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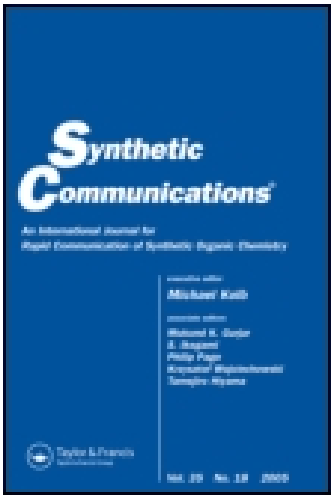

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A Novel Route to Pyrimidine Isodideoxynucleosides via Michael-Type Addition on Unsaturated Modified Sugars

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A NOVEL ROUTE TO PYRIMIDINE *ISO*DIDEOXYNUCLEOSIDES *VIA* MICHAEL-TYPE ADDITION ON UNSATURATED MODIFIED SUGARS

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Abstract : A short, stereocontrolled synthesis of isonucleosides is described. This approach is based on the Michael-Type addition of silylated uracil or thymine with an appropriate acceptor as pyranoside precursor. The alkylated products obtained allow carbonyl reduction, providing a straightforward way to prepare new sugar-modified nucleosides.

We recently reported a new synthesis of optically active α-alkyl-2-furylcarbinols **1** which is based on intramolecular sulfoxide group asymmetric induction[1]. This approach, from furaldehyde (Figure 1), which has been then applied by others[2], completes the classical induction by optically active aminoalcohols[3] or by kinetically controlled deracemization[4] . Oxidation of these compounds, as enantiomers or not, into hydroxypyranones **2** have been the subject of numerous reports. Here we would like to report some studies directed towards the transformation of **3** (R = methyl or hydroxymethyl) as a racemic or a pure enantiomer, by a Michael-type reaction into *iso*ketonucleosides with the nucleobase attached to C-2' (type II). Both types, **I** and **II**, are known to present antiviral activities[5].

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These ketopyranosyl compounds are formally unsaturated sugars[6], so, it is not surprising that an alternative route to **2** or **3** starts from commercial tri-*O*-acetylglucal using the well known Ferrier rearrangement[7]. In a previous study, we observed that glycosyl derivatives of **3** (R' = Acetyl) could be transformed into 2',3'-unsaturated-2,3'- dideoxynucleosides[8] (type I *pseudo* nucleosides).

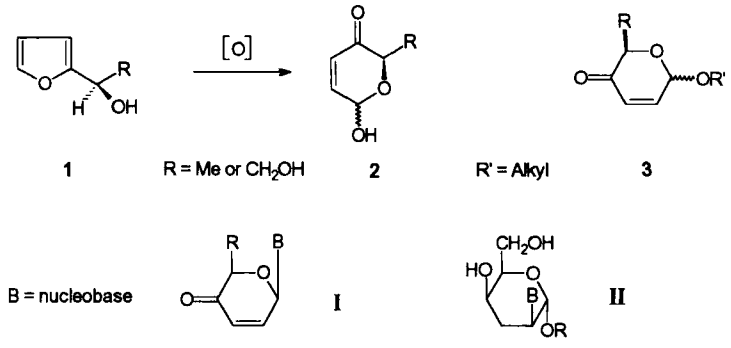

FIG. 1

For this purpose, racemic **6**, chosen as test substrate for its easy access, was at first prepared from α-methyl-2-furylcarbinol **4**[9] in two steps (Figure 2). Separation of the most abundant *trans*-isomer (the so-called "α-anomer"), was accomplished by silica gel column. This compound was then allowed to react in the presence of trimethylsilyl triflate as a Lewis acid with *bis*-trimethylsilyl uracil[10] obtained *in situ* just before, with an excess of N,O-*bis*-trimethylsilylacetamide (BSA). Although we used Vorbrüggen conditions[11] known to attack the anomeric position, **7** was obtained in 45% yield[12]. This nucleophilic conjugate addition appeared to be under stereoelectronic control, giving a single isomer for which N-1 was involved in the glycosidic bond from the ^{1}H and ^{13}C NMR data[13], with no trace of *O*-alkylation[14]. In a comparative study, when there is an acetate instead of an alkoxy group, the oxocarbonium ion is more favourably formed. For instance when **8** replaced **6**, **9** was formed as a 1:1 mixture of α- and β-anomer linkages[8].

