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Stereoselective Synthesis of 3′-*C*-Allyluridines and 3′-Spiro-γ-lactone Uridine Analogues

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Grignard reactions of 3′-ketouridines **1a–e** with allylmagnesium bromide and $CeCl_3$ afforded novel 3′-*C*-allyluridines **2a–e** and **3d–e**. The diprotected 3′-keto nucleosides **1a–c** afforded *xylo*-configurated compounds **2a–c** and the 5′-unprotected 3′-keto nucleosides **1d–e** afforded mixtures of *xylo*- and *ribo*-configurated compounds **2d/3d** and **2e/3e**. The allyluridine **2a** was converted into the diol **4** by standard hydroboration and further oxidised to the 3′-spiro-γ-lactone nucleoside **5**. This compound and its deprotected analogue **6** are the first examples of a novel class of 3′-spiro nucleoside analogues.

In the search for new antiviral and anticancer agents, a large number of novel nucleosides have been prepared and biologically evaluated over the last decade.[1–3] Recently, nucleoside analogues with 3′-spiro functionalities have been prepared.[4–9] Among these are TSAO-T { [1- (2′,5′-di-*O*-*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]thymine}-3′-spiro-5″-(4″-amino-1″,2″-oxathiole 2″, 2″-dioxide) and its derivatives containing a 3′-oxathiole ring system and a 2′-*O*-*tert*-butyldimethylsilyl (TBDMS) group as essential pharmacophores for anti-HIV-1 activity.[4–8] We consider cyclisations of 3′-*C*-branched nucleosides as a possible route to other classes of 3′-spiro nucleosides and we therefore studied recently published reports on the addition of carbon nucleophiles to 3′-ketonucleosides.[10–20] These include Wittig reactions on 3′-ketonucleosides,[10,11] Lombardo reactions[12] on 3′-ketodeoxynucleosides,[13] additions of a cyano group[14] and Grignard reactions on either 3′-keto-2′-deoxynucleosides[15,16] or 3′-ketonucleosides.[17–20] Preferential α-facial attack afforded in all reactions (except one[17]) β-D-*xylo* nucleosides as major products.[14–20] In this report, the possibility of stereochemical control of the cerium-assisted Grignard addition of an allyl group to 3′-ketouridines is evaluated. Furthermore, the nucleoside analogues **5** and **6** are reported as the first examples of a novel class of nucleoside analogues with a 3′-spiro-γ-lactone structure.

Results and discussion

It has recently been described[17] that 3′-*C*-alkynylnucleosides can be stereoselectively synthesised from the corresponding 3′-ketonucleosides using organocerium reagents. Thus, a *xylo*-isomer was obtained as the only product from the diprotected 3′-ketonucleoside **1a**, and a *ribo*-isomer was formed almost exclusively from the 5′-unprotected analogue **1d**. Here we report results for five differently protected 3′-ketouridines **1a–e** (Scheme 1), namely three 2′,5′-di-*O*-protected analogues **1a–c** and two 2′-*O*-monoprotected **1d–e**. 2′,5′-Di-*O*-TBDMS derivative **1a** was synthesised as reported[21–23] from disilylated uridine.[24] Ketones **1b** and **1c** were synthesised analogously from 5′-*O*-DMT-2′-*O*-TBDMS-uridine[24] and 5′-*O*-DMT-2′-*O*-TBDPS-uridine **7**, respectively (DMT = 4,4′-dimethoxytrityl, TBDPS = *tert*-butyldiphenylsilyl). Compound **7**, a novel compound used as starting material for the preparation of **1c**, was obtained in 55% yield by regioselective silylation of 5′-*O*-DMT-uridine with TBDPSCl, $AgNO_3$ and pyridine in THF followed by column chromatography. All oxidations afforded 3′-ketonucleosides **1a–e** in high yields (90–95%). The 5′-deprotected 3′-ketonucleosides **1d** and **1e** were synthesised from **1b** in 75% yield and **1c** in 80% yield, respectively, by standard detritylation (1.5% trichloroacetic acid in 1,2-dichloroethane).

Grignard addition of the allylmagnesium bromide/$CeCl_3$ reagent to 2′,5′-di-*O*-TBDMS-uridine **1a** afforded as expected exclusively the 3′-*C*-allyl *xylo*-nucleoside **2a** after column chromatography. Analogously, only **2b** and **2c** were obtained as the Grignard products from 5′-*O*-DMT-2′-*O*-TBDMS derivative **1b** and 5′-*O*-DMT-2′-*O*-TBDPS derivative **1c**, respectively. These reactions were accomplished in moderate to high yields (52–80%). When the addition was performed on 5′-*O*-deprotected 2′-*O*-silylated 3′-ketonucleosides **1d** or **1e**, mixtures of *xylo*- and *ribo*-nucleosides were obtained in moderate yields,

