New Synthetic Routes for the Preparation of 2′-*C*-Methylene Nucleosides

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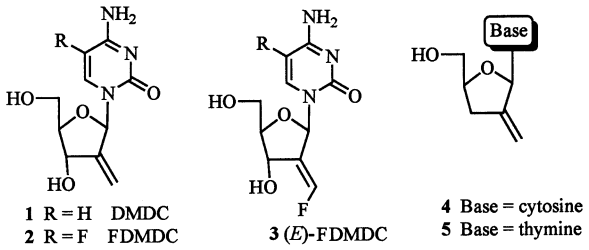
Two new routes to 2′,3′-dideoxy-2′-*C*-methylene nucleoside analogs have been developed. The first is based upon the coupling reaction of a 1-*O*-acetyl 2-*C*-(methylphenylsulfinyl) sugar with a silylated base under Vorbrüggen conditions, followed by thermal elimination of phenylsulfinic acid. The second route involved a condensation of a silylated base with a (π-allyl)palladium complex derived from a 2-*C*-acetoxymethyl furanoid glycal.

Introduction

Ribonucleoside diphosphate reductase (RDPR) is a metalloenzyme[1] that catalyzes the reduction of ribonucleotides to their corresponding 2-deoxy derivatives, essential monomers for DNA biosynthesis. Since RDPR is intimately involved in tumor progression, inhibition of this enzyme represents an attractive strategy in anticancer chemotherapy. Among the nucleosides which after conversion into their diphosphate derivatives are cytotoxic by inhibiting the RDPR, 2′-deoxy-2′-methylidenecytidine (DMDC, **1**)[2] and 5-fluoro- (5-FDMDC, **2**)[3] or 2′-fluoromethylene analogs [2′-(*E*)-FDMDC, **3**] are the most potent compounds.[4] In this context we report here the synthesis of the 3′-deoxy-DMDC (**4**) and its thymine congener **5** (Scheme 1).

Scheme 1



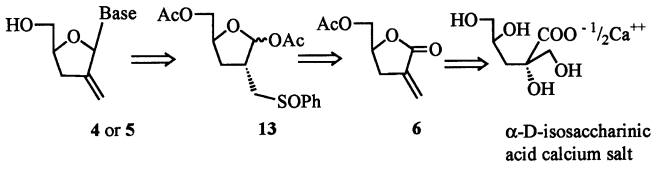
Results and Discussion

Synthesis from 2-*C*-[(Phenylsulfinyl)methyl]furanose

As represented in Scheme 2, the first strategy adopted to synthesize a 2′-*C*-methylene-2′,3′-dideoxy nucleoside is based upon the preparation and glycosylation of the key intermediate 1,5-di-O-acetyl-2,3-dideoxy-2-C-[(phenylsulfinyl)methyl]-erythro-furanose (**13**).

The 2-phenylsulfinyl group at C-2 of compound **13** was introduced in order both to control the β-stereoselectivity during the glycosidation step with the nucleobase and to serve as a precursor of the 2-*C*-methylene function on thermolytic elimination of PhSOH. Compound **13** itself could be prepared by addition of thiophenol to the 2′-*C*-methylenelactone **6**.

Scheme 2



α-Methylenelactone **6** was synthesized in two steps from α-D-isosaccharinolactone[5] as previously reported by Bock et al.[6]. Addition of thiophenol was carried out under thermodynamic conditions (PhSH, Et_3N at reflux in EtOH, condition **A**) as reported by Bernardi et al. for a closely related system[7]. Two compounds were obtained from Michael addition of thiophenol and from simultaneous deacetylation at C-5 in a 7:3 ratio (HPLC of the crude *erythro*/*threo* mixture). These compounds were partially separated (65−70% of diastereoisomeric purity) by column chromatography on silica gel. As expected, each isolated diastereoisomer reequilibrated to give the same ratio of *threo* and *erythro* compounds when separately submitted to these reaction conditions. Under condition **B** (no heat) (Table 1), condition **C** (no heat, no base) or condition **D** (PHS^-Na^+, 0°C to room temp.) similar ratios of diastereoisomers were obtained; however, in these cases no reequilibration could be realised.

It was expected that the use of thermodynamic conditions should lead predominantly to compound **8a** with *erythro* configuration. However, a chemical correlation demonstrated that this was not the case. When the major compound obtained, **7a**, was desulfurized with Raney Nickel in boiling EtOH the 2′-methyllactone **9** was ob-

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Scheme 3

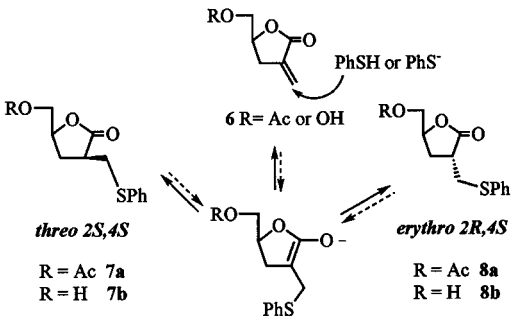


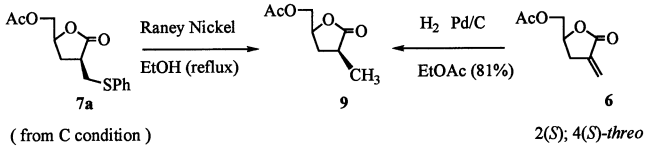
Table 1. Conditions and yields

Condition[a]	*threo*[b]		*erythro*[b]		yield (%)
	7a	**7b**	**8a**	**8b**	
A		70		30	80
B	63	7	27	3	65
C	70		30		78
D	75		25		75

[a] **A**: PhSH in EtOH with Et_3N at reflux. **B**: PhSH in EtOH with Et_3N at room temperature. **C**: PhSH in EtOH at room temperature. **D**: PhS^-Na^+ in EtOH, 0°C to room temperature. – [b] Ratio determined by HPLC analysis of the products (see Experimental Section).

tained. Its NMR data and physical properties were identical with those of the known product of hydrogenation (H_2, Pd/C, EtOAc, room temp.) of α-methylenelactone **6**[6]. Thus, the *threo* configuration of major product **7a** of the addition of thiophenol to methylenelactone **6** was by this way unambiguously determined.

