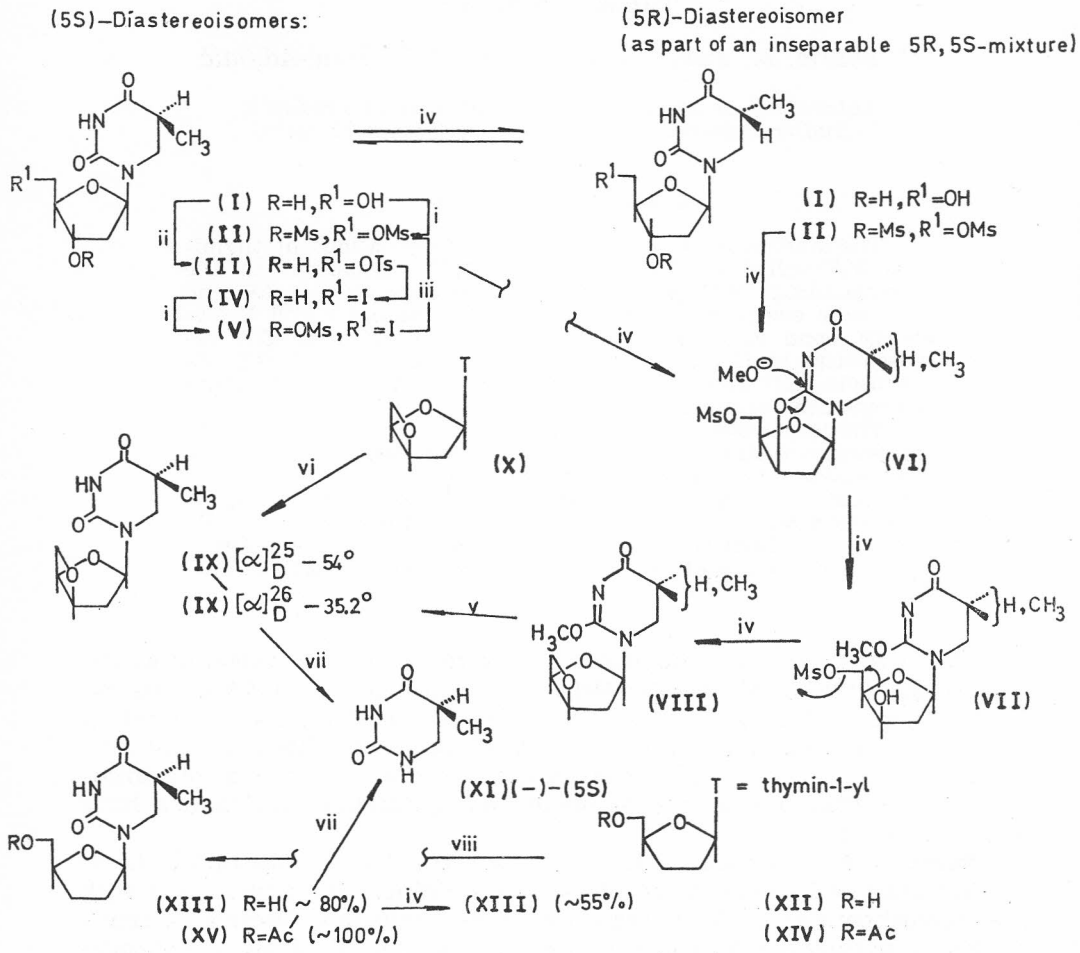
The intramolecular cyclisation of (5S)-3′,5′-dimesyloxy-5,6-dihydrothymidine (II) by NaOMe afforded (5R,5S)-5′-O-mesyl-2,3′-anhydro-5,6-dihydrothymidines (VI), which concomitantly proceeded to ring opened (5R,5S)-1-(2-deoxy-5-O-mesyl-β-D-threo-pentofuranosyl)-2-O-methyl-5,6-dihydrothymine (VII) and, finally, from the latter into (5R,5S)-1-(2-deoxy-3,5-anhydro-β-D-threo-pentofuranosyl)-2-O-methyl-5,6-dihydrothymine (VIII).

5,6-Dihydropyrimidine nucleosides have received a great deal of attention as constituents of transfer-RNAs[1] and chromosomal RNA of the rat ascites tumor.[2] Moreover, many pyrimidine nucleosides, fuctionalized at the C(5), have been investigated at various levels of biochemical criteria.[3–5] So far, however, no detailed investigations concerning the diastereoisomeric differentiations of the 5-substituted pyrimidine nucleosides have been published.

Recently we evidenced (5R)- and (5S)-5-methyl-5,6-dihydrouridines[6] by the catalytic hydrogenation of 5-methyluridine. This paper deals with the stereochemistry of 5,6-dihydrothymidine analogues. Various susceptibilities of pyrimidine nucleosides, upon the employed catalytic hydrogenations, generate 5,6-dihydro-,[7,8] tetrahydro-, hexahydro-, and from them derived ring opened products.[9,10]

Our attempted hydrogenation of thymidine in the presence of 5% Rh/C led to four products (see Experimental). On the other hand the efficient and stereoselective hydrogenation of thymidine over 5% Rh/Al_2O_3[10] into (5S)-diastereoisomer (I) was proved by inspection of the ^{13}C-NMR spectrum which exhibited single carbon-13 shifts in good accordance with the data on model compounds.[11,12]

The stereochemical integrity of (5S)-diastereoisomer I was lost under basic conditions (NaOMe/MeOH), apparently *via* a C(4)-C(5) keto-enol tautomerization and epimerization at the C(5) chiral centre. Judging from the relative intensities of the two sets of carbon-13 bands, a mixture of two diastereoisomers I appeared in a ratio of 55 : 45. In spite of all our attempts these diastereoisomers, even as sulphonyloxy compounds (*vide infra*), suited for chromatographic separations, have not yet been separated.



