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Synthesis of 4′-aryl-2′,3′-dideoxynucleoside analogues

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ABSTRACT

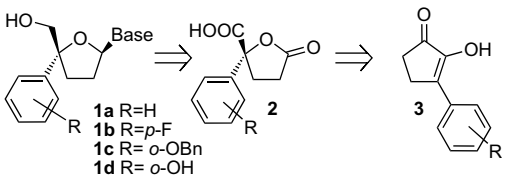
A series of 4′-aryl-2′,3′-dideoxynucleoside analogues were synthesized from optically pure 5-oxo-2-aryl-tetrahydrofuran-2-carboxylic acids up to 62% overall yield. 5-Oxo-2-aryl-tetrahydrofuran-2-carboxylic acids were obtained from 2-hydroxy-3-arylcyclopent-2-en-1-ones by asymmetric oxidation in up to 38–57% yield.

1. Introduction

Many therapeutic agents against AIDS and cancer have the structure of modified nucleosides.[1] One of the possibilities to modify the sugar ring is to introduce substituents to the position 4′.[2] Some of these 4′-substituted compounds have found to be effective against HIV-drug resistant reverse transcriptase variants.[3] On the other hand, many natural aryl-substituted tetrahydrofurans possess pharmacological activity.[4a–c] Also, certain α-methylene-γ-(4-substituted phenyl)-γ-butyrolactones bearing thymine, uracil and 5-bromouracil have anticancer activity,[4d,e] and phenyl-substituted γ-lactone acids and their derivatives act on the central nervous system.[4f–h]

Recently we published the synthesis of optically active 3-aryl-substituted γ-lactone acids from 3-aryl-2-hydroxy-2-cyclopenten-1-ones.[5]

In the present work we describe a stereoselective preparation of 4′-aryl-2′,3′-dideoxynucleoside analogues from 3-aryl-substituted γ-lactone acids, using the method, which has been developed for the synthesis of optically active 4′-benzyl-substituted nucleoside analogues[6] (Scheme 1). Introduction of the bulky phenyl or substituted phenyl substituents in the position 4′ changes the hydrophobic properties of the nucleoside analogue and also its steric accession to the enzyme active site. On the other hand, the electron donor/acceptor properties of different substituents in the phenyl ring change the electron density in the sugar ring, which may also influence the biological activity of the compound.



Scheme 1. Retrosynthetic route to 4′-aryl-2′,3′-dideoxynucleoside analogues.

2. Results and discussion

In the preparation of 4′-aryl-2′,3′-dideoxynucleoside analogues **1** with phenyl, *p*-*F*-phenyl and *o*-BnO-phenyl groups in the 4′ position, γ-lactone acids **2a–c** serve as key intermediates. The preparation of compounds **2a** and **2b** by the asymmetric oxidation of 2-hydroxy-3-arylcyclopent-2-en-1-ones **3a** and **3b** is described by us earlier.[5] To synthesize **2c**, the starting enone **3c** was prepared according to the literature procedure from the corresponding benzaldehyde in 21% overall yield.[7] Compound **3c** was subjected to asymmetric oxidation, analogously to that of **3a** and **3b**, resulting in the corresponding γ-lactone acid **2c** in 57% yield and 81% ee (Table 1).

The yield of **2c** was higher, however, the enantiomeric purity was slightly lower than that for lactone acids **2a** and **2b** (Table 1). The enantiomeric purity of initial γ-lactone acids **2a–c** was increased to ≥99% ee by a simple re-crystallisation from petroleum ether–ethyl acetate. 5-Oxo-2-aryl-tetrahydrofuran-2-carboxylic acids **2a–c** were transformed to 4′-aryl-2′,3′-dideoxynucleoside analogues **1a–c** in the reaction sequence presented in Scheme 2.

The reduction of the carboxylic group of γ-lactone acids **2a–c** was accomplished using a borane complex in dimethylsulfide.[8] In the case of unsubstituted phenyl and *p*-*F*-phenyl derivatives, the corresponding lactone alcohols **4a**,**b** were prepared in 84–86% yield. In the case of *o*-BnO-Ph-derivative **2c** the yield of lactone alcohol **4c** was only 12%, together with 61% of unreacted starting compound. The steric hindrance of the bulky *ortho*-benzyloxy substituent may be the reason why the reduction of the carboxylic acid requires higher temperature. The reaction at 50 °C for 30 min results in lactone alcohol **4c** with 44% yield. However, at the same

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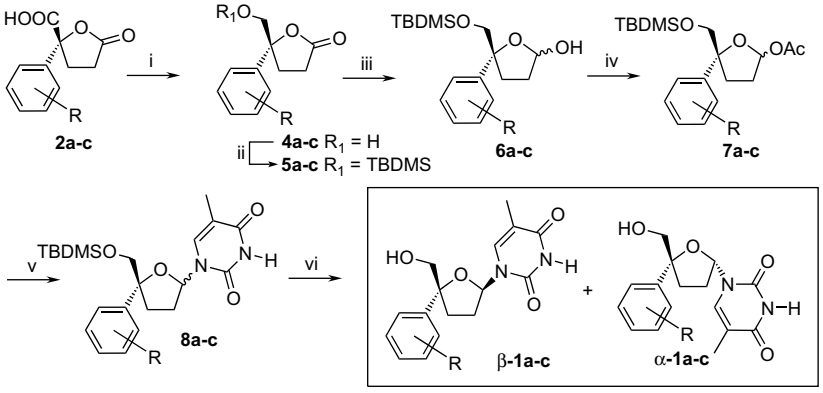
Table 1
Synthesis of 4′-aryl-2′,3′-dideoxynucleoside analogues

Entry	Substrate	Substituent R	Yield % (ratio 2*R*/2*S*)						
			2 [ee%]	**4**	**5**	**6**	**7**	**8**	**β-1+α-1**
1	a	Ph	38 [86][5]	86	100	92 (3.8:1.0)	90 (3.8:1.0)	87 (1.0:1.0)	100
2	b	*p*-F-Ph	43 [86][5]	84	93	93 (4.0:1.0)[a]	81 (3.1:1.0)	100 (1.0:1.1)	78
3	c	*o*-BnO-Ph	57 [81]	44	78	88 (2.6:1.0)	67 (1.7:1.0)	91 (1.3:1.0)	100

[a] In the initial solution of **6b** the ratio of 2*R*/2*S*=1.0:1.3, after 12 h the ratio changed to 4.0:1.0.



Scheme 2. Synthesis of 4′-aryl-2′,3′-dideoxynucleoside analogues **1**. Reagents: (i) $BH_3{\cdot}SMe_2$/THF, (ii) TBDMSCl, imidazole/CH_2Cl_2, (iii) DIBAH/toluene, (iv) $Ac_2O/Et_3N/CH_2Cl_2$, (v) thymine, BSA, TMSOTf/CH_3CN, (vi) TBAF/THF.

time, the formation of a considerable amount (33%) of lactone-reduced product, dihydroxy acid **9c**, was observed. Under the acidic conditions this compound lactonizes affording δ-lactone **10c** in 50% yield (Scheme 3).

The hydroxyl group in **4c** was protected with a TBDMS group using TBDMSCl and imidazole in CH_2Cl_2[9] and compounds **5a–c** were reduced with DIBAH at −78 °C. A mixture of anomeric lactols **6a–c** was obtained in 88–93% yield (the ratio of 2*R*/2*S* diastereomers for compounds **6a–c** according to ^{1}H NMR spectra from CH_2–OSi– group is given in Table 1). In the case of the large *ortho*-benzyloxy-substituted phenyl derivative **6c**, the 2*R*/2*S* ratio was 1.2:1.0, while in the case of the unsubstituted phenyl derivative **6a** the ratio was 3.8:1.0 and for the *para*-fluorophenyl derivative **6b** even 1.0:1.3, which changed after 12 h to 4.0:1.0 (Scheme 2; Table 1).