Scheme 4



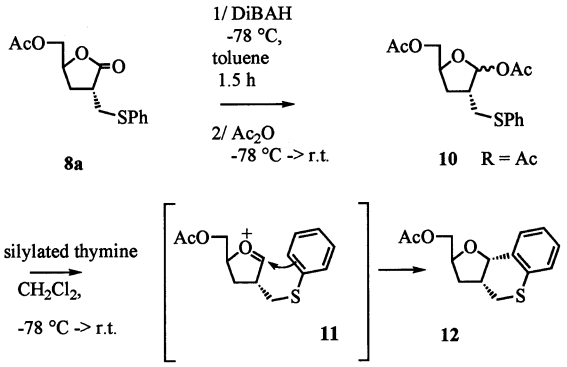
These results indicate that the two isomers were very close in energy, and this was confirmed by MNDO calculations under vacuum, showing only a small difference of energy (ca. 0.02 kcal/mol).[8]

In order to scale up the preparation of the *erythro* isomer **8a**, the 2′-*C*-methylenelactone **6** was treated according to condition C. After flash chromatography, the *threo* (**7a**) and *erythro* (**8a**) isomers were isolated in a 7:3 ratio (65 and 70% of diastereoisomeric purity, respectively, in 78% overall yield). However, the useless *threo* isomer **7a** could be reequilibrated under the same reaction conditions, giving additional amounts of **8a** (80% diastereoisomeric purity). Finally, compound **8a** was directly engaged in the next step.

Reduction of **8a** with DIBAH (2 equiv.) at −78°C in toluene, followed by in situ acetylation of the anomeric hydroxy group by addition of acetic anhydride, gave compound **10** (Scheme 5).

An attempt to condense **10** with 2,4-bis(trimethylsilyloxy)thymine using TMSOTf as the catalyst under Vorbrüggen conditions[9], did not give the desired nucleoside but the thioisochromane compound **12**. Compound **12** probably results from the trapping of the intermediary oxonium ion **11** generated by the Lewis acid (Scheme 5). This reaction may be compared to the formation of isochromane from 1-*O*-acetyl-2-benzylfuranose under Friedel–Crafts conditions as reported by Martin[10] and Araki et al.[11]

Scheme 5



Hence (Scheme 6), we oxidized the phenylthio substituent into a phenylsulfinyl group which could eventually participate during the glycosidation step[12], stereoselectively providing a β-D-nucleoside. Oxidation of compound **10** (80% diastereoisomeric purity) with sodium periodate quantitatively gave **13** which, under coupling reaction with 2,4-bis(trimethylsilyloxy)thymine as previously described (vide supra), gave an unseparable mixture of 2′-*C*-methylsulfinyl nucleoside diastereoisomers **14** and **15**. The minor *threo* isomer present in the starting *erythro* material **13** explains the formation of β isomer **15** as minor byproduct. However, as expected after thermolysis (15 h at reflux in xylene[13]) elimination of sulfinic acid occurred and an α/β anomer mixture of the 2′-*C*-methylene nucleosides **16** and **17** was obtained in 49% yield.

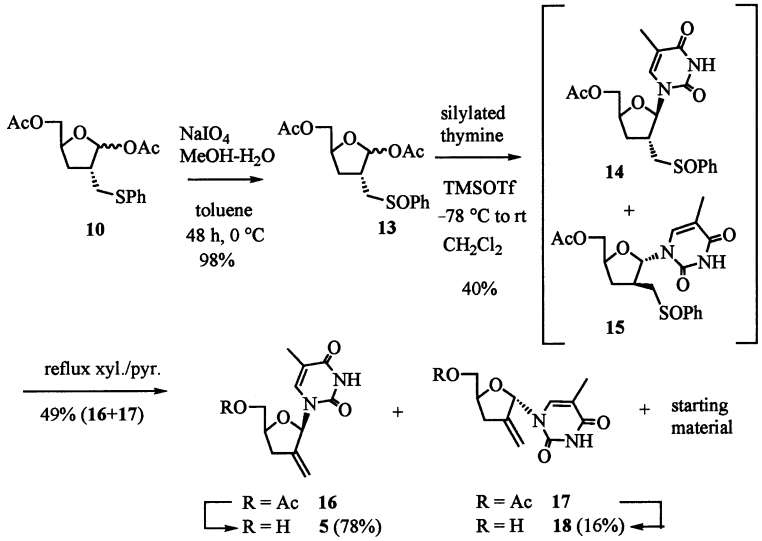
After treatment with MeONa/MeOH, and further separation by column chromatography, the β-D-2′,3′-dideoxy-5-methyl-2′-*C*-methyleneuridine (**5**) and its α-D-anomer **18** were isolated in a 78:16 ratio. The ^{1}H-NMR data of compound **5** were identical to those reported by Matsuda et al.[14]

Synthesis from a 2-(Acetoxymethyl)furanoid Glycal or (2*S*),4-Diacetoxymethyl-2,3-dihydrofuran (23) (see Scheme 7)

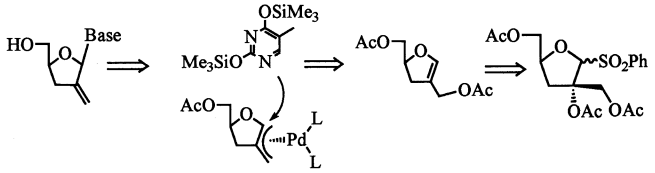
The difficulties encountered to control the C-2 asymmetry and to purify some compounds during this approach led us to explore a second route[15] based on the preparation of a 2-(acetoxymethyl)furanoid glycal as allyl acetate equivalent and to study its reactivity with a silylated base as the nucleophile in the presence of Pd^0 as the catalyst (Scheme 7).