Reagents: i, MsCl-py; ii, TsCl-py; iii, NaI-EtCOMe; iv, NaOMe-MeOH; v, HOAc--Me_2CO; vi, [H_2]- 5% Rh/Al_2O_3-H_2O; vii, 2.3% HCl; viii, [H_2] -5% Rh/Al_2O_3-H_2O--MeOH.

We then examined the option of regioselective sulphonylations of (5S)-diastereoisomer I, assuming that keto-enol prototropies of fully ketonized 5,6-dihydrothymidine (I) should not be affected by pyridine as solvent. In contrast to the mesylation of (5S)-I, which proceeded to

(5S)-3′,5′-dimesyloxy-5,6-dihydrothymidine (II) in very high yields, the regioselective tosylation afforded (5S)-5′-O-tosyl-5,6-dihydrothymidine (III).

The diastereoisomeric purities of (5S)-II and (5S)-III were evidenced by NMR spectroscopies. While (5S)-3′,5′-dimesyloxy compound II exhibited single bands in the ^{13}C-NMR spectrum at δ 173.0, 152.9, 83.2, 33.5, and 12.3 for the carbon-13 shifts of C(4), C(2), C(1′), C(5), and Me-(5) respectively, a standardized mesylation of (5R,5S)-5,6-dihydrothymidine (I) into (5R,5S)- II evidenced two sets of bands appearing at δ 173.0 and 172.8 for C(4), at 152.9 and 152.5 for C(2), at 83.5 and 83.2 for C(1′), at 33.6 and 33.3 for C(5), and at 12.3 and 12.0 for Me-(5), in a ratio of 60 : 40 (based on their intensities).

The treatment of (5S)-5′-O-tosyl derivative III with NaI in boilling 2-butanone gave the configurationally pure (5S)-5′-deoxy-5′-iodo-5,6-dihydrothymidine (IV). It is worth noting that the same, but regioselective, iodination of (5S)-3′,5′-dimesyloxy compound II gave (5S)-5′-deoxy-5′-iodo-3′-O-mesyl-5,6-dihydrothymidine (V), the latter being alternatively obtained by the mesylation of the 5′-iodo compound IV.

All attempts to proceed with (5S)-sulphonyloxy compounds II and V to respective (5S)-2,3′-anhydro structures resulted in unwanted mixtures of (5R)- and (5S)-diastereoisomers. Thus, a typical cyclisation reaction of (5S)-3′,5,-dimesyloxy compound II with equimolar amount of NaOMe in MeOH resulted in a mixture of (5R)- and (5S)-5′-O-mesyl-2,3′- (rather than 3′-O-mesyl-2,5′-[13]) anhydro-5,6-dihydrothymidine (VI) (44.5%), which concomitantly cleaved into (5R,5S)-1-(2-deoxy-5-O-mesyl-β-D-threo-pentofuranosyl)-2-O-dihydrothymine (VII) (13%) to give (5R,5S)-1-(2-deoxy-3,5-anhydro-β-D-threo-pentofuranosyl)-2-O-methyl-5,6-dihydrothymine (VIII) (6%). The latter was most conveniently prepared (in 70% yield) from (5R,5S)-3′,5′-dimesyloxy compound II in reaction with two equivalents of NaOMe in MeOH.

In good accordance with earlier reported transformations in pyrimidine nucleoside series,[14–16] the above described conversions proceeded through dihydrothyminyl-O(2) fission of the (5R,5S)-2,3′-anhydro intermediate VI by nucleophilic attack of the methoxide ion at C(2) and then by the intramolecular displacement of the 5′-mesyloxy group of the thus formed VII in reaction with the cis-situated 3′-alkoxide. Elemental analyses and spectroscopic data of VII and VIII were in good accordance with their structures. The intensities of the two sets of signals in the ^{1}H-NMR spectra, especially for H(1′) and H(5) in compound VII, and for H_a(6) and H_b(6) in VIII, evidenced the mixtures of diastereoisomers in ratios of 6 : 4. The threo-configuration of VII, particularly of (5S)-diastereoisomer, can be deduced from the characteristic ^{1}H-NMR signal of H(1′),[17,18] appearing 1′,2′ b (J = 8.5 Hz) at δ 5.98 as a doubled doublet due to 1′,2′ a (J = 4.4) and couplings.

At this point it seemed desirable to evaluate the preferences for the stereocontrolled synthesis of (5S)-1-(2-deoxy-3,5-anhydro-β-D-threo-pentofuranosyl)-5,6-dihydrothymine (IX), a good precursor for a series of stereospecific transformations of the corresponding sugar part of the molecule. In these considerations it was assumed that the demethylation reaction of (5R,5S)-2-O-methyl derivative VIII with HOAc[19] leading to (5R,5S)-1-(2-deoxy-3,5-anhydro-β-D-threo-pentofuranosyl)-5,6-dihydro-

thymine (IX) could not proceed to some of the desired diastereoisomers. Indeed, this was proved by the ^{1}H-NMR spectrum of the thus obtained diastereoisomeric mixture, $[\alpha]_D^{26} = -35°$ (c 0.48), indicating a ratio of 55 : 45.