The acetylation of lactols **6a–c** was performed using acetic anhydride and triethylamine in CH_2Cl_2 to afford the corresponding acetates **7a–c** in 67–92% yield (Scheme 2; Table 1).

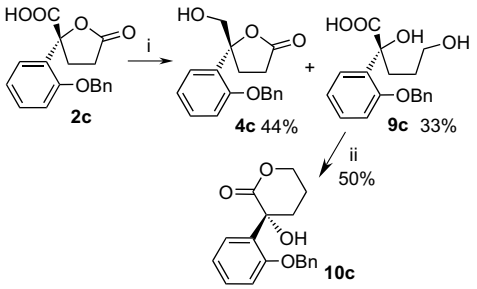
The base was introduced to acetates **7a–c** by coupling with thymine, using *N*,*O*-bis(trimethylsilyl)-acetamide (BSA) and trimethylsilyltriflate (TMSOTf) as Lewis acids,[9] resulting in the silylated nucleoside analogues **8a–c** in 87–100% yield as a mixture β- and α-anomers. The ratio of nucleoside anomers depends on the substituents in the ribose ring.[10,11] In the case of nucleoside analogues **8a–c**, which do not bear substituents in positions 2′ and 3′, the difference in 2*R*/2*S* ratio (position 1′ according to the numeration of nucleosides and position 2 according to that of substituted furans) is caused by the substituents in the position 4′ of ribose. The highest 2*R*/2*S* ratio was observed for *ortho*-benzyloxy-substituted nucleoside analogue **8c** (2*R*/2*S*=1.3:1.0; Table 1).

The last step—the removal of the protective silyl group with tetrabutylammonium fluoride (TBAF),[9] afforded nucleoside analogues **α-1a–c** and **β-1a–c** as a mixture of anomers, in 78–100% overall yield. The β- and α-anomers were separated by column chromatography, affording separately β-anomers **β-1a**,**b** and α-anomers **α-1a**,**b** at an approximately 1:1 ratio. In the case of **β-1c** and **α-1c** the ratio was 1.3:1.0 (Scheme 2).

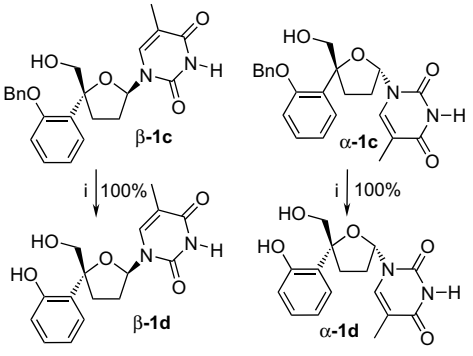
The benzyl group of compounds **β-1c** and **α-1c** was removed, using H_2 on Pd/C to give the nucleoside analogues **β-1d** and **α-1d** in quantitative yield (Scheme 4).

3. Conclusion

The asymmetric oxidation of 2-hydroxy-3-arylcyclopent-2-en-1-ones offers a simple route to both enantiomers of 5-oxo-2-aryl-



Scheme 3. Reduction of γ-lactone acid **2c** by a borane complex. Reagents: (i) $BH_3{\cdot}Me_2S$/THF, (ii) HCl/CH_2Cl_2.



Scheme 4. Synthesis of 4′-(2-hydroxyphenyl)-2′,3′-dideoxythymidines **1d**, where (i) H_2, 10%Pd/C/MeOH.

tetrahydrofuran-2-carboxylic acids, suitable key intermediates for the preparation of the analogues of 4′-aryl-2′,3′-dideoxynucleosides. The usefulness of the approach is demonstrated by the synthesis of eight new optically active 4′-aryl nucleoside analogues whose antiviral and anticancer properties are currently under study.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded using deuterated solvents ($CDCl_3$, δ 7.27 ppm and 77.00 ppm, CD_3OD, δ 3.30 ppm and 49.00 ppm, or DMSO-d_6, δ 2.50 ppm and 39.50 ppm) on a Bruker AMX-500 spectrometer. 2D FT methods were used for the full assignment of ^{1}H and ^{13}C chemical shifts. Mass spectra were determined on a Hitachi M80B spectrometer using the EI (70 eV) mode. Elemental analyses were performed on a Perkin–Elmer C, H, N, S-Analyzer 2400. Optical rotations were measured using an A. Krüss Optronic GmbH polarimeer P 3002. The enantiomeric purity of compounds was determined using a Daicel Chiracel ODH chiral column. IR spectra were recorded on a Perkin–Elmer Spectrum BX FTIR spectrometer. TLC analysis was performed using DC-Alufolien Kieselgel 60 F254 (Merck) plates. For column chromatography Merck Silica gel 60 (0.063–0.200 mm) was used. The reagents were purchased from Aldrich and used without purification. CH_2Cl_2 and CH_3CN were distilled from CaH_2 before use. THF was distilled from $LiAlH_4$ before use. The petroleum ether fraction (bp 40–60 °C) was used.

4.2. 2-Hydroxy-3-(2-benzyloxyphenyl)-cyclopent-2-en-1-one 3c

Acetic acid 5-(2-benzyloxyphenyl)-2,5-dioxopentyl ester (9.05 g, 66%) was prepared from 2-benzyloxyphenylbenzaldehyde (8.48 g, 40.0 mmol) and 1-acetoxy-3-buten-2-one (8.7 g, 68.0 mmol) according to the literature[7] as colourless crystals.

The title compound **3c** (2.28 g, 31%) was prepared from acetic acid 5-(2-benzyloxyphenyl)-2,5-dioxopentyl ester (8.93 g, 26.3 mmol) according to the method described in Ref. 5 as colourless crystals; mp=138–140 °C; IR (KBr): 3277, 3033, 2958, 1683, 1634, 1597, 1488, 1451, 1387, 1286, 1224, 1116, 1018, 753, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, J=1.6 and 7.7 Hz, 1H, Ph H-6), 7.38 (m, 4H, *o*,*m*-Bn), 7.35 (m, 2H, *p*-Bn and Ph H-4), 7.09 (m, 1H, Ph H-5), 7.08 (m, 1H, Ph H-3), 6.81 (s, 1H, OH), 5.16 (s, 2H, CH_2-Ph), 2.92 (m, 2H, H-4), 2.51 (m, 2H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7 (C-1), 155.8 (Ph C-2), 148.8 (C-2), 138.2 (C-3), 135.7 (*s*-Bn), 130.4 (Ph C-4), 129.6 (Ph C-6), 128.7 (*m*-Bn), 128.4 (*p*-Bn), 127.8 (*o*-Bn), 124.4 (Ph C-1), 121.9 (Ph C-5), 114.0 (Ph C-3), 71.9 (CH_2–Ph), 32.0 (C-5), 25.6 (C-4); MS (EI): *m*/*z* (%)=280 (4.08, M$^+$), 224 (0.50), 210 (0.66), 165 (0.10), 147 (0.74), 131 (0.93), 119 (2.51), 105 (1.61), 91 (100, Bn$^+$). Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.84; H, 5.73.