It is to note that Michael-type additions have not been exploited until recently for the preparation of nucleosides analogues[16-17]. In order to point out the usefulness of this behaviour in isonucleoside synthesis, we wish to disclose a novel entry to

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galactoses derivatives, starting with **12** (or **13**), described as representative examples and model reactions (Figure 3). It was initiated from tri-O-acetyl-D-glucal **10** which was converted into the known pseudoglycals **11a** or **11b** by iodine catalyzed Ferrier glycosylation[18] of isopropanol (**11a**) or ethanol (**11b**), followed by hydrolysis[19]. Selective protection with a bulky reagent of the primary alcohol as *tert*-butyldimethylsilyl-group[20] (for **11a**) or pivalate[21] (for **11b**), followed by pyridinium dichromate oxydation[21,22] (better yield than with MnO_2 owing to a difficult filtration step) gave respectively **12** and **13**[12,23].

Likewise, pyrimidine nucleoside bases gave, after bis-silylation as above mentionned, nitrogen glycosylation reactions under the same conditions[10] (see, for example, **14**).

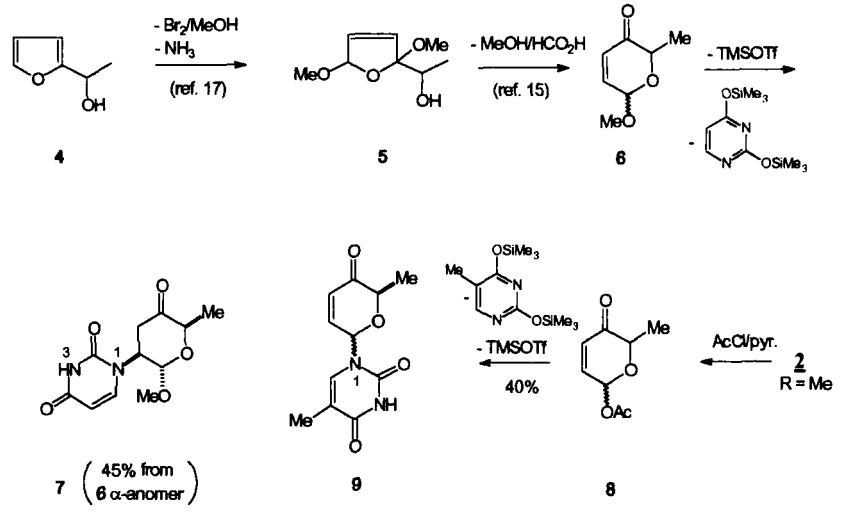

FIG. 2

By some aspects these results confirm very recent examples on the diastereoselective conjugate addition to oxygenated αβ-unsaturated δ-lactones, as described by Herradon[24]. The reduction of the keto function of Michael-type adducts was then investigated with respect to the stereochemical outcome[16]. It was observed that an inversion at C-4' took place during the $NaBH_4$ reduction, giving a 2'3'-dideoxy isopropyl O-α-galactonucleoside, as revealed the equatorial position of the H-4' and

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nOe difference spectroscopy (table I). Cleavage of the silyl-group by tetrabutylammonium fluoride, finally gave the single diastereoisomer **15**, as did also pivalate **13** in basic conditions[25]. Syntheses of uracil, thymine and 5-fluorouracil derivatives of the foregoing type of nucleosides have also been prepared.

Although the yields are unoptimized, diastereoselective syntheses can be achieved *via* simple strategy from readily available hexenopyranosiduloses as starting materials. Our method may be compared with the few other ones that lead to regioisomeric nucleosides analogues on C-2' [26-28].