All attempts to separate (5S)- and (5R)-3′,5′-anhydro compound IX were also unsuccessful. Therefore, we decided to examine the corresponding thymidine structure for a direct and stereoselective hydrogenation into (5S)-diastereoisomer IX. For this purpose 1-(2-deoxy-3,5-anhydro-β--D-threo-pentofuranosyl)thymine (X) was prepared according to the literature procedure[14] to be hydrogenated in the presence of 5% Rh/Al_2O_3 as catalyst. The thus obtained 5,6-dihydro compound IX, $[\alpha]_D^{25} = -54°$ (c 1), as a (85%) (5S)-diastereoisomer, was evidenced by ^{1}H- and ^{13}C-NMR spectral data and cleavage on treatment with a solution of HCl yielding (-)-(S)-5,6-dihydrothymine (XI), $[\alpha]_D^{22} = -10°$ (c 1), (Lit.[10] : $[\alpha]_D^{23} = -11.3°$).

The stereoselective hydrogenation of 3′-deoxythymidine[20] (XII) was then conveniently elaborated in 50% MeOH with 5% Rh/Al_2O_3 as catalyst. The diastereoisomeric differentiation was ascertained by spectroscopic methods indicating predominancy (80%) of (5S)-3′-deoxy-5,6-dihydrothymidine (XIII), $[\alpha]_D^{22} = -38°$. A much better access to the configurational purity of (5S)-diastereoisomer was found when 5′-O-acetyl-3′-deoxythymidine[20] (XIV) was reduced under the same conditions and then recrystallized from EtOH/Et_2O. The thus obtained (5S)-5'-O-acetyl-5'-deoxy-5,6--dihydrothymidine (XV), $[\alpha]_D^{27} = -33°$, on treatment with a solution of HCl afforded pure (-)-(S)-5,6-dihydrothymine, $[\alpha]_D^{26} = -12°$ (Lit.[10] : $[\alpha]_D^{23} = -11.3°$).

It is worth noting that the epimerization of the (5S)-XIII took place on treatment with basic reagent (NaOMe/MeOH), yielding a diastereoisomeric mixture, evidenced by optical rotation ($[\alpha]_D^{28} = -4°$ (c 1)), and two sets of ^{1}H-NMR bands in a ratio of 55 : 45.

EXPERIMENTAL

Melting points, uncorrected, were taken on a Kofler hot stage. IR spectra were obtained for potassium bromide pellets on a Perkin-Elmer 297 spectrophotometer. UV spectra were taken for solution in ethanol with a Perkin-Elmer 124 spectrophotometer. ^{13}C-NMR spectra were measured for solution in DMSO-d_6, unless otherwise stated, on a »JEOL JNM-FX 100« FT-NNM spectrophotometer. ^{1}H-NMR spectra were measured on a Varian A 60A spectrophotometer. Chemical shifts are given in δ (ppm), relative to tetramethylsilane as an internal standard. Signals of 2′-H_2 and 5-H were obscured in some spectra by those of DMSO. Optical rotations were measured in acetone, unless otherwise stated, using a Zeiss--Winkel 179707 apparatus. The silica gel (Merck HF_{254}, type 60) for TLC and for preparative TLC was activated at 110 °C for 60 min. The products were developed in CH_2Cl_2-MeOH 30:1, four developments, and recovered from TLC chromatographic plates with acetone, unless otherwise stated. The products were rendered visible by UV illumination, and anisaldehyde or iodine vapour.

(5S)-5,6-Dihydrothymidine (I)

a) A solution of thymidine (750 mg, 3.1 mmol) in H_2O (150 ml) containing 5% Rh/Al_2O_3 (247 mg) as stirred in H_2 atmosphere under 0.12 MPa at room temperature for 8 h. The catalyst was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue crystallized as the product I (650

mg, 86,2%), m.p. 150—152 °C (from EtOH), (Lit.[8] m.p. 152—153 °C; Lit.[10] m.p. 155—156°C, $[\alpha]_D^{22} = -23°$ (c 1, H_2O), Lit.[10] $[\alpha]_D^{23} = -20.5°$ (c 1.1, H_2O). The spectroscopic data (IR and ^{1}H-NMR spectra) were identical to those reported earlier.[10] ^{13}C-NMR spectrum: δ 173.1 (C-4), 152.9 (C-2), 85.8 (C-4'), 82.7 (C-1'), 70.5 (C-3'), 61.7 (C-5'), 36.0 (C-6), 34.6 (C-5), 12.5 (Me-5). ^{13}C-NMR spectrum of a sample isolated after treatment with NaOMe in MeOH: δ 173.1/*172.9* (C-4), 152.9/*152.4* (C-2), 85.8 (C-4'), *83.0*/82.7 (C-1'), 70.5 (C-3'), 61,7/*61.6* (C-5'), 41.2 (C-2'), 36.0/*35.8* (C-6), 34.5, (C-5), 12.5/*12.2* (Me-5). The bands in italics appeared in a 55% proportion.

b) To a solution of thymidine (1.0 g, 4.13 mmol) in anhydrous MeOH (50 ml) 5% Rh/C (300 mg) was added and stirred in H_2 atmosphere under 0.34 MPa at room temperature for 20 h. The catalyst was filtered off and the filtrate evaporated to a residue, $[\alpha]_D^{25} = -30°$ (c 0.95, MeOH). Preparative TLC separated four components, among them a mixture of (5R)- and (5S)- diasteroisomers.