4.3. (*R*)-5-Oxo-2-(2-benzyloxyphenyl)-tetrahydrofuran-2-carboxylic acid 2c

Compound **2c** (2.99 g, 57%) was prepared from 2-hydroxy-3-(2-benzyloxyphenyl)-cyclopent-2-en-1-one (4.71 g, 16.8 mmol) **3c** according to the general procedure described in Ref. 5 as white powder; mp=44–47 °C; $[\alpha]_D^{25}$ +67.7 (*c* 1.73, MeOH); ee=81%; IR (KBr): 3036, 2950, 2627, 1785, 1748, 1602, 1492, 1453, 1382, 1224, 1175, 1045, 997, 906, 755, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (br s, 1H, COOH), 7.52 (d, J=7.6 Hz, 1H, Ph H-6), 7.32 (m, 6H, *o*,*m*,*p*-Bn, Ph H-4), 7.03 (t, J=7.6 Hz, 1H, Ph H-5), 6.96 (d, J=8.1 Hz, 1H, Ph H-3), 5.03 and 4.99 (both d, J=11.7 Hz, 2H, CH_2–Ph), 3.16 (ddd, J=4.4, 9.5 and 14.0 Hz, 1H, H-3), 2.78 (ddd, J=9.2, 9.5 and 17.5 Hz, 1H, H-4), 2.52 (ddd, J=4.4, 9.6 and 17.5 Hz, H-4), 2.38 (ddd, J=9.2, 9.6 and 14.0 Hz, 1H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9 (C-5), 173.8 (COOH), 154.9 (Ph C-2), 136.0 (*s*-Bn), 130.0 (Ph C-4), 128.5 (*m*-Bn),128.1 (*p*-Bn), 127.3 (Ph C-1), 127.2 (*o*-Bn), 125.2 (Ph C-6), 120.9 (Ph C-5), 112.1 (Ph C-3), 86.0 (C-2), 70.4 (CH_2-Ph), 31.2 (C-3), 28.0 (C-4); MS (EI): *m*/*z* (%)=312 (0.99, M$^+$), 294 (0.02), 267 (0.25), 249 (0.05), 224 (0.04), 207 (0.08), 188 (0.06), 178 (1.53), 149 (0.78), 131 (0.81), 121 (5.14), 91 (100, Bn$^+$). Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.29; H, 5.17.

4.4. (*R*)-5-Phenyl-5-hydroxymethyl-dihydro-furan-2(3*H*)-one 4a

Compound **4a** (1.33 g, 86%) was obtained from **2a** (1.66 g, 8.07 mmol) according to the procedure described in Ref. 8 as white crystals; mp=112–114 °C; $[\alpha]_D^{23}$ +62.9 (*c* 3.03, $CHCl_3$); IR (KBr): 3412, 3036, 2924, 1737, 1494, 1451, 1213, 1072, 1006, 764, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 4H, *o*-Ph, *m*-Ph), 7.33 (m, 1H, *p*-Ph), 3.90 (dd, J=5.4 and 12.4 Hz, 1H, CH_2O), 3.73 (dd, J=8.0 and 12.4 Hz, 1H, CH_2O), 3.33 (dd, J=5.4 and 8.0 Hz, 1H, OH), 2.85 (m, 1H, H-4), 2.80 (m, 1H, H-3), 2.52 (m, 1H, H-3), 2.38 (m, 1H, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3 (C-2), 140.6 (*s*-Ph), 128.6 (*m*-Ph), 128.0 (*p*-Ph), 124.7 (*o*-Ph), 89.7 (C-5), 69.2 (CH_2OH), 30.3 (C-4), 29.2 (C-3); MS (EI): *m*/*z* (%)=161 (100.0, M−CH_2OH), 133 (20.6), 115 (26.1), 105 (89.8), 91 (13.7), 77 (57.2). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.67; H, 6.22.

4.5. (*R*)-5-(4-Fluorophenyl)-5-hydroxymethyl-dihydro-furan-2(3*H*)-one 4b

Compound **4b** (1.29 g, 84%) was obtained from **2b** (1.64 g, 7.34 mmol) according to the procedure described in Ref. 8 as white crystals; mp=79–80 °C; $[\alpha]_D^{23}$ +48.7 (*c* 3.01, $CHCl_3$); IR (KBr): 3424, 3045, 2947, 1749, 1614, 1602, 1516, 1454, 1212, 1078, 1009, 830 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, J=5.4 and 8.0 Hz, 2H, Ph H-2,6), 7.06 (dd, J=8.0 and 9.0 Hz, 2H, Ph H-3,5), 3.84 and 3.70 (both d, J=12.4 Hz, 2H, CH_2–O), 3.29 (br s, 1H, OH), 2.83 and 2.79 (m, 2H, H-3), 2.52 and 2.34 (m, 2H, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1 (C-2), 162.4 (d, J_{CF}=247.1 Hz, Ph C-4), 136.4 (d, J_{CF}=2.6 Hz, Ph C-1), 126.6 (d, J_{CF}=8.1 Hz, Ph C-2,6), 115.5 (d, J_{CF}=21.6 Hz, Ph C-3,5), 89.2 (C-5), 69.3 (CH_2O), 30.3 (C-4), 29.2 (C-3); MS (EI): *m*/*z* (%)=210 (0.95, M$^+$), 179 (88.1), 151 (17.5), 133 (13.2), 123 (100.0), 109 (15.6), 95 (42.2), 75 (17.4). Anal. Calcd for $C_{11}H_{11}FO_3$: C, 62.85; H, 5.27. Found: C, 62.86; H, 5.22.

4.6. (*R*)-5-(2-Benzyloxyphenyl)-5-hydroxymethyl-dihydro-furan-2(3*H*)-one 4c

To a solution of **2c** (2.50 g, 8.0 mmol) in THF (6.0 mL) at 0 °C $BH_3 \cdot Me_2S$ complex in THF (1.23 mL, 11.2 mmol) was added dropwise over a period of 8 min. The reaction mixture was stirred at room temperature for 2 h and then heated at 50 °C for 30 min. After cooling, the reaction mixture was treated with methanol (3.0 mL). The mixture was concentrated in vacuum and purified by column chromatography (petroleum ether/acetone=10:1 to 10:3) affording compounds **4c** and **9c**.

Compound **4c** (1.05 g, 44%) was obtained as white crystals; mp=95–97 °C; $[\alpha]_D^{24}$ +76.6 (*c* 3.01, $CHCl_3$); IR (KBr): 3410, 3032, 2941, 2920, 1733, 1600, 1584, 1492, 1445, 1222, 1086, 998, 770, 740, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, J=1.7, 7.7 Hz, 1H, Ph H-6), 7.41 (m, 4H, *o*,*m*-Bn), 7.37 (m, 1H, *p*-Bn), 7.31 (ddd, J=1.7, 7.7 and 8.3 Hz, 1H, Ph H-4), 7.01 (m, 1H, Ph H-3), 7.00 (m, 1H, Ph H-5), 5.12 and 5.10 (both d, J=11.5 Hz, 2H, CH_2-Ph), 4.10 and 3.91 (both d, J=12.2 Hz, 2H, CH_2O), 2.66 (br s, 1H, OH), 2.78 and 2.50 (m, 2H, H-3), 2.69 and 2.47 (m, 2H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4 (C-1), 154.5 (Ph C-2), 136.2 (*s*-Bn), 129.4 (Ph C-4), 128.7 (Ph C-1 and *m*-Bn),

128.2 (*p*-Bn), 127.4 (*o*-Bn), 126.6 (Ph C-6), 121.0 (Ph C-5), 112.2 (Ph C-3), 89.6 (C-4), 70.3 (CH_2-Ph), 67.1 (CH_2OH), 29.5 (C-3), 29.2 (C-2); MS (EI): *m*/*z* (%)=298 (0.89, M^+), 281 (0.36), 267 (7.5), 249 (0.89), 221 (0.66), 207 (2.2), 189 (2.8), 177 (10.0), 161 (2.0), 147 (2.1), 131 (1.7), 121 (6.8), 105 (1.2), 91 (100.0, Bn^+). Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.25; H, 6.06.