The first step was the preparation of a furanoid glycal. Such glycals usually suffer from relative instability, especially when a leaving group in allylic position is present. As few

Scheme 6



Scheme 7



methods exist for their preparation,[16] we decided to extend the methodology recently reported by Sinaÿ et al.[17] for the preparation of pyranoid glycals which is based on the reductive elimination of glycosyl phenyl sulfone by samarium diiodide (SmI_2) (Scheme 8).

Reduction of α-D-isosaccharinolactone **19**[5] with $NaBH_4$ in H_2O,[18] followed by acetylation of the crude mixture, led to the hemiacetal **20** (39%) as main product along with peracetylated alditol. Compound **20** was next converted into the phenylthio glycoside **21** by treatment with thiophenol and boron trifluoride–diethyl ether as catalysts. Sulfide **21** was then oxidized with *meta*-chloroperbenzoic acid (2 equiv.) to give the sulfone **22**. Reductive samariation of **22** with SmI_2 in the presence of HMPA, followed by elimination of the tertiary acetate afforded the 2-acetoxymethyl glycal **23** (as deduced from examination of the ^{1}H-NMR spectrum of the crude material). However, during the purification by chromatography on silica gel, unexpected partial isomerization was observed which led to the unstable 2-*C*-methylene furanoside **24**. This isomerization probably occurred by a rearrangement process via a six-membered ring leading to the thermodynamically more stable compound **24**. It is noteworthy, however, that this rearrangement was not observed in the case of 2-*C*-acetoxymethylpyranoid glycals.[19]

Condensation of crude allylic acetate **23** with 2,4-bis(trimethylsilyloxy)thymine in the presence of tris(dibenzylideneacetone)dipalladium(0) and triphenylphosphane gave, as main product, the expected β-nucleoside **16** in 21% overall yield along with recovered starting material[20] (Scheme 9). Deprotection by ammonolysis led to the 2′,3′-dideoxy-5-methyl-2′-*C*-methyleneuridine (**5**, 80%), which displayed spectral data identical to those of the same compound already prepared by the precedent method. Under identical conditions but using silylated cytosine, the β-nucleoside **25** was isolated after column chromatography along with the corresponding α-anomer (40% overall yield and β.α ratio = 8:2). Similar removal of the acetyl group from **25** gave 3′-deoxy-DMDC (**4**) in 73% yield[21].

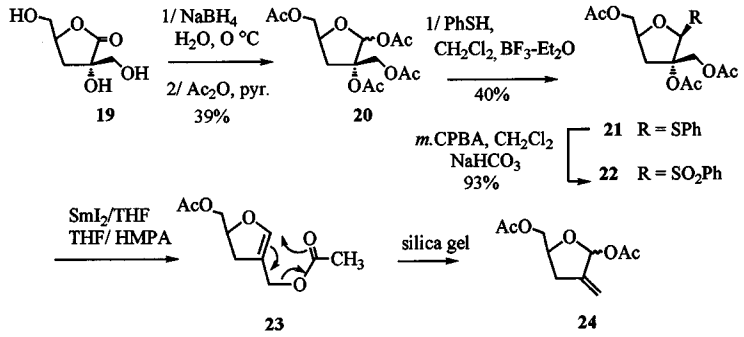
Conclusion

Two routes have been described to gain access to 2′-*C*-methylene nucleoside analogs from readily available α-D-isosaccharinolactone. This represents the first synthesis of nucleosides utilizing the (π-allyl)palladium complex prepared from an unsaturated furanoside. Extension of this work to the synthesis of DMDC may be considered using D-hamamelose as starting material (2-*C*-hydroxymethylribose, readily available from ribose[22]).

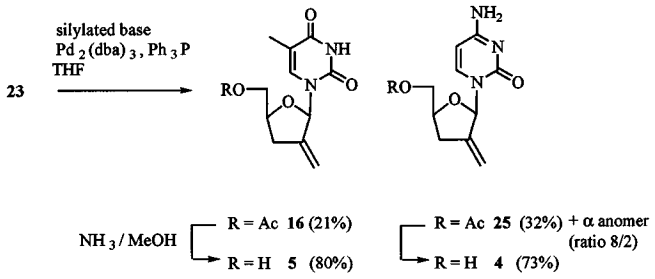
Experimental Section

General: Melting points, uncorrected: Electrothermal apparatus. – UV/Vis: Varian–Cary/3E spectrophotometer. – IR: Perkin–Elmer 1710 spectrophotometer. – ^{1}H NMR: Bruker AC 250- or 300-MHz and Varian 90-MHz spectrometers, solvents are given.

Scheme 8



Scheme 9



Chemical shifts are reported as δ values in ppm. Splitting-pattern abbreviations: s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, br = broad, m = multiplet. − CI (chemical ionization) MS: Nermag R 10,10C spectrometer. − Elemental analyses: Service de Microanalyse du CNRS (Vernaison-Lyon, France), values within 0.4% of the calculated values for C, H and N. − TLC: Precoated silica gel ($60F_{254}$) plates, the spots were examined with UV/Vis light and phosphomolybdic acid spray. − CC: Merck silica gel (230−240 mesh). Extraction in the usual manner refers to washing the organic layer with water, drying it with $MgSO_4$ and evaporating the solvent under reduced pressure. − HPLC: Gilson apparatus.

Addition Reaction of PhSH with α-Methylenelactone **6**. − *General Conditions:* To a solution of compound **6** (5.0 g, 30 mmol) in anhydrous EtOH (150 ml), PhSH (1.1 equiv., 3.3 ml) was added. After stirring for 18 h (see Scheme 3 for temperature and time conditions), the reaction mixture was concentrated under reduced pressure and purified.

*Condition **A**:* General conditions, in the presence of 1.1 equiv. of Et_3N at reflux for 18 h.

*Condition **B**:* Same as **A** , but at room temp.

*Condition **C**:* Same as general conditions but at room temp.