(5S)-3',5'-Dimesyloxy-5,6-dihydrothymidine (II)

To a solution of (5S)-5,6-dihydrothymidine I (2.25 g, 9.21 mmol) in cooled (8 °C), dry pyridine (27 ml) mesyl chloride (1.54 ml, 19.4 mmol) was added. The mixture was kept aside at 8 °C for 16 h and then the solvent removed azeotropically under reduced pressure in the presence of MeOH. It afforded the product II (3.57 g, 96.8%), R_F ca. 0.64, m.p. 139—140 °C (from MeOH), $[\alpha]_D^{24} = -7.8°$ (c 0.58).

Anal. $C_{12}H_{20}N_2O_9S_2$ (400.42) calc'd.: C 35.99; H 5.03; N 7.00%
found: C 36.24; H 4.85; N 6.80%

IR spectrum: υ_{max} 3422br, 3212br, 3017, 2967, 2932, 1722, 1687, 1662, 1347, 1177, and 942 cm^{-1}. ^{1}H-NMR spectrum: δ 10.36 (1H,s,3-NH), 6.2 (1H,t,1'-H; $J_{1',2'}$ 6.8 Hz), 5.33-5.03 (1H,m,3'-H), 4.50-4.11 (1H, and 2H,m,4'-H and 5'-H_2), 3.37 and 3.25 (each 3H,2xs,2xMsMe), 3.07-2.67 (2H,m,6-H_2; obscured by those of DMSO), 1.1 (3H,d,5-Me; $J_{Me,5}$ 6.4 Hz). ^{13}C-NMR spectrum: δ 173.0 (C-4), 152.9 (C-2), 83.2 (C-1'), 79.6 (C-4'), 79.2 (C-3'), 68.5 (C-5'), 37.6 and 36.7 (2xMsMe), 34.5 (C-6), (C-1'), 79.6 (C-4'), 79.2 (C-3'), 68.5 (C-5'), 37.6 and 36.7 (2xMsMe), 34.5 (C-6), 33.5 (C-5), 12.3 (Me-5).

^{13}C-NMR spectrum of a sample which was prepared from (5R, 5S)-I: δ 173.0/*172.8* (C-4), 152.9/*152.5* (C-2), *83.5*/83.2 (C-1'), 79.7/*79.6* (C-4'), 79.3 (C-3'), 68,6 (C-5'), 41.4 (C-2'), 37.6 and 36.8 (2xMsMe), 34.5 (C-6), 33.6/*33.3* (C-5), 12.3/*12.0* (Me-5). The bands in italics appeared in a 60% proportion.

(5S)-5'-O-Tosyl-5,6-dihydrothymidine (III)

To a cooled (8 °C) solution of (5S)-5,6-dihydrothymidine (I) (700 mg, 2.86 mmol) in dry pyridine (6.5 ml) tosyl chloride (687 mg, 3.6 mmol) was added. The mixture was kept aside at 8°C for 17 h and then the solvent removed under reduced pressure. The crystalline product III (599 mg, 52.4%) was purified by preparative TLC (in CH_2Cl_2-MeOH 7.5:1), R_F ca. 0.23 (494 mg, 43.3%), m.p. 123-125°C (from MeOH), $[\alpha]_D^{26} = +4.4°$ (c 0.46).

Anal. $C_{17}H_{22}N_2O_7S$ (398.43) calc'd.: C 51.24; H 5.57; N 7.03%
found: C 51.38; H 5.52; N 6.81%

IR spectrum: υ_{max} 3440, 3212, 3096, 2956, 2900, 1720, 1703, 1690, 1595, 1357, 1173, 784, and 757 cm^{-1}. ^{1}H-NMR spectrum: δ 10.20 (1H,s,3-NH), 7.9-7.32 (4H,m,ArH), 6.03 (1H,t,1'-H; $J_{1',2'}$ 7.2 Hz). 5.3 (1H,d,3'-OH; $J_{OH,3}$ 4.0 Hz), 4.21-3.63 (1H, 1H, and 2H,m,3'-H,4'-H, and 5'-H_2), 3.0-2.6 (2H,m,6-H_2; partly obscured by those of DMSO), 2.43 (3H,s,Ts-Me), 2.17-1.80 (2H,m,2'-H_2), 1.03 (3H,d,5-Me; $J_{Me,5}$ 6.0 Hz).

(5S)-5'-Deoxy-5'-iodo-5,6-dihydrothymidine (IV)

A suspension of 5'-O-tosyl derivative II (240 mg, 0.602 mmol) in 2-butanone (8 ml) was treated with NaI (248 mg, 1.66 mmol) and then heated under reflux for 3 h. The precipitate was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was partitioned between CH_2Cl_2 and a 5% solution of $Na_2S_2O_3$. The organic layer was dried (Na_2SO_4) and then the solvent removed under reduced pressure. The residue afforded the crystalline product IV (190 mg, 88.7%), m.p. 120°C (extended to 200°C) (from MeOH), R_F ca. 0.17, $[\alpha]_D^{23} = -8.8°$ (c 0.40).