4.7. (*R*)-3-(2-Benzyloxy-phenyl)-3-hydroxy-tetrahydro-*2H*-pyran-2-one 10c

Compound **10c** (0.393 g, 50%) was obtained as white crystals from **9c** (0.834 g, 2.64 mmol); mp=150–151 °C; $[\alpha]_D^{25}$ +121.3 (*c* 3.00, $CHCl_3$); IR (KBr): 3424, 3323, 3029, 2969, 2940, 1702, 1601, 1588, 1483, 1450, 1403, 1280, 1225, 1074, 1014, 964, 753, 732, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J*=1.7 and 7.8 Hz, 1H, Ph H-6), 7.47 (m, 2H, *o*-Bn), 7.42 (m, 2H, *m*-Bn), 7.39 (m, 1H, *p*-Bn), 7.30 (dt, *J*=1.7 and 2×7.8 Hz, 1H, Ph H-4), 7.05 (dt, *J*=1.0 and 2×7.8 Hz, 1H, Ph H-5), 6.98 (dd, *J*=1.0 and 7.8 Hz, 1H, Ph H-3), 5.05 (s, 2H, Ph-CH_2), 4.16 (m, 1H, H-6eq), 3.72 (m, 1H, H-6ax), 2.95 (s, 1H, OH), 2.15 (m, 2H, H-4 and H-5), 2.01 (m, 1H, H-4), 1.60 (m, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0 (C-2), 153.9 (Ph C-2), 135.8 (*s*-Bn), 133.2 (Ph C-1), 129.0 (Ph C-4), 128.6 (*o*-Bn), 128.5 (*m*-Bn), 128.4 (*p*-Bn), 125.1 (C-6), 121.1 (Ph C-5), 111.7 (Ph C-3), 73.7 (C-3), 70.8 (CH_2–Ph), 69.9 (C-6), 34.7 (C-4), 20.4 (C-5); MS (EI): *m*/*z* (%)=298 (1.2, M^+), 280 (0.05), 270 (0.28), 252 (0.70), 226 (0.90), 207 (1.3), 192 (2.7), 174 (0.95), 163 (17.5), 146 (1.1), 136 (1.7), 121 (27.8), 107 (2.3), 91 (100.0). Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.23; H, 6.06.

4.8. Typical procedure for preparation of 5a–c

To a solution of **4a–c** (3.0 mmol) and imidazole (0.274 g, 4.03 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C TBDMSCl (0.552 g, 3.66 mmol) was added. Stirring was continued at 0 °C for 15 min and then for 2 h at room temperature. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (4×20 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuum. The residue was purified by column chromatography (petroleum ether/acetone=30:1) to give compounds **5a–c**.

*4.8.1. (R)-5-Phenyl-5-(tert-butyl-dimethyl-silyloxymethyl)-dihydro-furan-2(3H)-one **5a***

Compound **5a** (0.933 g, 100%) was obtained as white crystals; mp=60–61 °C; $[\alpha]_D^{23}$ +25.2 (*c* 2.01, $CHCl_3$); IR (KBr): 3034, 2951, 2931, 2859, 1771, 1604, 1499, 1464, 1252, 1215, 1101, 1012, 842, 777, 766, 704 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 7.38 (m, 4H, *o*-Ph and *m*-Ph), 7.33 (m, 1H, *p*-Ph), 3.77 and 3.72 (2d, *J*=10.9 Hz, 2H, OCH_2), 2.83 and 2.36 (2m, 2H, H-4), 2.82 and 2.51 (2m, 2H, H-3), 0.90 (s, 9H, $(CH_3)_3C$–Si), 0.06 and 0.05 (2s, 6H, $(CH_3)_2$–Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7 (C-2), 141.1 (*s*), 128.4 (*m*), 128.0 (*p*), 124.9 (*o*), 89.0 (C-5), 70.9 (CH_2O), 30.8 (C-4), 29.7 (C-3), 25.8 ($(CH_3)_3C$–Si), 18.2 ($(CH_3)_3C$–Si), −5.6 and −5.7 ($(CH_3)_2$–Si); MS (EI): *m*/*z* (%)=291 (0.58, M^+-CH_3), 276 (2.0), 249 (56.4), 231 (3.3), 221 (3.4), 207 (8.4), 189 (0.82), 175 (1.5), 161 (23.5), 145 (3.8), 129 (12.8), 115 (9.3), 105 (15.8), 89 (12.3), 75 (100.0). Anal. Calcd for $C_{17}H_{26}SiO_3$: C, 66.62; H, 8.55. Found: C, 66.60; H, 8.62.

*4.8.2. (R)-5-(4-Fluorophenyl)-5-(tert-butyl-dimethyl-silyloxymethyl)-dihydro-furan-2(3H)-one **5b***

Compound **5b** (0.904 g, 93%) was obtained as white crystals; mp=77–81 °C; $[\alpha]_D^{23}$ +20.3 (*c* 1.01, $CHCl_3$); IR (KBr): 3047, 2955, 2931, 2859, 1766, 1602, 1512, 1472, 1464, 1255, 1214, 1114, 1010, 837, 781 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 7.37 (dd, *J*=5.2 and 8.8 Hz, 2H, Ph H-2,6), 7.06 (t, *J*=2×8.8 Hz, 2H, Ph H-3,5), 3.73 and 3.67 (2d, *J*=11.0 Hz, 2H, OCH_2), 2.81 and 2.32 (2m, 2H, H-4), 2.79 and 2.51 (2m, 2H, H-3), 0.90 (s, 9H, $(CH_3)_3C$–Si), 0.05 and 0.04 (2s, 6H, $(CH_3)_2$–Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5 (C-2), 162.3 (d, J_{CF}=247.0 Hz, Ph C-4), 137.0 (d, J_{CF}=3.0 Hz, Ph C-1), 126.7 (d, J_{CF}=8.1 Hz, Ph C-2,6), 115.3 (d, J_{CF}=21.4 Hz, Ph C-3,5), 88.5 (C-5), 70.8 (CH_2O), 30.8 (C-4), 29.6 (C-3), 25.7 ($(CH_3)_3C$–Si), 18.2 ($(CH_3)_3C$–Si), −5.6 and −5.8 ($(CH_3)_2$–Si); MS (EI): *m*/*z* (%)=325 (0.11, M^++1), 309 (1.0), 299 (0.55), 281 (1.9), 267 (48.8), 253 (0.44), 239 (4.6), 225 (9.7), 207 (2.2), 193 (2.8), 179 (18.2), 165 (4.6), 147 (8.9), 129 (5.8), 123 (19.0), 109 (18.1), 89 (19.9), 75 (100.0). Anal. Calcd for $C_{17}H_{25}FO_3Si$: C, 62.93; H, 7.77. Found: C, 62.86; H, 7.78.

*4.8.3. (R)-5-(2-Benzyloxyphenyl)-5-(tert-butyl-dimethyl-silyloxymethyl)-dihydro-furan-2(3H)-one **5c***

Compound **5c** (0.964 g, 78%) was obtained as a colourless syrup; $[\alpha]_D^{25}$ +35.4 (*c* 1.01, $CHCl_3$); IR (neat): 3035, 2953, 2929, 2857, 1779, 1601, 1586, 1489, 1471, 1454, 1243, 1104, 1010, 839, 779, 754, 698 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 7.63 (dd, *J*=1.7 and 8.1 Hz, 1H, Ph H-6), 7.43 (m, 4H, *o*-Bn and *m*-Bn), 7.39 (m, 1H, *p*-Bn), 7.31 (ddd, *J*=1.7, 7.5 and 8.1 Hz, 1H, Ph H-4), 7.02 (m, 1H, Ph H-5), 7.01 (m, 1H, Ph H-3), 5.10 and 5.08 (2d, *J*=11.3 Hz, 2H, CH_2-Ph), 4.15 and 3.71 (2d, *J*=10.6 Hz, 2H, OCH_2), 2.86 and 2.36 (2m, 2H, H-4), 2.72 and 2.43 (2m, 2H, H-3), 0.87 (s, 9H, $(CH_3)_3C$–Si), 0.01 and 0.00 (2s, 6H, $(CH_3)_2$–Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0 (C-2), 154.6 (Ph C-2), 136.4 (*s*-Bn), 129.4 (Ph C-1), 129.3 (Ph C-4), 128.7 (*m*-Bn), 128.2 (*p*-Bn), 127.6 (*o*-Bn), 126.7 (Ph C-5), 121.0 (Ph C-5), 112.0 (Ph C-6), 89.2 (C-5), 70.3 (CH_2-Ph), 68.4 (CH_2OSi), 30.4 (C-4), 29.9 (C-3); 25.8 ($(CH_3)_3C$–Si), 18.2 ($(CH_3)_3C$–Si), −5.6 and −5.8 ($(CH_3)_2$–Si); MS (EI): *m*/*z* (%)=355 (0.48, $M^+-{}^t$Bu), 337 (5.0), 309 (0.21), 295 (0.72), 277 (0.25), 263 (2.1), 249 (0.40), 235 (0.71), 221 (6.3), 205 (1.5), 193 (0.43), 177 (0.39), 161 (1.0), 145 (0.71), 131 (2.0), 121 (1.5), 103 (0.46), 91 (100.0). Anal. Calcd for $C_{24}H_{32}O_4Si$: C, 69.87; H, 7.82. Found: C, 69.82; H, 7.85.