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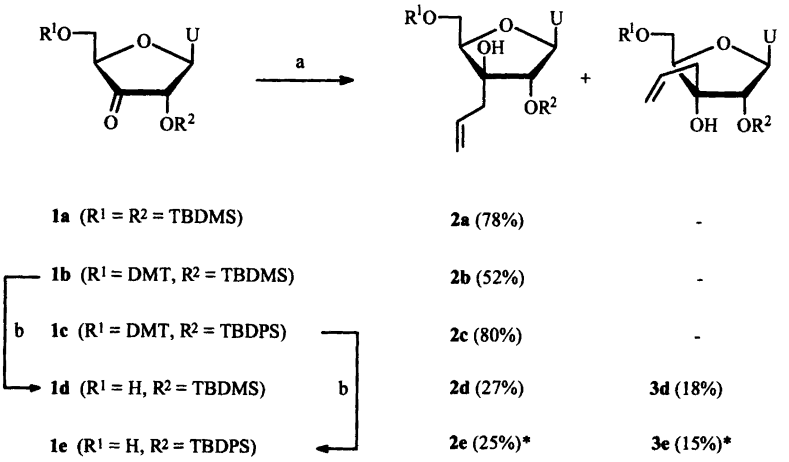
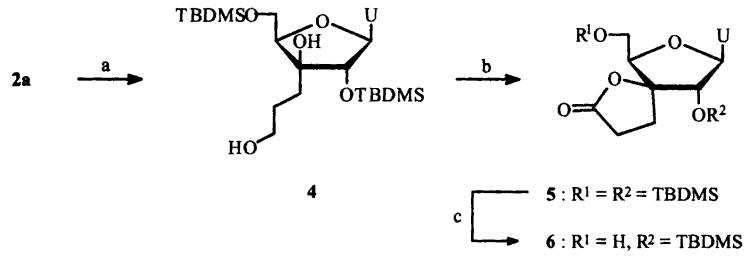


Scheme 1. a, AllylMgBr, $CeCl_3$, Et_2O, THF; b, 1.5% Cl_3CCOOH in $ClCH_2CH_2Cl$ (v/v). U = uracil-1-yl. *Not separated, yields estimated by ^1H NMR spectroscopy.

and to our surprise the *xylo*-isomers **2d** and **2e** were the major products. Thus, the essentially complete stereoselectivity reported for other cerium-assisted Grignard reagents on **1d**[17] was not observed here using allylmagnesium bromide. From the results depicted in Scheme 1 there seems to be no possibility of influencing the stereochemistry of the Grignard-products by using the larger 2′-*O*-TBDPS group instead of a 2′-*O*-TBDMS group.

The stereochemistry of the Grignard products were confirmed by ^1H–^1H COSY and ^1H NOE difference NMR experiments. Thus, e.g., the *xylo*-configuration of **2d** was confirmed by mutual NOE contacts between 3′-*C*-CH_2 and H-4′ and between 3′-OH and H-5′. NOE contacts between H-2′, H-5′ and 3′-*C*-CH_2 confirmed the *ribo*-configuration of **3d**. In addition, the small coupling constants between H-1′ and H-2′ observed for the *xylo*-isomers **2** ($J_{1'2'} \sim 0$–4.6 Hz) confirmed the conformation of the sugar ring as being predominantly a 3′-*endo*-conformer.[18] As reported for 3′-*C*-methyl-*ribo*- and -*xylo*-nucleosides,[18] the methyl substituent dictates the conformation as it prefers the equatorial position. Therefore, the *xylo*-configuration results in a 3′-*endo*-conformation and the *ribo*-configuration in a 2′-*endo*-conformation. As these relations are assumed to be similar for 3′-*C*-allylnucleosides and as the observed coupling constants between H-1′ and H-2′ for the *ribo*-isomers **3** are significantly larger ($J_{1'2'} \sim 6.9$–7.7 Hz, confirming a 2′-*endo*-conformation[18]) than for the *xylo*-configurated products, the *xylo*- and *ribo*-isomers can be identified by these coupling constants. Finally, significantly different ^{13}C-shifts for C-3′ are observed. These signals (identified from INEPT experiments) are at ~81 ppm for the *xylo*-isomers and at ~77 ppm for the *ribo*-isomers. To confirm further the configurations of the Grignard addition products the following transformations were performed on an analytical scale. As epimers **2d** and **3d** are easily separated, the 5′-*O*-DMT-protected analogue **3b**[25] [selected ^{13}C NMR shifts (61.71, 78.29, 84.84, 86.54) proved to be different from **2b**] was obtained by standard chemistry (DMTCl and pyridine) from **3d**. Attempts to separate **2e** and **3e** using column chromatography failed, but the *xylo*-isomer **2e** was obtained from **2c** by standard detritylation (1.5% trichloroacetic acid in 1,2-dichloroethane). Likewise, **2d** was prepared from **2b** by detritylation, and from **2a** by selective 5′-*O*-desilylation (80% AcOH).

As the first step in the synthesis of 3′-spiro derivatives **5** and **6** (Scheme 2), hydroboration of **2a** afforded **4** in 46% yield. Attempts to use the reagent $MgCl(CH_2)_3OMgCl$[26] together with $CeCl_3$ and **1a** to produce **4** in one step did not work in our hands. Compound **4** was oxidised with PCC (pyridinium chlorochromate) to give the spirolactone nucleoside **5** in 80% yield. The conditions used were as reported for carbohydrate derivatives by Marquez *et al.*[27] Lactone **5** was selectively deprotected by aqueous acetic acid to give the 2′-*O*-monosilylated derivative **6**. The configuration of **5** (and thus **2**, **4** and **6**) was confirmed by another NOE experiment, as mutual contacts between 3′-*C*-CH_2 and H-4′ were observed.



Scheme 2. a, 1. BH_3–oxathiane, THF, 2. NaOH, H_2O_2; b, PCC, 4 Å molecular sieves, CH_2Cl_2; c, 80% AcOH. U = uracil-1-yl.

In summary, Ce^{III}-assisted Grignard addition of an allyl group to the 3′-position of differently protected nucleosides has been evaluated and preferential α-attack of the nucleophile has been observed. Contrary to an earlier report using another Grignard reagent,[17] we did not obtain highly selective β-attack on 5′-*O*-unprotected *ribo*-nucleosides **1d** and **1e**. An effective and stereoselective route to a new class of *xylo*-configurated 3′-spiro-γ-lactone nucleoside analogues having structural similarities with the anti-HIV-1 active TSAO-compounds[4–8] has been developed.

