Nucleoside synthesis from 3-alkylated sugars: role of 3β-oxy substituents in directing nucleoside formation

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Using Vorbrüggen's protocol, reaction of persilylated uracil with xylofuranose derivatives having 3β-oxy-3α-alkyl substitution produced both α- and β-nucleosides. Only the β-nucleosides were formed from substrates having the reverse stereochemistry at C-3 or lacking the 3-alkyl substituent. Participation of the 3β-oxy substituent in stabilizing the incipient C-1 carbonium ion (or oxonium ion) intermediate has been suggested from analysis of energy-minimized conformations.

Introduction

Since the discovery of human immunodeficiency virus (HIV), the causative agent for acquired immunodefiency syndrome (AIDS), there has been intense research for identifying HIV inhibitors, among which nucleoside analogues remain in the forefront. At present acyclovir[1] and ganciclovir[2] are used clinically for the treatment of herpes simplex virus (HSV), while AZT,[3] ddC,[4] ddI,[5] d4T,[6] (−)-3TC[7] and avacavir[8] have been approved as drugs for AIDS and AIDS-related diseases. However, the toxicity of these drugs on prolonged use has emerged as a major concern. Thus, in search of more effective inhibitors against HIV, various alterations have been made in the carbohydrate moiety of the naturally occurring nucleosides.

Virtually all nucleoside inhibitors (NIs) of virally encoded polymerases described thus far elicit their effect through 'chain termination'. In order for a nucleoside triphosphate (NTP) to effect chain termination, it would need to serve initially as a substrate for the virus polymerase, leading to its incorporation and subsequent translocation within the active site in preparation for extension of the growing RNA chain. Secondly, the NTP would need to encompass one or more structural elements that would cause 'chain termination' or significantly impede further elongation of the RNA chain. Structural elements that influence the 3′-position sterically or electronically would be expected to affect elongation efficiency because of the fact that the 3′-hydroxyl group participates directly in phosphodiester formation as part of the elongation process. Thus, nucleosides carrying a 3-alkyl-3-OH sugar rather than a 3-deoxy one could prove more useful. A bulky alkyl group at C-3′ will occupy more space affecting the conformation of the furanose ring, and the product would be expected to play a different role in biochemical reactions. A survey of the literature[9] reveals that the synthetic C-2′β-methyl–C-2′α-OH and C-3′β-methyl–C-3′α-OH nucleosides show the ability to inhibit the growth of many virus cells.[10] However, to the best of our knowledge, nucleosides with α-methyl and β-OH at either C-2′ or C-3′ are yet to be reported. The present communication will focus on the synthesis of C-3′α-alkyl–3′β-OH substituted nucleoside analogues starting from D-glucose. The role of the tertiary hydroxy group at the quaternary carbon (C-3′) to trigger the formation of α-nucleosides will also be demonstrated.

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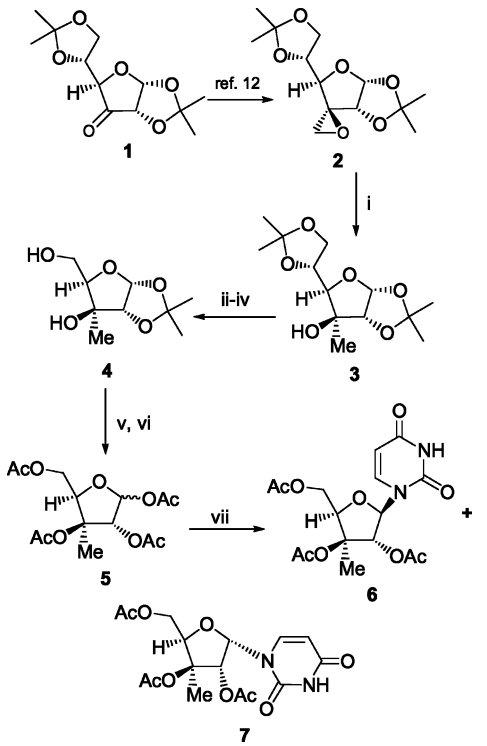
Results and discussion