4.9. Typical procedure for preparation of 6a–c

To a solution of **5a–c** (2.6 mmol) in toluene (5.2 mL) at −78 °C 1.5 M solution of DIBAH in toluene (1.91 mL, 2.87 mmol) was added dropwise. The reaction mixture was stirred at −76 °C for 15 min, then methanol (0.6 mL) was added dropwise and the mixture was allowed to warm to room temperature. EtOAc (4.0 mL) and saturated $NaHCO_3$ solution (0.5 mL) were added and stirring was continued for 2 h. Powdered Na_2SO_4 (3.0 g) was added and the mixture was stirred overnight. The precipitate was filtered off and washed with EtOAc. The solvent was removed in vacuum and the residue was purified by column chromatography (petroleum ether/acetone=40:1 to 30:1) to give compounds **6a–c**.

*4.9.1. (R)-5-Phenyl-5-(tert-butyl-dimethyl-silyloxymethyl)-tetrahydro-furan-2-ol **6a***

Compound **6a** (0.736 g, 92%) was obtained as white crystals; mp=87–89 °C; $[\alpha]_D^{22}$ +35.4 (*c* 10.0, $CHCl_3$); 2*R*/2*S*=3.8:1.0; IR (KBr): 3274, 3026, 2956, 2930, 2858, 1603, 1492, 1472, 1251, 1138, 1117, 1067, 971, 836, 782, 763, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, data for 2*S* isomer labelled with *) δ 7.43 and 7.46* (d, *J*=7.6 Hz, 2H, *o*-Ph), 7.35 and 7.32* (t, *J*=7.6 Hz, 2H, *m*-Ph), 7.27 and 7.24 (t, *J*=7.6 Hz, 1H, *p*-Ph), 5.70* (t, *J*=4.0 Hz, 1H, H-2), 5.56 (dd, *J*=4.1 and 9.4 Hz, 1H, H-2), 4.10 (d, *J*=9.4 Hz, 1H, OH), 3.68 and 3.63 (2d, *J*=10.5 Hz, 2H, CH_2–OSi), 3.57* and 3.55* (2d, *J*=10.6 Hz, 2H, CH_2–OSi), 2.62* (d, *J*=4.0 Hz, 1H, OH), 2.61 and 2.07 (2m, 2H, H-4), 2.52* and 2.27* (2m, 2H, H-4), 2.25* and 1.90* (2m, 2H, H-3), 1.92 and 1.93 (2m, 2H, H-3), 0.95 (s, 9H, $(CH_3)_3C$–Si), 0.88* (s, 9H, $(CH_3)_3C$–Si), 0.13, 0.12, −0.02* and −0.04* (4s, 4×3H, $(CH_3)_2$–Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7* and 143.6 (*s*), 128.0 and 127.8* (*m*), 127.1 and 126.8* (*p*), 125.7* and 125.5 (*o*), 99.56* and 98.8 (C-2), 88.7* and 88.5 (C-5), 70.8* and 69.6 (CH_2O), 34.7 and 34.2* (C-3), 31.8* and 30.3 (C-4), 26.0 and 25.8* ($(CH_3)_3C$–Si), 18.4 and 18.3* ($(CH_3)_3C$–Si), −5.5 and −5.6, −5.5* and −5.7* ($(CH_3)_2$–Si); MS (EI): *m*/*z* (%)=291 (0.19, M^+-OH), 275 (0.62), 251 (1.0), 233 (21.6), 207 (10.5), 189 (0.9), 177 (4.0), 163 (100.0), 145 (8.8), 129 (21.5), 117 (57.6), 105 (11.4), 91

(24.5), 75 (57.0). Anal. Calcd for $C_{17}H_{28}SiO_3$: C, 66.19; H, 9.15. Found: C, 65.95; H, 9.22.

4.9.2. (R)-5-(4-Fluorophenyl)-5-(tert-butyl-dimethyl-silyloxymethyl)-tetrahydro-furan-2-ol **6b**

Compound **6b** (0.788 g, 93%) was obtained as white crystals; mp=65–77 °C; $[\alpha]_D^{23}$ +26.4 (*c* 10.1, $CHCl_3$); 2*R*/2*S*=4.0:1.0; IR (KBr): 3306, 2932, 2859, 1606, 1509, 1472, 1251, 1136, 1116, 1096, 1065, 973, 838, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, data for 2*S* isomer labelled with *) δ 7.42* and 7.39 (dd, *J*=5.5 and 8.7 Hz, 2×2H, *o*-Ph), 7.02 and 6.99* (t, 6.97, *J*=8.7 Hz, 2×2H, *m*-Ph), 5.68* (br t, *J*=4 Hz, 1H, H-2), 5.55 (dd, *J*=4.4 and 9.0 Hz, 1H, H-2), 4.01 (d, *J*=9.0 Hz, 1H, OH), 3.63 and 3.60 (2d, *J*=10.4 Hz, 2H, CH_2–OSi), 3.54* and 3.50* (2d, *J*=10.4 Hz, 2H, CH_2–OSi), 2.66* (d, *J*=4.0 Hz, 1H, OH), 2.59 and 2.03 (2m, 2H, H-4), 2.50 and 2.24 (2m, 2H, H-4*), 2.20 and 1.92 (2m, 2H, H-3*), 1.94 and 1.91 (m, 2H, H-3), 0.94 and 0.86* (2s, 2×9H, $(CH_3)_3C$–Si), 0.12, 0.11, −0.03* and −0.06* (4s, 4×3H, $(CH_3)_2Si$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 (d, J_{CF}=245.4 Hz, *p*), 161.8* (d, J_{CF}=244.8 Hz, *p*), 141.6* (d, J_{CF}=2.7 Hz, *s*), 139.4 (d, J_{CF}=2.7 Hz, *s*), 127.4* and 127.2 (2d, J_{CF}=7.8 Hz, *o*), 114.8 and 114.5* (2d, J_{CF}=21.2 Hz, *m*), 99.5* and 98.8 (C-2), 88.3* and 88.2 (C-5), 70.5* and 69.6 (CH_2O), 34.6 and 34.0* (C-3), 31.9* and 30.6 (C-4), 25.9 and 25.8* (($CH_3)_3$C–Si), 18.4 and 18.2* (($CH_3)_3$C–Si), −5.5, −5.6, −5.6* and −5.7* (($CH_3)_2$–Si); MS (EI): *m*/*z* (%)=309 (0.25, M^+−OH), 293 (0.72), 269 (1.4), 253 (1.7), 251 (20.9), 225 (10.9), 223 (3.5), 207 (0.71), 195 (2.4), 181 (70.23), 163 (4.7), 149 (6.2), 135 (47.6), 123 (9.7), 109 (37.7), 85 (18.1), 75 (100.0). Anal. Calcd for $C_{17}H_{27}FO_3Si$: C, 62.54; H, 8.34. Found: C, 62.53; H, 8.37.