Experimental

NMR spectra were recorded at 250 and 500 MHz for ^1H and at 62.9 and 125 MHz for ^{13}C. ^1H NMR chemical shifts are in ppm relative to tetramethylsilane as internal standard. ^1H NMR peak assignments for compounds **2d**, **3d** and **5** were derived from ^1H–^1H COSY and NOE NMR experiments. ^{13}C NMR peak assignments for compound **5** were derived from INEPT and ^1H–^{13}C COSY NMR experiments. Microanalyses were performed at the Department of Chemistry, University of Copenhagen. The silica gel used for column chromatography (0.040–0.063 mm) was purchased from Merck. To verify the purity and identity of compounds **2b–2e** and **3d**, copies of the ^{13}C NMR spectra were enclosed on submission of this manuscript.

*General procedure for preparation of 2′,5′-di-*O*-protected 3′-ketouridines.* **1a–1c.** The standard procedure is illustrated by the oxidation of 2′-*O*-(*tert*-butyldimethylsilyl)-5′-*O*-(4,4′-dimethoxytrityl)uridine to give **1b**. CrO_3 (1.52 g, 15.2 mmol) as a powder was dried with molecular sieves (3 Å, powder, 1.9 g) and CH_2Cl_2 (27 ml) was added. To the suspension were added acetic anhydride (1.52 ml, 16.1 mmol) and pyridine (2.67 ml, 33.1 mmol) and the mixture was stirred for 0.5 h. A solution of 2′-*O*-(*tert*-butyldimethylsilyl)-5′-*O*-(4,4′-dimethoxytrityl)uridine[24] (2.00 g, 3.04 mmol) in CH_2Cl_2 (9 ml) was added slowly, and the mixture was stirred for 1 h and poured into EtOAc (300 ml). This mixture was filtered through a layer of silica gel, evaporated and coevaporated with toluene and $CHCl_3$.

*1-[2′,5′-Di-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuran-3-ulosyl]uracil.* **(1a).**[21] Amounts used: CrO_3 (3.01 g, 30.1 mmol), molecular sieves (3 Å, powder, 3.7 g), acetic anhydride (3.01 ml, 31.9 mmol), pyridine (5.26 ml, 66.2 mmol), 2′,5′-Di-*O*-(*tert*-butyldimethylsilyl)-uridine[24] (4.74 g, 10.0 mmol) and CH_2Cl_2 (27 ml). Yield: 4.50 g (95%). R_f=0.66 (5% MeOH in CH_2Cl_2, v/v). ^1H NMR ($CDCl_3$): δ 0.01, 0.07, 0.09, 0.10 (12 H, 4×s), 0.86–0.94 (18 H, m), 3.92 (2 H, m), 4.18 (1 H, d, J=8.0 Hz), 4.23 (1 H, m), 5.82 (1 H, d, J=8.1), 6.27 (1 H, d, J=8.0 Hz), 7.83 (1 H, d, J=8.1 Hz), 9.27 (1 H, br s). ^{13}C NMR ($CDCl_3$): δ −5.78, −5.63, −5.44, −4.79, 18.12, 18.19, 25.36, 25.73, 62.81, 77.33, 81.89, 84.90, 103.67, 138.97, 150.27, 162.74, 208.21.

*1-[2′-*O*-(tert-Butyldimethylsilyl)-5′-O-(4,4′-dimethoxytrityl)-β-D-*erythro*-pentofuran-3-ulosyl]uracil.* **(1b).** Yield: 1.79 g (90%). R_f=0.67 (5% MeOH in CH_2Cl_2, v/v). ^1H NMR ($CDCl_3$): δ 0.10, 0.18 (6 H, 2×s), 0.91 (9 H, s), 3.41 (1 H, dd, J=2.3, 10.5 Hz), 3.62 (1 H, dd, J=2.2, 10.6 Hz), 3.79 (6 H, s), 4.25 (1 H, m), 4.53 (1 H, d, J=8.0 Hz), 5.42 (1 H, d, J=8.1 Hz), 6.24 (1 H, d, J=8.0 Hz), 6.82–7.31 (13 H, m), 7.65 (1 H, d, J=8.2 Hz), 8.73 (1 H, br s). ^{13}C NMR ($CDCl_3$): δ −5.32, −4.67, 18.20, 25.42, 55.24, 63.08, 76.71, 80.59, 85.12, 87.42, 103.51, 113.43, 127.32, 127.98, 128.09, 129.95, 130.11, 134.65, 134.89, 139.28, 144.13, 150.17, 158.92, 162.43, 208.45.

*1-[2′-*O*-(tert-Butyldiphenylsilyl)-5′-O-(4,4′-dimethoxytrityl)-β-D-*erythro*-pentofuran-3-ulosyl]uracil.* **(1c).** Amounts used: CrO_3 (1.68 g, 16.8 mmol), molecular sieves (3 Å, powder, 2.0 g), acetic anhydride (1.68 ml, 17.8 mmol), pyridine (2.94 ml, 36.4 mmol), nucleoside **7** (2.65 g, 3.34 mmol) and CH_2Cl_2 (29 ml). Yield: 2.50 g (94%). R_f=0.73 (5% MeOH in CH_2Cl_2, v/v). ^1H NMR ($CDCl_3$): δ 1.13 (9 H, s), 3.28 (1 H, dd, J=2.3, 10.4 Hz), 3.61 (1 H, dd, J=2.1, 10.4 Hz), 3.76, 3.77 (6 H, 2×s), 4.25 (1 H, m), 4.65 (1 H, d, J=8.0 Hz), 4.94 (1 H, d, J=8.1 Hz), 6.27 (1 H, d, J=8.0 Hz), 6.66–7.85 (24 H, m), 8.62 (1 H, br s). ^{13}C NMR ($CDCl_3$): δ 19.02, 26.59, 55.12, 63.07, 75.74, 80.28, 84.78, 87.24, 103.08, 113.19, 113.23, 127.06, 127.83, 127.90, 127.90, 128.91, 129.04, 129.86, 130.24, 130.27, 131.89, 132.24, 134.35, 134.90, 135.59, 135.88, 138.65, 143.57, 149.86, 158.64, 162.45, 208.63.