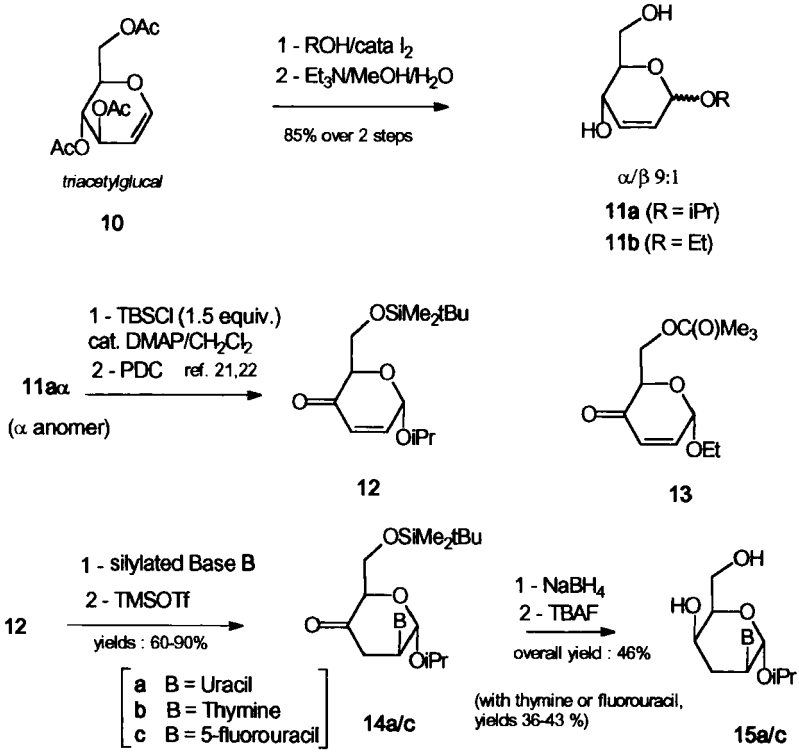

FIG. 3

Experimental section.

^1H and ^{13}C NMR were obtained for solutions in $CDCl_3$ on a Bruker AC 400 spectrometer and were typically referenced using the TMS peak. Coupling constants (J)

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Table 1 — nOe spectroscopy for the silylated precursor 16 of 15a.

signal	origin	H6	H1'	H2'	H4'	H5'	H3"	H3'
var.	δ ppm(CDCl$_3$)	8.3	5,02	4,46	4,1	3,91	2,22	2,09
H6			7,9					
H5		11,1						
H1'		6,7		4,9				
H2'							10,1	4,3
H3'				1,3	2,2		20	
H3"				2,9		1,9		20
H4'						3,7	5,9	3,3
H5'					6,6		3,6	

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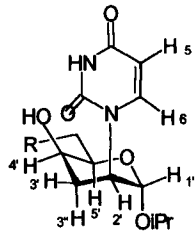

are given in Hz with the following abbreviations for splitting patterns : s = singlet, ps = pseudo-singlet, d = doublet, t = triplet, q = quartet and m = multiplet. The IR spectra were recorded on a Unicam Genesis FTIR spectrometer. The mass spectra were recorded on a Mat CH7 spectrometer. Optically rotations were measured on a Perkin-Elmer model 240 polarimeter. All reactions were monitored on TLC plates (Merck silica gel 60F254, 0.25 mm thickness). Elemental analyses were performed at the CNRS Institute of Gif-sur-Yvette (F-91198). Commercially available chemicals were used without further purification. Products were purified by flash chromatography prior to analysis and yields are not optimized.

Experimental procedures are illustrated by the following examples.

6-methoxy-2-methyl-2H-pyran-3(6H)-one **6** (cis/trans mixture of isomers) was obtained from methyl-(2-furyl) methanol according to ref. 15.