*Condition **D**:* To a solution of **6** (30 mmol) in anhydrous EtOH (170 ml) at 0°C was added dropwise a solution of sodium phenyl sulfide [prepared from thiophenol (3 ml) in EtOH (100 ml) at 0°C and sodium (1.09 g)]. After stirring while warming from 0°C to room temp. for 1 h, the reaction mixture was neutralized with 10% aq. AcOH and extracted with Et_2O. The organic layers were washed with H_2O, with brine and dried ($MgSO_4$). After concentration under reduced pressure, the residue obtained was purified as described below.

Purification of Compounds **7a**/**7b**/**8a**/**8b**: The crude mixture obtained from conditions **A**, **B**, **C** or **D** was purified by flash chromatography on silica gel with a mixture of cyclohexane/ethyl acetate (2:1 then 1:1).

HPLC Conditions for Silica Gel Chromatography Control: Solvents: cyclohexane/EtOAc (4:1) for compounds **7a**/**7b**, and cyclohexane/EtOAc (2:1) for **7b**/**8b**. Flow rate: 0.5 ml/min. Column: l = 20 cm, d = 0.5 cm; normal phase LiChrosorb Si 60 dp = 7 μm. UV/Vis detection: 254 nm.

(2S,4S)-5-O-Acetyl-4,5-dihydroxy-2-phenylthiomethyl-4-pentanolide (**7a**): IR (film): $\tilde{\nu}$ = 1750 cm^{-1} (CO ester), 1780 (CO lactone). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.20 (m, 5 H, arom), 4.50 (m, 1 H, 4-H), 4.25 (dd, 1 H, J = 12 Hz, J' = 6 Hz, 5a-H), 4.05 (dd, 1 H, J'' = 12 Hz, J' = 6 Hz, 5b-H), 3.50 (d, 1 H, J = 10 Hz, 2-H), 2.85 (m, 2 H, 2′a-H and 2′b-H), 2.45−2.2 (m, 2 H, 3a-H/3b-H), 2.05 (s, 3 H, Me). − MS (DCI/NH_3): m/z = 298 $(M + NH_4)^+$, 190 $[(M + NH_4)^+ - PhS]$. − $C_{14}H_{16}O_4S$ (280.3): calcd. C 59.98, H 5.75; found C 59.70, H 5.68.

(2S,4S)-4,5-Dihydroxy-2-phenylthiomethyl-4-pentanolide (**7b**): − IR (film): $\tilde{\nu}$ = 1769 cm^{-1} (CO lactone). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.35 (m, 5 H, arom), 4.50 (m, 1 H, 4-H), 3.90 (dd, 1 H, J = 12 Hz, J' = 2 Hz, 5a-H), 3.60 (m, 2 H, 5b-H), 3.48 (d, 5 Hz, 2-H), 3.00 (m, 2 H, 2′-H), 2.50−2.30 (m, 2 H, 3a-H/3b-H), 2.00 (s, 1 H, OH). − MS (DCI/NH_3): m/z = 256 $(M + NH_4)^+$.

(2R,4S)-5-O-Acetyl-4,5-dihydroxy-2-phenylthiomethyl-4-pentanolide (**8a**): IR (film): $\tilde{\nu}$ = 1750 cm^{-1} (CO ester), 1780 (CO lactone). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.30 (m, 5 H, arom), 4.68 (m, 1 H, 4-H), 4.17 (dd, 1 H, J = 12 Hz, J' = 4 Hz, 5a-H), 4.05 (dd, 1 H, J = 12 Hz, J' = 4 Hz, 5b-H), 3.45 (m, 1 H, 2-H), 2.85 (m, 2 H, 2′a-H and 2′b-H), 2.23 (m, 1 H, 3-H), 1.90 (s, 3 H, Me). − MS (DCI/NH_3): m/z = 298 $(M + NH_4)^+$, 190 $[(M + NH_4)^+ - PhS]$. − $C_{14}H_{16}O_4S$ (280.3): calcd. C 59.98, H 5.75; found C 60.05, H 5.70.

(2R,4S)-4,5-Dihydroxy-2-phenylthiomethyl-4-pentanolide (**8b**): IR (film): $\tilde{\nu}$ = 1769 cm^{-1} (CO lactone). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.40 (m, 5 H, arom), 4.65 (m, 1 H, 4-H), 3.90 (dd, 1 H, J = 12 Hz, J' = 2 Hz, 5b-H), 3.70 (dd, 1 H, J = 12 Hz, J' = 4 Hz, 5a-H), 3.50 (dd, 1 H, J = 12 Hz, J' = 2 Hz, 2-H), 3.00 (m, 2 H, 2′-H), 2.42 (m, 1 H, 3a-H), 2.24 (s, 1 H, OH), 2.00 (m, 1 H, 3b-H). − MS (DCI/NH_3): m/z = 256 $(M + NH_4)^+$.

(2S,4S)-4-Acetoxymethyl-2-methyl-γ-butyrolactone (**9**) (from lactone **6**): A solution of **6** (500 mg, 1.78 mmol) in EtOAc (20 ml) was stirred for 3 h at room temperature and under H_2 in the presence of palladium on charcoal (10%). After filtration through a Celite pad and concentration of the filtrate, a residue was obtained, which was purified by flash column chromatography [cyclohexane/ethyl acetate (2:1)] to give 250 mg (81%) of **9**. − $[\alpha]_D^{20}$ = +45 (c = 1, $CHCl_3$); ref.[6]: +45 (c = 0.7, $CHCl_3$). − ^1H NMR (250 MHz, $CDCl_3$): δ =

4.59 (m, 1 H, 4-H), 4.40 (m, 2 H, 5-H), 2.70 (m, 3 H, 2-H, 3a-H), 2.11 (s, 3 H, OAc), 1.81 (dd, 1 H, J = 12 Hz, J' = 10 Hz, 3b-H), 1.33 (d, 3 H, J = 6.5 Hz, CH_3). − $C_8H_{12}O_4$ (172.1): calcd. C 55.81, H 7.02; found C 55.67, H 6.95. − **9** (from lactone **7a**): To a solution of **7a** (500 mg, 1.78 mmol, 80% d.e.) in EtOH (20 ml), obtained by addition of thiophenol to compound **6** according to condition C, Raney Nickel (100 mg) was added and the suspension was refluxed for 6 h. After filtration and evaporation of the solvent, compound **9** was obtained (300 mg, 88%).