Anal. $C_{10}H_{15}IN_2O_4$ (354.16) calc'd.: C 33.91; H 4.27; N 7.91%
found: C 34.10; H 4.33; N 8.02%

IR spectrum: υ_{max} 3355, 3182, 3137, 1727, and 1690br cm^{-1}. ^{1}H-NMR spectrum: δ 10.14 br (1H,s,3-NH), 6.21 (1H,t,1'-H; $J_{1',2'}$ 7.2 Hz), 5.3 (1H,d,3'-OH; $J_{OH,3'}$ 4.4 Hz), 4.39-3.80 (1H,m,3'-H), 3.80-2.98 (1H and 2H,m,4'-H and 6-H_2), 3.39 (2H,d, 5'-H_2; $J_{4',5'}$ 4.7 Hz), 2.98-1.75 (1H and 2H,m,5-H and 2'-H_2), 1.09 (3H,d,5-Me; $J_{Me,5}$ 6.5 Hz).

(5S)-5'-Deoxy-5'-iodo-3'-O-mesyl-5,6-dihydrothymidine (V)

a) To a suspension of (5S)-3',5'-dimesyloxy compound II (500 mg, 1.25 mmol) in 2-butanone (17 ml) NaI (515 mg, 3.44 mmol) was added. The mixture was refluxed for 2 h, and worked up as described for the preparation of (5S)-5'-iodo compound IV. The crystalline product V (355 mg, 66%) was subjected to TLC (in CH_2Cl_2-MeOH 20:1), R_F ca. 0.71, m.p. 119-121°C (from MeOH), $[\alpha]_D^{21.5} = -11.3°$ (c 0.75).

Anal. $C_{11}H_{17}IN_2O_6S$ (432.25) calc'd.: C 30.56; H 3.96; N 6.48%
found: C 30.78; H 4.23; N 6.72%

IR spectrum: υ_{max} 3334, 3032, 2975, 2936, 2882, 1722, and 1705br cm^{-1}. ^{1}H-NMR spectrum: δ 10.57 (1H,s,3-NH), 6.3 (1H,t,1'-H; $J_{1',2'}$ 7.4 Hz), 5.27-4.97 (1H,m,3'-H), 4.3-3.92 (1H,m,4'-H), 3.4 (3H,s,Ms-Me), 3.1-2.7 (2H,m,6-H_2), 1.15 (3H,d,5-Me; $J_{Me,5}$ 6.4 Hz).

b) The (5S)-5'-iodo compound IV (120 mg, 0.339 mmol) was disolved in dry pyridine (1 ml) under reflux. To the cooled (8 °C) solution mesyl chloride (0.057 ml, 0.73 mmol) was added, kept aside at 8°C for 16 h, and worked up following the standard procedure. The product V was purified by TLC (in CH_2Cl_2-MeOH 15:1), R_F ca. 0.71 (110 mg, 75.4%), m.p. 119-120°C (from MeOH) identical (mixed m.p., IR and ^{1}H-MNR spectra) to that obtained under a).

(5R,5S)-5'-O-Mesyl-2,3'-anhydro-5,6-dihydrothymidine (VI)

To a suspension of (5S)-3',5'-dimesyloxy compound II (450 mg, 1.124 mmol) in anhydrous MeOH (50 ml) methanolic 0.5 mol dm^{-3} NaOMe (2.25 ml, 1.125 mmol) was added and heated under reflux for 1 h. To the cooled solution silica gel (6.6 g) and EtOH (60 ml) were added to a neutral reaction, filtered, and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in Me_2CO (15 ml) and concentrated to a volume of 7.5 ml from which the product VI crystallized (152 mg, 44.5%), m.p. 178-180°C (from EtOH), R_F ca. 0.10, $[\alpha]_D^{24} = -57°$ (c 0.5, MeOH).

Anal. $C_{11}H_{16}N_2O_6S$ (304.32) calc'd.: C 43.41; H 5.30; N 9.21%
found: C 43.18; H 4.99; N 9.01%

UV spectrum: λ_{max} 244 nm (log ε 4.09). IR spectrum: υ_{max} 3430br, 3080, 2937, 2875, 1680, and 1562br cm^{-1}. ^{1}H-NMR spectrum: δ 5.5-5.34 (1H,m,1'-H), 5.34-5.32 (1H,m,3'-H), 4.65-4.18 (1H,m,4'-H), 4.39 (2H,d,5'-H_2; $J_{5',4'}$ 6.0 Hz), 3.65-3.08 (2H,m,6-H_2), 3.21 (3H,s,Ms-Me), 1.0 (3H,d,5-Me; $J_{Me,5}$ 6.7 Hz).

From the mother liquor two components (at R_F ca. 0.16 and 0.45) were separated by preparative TLC (in CH_2Cl_2-MeOH 20:1). The fraction, R_F ca. 0.16, was identified as (5R, 5S)-1-(2-deoxy-5-O-mesyl-β-D-threo-pentofuranosyl)-2-O--methyl-5,6-dihydrothymine (VII) (25.2 mg, 13.2%), m.p. 174-177 °C (from MeOH), $[\alpha]_D^{24} = -10.2°$ (c 0.98, DMSO).