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methyl 2-uracil-2'3'6'-trideoxy-α-D-erythro-hexopyranoside-4-ulosyle **7**.
In a two-neck round-bottom flask (25 mL) equipped with a magnetic stirrer and a drying tube connected to a nitrogen atmosphere, a mixture of uracil (1 g, 9 mmol) in dry acetonitrile (120 mL) was prepared. *N,O*-bis(trimethylsilyl) acetamide (BSA) (6.1 mL, 25 mmol) was added *via* a syringe and the suspension stirred at r.t. until complete dissolution of uracil. Ketone **6** (923 mg, 6.5 mmol) was added over 2 min followed by trimethylsilyltrifluoromethanesulfonate (TMSOTf) (1.25 mL, 7 mmol) *via* the syringe. The resulting solution was stirred for 2 h at ambient temperature, then water (100 mL) was added. After concentration *in vacuo*, the aqueous solution was partitioned with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), filtered and again concentrated *in vacuo*. The pale yellow solid (0.739 g, 45 % yield) consisted of the crude **7** as a single isomer, that could not be chromatographied on silica-gel without an important degradation by retro-Michael reaction, but was used as such in the next step. Data for **7** : mp 295-96°C ; ^{1}H NMR (400 Mhz, Me_2SO-*d6*) δ = 11.29 (br s, NH), 7.48 (d, J=8.0 Hz, 6-H), 5.55 (dd, J = 8, 2.1 Hz, 5-H), 4.9 (d, J = 4.5 Hz, 1'-H), 4.64 (m, 2'-H), 4.17 (q, J = 6.7 Hz, 5'-H), 3.29 (s, OMe), 3.00 (dd, J = 16.6, 9.3 Hz, 3"-H), 2.6 (dd, J = 16.6, 5.7 Hz, 3'-H), 1.16 (d, J = 6.72 Hz, Me).^{13}C NMR (100 Mhz, Me_2SO-*d6*) δ = 208.3, 164, 151.7, 144.5, 102.8, 99.8, 71.4, 57.2, 55.9, 39.0, 15.6. HRMS obs. 254.0912. Calc. for $C_{11}H_{14}N_2O_5$: 254.0903.

6-acetoxy-2-methyl-2H-pyran-3(6H)-one **8.** A mixture of *cis/trans* isomers **2** (R = Me, 2.56 g, 2 mmol), acetic anhydride (0.7 mL, 7.4 mmol) and pyridine (0.25 mL) was stirred at r.t. for 5 min. CH_2Cl_2 (10 mL) was added and pyridine was eliminated by an aqueous solution (10 g/L) of $CuSO_4$ (3 × 6 mL). The organic layer was washed by water (6 mL) dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product which was flash chromatographied on silica-gel. Evaporation of the solvent gave an isomeric mixture of *cis*- (28 %) and *trans*- (72 %) acetates **8**.

2,4-bis(trimethylsiloxy)-5-thymine. A suspension of 1.9 g (15 mmol) of thymine and 30 mL of hexamethyldisilazane (HMDS) was heated to 120°C under argon during 1 h with stirring. After cooling to r.t. Me_3SiCl (0.2 mL, 1.6 mmol) was then added and the reaction was allowed to proceed again for 2 h at reflux. Evaporation *in vacuo* left a partially crystallized residue which was distillated cold water was not circulated through the condenser, since the product tended to solidify). The title compound (3.5 g, 80 % yield) was obtained at bp 78-80 °C/0.5 mm.

1-(5'-methyl-2',3'-dideoxy-α/β-glycero-pent-2'-enopyranos-4'-ulosyl) thymine **9**
In a two-neck round-bottom flask (25 mL) equipped with a magnetic stirrer and a drying tube connected to a nitrogen atmosphere, a mixture of 2.4-bis(trimethylsiloxy)-thymine (168 mg, 0.62 mmol) in dry 1,2-dichloroethane (11 mL). 95 mg (0.56 mmol) of acetates **8** were added, followed by trimethylsilyltrifluoromethanesulfonate (TMSOTf) (130 µL, 0.56 mmol) *via* a syringe. The resulting solution

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was stirred for 2 h at ambient temperature, then poured on a cold aqueous solution of $NaHCO_3$. The pink precipitate was filtrated on a sintered disk, and the aqueous layer extracted with CH_2Cl_2 (3 ×40 mL). The organic layer was washed with water, (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The pale yellow solid (0.112 g ,85 % yield) consisted of **9** as an anomeric mixture of isomers.
^1H NMR (400 MHz, $CDCl_3$) δ = 9.31 (s, 3-H); 7.17 (+ 7.07) (s, 6-H); 6.88 (d, J = 10.2 Hz, 2'-H); 6.78 (+6.74) (s, 1'-H); 6.43 (+6.41) (d,10.2 Hz, 3'-H); 4.47 (+4.40) (d, J = 7 Hz, 5'-H); 1.97 (+1.93) (s, 5-Me); 1.45 (1.37) (d, J = 7 Hz, 6'-Me).

isopropyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside **11aα**. To a solution of 3,4,6-tri-*O*-acetyl-D-glucal (5g, 18.4 mmol) and isopropanol (1.4 mL) in tetrahydrofuran (100 mL) was added 0.932 g of iodine (20 mol %). After being stirred at r.t. for 1.5 h, under nitrogen atmosphere the mixture was diluted with ether (75 mL). The resulting dark-red colored mixture was washed with 50 mL of a 10 % aqueous sodium thiosulfate under stirring until the solution becomes colorless. The aqueous phase was extracted with ether (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. Silica-gel column chromatography of the residues (15 % EtOAc/cyclohexane) afforded 4.74 g (95 % yield) of the glycosylated derivative as an oily α/β mixture (85/15). This mixture (4.38 g) was dissolved in methanol (84 mL) and stirred at r.t. Water (67 mL) and triethylamine (16 mL) were added, then the solution was concentrated by rotary evaporation. Azeotropic elimination in boiling toluene of the traces of water, followed by recrystallization from ether yielded the pure α–anomer, mp 99-102 °C, identical in every way with literature description[18].

isopropyl 6-O-tert-butyldimethylsilyl-4-keto-2,3-dideoxy-α-D-erythro-hex-2-eno pyranoside **12**. In an oven-dried 250 mL flask, protected by a drying tube and nitrogen atmosphere, was added under stirring the diol **11aα** (1.924 g, 10.22 mmol), *tert*-butyldimethylsilylchloride (TBSCl, 2.74 g, 18.2 mmol) followed by anhydrous triethylamnine (2.75 mL) then by a catalytic amount of dimethylaminopyridine (DMAP). The resulting solution was stirred for 1 h at r.t., and washed with saturated aqueous $NaHCO_3$, then NaCl, and finally dried (Na_2SO_4). The solvent was removed *in vacuo*. Purification by column chromatography afforded by careful elution with a gradient of EtOAc in cyclohexane (2 to 5 %) 2.45 g (8.1 mmol) of the monosilylated alcohol (yield 79 %). *isopropyl 6-O-tert-butyldimethyl silyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside* : $[\alpha]_D$ = + 64° (C = 1.0, acetone). ^1H NMR (400 MHz, $CDCl_3$) δ = 5.92 (d, J = 10.2 Hz, 2'-H), 5.71(dd, J = 10.2, 2.3 Hz, 3'-H), 5.05 (m,1'-H), 4.17 (m, 4'-H), 3.96 (sept., J = 6.2, Hz 7'-H), 3.94-3.75 (m, 5'-H, 6'-H, 6"-H), 2.80 (d, J = 4 Hz, H-O), 1.24 (d, J = 6.2 Hz, 8'-Me), 1.17 (d, J = 6.1 Hz, 9'-Me), ^{13}C NMR (100 Mhz, $CDCl_3$) δ = 132.3 ; 126.3 ; 92.2 ; 76.2 ; 69.9 ; 66.9 ; 65.2 ; 26.7 ; 25.6 ; 23.5 ; 21.8 ; 18.1 ; -5.4.

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A solution of this alcohol (2.62 g, 7.47 mmol) in CH_2Cl_2 (19 mL) was added dropwise over a 10 min period to a suspension of pyridinium dichromate (PDC, 3.86 g, 10.26 mmol). This mixture was stirred for 48 h at r.t. before being filtered through celite to remove pyridinium salts. The resulting solution was purified by flash chromatography on a silica-gel column. Elution (5 % EtOAc/cyclohexane) gave 1.75 g (5.83 mmol, 78 % yield) of ketone **12** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.84 (dd, J = 10.1, 3.5 Hz, 2'-H), 6.09 (d, J = 10.3 Hz, 3'-H), 5.41 (d, J = 3.5 Hz, 1'-H), 4.5 (dd, J = 5.8, 2.6 Hz, 5'-H), 4.08 (dd, J = 11.3, 2.7 Hz, 6"-H), 4.08 (sept., J = 6.37, Hz 7'-H), 3.98 (dd, J = 11.3, 5.8 Hz, 6'-H), 1.28 (d, J = 6.2 Hz, 8'-Me), 1.22 (d, J = 6.2 Hz, 9'-Me), 0.9 (s, Me_3Si), 0.1 (s, 2MeSi). ^{13}C NMR (100 Mhz, $CDCl_3$) δ = 195.0 ; 144.6 ; 127.9 ; 91.4 ; 76.0 ; 71.0 ; 62.6 ; 25.8 ; 23.2; 21.8 ; 18.3 ; -5.4.

isopropyl 2'-thymine-6'-O-tert-butyldimethylsilyl-2'3'-dideoxy-α-D-erythro-hexopyranoside **14b**.