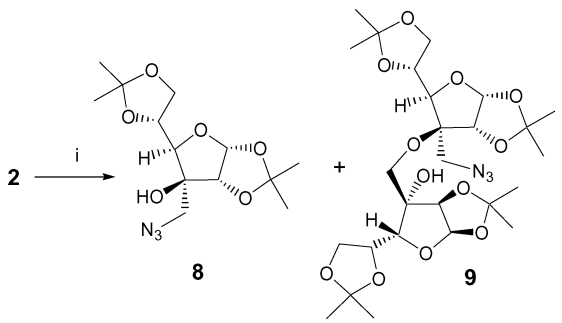
Since 1,2:5,6-di-*O*-isopropylidene-α-D-ribo-hexofuran-3-ulose (**1**) can be easily converted to the 3,3-epoxymethylene derivative **2**,[11] we envisioned a strategy involving its elaboration into a variety of derivatives with 3α-alkyl substitution through nucleophilic opening of the epoxide ring. The reaction sequence for the synthesis of **2** included Wittig reaction of **1** with methylene triphenylphosphorane and stereoselective epoxidation of the double bond using a peracid. We initially decided to generate α-methyl substitution at C-3 for obtaining the precursor towards nucleoside synthesis. For this, the epoxide ring in **2** was opened up by treatment with lithium aluminium hydride in refluxing diethyl ether to afford C-3 methyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**)[12] in 70% yield. Selective removal of the 5,6-acetonide functionality from **3** by treatment with dilute HOAc (Scheme 1) and subsequent sodium metaperiodate cleavage followed by reduction with sodium borohydride furnished **4**. Deprotection of the 1,2-hydroxy groups with 4% H_2SO_4 in aqueous acetonitrile and acetylation thereafter with Ac_2O/Py in presence of 4-dimethylaminopyridine (cat. amount) furnished an anomeric mixture of peracetylated furanose derivatives **5**. Introduction of a uracil moiety at C-1 of **5** could be smoothly effected under Vorbrüggen glycosidation[13] conditions using persilylated uracil and TMS–OTf as the Lewis acid, affording a mixture of **6** and **7** in the ratio of 1 : 2 with a combined yield of 70%.

A distinction between α- and β-nucleosides could be made on the basis of the chemical shift of the H-4′ signal, which was observed at δ 5.40 (dd, J = 6.0, 10.0 Hz) for **6** and at δ 6.45 (dd, J = 6.0, 10.8 Hz) for **7** in their ^{1}H NMR spectra taken in pyridine-d_5. Reports in the literature[14–16] reveal that the H-4′ signal of the α-anomer resonates more downfield than the β-anomer, suggesting **6** as the β-nucleoside and **7** as the α-isomer.

We next decided to open the epoxide ring through nucleophilic attack by azide followed by functional group manipulation to generate appropriate substrates for nucleoside synthesis. Thus, treatment of **2** with sodium azide in dry DMF at 60 °C furnished (Scheme 2) a mixture of the C-3 azidomethyl derivative **8** (42%)



Scheme 1 *Reagents*: i, $LiAlH_4$, dry diethyl ether; ii, dil. HOAc; iii, $NaIO_4$, aq. MeOH; iv, $NaBH_4$; v, 4% H_2SO_4, aq. CH_3CN; vi, Py/Ac_2O/DMAP; vii, 2,4-bis(trimethylsilyloxy)pyrimidine, TMS–OTf, CH_3CN.

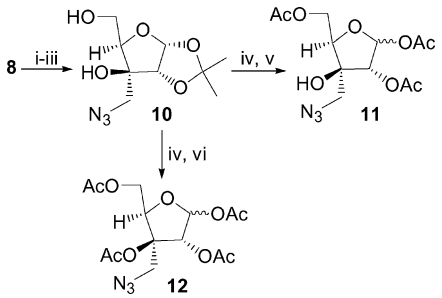


Scheme 2 *Reagents and conditions*: i, NaN_3, DMF, 60 °C or 100 °C.

and the pseudo-dimeric compound **9** (28%), which were separated and purified by column chromatography. The yields of the two products were almost reversed when the reaction was carried out at 100 °C. The formation of the dimeric compound **9** could be explained by assuming that the alkoxide ion generated at C-3 after the nucleophilic attack of the azide group on the epoxide reacted in tandem with a second molecule of the epoxide.