1,5-Di-O-acetyl-2-C-phenylthiomethyl-2,3-dideoxy-D-erythro-pentofuranose (**10**): To a cooled solution (−78°C) of compound **8a** (80% d.e., 2 g, 7.4 mmol) in anhydrous toluene (100 ml), was added 10 ml of a 1.5 M solution of DIBAH in toluene. The reaction was stirred for 1.5 h, then acetic anhydride (5 ml) was added and the mixture was allowed to reach room temp. under stirring. The mixture was stirred at the same temperature for 12 h, quenched by addition of water (100 ml) and extracted with EtOAc. The organic layers were washed with an aq. saturated solution of $NaHCO_3$, with brine and dried (Na_2SO_4), giving 1.7 g of compound **10** (71%) after concentration under reduced pressure. R_f = 0.6 [cyclohexane/ethyl acetate (1:1)]. − IR (film): $\tilde{\nu}$ = 1740 (ester), 1720 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.40 (m, 5 H, H-arom), 6.30 (d, 0.5 H, J = 3 Hz) and 6.28 (br s, 0.5 H) [1-H], 4.75 (m, 0.5 H) and 4.23 (m, 0.5 H) [4-H], 4.00 (m, 1 H) and 3.70 (m,1 H) [5-H], 3.25−2.60 (m, 3 H, 2′-H and 2-H), 2.23 (m, 2 H, 3-H), 2.06−1.90 (m, 6 H, OAc). − MS (DCI/NH_3): m/z = 342 $(M + NH_4)^+$, 282 $(M^+ - Ac)$, 265 $(M + H - OAc)^+$. − $C_{16}H_{20}O_5S$ (324.3): calcd. C 59.24, H 6.21; found C 59.01, H 6.15.

2-Acetoxymethyl-2,3,3a,9b-tetrahydro-4H-1-oxa-5-thiacyclopenta[a]naphthalene (**12**): A suspension of thymine (252 g, 2 mmol) in hexamethyldisilazane (10 ml) and pyridine (5 ml) was refluxed for 4 h. After concentration under reduced pressure and repeated co-evaporations with toluene, a residue was obtained. The latter was further dissolved in dichloromethane (5 ml) and added to a solution of **10** (324 mg, 1 mmol) in dichloromethane (25 ml). Then, at −78°C, a 1 M solution of TMSOTf in dichloromethane (5 ml) was added dropwise and the resulting mixture was stirred for 24 h at room temp. After addition of a saturated aq. solution of $NaHCO_3$ (10 ml), the reaction mixture was extracted with ethyl acetate. The organic layers were washed with water, brine and dried ($MgSO_4$). Concentration under reduced pressure afforded a residue which was purified by flash chromatography to give 105 mg (40%) of compound **12** as an oil. − ^1H NMR (90 MHz, $CDCl_3$): δ = 7.50−6.90 (m, 4 H, H-arom), 4.75 (d, 1 H, J = 6 Hz, 1-H), 4.40 (m, 2 H, 5-H),4.10 (m, 1 H, 4-H), 2.8 (m, 2 H, 2′-H), 2.5 (m, 1 H, 3a-H), 2.45−2.02 (m, 2 H, 3-H), 2.02 (s, 3 H, OAc), 1.60 (m, 1 H, 3-H). − MS (DCI/NH_3): m/z: 265 $(M + H)^+$, 282 $(M+ NH_4)^+$. − $C_{14}H_{16}O_3S$ (264.3): calcd. C 63.61, H 6.10; found C 63.40, H 5.95.

1,5-Di-O-acetyl-2,3-dideoxy-2-C-(phenylsulfoxymethyl)-D-erythro-pentofuranose (**13**): To a cooled solution (0°C) of compound **10** (648 mg, 2 mmol) in a mixture of MeOH/toluene (1:1, 60 ml) was added dropwise an aq. solution of $NaIO_4$ (600 mg, 2.8 mmol, 12 ml). The mixture was stirred for 48 h at 0°C and extracted with EtOAc after addition of water (10 ml). The organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, giving 670 mg (98%) of compound **13**. − IR (film): $\tilde{\nu}$ = 1740, 1720 cm^{-1}. − ^1H NMR (270 MHz, $CDCl_3$): δ = 7.60 (br s, 2 H, H-arom, J < 1 Hz), 7.50 (br s, 3 H, H-arom, J < 1 Hz), 6.30 (d, 0.3 H, J = 5 Hz) and 6.20 (d, 0.3 H, J = 5 Hz) and 5.95 (m, 0.4 H) [1-H], 4.80 (m, 0.5 H, 4-H), 4.5−4.2 (m, 0.5 H, 4-H), 4.2−3.8 (m, 2 H, 5-H), 3.2−2.5 (m, 3 H, 2-H and 2′-H), 2.50−2.00 (m, 2 H, 2-H, 3-H), 2.01 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3). − $C_{16}H_{20}O_6S$ (340.3): calcd. C 56.46, H 5.92; found C 56.07, H 5.85.