In a two-neck round-bottom flask (100 mL) equipped with a magnetic stirrer and a drying tube connected to a nitrogen atmosphere, a mixture of thymine (0.50 g, 3.3 mmol) in dry acetonitrile (45 mL) was prepared. *N,O*-bis(trimethylsilyl) acetamide (BSA) (2.48 mL, 10 mmol) was added *via* a syringe and the suspension stirred at r.t. until complete dissolution of thymine. Ketone **12** (1 g, 3.33 mmol) was added over 2 min followed by trimethylsilyltrifluoromethanesulfonate (TMSOTf) (1.34 mL, 7.4 mmol) *via* the syringe. The resulting solution was stirred for 3 h at ambient temperature, then water (60 mL) was added. After concentration *in vacuo* to remove the acetonitrile, the aqueous solution was partitioned with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), filtered and again concentrated *in vacuo*. The pale yellow oil (1.34 g, 94 % yield) consisted of the crude **14b** as a single isomer, that could not be chromatographied on silica-gel without an important degradation by retro-Michael reaction, but was used as such in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39 (s, large, 3-H), 7.40 (d, J = 1.05 Hz, 6-H), 5.13 (d, J = 2.06 Hz, 1'-H), 4.85 (ddd, J = 7.3, 7.04, 2.06 Hz, 2'-H), 4.17 (pseudo-t, J = 3.18, 2.95 Hz, 5'-H), 4.04 (dd, J = 11.2, 3.81 Hz, 6'-H), 3.99 (dd, J = 11.8, 2.54 Hz, 6"-H), 3.97 (sept., J = 6.2 Hz, 7'-H), 2.98 (dd, J = 16.3, 7.76 Hz, 3"-H), 2.7 (dd, J = 16.4, 6.9 Hz, 3'-H), 1.26 (d, J = 6.3 Hz, 8'-Me), 1.19 (d, J = 6.2 Hz, Me-9'), 0.90 (s, Me_3CSi), 0.08 (s, Me_2Si). ^{13}C NMR (100 Mhz, $CDCl_3$) δ = 205.4 ; 163.8 ; 150.8 ; 137.2 ; 111.8 ; 96.1 ; 76.9 ; 70.2 ; 62.9 ; 55.9 ; 40.7 ; 25.8 ; 22.8 ; 21.2 ; 18.4 ; 12.7 ; -5.4.

14a. This was carried out analogously to the preparation of **14b** on a 4 mmol scale starting from uracil (0.56 g, 5 mmol), BSA (3.43 mL, 13.86 mmol), acetonitrile (67 mL), TMSOTf (1.3 mL, 7.4 mmol) and ketone 12 (1.13 g, 3.76 mmol) to yield a crude colourless oil (1.12 g, 72 % yield). ^{1}H NMR (400 Mhz,) 8.77 (s,NH); 7.77 (d, J = 8.0 Hz, 6-H); 5.73 (d, J = 8.0 Hz, 5-H); 5.06 (m, 2'-H); 5.04 (m, 1'-H); 4.20

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(m, 5'-H); 3.99 (sept., J = 6.1 Hz, 7'-H); 3.99 (dd, J = 10.8, 5.6 Hz, 6'-H); 3.91 (dd, J = 10.8, 1.5 Hz, 6"-H); 3.11 (dd, J = 18.2, 8.6 Hz, 3"-H); 2.56 (dd, J = 18.5, 3.6 Hz, 3'-H); 1.28 (d, J = 6.1 Hz, 8'-Me); 1.22 (d, J = 6.1 Hz, 9'-Me); 0.9 (s, Me_3CSi); 0.1 (s, Me_2Si). RMN ^{13}C ($CDCl_3$) 204.2 ; 163.2 ; 150.9 ; 142.2 ; 103 ; 95.4 ; 77.2 ; 70.3 ; 62.7 ; 54.3 ; 39.4 ; 25.8 ; 22.8 ; 21.2 ; 18.5 ; -5.4.