*1-[2′-*O*-(tert-Butyldimethylsilyl)-β-D-*erythro*-pentofuran-3-ulosyl]uracil.* **(1d).**[23] Ketone **1b** (500 mg, 0.76 mmol) was dissolved in 1.5% Cl_3CCOOH in $ClCH_2CH_2Cl$ (8.27 ml, 0.76 mmol, v/v) and stirred for 1 h. After this time, the mixture was added to a column of silica gel packed in CH_2Cl_2. After being washed with CH_2Cl_2, the product was eluted with 2–4% MeOH in CH_2Cl_2 (v/v). Yield: 217 mg (80%). R_f=0.59 (10% MeOH in CH_2Cl_2, v/v). ^1H NMR ($CDCl_3$): δ 0.04, 0.12 (6 H, 2×s), 0.86 (9 H, s), 3.93–3.98 (2 H, m), 4.26 (1 H, m), 4.67 (1 H, d, J=7.7 Hz), 5.80 (1 H, d, J=7.7 Hz), 5.86 (1 H, d, J =8.1 Hz), 7.55 (1 H, d, J=8.1 Hz), 9.46 (1 H, br s). ^{13}C NMR ($CDCl_3$): δ −5.36, −4.64, 18.09, 25.43, 61.73, 74.94, 82.28, 90.04, 103.59, 141.67, 150.41, 162.94, 208.28.

*1-[2′-*O*-(tert-Butyldiphenylsilyl)-β-D-*erythro*-pentofuran-3-ulosyl]uracil.* **(1e).** Ketone **1c** (500 mg, 0.64 mmol) was dissolved in 1.5 % Cl_3CCOOH in $ClCH_2CH_2Cl$ (6.96 ml, 0.64 mmol, v/v). After being stirred for 1 h, the mixture was added to a column of silica gel packed in CH_2Cl_2. After being washed with CH_2Cl_2, the product was eluted with 2% MeOH in CH_2Cl_2 (v/v). Yield: 231 mg (75%). R_f=0.22 (5% MeOH in CH_2Cl_2, v/v). ^1H NMR ($CDCl_3$): δ 1.10, 1.11 (9 H, 2×s), 3.79 (1 H, m), 3.87 (1 H, m), 4.24 (1 H, m), 4.70 (1 H, d, J=7.4 Hz), 5.38 (1 H, d, J=7.7 Hz), 5.85 (1 H, d, J=

7.2 Hz), 6.99 (1 H, d, J=7.7 Hz), 7.26–7.71 (10 H, m), 9.08 (1H, br s). ^{13}C NMR ($CDCl_3$): δ 19.16, 26.70, 61.71, 74.64, 82.17, 89.13, 103.31, 127.88, 127.91, 130.34, 135.63, 135.92, 140.49, 149.98, 162.66, 208.28.

General procedure for the preparation of 3′-allyluridines. **2a–e, 3d and 3e.** The standard procedure is illustrated by the preparation of **2a** from ketone **1a**. $CeCl_3 \cdot 7\,H_2O$ (6.18 g, 16.6 mmol) was dried under vacuum at 140 °C for 4 h and the residue was stirred in anhydrous THF (195 ml) for 2 h and then cooled to −78 °C. Allylmagnesium bromide (1 M) in anhydrous ether (16.6 ml, 16.6 mmol) was added dropwise, and the mixture was stirred for another 2 h at −78 °C. A solution of **1a** (1.30 g, 2.8 mmol) in anhydrous THF (40 ml) was added dropwise and stirring was continued for 1 h. The reaction was quenched by addition of glacial acetic acid (2.2 ml) and the mixture was allowed to warm to room temperature. The mixture was poured into EtOAc (400 ml) and washed with water (3 × 200 ml) and brine (3 × 200 ml). The organic phase was separated, dried (Na_2SO_4) and concentrated. Purification using silica gel column chromatography (0–1% MeOH in CH_2Cl_2, v/v) afforded **2a** as a white solid.

*1-[3′-C-Allyl-2′,5′-Di-O-(*tert*-butyldimethylsilyl)-β-D-xylofuranosyl]uracil.* **(2a).** Yield 1.11 g (78 %). R_f=0.38 (5% MeOH in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$): δ 0.14, 0.15, 0.15, 0.23 (12 H, 4 × s), 0.91, 0.93 (18 H, 2 × s), 2.32 (1 H, dd, J=8.7, 14.2 Hz), 2.58 (1 H, dd, J=5.6, 14.2 Hz), 3.97 (1 H, m), 4.11 (1 H, dd, J=2.4, 12.0), 4.23 (1 H, dd, J=2.5, 12.0), 4.43 (1 H, s), 5.17 (1 H, m), 5.22 (1 H, m), 5.61 (1 H, dd, J=1.9, 8.2 Hz), 5.68 (1 H, s), 5.89 (1 H, m), 7.97 (1 H, d, J=8.2 Hz), 9.36 (1 H, br s). ^{13}C NMR ($CDCl_3$): δ −5.83, −5.67, −5.44, −4.22, 17.95, 17.98, 25.64, 25.74, 37.33, 62.72, 81.28, 82.58, 82.96, 91.08, 100.75, 119.21, 132.41, 141.07, 150.46, 163.73. Anal. Calcd. for $C_{24}H_{44}N_2O_6Si_2$: C, 56.21; H, 8.65; N, 5.46. Found: C, 56.63; H, 8.87; N, 5.12.