1-[5-O-Acetyl-2,3-dideoxy-2-C-(phenylsulfoxy)methyl-β-D-erythro- and -α-D-threo-pentanofuranosyl]thymine (**14** and **15**): A solution of compound **13** (340 mg, 1 mmol) in anhydrous dichloromethane (25 ml), kept under argon, was added to silylated thymine (1 mmol) in dichloromethane (15 ml) at −78°C. Then, a 1 M solution of TMSOTf (5 ml) was added. After stirring at room temperature for 24 h and addition of an aq. solution of $NaHCO_3$ (10 ml), the reaction mixture was extracted with EtOAc (3 × 50 ml). The organic layers were washed with H_2O, brine and dried ($MgSO_4$). Concentration under reduced pressure furnished 162 mg (40%) of **14** and **15** as a complex mixture of diastereoisomers (asymmetric sulfoxide and *erythro/threo* isomers). − IR (film): $\tilde{\nu}$ = 1740 (CO ester), 1720, 1700 (CO base) cm^{-1}. − MS (DCI/NH_3): m/z = 407 $(M + H)^+$, 281 $(M - PhSO)^+$, 155 $(M - Base - PhSO)^+$, 127 $(Base + H)^+$. − ^1H NMR (250 MHz, $CDCl_3$): δ = 9.50 (s, 1 H, NH), 7.60 (m, 5 H, H-arom), 7.35 (s, 0.2 H, 6-H), 7.32 (s, 0.2 H, 6-H), 7.09 (s, 0.5 H, 6-H), 6.00−5.7 (m, 1 H, 1-H), 4.92 (m, 0.2 H) and 4.63 (m, 0.8 H) [4′-H], 4.40−3.80 (m, 2 H, 5′-H), 3.20−2.50 (m, 3 H, 2-H and 2′-H), 2.5−2.20 (m, 2 H, 3-H), 2.25, 2.23, 2.15, 2.13 (4 s, 3 H, OAc), 2.03, 2.01, 1.97, 1.94 (4 s, 3 H, Me). − $C_{19}H_{22}N_2O_6S$ (406.4): calcd. C 56.15, H 5.46; found C 55.90, H 5.39.

α- and β-D-(5′-O-Acetyl-2′,3′-dideoxy-5-methyl-2′-C-methyleneuridine) (**16** and **17**): A mixture of compounds **14** and **15** (89 mg, 0.2 mmol) in xylene (60 ml) was stirred at reflux for 15 h in the presence of pyridine (16 ml). After concentration under reduced pressure, the solid obtained was purified by flash chromatography to give 30 mg (49%) of a mixture of unseparable anomers β-**16** and α-**17**, along with 30 mg of starting material **14** and **15**.

Compounds **16** *and* **17**: IR (film): $\tilde{\nu}$ = 1740 (CO ester), 1720, 1700 (CO base) cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 9.50 (s, 0.7 H, NH), 9.10 (s, 0.3 H, NH), 7.07 (s, 0.3 H, 6-H), 7.00 (s, 0.7 H, 6-H), 5.40 (s, 1 H, 2″a-H), 5.20 (m, 1 H, 2′b-H), 4.70 (m, 0.7 H, 4′-H), 4.50−4.15 (m, 2.3 H, 5′-H, 4′-H), 2.80−2.55 (m, 3′-H), 2.20, 2.10 and 1.90 (3 s, 6 H, OAc and 5-Me). − MS (DCI/NH_3): m/z = 298 $(M + 18)^+$, 281 $(M + H)^+$, 155, 127. − $C_{13}H_{16}N_2O_5$ (280.2): calcd. C 55.71, H 5.75; found C 55.50, H 5.69.

β-D-(2′,3′-Dideoxy-5-methyl-2′-C-methyleneuridine) (**5**): A mixture of **16** and **17** (60 mg, 0.21 mmol) in MeOH (10 ml), saturated with ammonia, was stirred at room temperature for 5 h. The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography [ethyl acetate/MeOH (9:1)] to give 39 mg (78%) of more polar β-D (R_f = 0.4) nucleoside **5**, recrystallized from ethyl acetate, and 8 mg (16%) of less polar (R_f = 0.46) α-D nucleoside **18** as an oil. − **5**: M.p. 134−135°C (ref.[14]: 135°C; ref.[21]: 132−134°C); $[\alpha]_D^{20}$ = −74 (c = 1, MeOH). − UV/Vis (MeOH): λ_{max} = 266 nm (ε = 8800), λ_{min} = 235 nm. − UV/Vis (NaOH, 0.01 N): λ_{max} = 266 nm (ε = 7700), λ_{min} = 246 nm [ref.[21]: UV/Vis (MeOH): λ_{max} = 267 nm (ε = 9700); UV/Vis (NaOH, 0.01 N): λ_{max} = 267 nm (ε = 8800), λ_{min} = 237 nm]. − ^1H NMR (300 MHz, $CDCl_3$): δ = 8.89 (s, 1 H, NH), 6.97 (d, 1 H, J = 1, 6-H), 6.58 (s, 1 H, 1′-H), 5.34 (m, 1 H, 2″a-H), 5.15 (m, 1 H, 2″b-H), 4.24 (m, 1 H, 4′-H), 3.97 (dd, 1 H, J = 2.5 Hz, J' = 12 Hz, 5′a-H), 3.68 (dd, 1 H, J = 4 Hz, J' = 12 Hz, 5′b-H), 2.82 (m, 1 H, 3′a-H), 2.70 (dd, 1 H, J = 6.5 Hz, J' = 16.5 Hz, 3′b-H), 1.88 (s, 3 H, CH_3). − MS (DCI/NH_3): m/z = 239 $(M + H)^+$, 130 $(sugar - 1+ NH_4)^+$, 127 $(thymine + H)^+$, 113. − $C_{11}H_{14}N_2O_4$ (238.2): calcd. C 55.4, H 5.92; found C 55.01, H 5.85. − **18**: $[\alpha]_D^{20}$ = +23 (c = 1, MeOH). − IR (film): $\tilde{\nu}$ = 3400 (OH), 1720, 1700 (CO base) cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 8.90 (s, 1 H, NH), 6.97 (d, 1 H, J = 1 Hz, 6-H), 6.58 (s, 1 H, 1-H), 5.36 (m, 1 H, 2′a-H), 5.12 (m, 1 H, 2′b-H), 4.48 (m, 1 H, 4′-

H), 3.77 (dd, 1 H, J = 12 Hz, J' = 3 Hz, 5′a-H), 3.57 (dd, 1 H, J = 12 Hz, J' = 5 Hz, 5′b-H), 2.84 (dd, 1 H, J = 16 Hz, J' = 5 Hz, 3′a-H), 2.65 (m, 1 H, 3′b-H), 2.10 (s, OH), 1.90 (s, 3 H, 5-Me). − MS (DCI/NH_3): m/z = 256 $(M + 18)^+$, 239 $(M + H)^+$, 113 (sugar). − $C_{11}H_{14}N_2O_4$ (238.2): calcd. C 55.4, H 5.92; found C 55.02, H 5.82.