Anal. $C_{12}H_{20}N_2O_7S$ (336.36) calc'd.: C 42.85; H 5.99; N 8.33%
found: C 42.58; H 5.91; N 7.94%

UV spectrum: λ_{max} 245 nm (log ε 4.08). IR spectrum: υ_{max} 3422br, 3252br, 2932, 1656, and 1547br cm^{-1}. ^{1}H-NMR spectrum: δ 5.98 (0.6H dxd,1'-H; $J_{1',2'a}$ 4.4 and $J_{1',2'b}$ 8.5 Hz), 6.07-5.85 (0.4H,m,1'-H), 5.41 (1H,d br.3'-OH; $J_{OH,3'}$ 3.1 Hz), 4.5-4.0 (1H,1H, and 2H,m,3'-H, 4'-H, and 5'-H_2), 3.8 (3H,s,OCH_3), 3.77 (1H,dxd br,6-H_a; $J_{a,b}$ 12.8 and $J_{a,5}$ 6.0 Hz), 3.17 (3H,s,Ms-Me), 2.09-1.88 (0.6 H,m,5-H), 1.88-1.67 (0.4H,m,5-H), 1.03 (3H,d br,5-Me; $J_{Me,5}$ 6.4 Hz).

The fraction, R_F ca. 0.45, m.p.70-71.5°C (from ether-n-hexane), was identified as (5R,5S)-1-(2-deoxy-3,5-anhydro-β-D-threo-pentofuranosyl-2-O-methyl-5,6-dihydrothymine (VIII) (15.4 mg, 5.7%), identical (m.p., IR and ^{1}H-NMR spectra) to that obtained from 3',5'-dimesyloxy compound II in reaction with two equivalents of NaOMe (*vide infra*).

(5R,5S)-1-(2-Deoxy-3,5-anhydro-β-D-threo-pentofuranosyl)--2-O-methyl-5,6-dihydrothymine (VIII)

A suspension of (5S)-3',5'-dimesyloxy derivative II (80.0 mg, 0.263 mmol) in anhydrous MeOH (8.8 ml) was treated with methanolic 0.5 mol dm^{-3} NaOMe (1.05 ml, 0.525 mmol) and heated under reflux for 3 h. The mixture was neutralized with silica gel (2 g) in EtOH (12 ml) and worked up as described for compound VI. Preparative TLC afforded the product VIII (44.0 mg, 69.6%), R_F ca. 0.45, m.p. 70-72°C (from ether-n-hexane), $[\alpha]_D^{24} = -19.5°$ (c 0.8, MeOH).

Anal. $C_{11}H_{16}N_2O_4$ (240.26) calc'd.: C 54.99; H 6.71; N 11.66%
found: C 55.41; H 7.05; N 11.25%

UV spectrum: λ_{max} 243 nm (log ε 4.04). IR spectrum: υ_{max} 3408br, 2985, 2938, 2873, 1690, 1680br, 1563, and 1545br cm^{-1}. ^{1}H-NMR spectrum: δ 6.53-6.2 (1H,m,1'--H), 5.41 (1H,dxd br,3'-H; $J_{3',2'}$ 3.6 and $J_{3',4'}$ 6.8 Hz), 4.74 (1H, dxd br,5'-H_b; $J_{b,a}$ 8.0 and $J_{b,4}$ 4.0 Hz), 4.31-4.03 (1H,m,4'-H), 3.98 (3H,s br, OMe), 3.85 (1H,dxd, 6-H_a; $J_{a,b}$ 11.8 and $J_{a,5}$; obscured by those of OMe), 3.4 (035H,dxd,6-H_b; $J_{b,a}$ 11.8 and $J_{b,5}$ 7.0 Hz), 3.27 (0.65H,dxd,6-H_b; $J_{b,a}$ 11.8 and $J_{b,5}$ 7.0 Hz), 2.84-2.21 (1 and 2H,m,5 -H and 2'-H_2), 1.27 (3H,d br, 5-Me; $J_{Me,5}$ 6.8 Hz).

(5R,5S)-1-(2-Deoxy-3,5-anhydro-β-D-threo-pentofuranosyl)--5,6-dihydrothymine (IX)

To a solution of (5R,5S)-1-(2-deoxy-3,5-anhydro-β-D-threo-pentofuranosyl)--2-O-methyl-5,6-dihydrothymine (VIII) (109 mg, 0.45 mmol) in Me_2CO (75. ml), HOAc (0.59 ml) was added. The mixture was heated in a sealed tube at 95°C for 24 h and then evaporated to dryness. The residue was dissolved in CH_2Cl_2 and subjected to preparative TLC (CH_2Cl_2-MeOH 25:1). The product IX, R_F ca. 0.47 (44.3 mg, 43.1%) was recrystallized from Me_2CO, m.p. 184-188°C (from Me_2CO), $[\alpha]_D^{26} = -35.2°$ (c 0.48, MeOH).