*1-[3′-C-Allyl-2′-O-(*tert*-Butyldimethylsilyl)-5′-O-(4,4′-dimethoxytrityl)-β-D-xylofuranosyl]uracil.* **(2b).** Amounts used: $CeCl_3 \cdot 7\,H_2O$ (1.36 g, 3.65 mmol), ketone **1b** (400 mg, 0.61 mmol), 1 M allylMgBr in ether (3.65 ml, 3.65 mmol) and THF (70 ml). Yield: 231 mg (52 %). R_f=0.36 (5% MeOH in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$): δ 0.15, 0.26 (6 H, 2 × s, 2 × $SiCH_3$), 0.89 (9 H, s, *t*-Bu), 2.04 (1 H, dd, J=8.8, 14.2 Hz, CH_2a), 2.48 (1 H, dd, J=5.6, 14.2 Hz, CH_2b), 3.48–3.55 (2 H, m, 2 × H-5′), 3.80 (6 H, s, 2 × OCH_3), 4.06 (1 H, s, H-2′), 4.09 (1 H, m, H-4′), 5.04 (1 H, m, H_2C=a), 5.10 (1 H, m, H_2C=b), 5.54 (1 H, d, J=8.3 Hz, H-5), 5.68 (1 H, m, –CH=), 5.70 (1 H, s, H-1′), 6.83–7.44 (13 H, m, DMT), 8.03 (1 H, d, J=8.2 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ −5.59, −4.06, 17.96, 25.81, 36.76, 55.25, 62.17, 80.81, 81.98, 83.91, 87.84, 91.78, 100.55, 113.41, 119.83, 127.21, 127.99, 128.11, 129.98, 130.01, 132.01, 134.85, 135.06, 141.39, 143.90, 150.40, 158.82, 163.62. FAB-MS m/z=723 (M+Na^+).

*1-[3′-C-Allyl-2′-O-(*tert*-butyldiphenylsilyl)-5′-O-(4,4′-dimethoxytrityl)-β-D-xylofuranosyl]uracil.* **(2c).** Amounts used: $CeCl_3 \cdot 7\,H_2O$ (2.84 g, 7.63 mmol), ketone **1c** (1.05 g, 1.27 mmol), 1 M allylMgBr in ether (7.63 ml, 7.63 mmol) and THF (130 ml). Yield: 883 mg (80 %). R_f=0.64 (5% MeOH in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$): δ 1.11 (9 H, s), 2.33 (1 H, dd, J=8.6, 14.4 Hz), 2.60 (1 H, dd, J=5.8, 14.4 Hz), 3.45 (1 H, dd, J=3.1, 11.1 Hz), 3.73 (1 H, dd, J=2.8, 11.2 Hz), 3.79 (6 H, s), 4.09 (1 H, m), 4.20 (1 H, d, J=3.1 Hz), 4.96–5.05 (2 H, m), 5.32 (1 H, dd, J=1.9, 7.2 Hz), 5.66 (1 H, m), 5.92 (1 H, d, J=3.1 Hz), 6.78–7.73 (24 H, m), 8.62 (1 H, br s). ^{13}C NMR ($CDCl_3$): δ 19.32, 26.98, 37.96, 55.20, 62.53, 80.73, 82.19, 82.82, 87.72, 89.66, 101.65, 113.32, 119.42, 123.67, 127.12, 127.76, 127.91, 128.01, 128.28, 129.98, 130.11, 132.32, 132.48, 134.82, 135.00, 135.93, 136.06, 141.37, 143.84, 149.73, 149.96, 158.73, 162.97. FAB-MS: m/z=847 (M+Na^+).