2-C-Acetoxymethyl-1,2,5-tri-O-acetyl-3-deoxy-D-erythro-pentofuranose (**20**): A solution of α-D-isosaccharinolactone (2,5-dihydroxy-2-hydroxymethyl-4-pentanolide, **19**, 5 g, 30 mmol) in water at 0°C was added to an aq. solution of 1 M $NaBH_4$. After stirring for 30 min, the reaction was neutralized by addition of Amberlite® IRC-50 ion-exchange resin, filtered and the filtrate was concentrated under vacuum and then co-evaporated with MeOH (4 × 50 ml). After purification by flash chromatography [CH_2Cl_2/MeOH (9:1 → 5/1)], 2 g of a syrup composed of a mixture of aldose and alditol was obtained. This crude material was treated with pyridine (20 ml) and Ac_2O (6 ml) at reflux for 19 h. After concentration under reduced pressure, the residue was purified by flash colum chromatography [cyclohexane/acetone (1:1)] to give 4 g of **20** (39% overall yield) as a syrup. − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 6.39 (s, 0.3 H, 1-H), 6.36 (s, 0.7 H, 1-H), 4.78−3.96 (m, 5 H, 2′-H, 4-H, 5-H), 2.73 (m, 1 H, 3a-H), 2.21 (m, 1 H, 3b-H), 2.01 (s, 12 H, OAc). − MS (DCI/NH_3): m/z = 350 $(M + NH_4)^+$, 306, 273. − $C_{14}H_{20}O_9$ (332.2): calcd. C 50.58, H 6.06; found C 50.70, H 5.95.

Phenyl 2-C-Acetoxymethyl-2,5-di-O-acetyl-3-deoxy-β-D-threo-thiopentofuranoside (**21**): To a solution of compound **20** (290 mg, 0.87 mmol) in anhydrous dichloromethane (4 ml) at 0°C under argon, were added thiophenol (100 µl, 0.97 mmol) and then BF3·Et2O (320 µl, 2.6 mmol). The reaction mixture was stirred for 2.5 h and poured into a cold saturated aq. solution of $NaHCO_3$ (10 ml). After extraction with dichloromethane, the organic layer was washed with H_2O, then with brine and dried ($MgSO_4$). Concentration under reduced pressure, followed by purification by flash chromatography [cyclohexane/EtOAc (7:3)] gave compound **21** (138 mg, 40%) as an oil. − $[\alpha]_D^{20}$ = −112 (c = 0.99, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3400 (OH), 1720, 1700 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55−7.58 (m, 2 H, Ph), 7.32−7.39 (m, 3 H, Ph), 5.90 (s, 1 H, 1-H), 4.78 and 4.90 (2 d, 2 H, J = 12 Hz, 2′-H), 4.52 (m, 1 H, 4-H), 4.42 (dd, 1 H, J = 11.5 Hz, J' = 4 Hz, 5a-H), 4.26 (dd, 1 H, J = 11.5 Hz, J' = 6 Hz, 5b-H), 2.66 (dd, 1 H, J = 13 Hz, J' = 6 Hz, 3a-H), 2.12 (s, 3 H, OAc), 2.11 (m, 1 H, 3b-H), 2.10 (s, 6 H, 2 × OAc). − MS (DCI/NH_3): m/z = 400 $(M + NH_4)^+$, 273 $(M - SPh)^+$. − $C_{18}H_{22}O_7S$ (382.4): calcd. C 56.53, H 5.80; found C 56.60, H 5.70.

Phenylsulfonyl 2-C-Acetoxymethyl-2,5-di-O-acetyl-3-deoxy-β-D-threo-pentofuranoside (**22**): To a solution of compound **21** (1.13 g, 2.96 mmol) in anhydrous dichloromethane (80 ml) under argon, 50% mCPBA (2.04 g, 6.51 mmol) and $NaHCO_3$ (1.24 g, 14.8 mmol) were added at 0°C. The reaction mixture was stirred for 5 h at room temp. After addition of a 10% aq. solution of sodium sulfite (10 ml), the organic layer was washed with an aq. saturated solution of $NaHCO_3$, then with water, brine and dried ($MgSO_4$). The residue obtained after evaporation of the solvent was purified by flash column chromatography [cyclohexane/acetone (7:3)] to give the crystalline sulfone **22** (1.14 g, 93%); M.p. = 94−96°C. − $[\alpha]_D^{20}$ = −43 (c = 1.03, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2929, 1747 (CO), 1371, 1325, 1235 and 1157 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (m, 5 H, arom H), 5.41 (s, 1 H, 1-H), 4.85 and 5.32 (2 d, 2 H, 2′-H), 4.51 (m, 1 H, 4-H), 4.44 (dd, 1 H, J = 7 Hz, J' = 11.5 Hz, 5a-H), 4.34 (dd, 1 H, J = 3.5 Hz, J' = 11.5 Hz, 5b-H), 2.58 (dd, 1 H, J = 5.5 Hz, J' = 13.5 Hz, 3a-H), 2.39 (dd, 1 H, J = 10.5 Hz, J' = 13.5 Hz, 3b-H), 2.11 (s, 6 H, 2 × OAc), 2.05 (s, 3 H, OAc). − MS (DCI/NH_3): m/z = 432 $(M + NH_4)^+$. − $C_{18}H_{22}O_9S$ (414.4): calcd. C 52.17, H 5.35; found C 52.34, H 5.19.