4.9.3. (R)-5-(2-Benzyloxyphenyl)-5-(tert-butyl-dimethyl-silyloxymethyl)-tetrahydro-furan-2-ol **6c**

Compound **6c** (0.947 g, 88%) was obtained as a colourless syrup, $[\alpha]_D^{24}$ +4.5 (*c* 10.0, $CHCl_3$); 2*R*/2*S*=2.6:1.0; IR (neat): 3428, 3034, 2955, 2930, 2857, 1600, 1584, 1498, 1486, 1449, 1253, 1223, 1103, 1053, 1004, 837, 778, 754, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, data for 2*S* isomer labelled with *) δ 7.79* (dd, *J*=1.8 and 7.8 Hz, 1H, Ph H-6), 7.74 (dd, *J*=1.8 and 7.8 Hz, 1H, Ph H-6), 7.46–7.36 (m, 2×5H, Bn from both isomers), 7.28 and 7.24* (2m, 2×1H, Ph H-4), 7.00 and 6.98* (2m, 2×1H, Ph H-5), 6.99 and 6.94* (2m, 2×1H, Ph H-3), 5.72* (t, *J*=4.0 Hz, 1H, H-2), 5.55 (ddd, *J*=2.3, 3.3 and 10.0 Hz, 1H, H-2), 5.09* and 5.08* (2d, *J*=11.4 Hz, 2H, Ph–CH_2), 5.08 (s, 2H, Ph–CH_2), 4.43 (d, *J*=10.0 Hz, 1H, OH), 4.20 and 3.51 (2d, *J*=10.1 Hz, 2H, CH_2–OSi), 3.96* and 3.57* (2d, *J*=10.4 Hz, 2H, CH_2–OSi), 2.60 and 2.30 (m, 2H, H-4*), 2.56 and 2.26 (m, 2H, H-4), 2.42* (d, *J*=4.0 Hz, 1H, OH), 2.19 and 1.84 (m, 2H, H-3*), 1.91 (m, 2H, H-3), 0.88 and 0.86* (2s, 2×9H, $(CH_3)_3$C–Si), 0.00, −0.02, −0.05*, −0.07* (4s, 4×3H, $(CH_3)_2$–Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7* and 154.6 (Ph C-2), 136.9* and 136.6 (*s*-Bn), 133.9* and 131.5 (Ph C-1), 128.7 and 128.6* (*m*-Bn), 128.6 and 128.2* (Ph C-4), 128.1 and 127.9* (*p*-Bn), 127.7 (2C, Ph C-6), 127.6 and 127.5* (*o*-Bn), 120.8 and 120.6* (Ph C-5), 111.6 (2C, Ph C-3), 99.4* and 99.3 (C-2), 88.6* and 87.8 (C-5), 70.1 and 70.0* (Ph–CH_2–), 68.8* and 67.1 (CH_2–OSi), 35.3 and 34.7* (C-3), 31.7* and 28.9 (C-4), 25.9* and 25.8 (($CH_3)_3$C–Si), 18.3 and 18.2* (($CH_3)_3$C–Si), −5.4*, −5.6, −5.7* and −5.7 (($CH_3)_2$–Si); MS (EI): *m*/*z* (%)=339 (0.44, $M^+-{}^t$Bu–OH), 311 (0.12), 295 (0.14), 283 (0.11), 269 (3.8), 251 (3.4), 233 (0.35), 221 (3.3), 205 (1.0), 192 (0.52), 173 (1.1), 161 (0.79), 149 (0.93), 131 (3.8), 115 (1.9), 107 (1.0), 91 (100.0), 85 (7.6), 73 (14.0). Anal. Calcd for $C_{24}H_{34}O_4Si$: C, 69.53; H, 8.27. Found: C, 69.48; H, 8.30.

4.10. Typical procedure for preparation of 1a–c

To a mixture of compounds **6a–c** (1.45 mmol) and Et_3N (0.610 mL, 4.35 mmol) in CH_2Cl_2 (1.5 mL) acetic anhydride (0.410 mL, 4.35 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature overnight. Water (5 mL) was added and the mixture extracted with EtOAc (4×5 mL). The combined extracts were dried over $MgSO_4$. After solvent evaporation in vacuum the residue was purified by column chromatography (petroleum ether/acetone=20:1) to afford compounds **7a–c**.

Yield: **7a** (0.458 g, 90%), **7b** (0.432 g, 81%), **7c** (0.443 g, 67%).

To a solution of thymine (0.171 g, 1.36 mmol) in dry CH_3CN (11.0 mL) BSA (0.998 mL, 3.88 mmol) and compounds **7a–c** (1.30 mmol) in CH_3CN (7.6 mL) were added at room temperature. After cooling to 0 °C TMSOTf (0.235 mL, 1.30 mmol) was added dropwise, the reaction mixture was stirred at room temperature for 2 h and poured into the mixture of CH_2Cl_2 (70 mL) and saturated $NaHCO_3$ solution (15 mL). The CH_2Cl_2 layer was removed and the water layer was extracted with CH_2Cl_2 (3×10 mL). The combined CH_2Cl_2 layers were dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (petroleum ether/acetone=10:1 to 10:2) to afford compounds **8a–c**.

Yield: **8a** (0.472 g, 87%), **8b** (0.564 g, 100%), **8c** (0.618 g, 91%).

To a solution of compounds **8a–c** (1.12 mmol) in THF (10.0 mL) 1.0 M TBAF solution in THF (2.32 mL, 2.32 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h and then concentrated in vacuum. α- and β-Anomers were separated by column chromatography on silica gel (CH_2Cl_2/MeOH=40:1 to 20:1) affording anomers **β-1a–c** and **α-1a–c**.

4.10.1. 1-(5-Phenyl-5-hydroxymethyl-tetrahydro-furan-2-yl)-5-methyl-1H-pyrimidine-2,4-diones **β-1a** (2R,5R) and **α-1a** (2S,5R)

1-(4′-Phenyl-2′,3′-dideoxy-D-ribo-pentofuranosyl)-thymines ***β-1a*** *and* ***α-1a***. Compound **β-1a** (0.170 g, 50%) was obtained as white crystals; mp=86–91 °C; $[\alpha]_D^{22}$ +9.1 (*c* 5.46, MeOH); IR (KBr): 3427, 3186, 3061, 2954, 1694, 1473, 1448, 1275, 1067, 763, 703 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 8.19 (s, 1H, H-6), 7.41 (d, *J*=7.7 Hz, 2H, *o*-Ph), 7.34 (t, *J*=7.7 Hz, 2H, *m*-Ph), 7.25 (t, *J*=7.7 Hz, 1H, *p*-Ph), 6.16 (dd, *J*=3.8 and 6.5 Hz, 1H, H-2′), 3.74 and 3.71 (2d, *J*=12.2 Hz, 2H, –CH_2OH), 2.60 and 2.17 (2m, 2H, H-4′), 2.17 and 2.07 (2m, 2H, H-3′), 1.90 (s, 3H, CH_3–C=); ^{13}C NMR (125 MHz, CD_3OD) δ 166.5 (C-4), 152.4 (C-2), 144.3 (*s*), 138.7 (C-6), 129.4 (*m*), 128.5 (*p*), 126.2 (*o*), 111.0 (C-5), 91.7 (C-5′), 86.4 (C-2′), 68.7 (–CH_2OH), 32.9 (C-3′), 31.9 (C-4′), 12.5 (CH_3–C=); MS (EI): *m*/*z* (%)=302 (0.59, M^+), 271 (40.3), 177 (46.7), 159 (31.5), 146 (50.4), 129 (100.0), 117 (69.4), 105 (94.6), 91 (85.4), 77 (75.3). HRMS-EI calcd for $(M-CH_2OH)^+$ $C_{15}H_{15}O_3N_2$: 271.1083; found: 271.1110.