*1-[3′-C-Allyl-2′-O-(*tert*-butyldimethylsilyl)-β-D-xylofuranosyl]uracil* **(2d)** *and 1-[3′-C-allyl-2′-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]uracil.* **(3d).** Amounts used: $CeCl_3 \cdot 7H_2O$ (0.98 g, 2.68 mmol), ketone **1d** (159 mg, 0.45 mmol), 1 M allylMgBr in ether (2.68 ml, 2.68 mmol) and THF (50 ml). **2d**: Yield: 48 mg (27 %). R_f=0.42 (5% MeOH in CH_2Cl_2, v/v). ^{1}H NMR (DMSO-d_6): δ 0.11, 0.16 (6 H, 2 × s, 2 × $SiCH_3$), 0.88 (9 H, s, *t*-Bu), 2.29 (1 H, dd, J=8.0, 14.4 Hz, CH_2a), 2.42 (1 H, dd, J=6.0, 14.4 Hz, CH_2b), 3.60–3.80 (2 H, m, 2 × H-5′), 3.91 (1 H, m, H-4′), 4.09 (1 H, d, J=1.3 Hz, H-2′), 4.81 (1 H, dd, J=5.4, 5.6 Hz, 5′-OH), 4.99 (1 H, s, 3′-OH), 5.07 (1 H, s, H_2C=a), 5.12 (1 H, d, J=5.3 Hz, H_2C=b), 5.51 (1 H, d, J=1.2 Hz, H-1′), 5.58 (1 H, dd, J=2.1, 8.2 Hz, H-5), 5.82 (1 H, m, –CH=), 7.79 (1 H, d, J= 8.2 Hz, H-6), 11.3 (1 H, d, J=1.5 Hz, NH). ^{13}C NMR (DMSO-d_6): δ −5.65, −4.40, 17.53, 25.58, 36.59, 59.60, 79.24, 81.55, 86.29, 90.34, 100.01, 117.92, 133.33, 140.92, 150.49, 163.24. FAB-MS m/z=421 (M+Na^+, 100%). **3d**: Yield: 32 mg (18 %). R_f=0.42 (5% MeOH in CH_2Cl_2, v/v). ^{1}H NMR (DMSO-d_6): δ −0.14, 0.01(6 H, 2 × s, 2 × $SiCH_3$), 0.83 (9 H, s, *t*-Bu), 2.41–2.49 (2 H, m, CH_2a, CH_2b), 3.57 (1 H, m, H-5′a), 3.68 (1 H, m, H-5′b), 3.82 (1 H, s, 5′-OH), 4.14 (1 H, d, J=7.6 Hz, H-2′), 4.62 (1 H, s, 3′-OH), 5.10–5.18 (2 H, m, H_2C=a, H_2C=b), 5.30 (1 H, m, H-4′), 5.75 (1 H, dd, J=2.1, 8.1 Hz, H-5), 5.95 (1 H, m, –CH–), 5.97 (1 H, d, J=7.6 Hz, H-1′), 8.13 (1 H, d, J=8.2 Hz, H-6), 11.3 (1 H, d, J=1.8 Hz, NH). ^{13}C NMR (DMSO-d_6): δ −5.08, −4.68, 17.51, 25.43, 37.48, 60.00, 77.76, 77.88, 85.14, 85.96, 102.41, 117.57, 133.85, 140.74, 150.96, 162.73.

*1-[3′-C-Allyl-2′-O-(*tert*-Butyldiphenylsilyl)-β-D-xylofuranosyl]uracil* **(2e)** *and 1-[3′-C-allyl-2′-O-(*tert*-butyldiphenylsilyl)-β-D-ribofuranosyl]uracil.* **(3e).** Amounts used: $CeCl_3 \cdot 7H_2O$ (0.91 g, 2.44 mmol), ketone **1e**

(195 mg, 0.41 mmol), 1 M allylMgBr in ether (2.44 ml, 2.44 mmol) and THF (55 ml). Yield: 128 mg (a mixture of **1e**:**2e**:**3e** 4:5:3). R_f=0.40 (5% MeOH in CH_2Cl_2, v/v). Data for **2e** (obtained from the analytical transformation described in the text): ^{1}H NMR ($CDCl_3$): δ 1.09 (9 H, s), 2.51 (1 H, dd, J=8.5, 14.4 Hz), 2.76 (1 H, dd, J=5.9, 14.4 Hz), 3.88–4.00 (3 H, m), 4.44 (1 H, d, J=4.6 Hz), 5.20 (1 H, s), 5.26 (1 H, d, J=3.0 Hz), 5.34 (1 H, d, J=8.1 Hz), 5.69 (1 H, d, J=4.6 Hz), 5.91 (1 H, m), 7.26–7.72 (11 H, m). ^{13}C NMR ($CDCl_3$): δ 19.30, 26.92, 38.47, 62.18, 80.91, 82.04, 82.29, 90.37, 102.19, 119.88, 127.82, 127.87, 128.04, 130.17, 130.22, 132.28, 132.36, 135.62, 135.80, 135.90, 135.97, 141.96, 149.93, 163.09.

1-[2′,5′-Di-O-*(*tert-*Butyldimethylsilyl)-3′*-C-*(3-hydroxypropyl)-β-*D-*xylofuranosyl]uracil* **(4).** To a stirred solution of nucleoside **2a** (1.08 g, 2.1 mmol) in anhydrous THF (7.5 ml) under argon was added a 7.8 M solution of BH_3 in oxathiane (0.26 ml, 2.0 mmol). The reaction was stirred for 45 min, after which a 2 M aqueous solution of NaOH (1.2 ml, 2.4 mmol) was added slowly. The mixture was cooled to 0 °C and 35% H_2O_2 (0.25 ml, 2.5 mmol) was added. The mixture was allowed to warm to rt, stirred for 60 min and then poured into a mixture of ether (100 ml) and water (100 ml). The organic phase was separated and washed several times with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and evaporated. Purification using silica gel column chromatography (0–2% MeOH in CH_2Cl_2, v/v) afforded **4** as a white solid. Yield 478 mg (43%). R_f=0.35 (5% MeOH in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$): δ 0.15, 0.16, 0.16, 0.25 (12 H, 4×s, 4×$SiCH_3$), 0.90, 0.93 (18 H, 2×s, 2×*t*-Bu), 1.55–1.97 (4 H, m, 3-*C*-CH_2CH_2), 3.61–3.76 (2 H, m, OCH_2), 3.97 (1 H, t, J=2.7 Hz, H-4′), 4.07 (1 H, s, H-2′), 4.09 (1 H, dd, J=2.7, 11.9 Hz, H-5′a), 4.23 (1 H, dd, J=2.7, 12.1 Hz, H-5′b), 5.60 (1 H, d, J=8.2 Hz, H-5), 5.65 (1 H, s, H-1′), 7.96 (1 H, d, J=8.2 Hz, H-6), 9.39 (1 H, br s, NH). ^{13}C NMR ($CDCl_3$): δ −5.76, −5.70, −5.59, −3.97, 17.92, 18.06, 25.70, 25.76, 26.87, 29.43, 62.25, 63.05, 81.56, 81.79, 83.99, 91.66, 100.43, 141.29, 150.47, 163.89. FAB-MS: m/z=531 (MH$^+$). Anal. Calcd. for $C_{24}H_{46}N_2O_7Si_2$: C, 54.31; H, 8.73; N, 5.28. Found: C, 54.26; H, 9.06; N, 5.11.