isopropyl 2'-thymine-2'3'-dideoxy-α-D-erythro-hexopyranoside-4'-ulosyle **15b**
A solution of **14b** (1.3 g, 3.04 mmol) dissolved in absolute ethanol (35 mL) was cooled to 0°C in a two-neck round bottom flask (100 mL). $NaBH_4$ (197 mg, 5.2 mmol) in ethanol (10 mL) cooled at 0°C was slowly added *via* a syringe and the resulting mixture was allowed to stir for 15 min at 0°C after which time a few drops of glacial acetic acid were added, causing the reaction mixture to hydrolyse. Water was added, and the solution extracted with ether (4×40 mL). The organic layers were washed with saturated $NaHCO_3$ until neutrality, water (3×20 mL), brine, dried ($MgSO_4$) and the solvents evaporated *in vacuo*. The crude resulting oil was purified by chromatography (20% EtOAc/cyclohexane). The pure compound (0.8 g, 1.87 mmol, 61 % yield) was obtained as a white powder mp = 179-181°C. $[\alpha]_D$ = 85°, de = 73% (C = 0.90, acetone).
In a three-neck round-bottom flask (50 mL) equipped with a magnetic stirrer under a nitrogen atmosphere the above reducted compound (200 mg, 0.466 mmol) was added with anhydrous THF (16 mL). Tetra-n-butylammonium fluoride (2.3 mL of a 1 M solution in THF) was added at r.t. and the resulting solution stirred for 1 h before being concentrated under reduced pressure. The resulting colourless oil was purified on a silica gel column (1/25 ratio) with 10 % MeOH/EtOAc, to give 140 mg (0.44 mmol, 95 % yield) of **15b** as a crystalline compound, mp. 98.5-100.2°C. $[\alpha]_D$ = +118°, de = 64% (C = 0.39, acetone). ^1H NMR (400 Mhz, Me_2SO-*d6*) δ, 11.18 (s, 3-H), 7.97 (s, 6-H), 5.02 (d, J = 2.3 Hz, 1'-H), 4.87 (d, J = 2.9 Hz, HO,4-C), 4.59 (t, J = 5.7 Hz, HO,6'-C), 4.20 (m, 2'-H), 3.92 (sept., J = 6.2 Hz, 7'-H), 3.76 (m, 5'-H, 4'-H), 3.58 (m, 6'-H, 6"-H), 2.00 (m, 3"-H), 1.84 (m, 3'-H), 1.73 (s, Me-7), 1.15 (d, J = 6.0 Hz, 8'-Me),1.05 (d, J = 6.0 Hz, 9'-Me). ^{13}C NMR (100 Mhz, Me_2SO-*d6*) δ = 163.6 ; 150.7 ; 139.8 ; 106.6 ; 94.3 ; 71.7 ; 67.8 ; 62.1 ; 59.9 ; 50.6 ; 30.3 ; 22.8 ; 20.9 ; 12.0.

15a. mp 212-15°C. ^1H NMR (400 Mhz, Me_2SO-*d6*) δ = 11.18 (s, NH), 8.15 (d, J = 8.1 Hz, 6'-H), 5.51 (dd, J = 8.1, 1.9 Hz, 5-H), 5.02 (s, 1'-H), 4.91 (d, J = 2.9 Hz, HO,4'C), 4.62 (t, J = 5.5 Hz, 6'-H), 4.2 (m, 2'-H), 3.92 (sept., J = 6.2 Hz, 7'-H), 3.75 (m, 5'-H, 4'-H), 3.55 (t, J = 5.2 Hz, 6'-H, 6"-H), 2.01 (m, 3"-H), 1.84 (m, 3'-H), 1.15 (d, J = 6.2 Hz, Me-8'), 1.07 (d, J = 6.1 Hz, 9'-Me). ^{13}C NMR (100 Mhz, Me_2SO-*d6*) δ = 164.2 ; 152 ; 145.2 ; 100.6 ; 95.5 ; 72.5 ; 68.9 ; 62.8 ; 61.3 ; 51.5 ; 31.1 ; 24 ; 22.1 .

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