Compound **α-1a** (0.170 g, 50%) was obtained as white crystals; mp=156–168 °C; $[\alpha]_D^{22}$ +4.0 (*c* 5.46, MeOH). IR (KBr): 3418, 3193, 3058, 2954, 1694, 1472, 1448, 1270, 1061, 763, 704 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.46 (d, *J*=7.7 Hz, 2H, *o*-Ph), 7.39 (t, *J*=7.7 Hz, 2H, *m*-Ph), 7.31 (t, *J*=7.7 Hz, 1H, *p*-Ph), 7.02 (q, *J*=1.2 Hz, 1H, H-6), 6.38 (dd, *J*=4.2 and 6.2 Hz, 1H, H-2′), 3.61 and 3.53 (2d, *J*=11.9 Hz, 2H, –CH_2OH), 2.64 and 2.34 (2m, 2H, H-4′), 2.61 and 2.06 (2m, 2H, H-3′), 1.58 (d, *J*=1.2 Hz, 3H, CH_3–C=); ^{13}C NMR (125 MHz, CD_3OD) δ 166.3 (C-4), 152.4 (C-2), 144.7 (*s*), 138.0 (C-6), 129.4 (*m*), 128.6 (*p*), 127.1 (*o*), 110.9 (C-5), 91.8 (C-5′), 88.6 (C-2′), 70.8 (–CH_2OH), 33.1 (C-3′), 32.4 (C-4′), 12.3 (CH_3–C=); MS (EI): *m*/*z* (%)=302 (0.94, M^+), 271 (58.0), 204 (4.0), 177 (47.6), 159 (33.4), 145 (40.3), 129 (100.0), 117 (60.6), 105 (76.8), 91 (69.2), 77 (63.5). HRMS-EI calcd for $(M-CH_2OH)^+$ $C_{15}H_{15}O_3N_2$: 271.1083; found: 271.1099.

4.10.2. 1-(5-(4-Fluorophenyl)-5-hydroxymethyl-tetrahydro-furan-2-yl)-5-methyl-1H-pyrimidine-2,4-diones **β-1b** (2R,5R) and **α-1b** (2S,5R)

1-(4′-(4-Fluorophenyl)-2′,3′-dideoxy-D-ribo-pentofuranosyl)-thymines ***β-1b*** *and* ***α-1b***. Compound **β-1b** (0.139 g, 39%) was obtained as white crystals; mp=80–86 °C; $[\alpha]_D^{24}$ +5.0 (*c* 4.2, MeOH); IR (KBr): 3426, 3192, 3063, 2956, 1690, 1604, 1509, 1473, 1275, 1225, 1070, 837 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 8.15 (s, 1H, H-6), 7.45 (dd, *J*=5.4 and 8.8 Hz, 2H, Ph H-2,6), 7.07 (t, *J*=8.8 Hz, 2H, Ph H-3,5), 6.17 (dd, *J*=4.2 and 6.3 Hz, 1H, H-2′), 3.72 and 3.70 (2d, *J*=12.2 Hz, 2H,

–CH_2O), 2.60 and 2.18 (2m, 2H, H-4′), 2.18 and 2.10 (2m, 2H, H-3′), 1.90 (s, 3H, CH_3–C═); ^{13}C NMR (125 MHz, CD_3OD) δ 166.5 (C-4), 163.6 (d, J_{CF}=244.5 Hz, Ph C-4), 152.4 (C-2), 140.4 (d, J_{CF}=2.9 Hz, Ph C-1), 138.7 (C-6), 128.3 (d, J_{CF}=8.1 Hz, Ph C-2,6), 116.0 (d, J_{CF}=21.5 Hz, Ph C-3,5), 111.1 (C-5), 91.3 (C-5′), 86.4 (C-2′), 68.8 (–CH_2–OH), 32.9 (C-3′), 32.1 (C-4′), 12.5 (CH_3–C═); MS (EI): *m*/*z* (%)=320 (0.27, M^+), 302 (0.12), 289 (33.9), 228 (1.1), 195 (24.8), 177 (17.9), 164 (37.0), 147 (47.7), 135 (75.6), 127 (79.0), 123 (100.0), 109 (98.9), 95 (47.7), 83 (17.9); HRMS-EI calcd for $(M-CH_2OH)^+$ $C_{15}H_{14}FO_3N_2$: 289.0988; found: 289.0990.

Compound **α-1b** (0.138 g, 39%) was obtained as white crystals; mp=191–196 °C; IR (KBr): 3408, 3208, 3072, 2946, 2921, 2864, 2816, 1715, 1668, 1604, 1511, 1474, 1454, 1421, 1274, 1258, 1065, 1052, 989, 961, 894, 839, 816, 776, 760, 724, 676 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.47 (dd, *J*=5.4 and 8.8 Hz, 2H, Ph H-2,6), 7.11 (t, *J*=8.8 Hz, 2H, Ph H-3,5), 7.03 (s, 1H, H-6), 6.38 (dd, *J*=4.1 and 6.1 Hz, 1H, H-2′), 3.58 and 3.52 (2d, *J*=11.8 Hz, 2H, –CH_2O), 2.62 and 2.33 (2m, 2H, H-4′), 2.62 and 2.08 (2m, 2H, H-3′), 1.63 (s, 3H, CH_3–C═); ^{13}C NMR (125 MHz, CD_3OD) δ 166.3 (C-4), 163.6 (d, J_{CF}=245.0 Hz, Ph C-4), 152.5 (C-2), 140.8 (d, J_{CF}=2.9 Hz, Ph C-1), 137.9 (C-6), 129.1 (d, J_{CF}=8.0 Hz, Ph C-2,6), 116.0 (d, J_{CF}=21.7 Hz, Ph C-3,5), 111.1 (C-5), 91.3 (C-5′), 88.5 (C-2′), 70.7 (–CH_2–OH), 32.9 (C-3′), 32.7 (C-4′), 12.4 (CH_3–C═); MS (EI): *m*/*z* (%)=320 (0.27, M^+), 302 (0.13), 289 (41.9), 195 (31.7), 177 (22.4), 164 (44.3), 147 (58.0), 135 (81.5), 127 (100.0), 123 (80.5), 109 (85.1), 95 (32.7), 83 (15.3); HRMS-EI calcd for $(M-CH_2OH)^+$ $C_{15}H_{14}FO_3N_2$: 289.0988; found: 289.0991.

4.10.3. 1-(5-(2-Benzyloxyphenyl)-5-hydroxymethyl-tetrahydro-furan-2-yl)-5-methyl-1H-pyrimidine-2,4-diones β-1c (2R,5R) and α-11c (2S,5R)

*1-(4′-(2-Benzyloxyphenyl)-2′,3′-dideoxy-D-ribo-pentofuranosyl)-thymines **β-1c** and **α-1c***. Compound **β-1c** (0.260 g, 57%) was obtained as white crystals; mp=96–101 °C; IR (KBr): 3419, 3188, 3063, 2953, 1690, 1599, 1484, 1447, 1276, 1218, 1067, 756, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H, NH), 7.70 (q, *J*=1.2 Hz, 1H, H-6), 7.62 (dd, *J*=1.7 and 7.7 Hz, Ph H-6), 7.41 (m, 4H, *o*-Bn and *m*-Bn), 7.36 (m, 1H, *p*-Bn), 7.27 (dt, *J*=1.7 and 2×7.7 Hz 1H, Ph H-4), 7.01 (dt, *J*=0.8 and 2×7.7 Hz, 1H, Ph H-5), 6.98 (dd, *J*=0.8 and 7.7 Hz, 1H, Ph H-3), 6.27 (dd, *J*=5.4 and 6.6 Hz, 1H, H-2′), 5.09 (s, 2H, Ph–CH_2), 4.17 and 3.86 (2d, *J*=11.7 Hz, 2H, –CH_2–OH), 2.80 (s, 1H, OH), 2.61 and 2.49 (2m, 2H, H-4′), 2.31 and 2.08 (m, 2H, H-3′), 1.93 (d, *J*=1.2 Hz, 3H, CH_3–C═); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0 (C-4), 154.7 (Ph C-2), 150.6 (C-2), 136.7 (C-6), 136.5 (*s*-Bn), 130.1 (Ph C-1), 129.1 (Ph C-4), 128.7 (*m*-Bn), 128.1 (*p*-Bn), 127.3 (*o*-Bn), 127.0 (Ph C-6), 121.1 (Ph C-5), 112.1 (Ph C-3), 110.8 (C-5), 89.2 (C-5′), 85.4 (C-2′), 70.1 (Ph–CH_2–), 66.3 (–CH_2–OH), 31.7 (C-3′), 31.0 (C-4′), 12.5 (CH_3–C═); MS (EI): *m*/*z* (%)=377 (9.3, M^+-CH_2OH), 282 (3.5), 252 (10.6), 221 (4.3), 207 (2.1), 195 (5.2), 175 (1.6), 161 (9.0), 145 (4.4), 131 (10.5), 126 (11.0), 121 (5.2), 105 (3.3), 91 (100.0), 83(1.9). Anal. Calcd for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.61; H, 5.90; N, 6.76.