*(5*S*,6*R*,8*R*,9*R*)-6-(*tert-*Butyldimethylsilyloxymethyl)-9-*(tert-*butyldimethylsilyloxy)-8-(uracil-1-yl)-1,7-dioxaspiro-2-oxo[4.4]nonane*) **(5).** To a suspension of predried PCC (308 mg, 1.43 mmol) and molecular sieves (4 Å, powder, 358 mg) in CH_2Cl_2 (2.3 ml) was added a solution of diol **4** (190 mg, 0.36 mmol) in CH_2Cl_2 (2.1 ml). The mixture was stirred for 1 h and then poured into EtOAc (40 ml) and filtered through a layer of silica gel. Purification using silica gel column chromatography (0–2% MeOH in CH_2Cl_2, v/v) afforded **5** as a white solid. Yield 176 mg (93 %). R_f=0.62 (5% MeOH in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$): δ 0.09, 0.10, 0.10, 0.13 (12 H, 4×s, 4×$SiCH_3$), 0.88, 0.89 (18 H, 2×s, 2×*t*-Bu), 2.21 (1 H, m, H-4b), 2.46–2.64 (3 H, m, H-3a, H-3b, H-4b), 3.90 (2 H, m, CH_2), 4.12 (1 H, dd, J=4.8, 6.0 Hz, H-6), 4.22 (1 H, d, J=2.8 Hz, H-9), 5.73 (1 H, dd, J=1.5, 8.1 Hz, H-5′), 5.81 (1 H, d, J=2.8 Hz, H-8), 7.65 (1 H, d, J=8.2 Hz, H-6′), 9.51 (1 H, br s, NH). ^{13}C NMR ($CDCl_3$): δ −5.74, −5.52, −5.22, −4.58 (4×$SiCH_3$), 17.85, 18.26 (2×*t*-Bu), 24.33 (C-4), 25.59, 25.77 (2×*t*-Bu), 27.38 (C-3), 60.56 (CH_2), 80.81 (C-9), 84.07 (C-6), 89.25 (C-8), 89.70 (C-5), 102.29 (C-5′), 139.93 (C-6′), 150.49 (C-2′), 163.29 (C-4′), 175.25 (C-2). FAB-MS: m/z=527 (MH$^+$). Anal. Calcd. for $C_{24}H_{42}N_2O_7Si_2$: C, 54.72; H, 8.04; N, 5.32. Found: C, 54.48; H, 8.15; N, 5.17.

*(5*S*,6*R*,8*R*,9*R*)-9-(*tert-*Butyldimethylsilyloxy)-6-hydroxymethyl-8-(uracil-1-yl)-1,7-dioxaspiro[4.4]nonane-2-one* **(6).** A solution of lactone **5** (70 mg, 0.13 mmol) in 80 % aqueous AcOH (2.0 ml) was stirred for 3 h at 60 °C. The solution was neutralised with saturated aqueous $NaHCO_3$ and the mixture was poured into CH_2Cl_2 (10 ml). The organic phase was separated and washed with saturated aqueous solutions of $NaHCO_3$ (3×5 ml), dried (Na_2SO_4) and evaporated. Purification using preparative TLC (7% MeOH in CH_2Cl_2, v/v) afforded **6** as a white solid. Yield 50 mg (91 %). R_f=0.44 (10% MeOH in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$): δ 0.11, 0.15 (6 H, 2×s), 0.90 (9 H, s), 2.21 (1 H, m), 2.51–2.74 (3 H, m), 3.91 (1 H, dd, J=5.4, 11.6 Hz), 4.02 (1 H, dd, J=4.5, 11.7 Hz), 4.22 (1 H, m), 4.31 (1 H, d, J=3.0 Hz), 5.77 (1 H, d, J=8.2 Hz), 5.84 (1 H, d, J=3.0 Hz), 7.72 (1 H, d, J=8.2 Hz), 9.44 (1 H, br s). ^{13}C NMR ($CDCl_3$): δ −5.29, −4.67, 17.77, 24.36, 25.51, 27.42, 60.01, 80.34, 84.21, 89.24, 90.00, 102.25, 140.18, 150.37, 163.38, 175.5. FAB-MS: m/z=413 (MH$^+$). Anal. Calcd. for $C_{18}H_{28}N_2O_7Si.0.5H_2O$: C, 51.29; H, 6.93; N, 6.65. Found: C, 51.23; H, 7.03; N, 6.40.