Anal. $C_{10}H_{14}N_2O_4$ (226.23) calc'd.: C 53.09; H 6.24; N 12.38%
found: C 52.99; H 6.15; N 12.12%

IR spectrum: υ_{max} 3201, 3089, 3001, 2936, 1719, and 1691br cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$): δ 8.2 (1H,s br,3-NH), 6.56 (0.55H,dxd,1'-H; $J_{1',2'a}$ 4.5 and $J_{1',2'b}$ Hz), 6.5 (0.45H, dxd,1'-H; $J_{1',2'a}$ 4.1 and $J_{1',2b}$ 8.1 Hz), 5.52-5.25 (1H,m,3'-H), 4.71 (1H,dxd,5'-H_b; $J_{b,a}$ 8.0 and $J_{b,4'}$ 4.0 Hz), 4.29-3.94 (1H,m,4'-H), 3.96 (0.55H,dxd,6-

-H_a; $J_{a,b}$ 12.0 and $J_{a,5}$ 5.8 Hz), 3.92 (0.45H,dxd,6-H_a; $J_{a,b}$ 12.0 and $J_{a,5}$ 5.6 Hz), 3.39 (0.55H,dxd,6-H_b; $J_{b,a}$ 12.0 and $J_{b,5}$ 8.0 Hz), 3.36 (0.45H,dxd,6-H_b; $J_{b,a}$ 12.0 and $J_{b,5}$ 9.8 Hz), 3.02-2.12 (3H,m,5-H and 2′-H_2), 1.31 (3H,d br, 5-Me; $J_{Me,5}$ 7.0 Hz).

(5S)-1-(2-Deoxy-3,5-anhydro-β-D-threo-pentofuranosyl)--5,6-dihydrothymine (IX)

To a solution of 1-(2-deoxy-3,5-anhydro-β-D-threo-pentofuranosyl)thymine[14] (X) (150 mg, 0.67 mmol) in H_2O (34 ml), 5% Rh/Al_2O_3 (42 mg) was added. The mixture was stirred under 0.35. MPa of H_2 at room temperature for 1.5 h. The catalyst was filtered off and the filtrate evaporated to dryness. Preparative TLC (in CH_2Cl_2-MeOH 25:1, three developments, elution with CH_2Cl_2) afforded the product IX (110 mg, 79.9%), mainly as (5S)-diastereoisomer, $[\alpha]_D^{25} = -54°$ (c 1, MeOH). The ^{1}H-NMR signals, comparable to those of (5R,5S) mixture IX, showed intensities in a ratio of 80:20. ^{13}C-NMR spectrum ($CDCl_3$): δ 172.6 (C-4), *153.3*/152.9 (C-2), 88.7 (C-4′), 86.6 (C-1′), *78.8*/78.5 (C-3′), 75.1 (C-5′), *42*/42.2 (C-6), *36.1*/36.6 (C-2′), 35.3 (C-5), *12.5*/12.8 (Me-5). The bands in italics appeared in a 85% proportion.

Cleavage of (5S)- IX into (-)-(5S)-5,6-Dihydrothymine (XI)

To a suspension of (85% 5S)-1-(3,5-anhydro-β-D-threo-pentofuranosyl)-5,6--dihydrothymine (IX) (36 mg, 0.15 mmol) in H_2O (3.5 ml) conc. HCl solution (0.25 ml) was added. The mixture was heated at 100 °C for 1 h, then diluted with H_2O (1 ml) and neutralized with Ag_2CO_3. A precipitate was filtered off and the excess Ag ion removed from the filtrate by precipitation with H_2S and filtration through a short Celite column. From the filtrate the product separated (7.0 mg, 61%), m.p. 259—261 °C (from MeOH), $[\alpha]_D^{22} = -10°$ (c 1, pyridine), Lit.[10]: m.p. 261—262 °C, $[\alpha]_D^{23} = -11.3°$ (c 0.49, pyridine).

(5S)-3′-Deoxy-5,6-dihydrothymidine (XIII)

To a solution of 3′-deoxythymidine[20] (XII) 226 mg, 1 mmol) in 50% MeOH (30 ml), 5% Rh/Al_2O_3 (80 mg) was added. The mixture was stirred under 0.3 MPa of H_2 at room temperature for 24 h. The catalyst was filtered off and the filtrate evaporated to dryness. Preparative TLC (CH_2Cl_2-MeOH (10 : 1) afforded the product XIII (200 mg, 88%), R_F ca. 0.35, which crystallized from CH_2Cl_2-Et_2O, m.p. 122—124 °C, $[\alpha]_D^{22} = -38°$ (c 1.5).

Anal. $C_{10}H_{16}N_2O_4$ (228.25) calc'd.: C 52.62; H 7.07; N 12.28%
found: C 52.41; H 6.88; N 12.37%

IR spectrum: ν_{max} 3346br, 3246br, 3100br, 2984, 2941, 2871, 1707br, 1691br and 1675 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$): δ 8.46 (1H,s br,3-NH), 6.24—6.05 (1H,m,1′-H), 4.14—3.89 (1H,m,4′-H), 3.85—3.55 (2H,m,5′-H_2), 3.41 (1H,dxd,6-H_a; $J_{a,b}$ 12.0 and $J_{a,5}$ 5.9 Hz), 3.19 (1H,dxd,6-H_b; $J_{b,a}$ 12.0 and $J_{b,5}$ 9.5 Hz), 2.71 (1H,dxdxd,5,H; $J_{5,6b}$ 9.5, $J_{5,6a}$ 5.9 and $J_{5,Me}$ 6.8 Hz), 2.32—1.75 (2H and 2H,m,2′-H_2 and 3′-H_2), 1.27 (3H,d,5-Me; $J_{Me,5}$ 6.8 Hz). ^{13}C-NMR spectrum: δ 173.1 (C-4), *153.2*/152.8 (C-2), 84.9 (C-4′), 79.3 (C-1′), 64.4 (C-5′), 42.8 (C-6), *35.4*/35.2 (C-5), *28.7*/28.3 (C-2′), 26.5 (C-3′), *12.9*/12.6 (Me-5). The bands in italics appeared in a 80% proportion.