Compound **α-1c** (0.196 g, 43%) was obtained as white crystals; mp=73–78 °C; $[\alpha]_D^{25}$ +57.3 (*c* 1.00, MeOH). IR (KBr): 3421, 3197, 3035, 2956, 1689, 1599, 1486, 1448, 1267, 1232, 1060, 757, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H, –NH), 7.61 (dd, *J*=1.7 and 7.8 Hz, 1H, Ph H-6), 7.41 (m, 4H, *o*-Bn and *m*-Bn), 7.36 (m, 1H, *p*-Bn), 7.30 (dt, *J*=1.7 and 2×7.7 Hz, 1H, Ph H-4), 7.09 (q, *J*=1.2 Hz, 1H, H-6), 7.02 (m, 1H, Ph H-5), 7.00 (m, 1H, Ph H-3), 6.53 (dd, *J*=5.2 and 6.4 Hz, 1H, H-2′), 5.10 (s, 2H, Ph-CH_2), 3.87 and 3.75 (2d, *J*=11.8 Hz, 2H, –CH_2OH), 2.91 (s, 1H, OH), 2.67 and 2.42 (2m, 2H, H-4′), 2.53 and 1.92 (m, 2H, H-3′), 1.77 (d, *J*=1.2 Hz 3H, CH_3C═); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9 (C-4), 154.6 (Ph C-2), 150.9 (C-2), 136.4 (*s*-Bn), 135.8 (C-6), 130.7 (Ph C-1), 129.1 (Ph C-4), 128.7 (*m*-Bn), 128.1 (*p*-Bn), 127.5 (Ph C-6), 127.4 (*o*-Bn), 120.7 (Ph C-5), 112.2 (Ph C-3), 110.8 (C-5), 89.4 (C-5′), 85.7 (C-2′), 70.2 ($PhCH_2$), 67.7 (–CH_2OH), 32.0 (C-3′), 31.8 (C-4′), 12.4 (CH_3–C═). Anal. Calcd for $C_{23}H_{24}N_2O_5$, C, 67.63; H, 5.92; N, 6.86. Found: C, 67.77; H, 5.90; N, 6.83.

4.11. 1-(5-(2-Hydroxyphenyl)-5-hydroxymethyl-tetrahydro-furan-2-yl)-5-methyl-1*H*-pyrimidine-2,4-diones β-1d (2*R*,5*R*) and α-1d (2*S*,5*R*)

*1-(4′-(2-Hydroxyphenyl)-2′,3′-dideoxy-D-ribo-pentofuranosyl)-thymines **β-1d** and **α-1d***. To a solution of **β-1c** (**α-1c**) (0.25 mmol) in CH_3OH (2.5 mL) 10% Pd/C powder (0.028 g) was added. Through the reaction mixture H_2 was bubbled at room temperature for 5 h. The reaction mixture was filtered off and concentrated in vacuum. The residue was purified by column chromatography (CH_2Cl_2/MeOH=30:1 to 20:1) affording compounds **β-1d** (**α-1d**).

Compound **β-1d** (0.080 g, 100%) was obtained as white crystals; mp=115–119 °C; IR (KBr): 3381, 3218, 1677, 1607, 1471, 1450, 1407, 1274, 1064, 1041, 762 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 8.17 (q, *J*=1.2 Hz, 1H, H-6), 7.40 (dd, *J*=1.7 and 7.7 Hz, Ph H-6), 7.08 (dt, *J*=1.7 and 2×7.7 Hz, 1H, Ph H-4), 6.80 (dt, *J*=0.8 and 2×7.7 Hz, 1H, Ph H-5), 6.76 (dd, *J*=0.8 and 7.7 Hz, 1H, Ph H-3), 6.19 (dd, *J*=4.5 and 6.2 Hz, 1H, H-2′), 4.18 and 3.71 (2d, *J*=12.0 Hz, 2H, –CH_2OH), 2.55 and 2.53 (2m, 2H, H-4′), 2.15 and 2.03 (m, 2H, H-3′), 1.91 (d, *J*=1.2 Hz, 3H, CH_3–C═); ^{13}C NMR (125 MHz, CD_3OD) δ 166.4 (C-4), 154.7 (Ph C-2), 152.3 (C-2), 138.6 (C-6), 129.7 (Ph C-4), 129.3 (Ph C-1), 127.6 (Ph C-6), 120.3 (Ph C-5), 117.0 (Ph C-3), 111.0 (C-5), 91.3 (C-5′), 86.1 (C-2′), 66.0 (–CH_2OH), 33.0 (C-3′), 30.4 (C-4′), 12.5 (CH_3–C═); MS (EI): *m*/*z* (%)=318 (0.23, M^+), 287 (25.3), 192 (22.6), 175 (11.2), 161 (56.6), 145 (29.0), 131 (100.0), 126 (36.3), 121 (44.1), 115 (23.8), 107 (51.2), 91 (45.0), 77 (46.0); HRMS-EI: calcd for $(M-CH_2OH)^+$ $C_{15}H_{15}O_4N_2$: 287.1032; found: 287.1027.

Compound **α-1d** (0.079 g, 99%) was obtained as white crystals; mp=93–97 °C; $[\alpha]_D^{22}$ +31.7 (*c* 1.00, MeOH); IR (KBr): 3381, 3065, 2957, 1690, 1605, 1473, 1451, 1404, 1268, 1059, 822, 758 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.42 (dd, *J*=1.7 and 7.7 Hz, 1H, Ph H-6), 7.20 (q, *J*=1.2 Hz, 1H, H-6), 7.12 (ddd, *J*=1.7, 7.7 and 8.0 Hz, 1H, Ph H-4), 6.82 (dt, *J*=0.8, 2×7.7 Hz, 1H, Ph H-5), 6.80 (dd, *J*=0.8 and 8.0 Hz, 1H, Ph H-3), 6.43 (dd, *J*=3.7 and 6.9 Hz, 1H, H-2′), 3.84 and 3.60 (2d, *J*=11.8 Hz, 2H, –CH_2OH), 2.76 and 2.41 (2m, 2H, H-4′), 2.59 and 2.03 (2m, 2H, H-3′), 1.65 (d, *J*=1.2 Hz, 3H, CH_3C═); ^{13}C NMR (125 MHz, CD_3OD) δ 166.3 (C-4), 155.1 (Ph C-2), 152.6 (C-2), 138.2 (C-6), 130.1 (Ph C-1), 129.8 (Ph C-4), 128.3 (Ph C-6), 120.2 (–Ph C-5), 117.2 (Ph C-3), 111.1 (C-5), 91.8 (C-5′), 88.0 (C-2′), 68.7 (–CH_2OH), 33.0 (C-3′), 32.8 (C-4′), 12.4 (CH_3–C═); MS (EI): *m*/*z* (%)=318 (0.53, M^+), 287 (23.1), 220 (2.6), 192 (32.1), 175 (14.6), 161 (58.8), 145 (17.4), 131 (100.0), 121 (46.5), 115 (15.3), 107 (42.8), 91 (2.4), 77 (32.0); HRMS-EI: calcd for $(M-CH_2OH)^+$ $C_{15}H_{15}O_4N_2$: 287.1032; found: 287.1054.

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