1-[2′-O-(tert-*Butyldiphenylsilyl)-5′*-O-*(4,4′-dimethoxytrityl)-β-*D-*ribofuranosyl]uracil* **(7).** To a stirred solution of 5′-*O*-DMT-uridine[25] (5.0 g, 9.2 mmol) in anhydrous THF (90 ml) and pyridine (2.8 ml, 33.8 mmol) was added $AgNO_3$ (1.83 g, 11.0 mmol) and TBDPSCl (3.07 ml, 11.8 mmol). After being stirred for 18 h, the mixture was filtered, poured into EtOAc (250 ml) and washed with $NaHCO_3$ (3×100 ml). The organic phase was dried (Na_2SO_4) and evaporated. Purification using silica gel column chromatography (0–10% EtOAc, 0.5 % pyridine, CH_2Cl_2, v/v/v) afforded **7** as a white solid which was used for preparation of **1c** without further purfication. Yield 4.32 g (55 %). R_f=0.60 (5% MeOH in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$): δ 1.13 (9 H, s), 3.30 (2 H, m), 3.77 (6 H, s), 4.15–4.18 (2 H, m), 4.57 (1 H, dd, J=5.0 Hz, 6.4 Hz), 5.03 (1 H, dd, J=1.8, 8.2 Hz), 6.20 (1 H, d, J=6.6 Hz), 6.65–7.61 (23 H, m), 7.67 (1 H, d, J=8.2 Hz), 8.66 (1 H, m). ^{13}C NMR ($CDCl_3$): δ 19.05, 26.85, 55.22, 63.77, 72.13, 75.95, 84.17, 87.17, 87.48, 102.49, 113.22, 123.22, 127.06, 127.90, 128.03, 128.16, 128.23, 129.99, 130.50, 131.52, 132.32, 134.78,

135.52, 135.63, 135.91, 140.09, 143.87, 149.80, 150.10, 158.64, 162.81. In addition, a mixture of **7** and the isomer 1-[3′-*O*-(*tert*-butyldiphenylsilyl)-5′-*O*-(4,4′-dimethoxytrityl)-β-D-ribofuranosyl]uracil was isolated in 30 % yield.

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References

1. Nasr, M., Litterst, C. and McGowan, J. *Antiviral Res.* 4 (1990) 125.
2. Schinazi, R. F., Mead, J. R. and Feorino, P. M. *AIDS Res. Human Retroviruses 8* (1992) 963.
3. De Clercq, E. *J. Med. Chem. 38* (1995) 2491.
4. Camarasa, M.-J., Pérez-Pérez, M.-J., San-Félix, A., Balzarini, J. and De Clercq, E. *J. Med. Chem. 35* (1992) 2721.
5. Pérez-Pérez, M. J., San-Félix, A., Balzarini, J., De Clercq, E. and Camarasa, M. J. *J. Med. Chem. 35* (1992) 2988.
6. Velázquez, S., San-Félix, A., Pérez-Pérez, M. J., Balzarini, J., De Clercq, E. and Camarasa, M. J. *J. Med. Chem. 36* (1993) 3230.
7. Alvarez, R., Velázquez, S., San-Félix, A., Aquaro, S., De Clercq, E., Perno, C.-F., Karlsson, A., Balzarini, J. and Camarasa, M. J. *J. Med. Chem. 37* (1994) 4185.
8. Balzarini, J., Pérez-Pérez, M.-J., San-Félix, A., Velázquez, K. S., Camarasa, M.-J., Vandamme, A.-M., Karlsson, A. and De Clercq, E. In: Krohn, K., Kirst, H.A. and Maag, H., Eds., *Antibiotics and Antiviral Compounds, Chemical Synthesis and Modification*, VCH, Weinheim 1993.
9. Samano, V. and Robins, M. J. *Tetrahedron Lett. 35* (1994) 3445.
10. Auguste, S. P. and Young, D. W. *J. Chem. Soc., Perkin Trans. 1* (1995) 395.
11. Samano, V. and Robins, M. J. *Synthesis* (1991) 283.
12. Sharma, M. and Bobek, M. *Tetrahedron Lett. 31* (1990) 5839.
13. Svendsen, M. L., Wengel, J., Dahl, O., Kirpekar, F. and Roepstorff, P. *Tetrahedron 49* (1993) 11341.
14. Camarasa, M.-J., Diaz-Ortiz, A., Calvo-Mateo, A., De las Heras, F. G., Balzarini, J. and De Clercq, E. *J. Med. Chem. 32* (1989) 1732.
15. Bender, S. L. and Moffett, K. K. *J. Org. Chem. 57* (1992) 1646.
16. Webb, T. R. *Tetrahedron Lett. 31* (1988) 3769.
17. Jung, P. M. J., Burger, A. and Biellmann, J.-F. *Tetrahedron Lett. 36* (1995) 1031.
18. Koole, L. H., Buck, H. M., Vial, J.-M. and Chattopadhyaya, J. *Acta Chem. Scand. 43* (1989) 665.
19. Huss, S., De las Heras, F. G. and Camarasa, M. J. *Tetrahedron 47* (1991) 1727.
20. Hayakawa, H., Tanaka, H., Itoh, N., Nakajima, M., Miyasaka, T., Yamaguchi, K. and Iitaka, Y. *Chem. Pharm. Bull. 35* (1987) 2605.
21. Hansske, F., Madej, D. and Robins, M. J. *Tetrahedron 40* (1984) 125.
22. Hansske, F. and Robins, M. J. *Tetrahedron Lett. 24* (1983) 1589.
23. Robins, M. J., Samano, V. and Johnson, M. D. *J. Org. Chem. 55* (1990) 410.
24. Hakimelahi, G. H., Proba, Z. A. and Ogilvie, K. K. *Can. J. Chem. 60* (1982) 1106.
25. Smith, M., Rammler, D. H., Goldberg, I. H. and Khorana, H. G. *J. Am. Chem. Soc. 84* (1962) 430.
26. Cahiez, G., Alexakis, A. and Normant, J. F. *Tetrahedron Lett. 33* (1978) 3013.
27. Lee, J., Sharma, R. and Marquez, V. E. *Carbohydrate Lett. 1* (1995) 285.

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