1,4-Anhydro-2-C-acetoxymethyl-4-O-acetyl-2,3-dideoxy-D-glycero-pent-1-enitol (**23**): Under argon, sulfone **22** (415 mg, 1.1 mmol) and HMPA (4.2 ml) were successively added, at room temp., to a 0.1 M solution of samarium iodide in THF (50 ml). After 30 min, the initially blue color of the reaction mixture turned to dark purple and 50 ml of ether and a saturated aq. solution of ammonium chloride (10 ml) were added. The organic layer was separated and washed with water (5 × 20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. This gave **23** as an oily residue (450 mg) directly treated for condensation with a silylated base. − IR (film): $\tilde{\nu}$ = 2956, 1741, 1640, 1250 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.44 (s, 1 H, 1-H), 4.93 (m, 1 H, 4-H), 4.70 (s, 2 H, 2′-H), 4.24 (m, 2 H, 5-H), 2.86 (m, 1 H, 3a-H), 2.46 (dd, 1 H, J = 7.5 Hz, J' = 15 Hz, 3b-H), 2.18−2.14 (2 s, 2 × 3 H, OAc). − MS (DCI/NH_3): m/z = 232 $(M + NH_4)^+$, 215 $(M + H)^+$, 172 $(M - Ac)^+$, 155 $(MH - AcOH)^+$.

5′-O-Acetyl-2′,3′-dideoxy-5-methyl-2′-methylideneuridine (**16**): To a solution of crude compound **23** (ca. 0.5 mmol) in anhydrous THF (4 ml), $Pd_2(DBA)_3$ (32 mg, 0.035 mmol) and triphenylphosphane (28 mg, 0.1 mmol) were successively added. After stirring for 15 min, a solution of 2,4-bis(trimethylsilyloxy)thymine (prepared from 0.5 mmol of thymine, NH_4SO_4 cat., and hexamethyldisilazane)[9], in anhydrous THF (2.5 ml) was added and the solution was heated and maintained at 60°C for 8 h. After cooling, the reaction mixture was diluted with ether (20 ml) and the organic layer was washed with a saturated aq. NaCl solution (10 ml) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash column chromatography [cyclohexane/EtOAc (3:7)] led to 29 mg of compound **16** (21%). − ^{1}H NMR (90 MHz, $CDCl_3$) δ = 9.10 (br s, 1 H, NH), 7.07 (s, 1 H, 6-H), 6.60 (s, 1 H, 1′-H), 5.37 (m, 1 H, 2″a-H), 5.20 (m, 1 H, 2″b-H), 4.50−4.15 (m, 3 H, 5′-H and 4′-H), 2.77 (m, 2 H, 3′-H), 2.10 (s, 3 H, OAc), 1.90 (s, 3 H, CH_3). − MS (DCI/NH_3): m/z = 298 $(M + NH_4)^+$, 281 $(M + H)^+$, 155 (sugar). − $C_{13}H_{16}N_2O_5$ (280.2): calcd. C 57.1, H 5.76, N 9.99; found C 57.22, H 5.73.

2′,3′-Dideoxy-5-methyl-2′-methylideneuridine (**5**): Compound **16** (28 mg, 0.10 mmol) in a MeOH/NH_3 solution (4 ml) was stirred for 5 h. The residue obtained after concentration under reduced pressure was purified by flash column chromatography [cyclohexane/EtOAc (4:6)] to give crystalline compound **5** (19 mg, 80%)

5′-O-Acetyl-2′,3′-dideoxy-2′-methylidenecytidine (**25**): This compound was prepared from crude **23** (0.5 mmol) and silylated cytosine [prepared by refluxing a mixture of cytosine (55 mg, 0.5 mmol), and ammonium sulfate (catal. amount) in HMDS (4 ml)] as described for compound **16**. The residue obtained after evaporation of the solvent was purified by flash column chromatography [EtOAc/MeOH (90:10)] giving the β nucleoside **25** (42 mg, 32%) and a mixture of α.β nucleoside anomers (10 mg, overall yield 39%, ratio β/α = 8:2).

Compound **25** (syrup): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, 1 H, J = 7.5 Hz, 6-H), 6.65 (s, 1 H, 1′-H), 5.90 (d, 1 H, J = 7.5 Hz, 5-H), 5.24 (m, 1 H, 2″a-H), 5.17 (m, 1 H, 2″b-H), 4.31 (m, 2 H, 4′-H, 5′a-H), 4.20 (dd, 1 H, J = 6, J' = 12.5 Hz, 5′b-H), 2.76 (dd, 1 H, J = 16, J' = 6.5 Hz, 3′a-H), 2.57 (m, 1 H, 3′b-H), 2.08 (s, 3 H, OAc). − MS (DCI/NH_3): m/z = 266 $(M + 1)^+$.

2′,3′-Dideoxy-2′-methylidenecytidine (**4**): A solution of compound **25** (18 mg, 0.068 mmol) in MeOH/NH_3 (3 ml) was stirred for 2 h. The residue obtained after evaporation of the solvent was purified by flash column chromatography [EtOAc/MeOH (90:10)] to give **4** (11 mg, 73%). − $[\alpha]_D^{20}$ = −24 (c = 0.85, MeOH). − UV/Vis (MeOH): λ_{max} = 272 nm (ε = 6230), λ_{min} = 255 nm. − UV/Vis (MeOH, HCl): λ_{max} = 282 nm (ε = 12000), λ_{min} = 244 nm. − ^{1}H NMR (300 MHz, DMSO): δ = 7.56 (d, 1 H, J = 7.5 Hz, 6-H),

7.20−7.15 (d, 2 H, NH_2), 6.47 (s, 1 H, 1′-H), 5.73 (d, 1 H, J = 7.5 Hz, 5-H), 5.19 (d, 1 H, J = 2 Hz, 2″a-H), 4.98 (d, 1 H, J = 2 Hz, 2″b-H), 4.95 (br s, 1 H, OH), 4.07 (m, 1 H, 4′-H), 3.61 (m, 1 H, 5′a-H), 3.51 (m, 1 H, 5′b-H), 2.64 (m, 2 H, 3′-H); identical to data in ref.[21]. − MS (DCI/NH_3): m/z = 224 $(M + H)^+$, 129, 113, 112. − $C_{10}H_{13}N_3O_3$ (223.2): calcd. C 53.81, H 5.87, N 18.82; found C 58.87, H 5.79, N 18.76.

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