A sample of (5S)- XIII (50 mg, 0.22 mmol) was dissolved in MeOH (3 ml) and treated with methanolic 0.1 mol dm^{-3} NaOMe (2 ml). The mixture was heated under reflux for 15 min, neutralized with 50% HOAc, and then evaporated to dryness under reduced pressure. Preparative TLC (in CH_2Cl_2-MeOH 10 : 1) afforded the product as a mixture of (5R)- and (5S)-diastereoisomers XIII (40 mg, 80%), m.p. 116—122 °C (from CH_2Cl_2-Et_2O), $[\alpha]_D^{28} = -4°$ (c 1,MeOH). The ^{1}H-NMR spectrum showed difference in the Me-(5) region, exhibiting two sets of bands at δ 1.26 (0.45 H,d; $J_{Me,5}$ 6.8 Hz) and at 1.25 (0.55 H,d; $J_{Me,5}$ 6,8 Hz).

(5S)-5'-O-Acetyl-3'-deoxy-5,6-dihydrothymidine (XV)

To a solution of 5'-O-acetyl-3'-deoxy-thymidine[20] (XIV) (173 mg, 0.65 mmol) in MeOH (10 ml) and water (30 ml) 5% Rh/Al_2O_3 (62 mg) was aded, hydrogenated under 0.3 MPa of H_2, and worked up as desribed for compound XIII. It afforded the product XV (160 mg, 92%, R_F ca. 0.32 (CH_2Cl_2-MeOH 20:1), m.p. 110—111°C (from EtOH-Et_2O), $[\alpha]_D^{27}$ = -33° (c, 1, MeOH).

Anal. $C_{12}H_{18}N_2O_5$ (270.28) calc'd.: C 53,32; H 6.71; N 10.37%
found: C 53,31; H 6.69; N 10.29%

IR spectrum: ν_{max} 3440br, 3275, 3224, 3110, 2980, 2941, 1738, 1727, 1711, and 1690 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$): δ 8.22 (1H,s br,3-NH), 6.28—6.09 (1H,m,1'-H), 4.30—4.07 (3H,m,4'-H and 5'-H_2), 3.39 (1H,dxd,6-H_a; $J_{a,b}$ 12.5 and $J_{a,5}$ 6.3 Hz), 3.18 (1H,dxd,6-H_b; $J_{b,a}$ 12.5 and $J_{b,5}$ 8.9 Hz), 2.81—2.51 (1H,m,5-H), 2.1 (3H,s,COMe), 2.36—1.56 (4H,m,2'-H_2 and 3'-H_2), 1.28 (3H,d,5-Me; $J_{Me,5}$ 7.07 Hz). ^{13}C-NMR spectrum: δ 173.0 (C-4), 170.7 (CO-Ac), *153.2*/152.8 (C-2), *84.5*/85.3 (C-4'), 76.1/77.1 (C-1'), *65.8*/66.4 (C-5'), 42.2 (C-6), 35.2 (C-5), *28.3*/27.7 (C-2'), *27.0*/27.4 (C-3'), 20.8 (Me-Ac), *13.0*/12.5 (Me-5). The bands in italics appeared in a 93% proportion. The weaker bands disappeared after the sample had been recrystallized 3 times from EtOH-Et_2O.

Cleavage of (5S)- XV into (-)-(5S)-5,6-Dihydrothymine (XI)

A suspension of recrystallized XV in water (8 ml) was treated with conc. HCl solution (0.55 ml) at 100 °C for 1 h, and worked up as for cleavage of compound IX. The crystalline product XI was obtained in 64% (28 mg) yield, m.p. 256—260 °C, $[\alpha]_D^{26}$ = -12° (c 0.5, pyridine), Lit.[10]: $[\alpha]_D^{23}$ = -11.3° (c 0.49, pyridine).

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SAŽETAK

Stereoselektivne transformacije timidina

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Stereoselektivna hidriranja timidina, 3,'5'-anhidro- X i 3 -deoksi- XII timidina, uz 5% Rh/Al_2O_3 kao katalizator, daju odgovarajuće derivate (5S)-5,6--dihidrotimidina I, IX, i XIII. Tijek transformacija potvrđen je ^1H- i ^{13}C-NMR analizama i cijepanjima njihovih *N*-glikozidnih veza do (-)-(S)-5,6-dihidrotimina. Regioselektivne sinteze konfiguracijski definiranih (5S)-5'-O-tosil- (III) i (5S)-5'-deoksi-5'-iodo (IV) 5,6-dihidrotimidina također su opisane.

Intramolekulska ciklizacija (5S)-3',5'-dimesiloksi-5,6-dihidrotimidina (II) s pomoću NaOMe daje (5R,5S)-5,-O-mesil-2,3'-anhidro-5,6-dihidrotimidina (VI), koji istovremeno prelazi u (5R,5S)-1-(2-deoksi-5-O-mesil-β-D-treo-pentofuranozil)-2-O-metil-5,6-dihidrotimin (VII) i konačno u (5R,5S)-1-(2-deoksi-3,5-anhidro-β-D-treo-pentofuranozil)-2-O-metil-5,6-dihidrotimin (VIII).