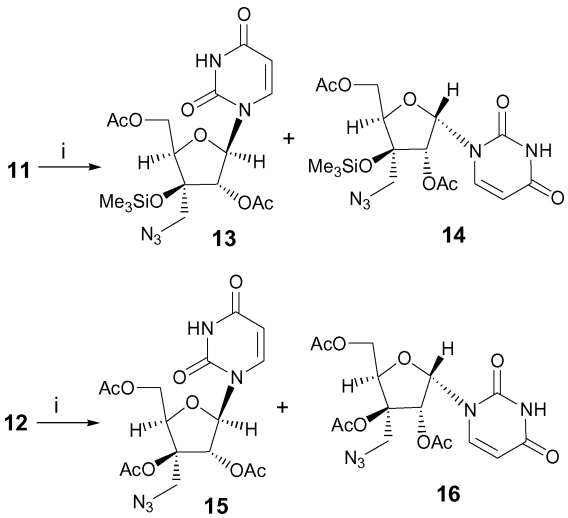
Selective removal of the 5,6-*O*-isopropylidene group of **8** followed by vicinal diol cleavage and reduction of the generated aldehyde produced **10**, which was treated with acid to deprotect the 1,2-hydroxyl groups (Scheme 3). Acetylation thereafter with Ac_2O/Py at room temperature yielded **11** (as an anomeric mixture). However, acetylation in the presence of 4-dimethylaminopyridine (cat. amount) furnished a mixture of peracetylated furanose derivatives **12**.

Introduction of a uracil moiety at C-1 of **11** and **12** under Vorbrüggen glycosidation conditions afforded a mixture of **13**



Scheme 3 *Reagents*: i, dil. HOAc; ii, $NaIO_4$, aq. MeOH; iii, $NaBH_4$ MeOH; iv, H_2SO_4 (4%), $CH_3CN–H_2O$; v, Py/Ac_2O; vi, Py/Ac_2O/DMAP.

(30%) and **14** (32%) from **11** and a mixture of **15** (15%) and **16** (48%) from **12** (Scheme 4). The appearance of the H-4′ signal at δ 5.06 (partly merged) in the ^1H NMR spectrum of **14** and at δ 4.41 in the spectrum of **13** identified them as the α- and β-nucleosides respectively based on literature precedence. Similar differences were also observed in the ^1H NMR spectra of the nucleosides **15** and **16** (H-4′ signal of **15** and **16** at δ 4.52 and 6.08 respectively).

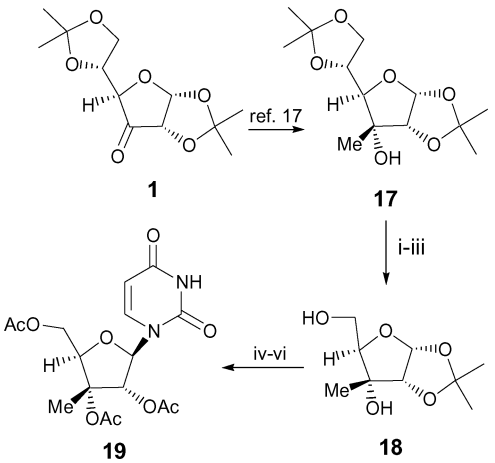


Scheme 4 *Reagents and conditions*: i, 2,4-bis(trimethylsilyloxy)-pyrimidine, TMS–OTf, CH_3CN, reflux, 4 h, N_2.

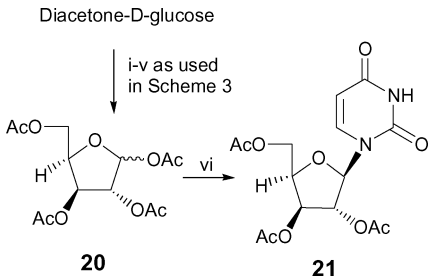
We then focused our attention on the synthesis of a nucleoside with C-3β alkyl groups to compare the result with that observed in the 3α-alkyl series. Thus, Grignard reaction of 1,2:5,6-di-*O*-isopropylidene-α-D-ribo-hexofuran-3-ulose **1** (Scheme 5) with methyl magnesium iodide in dry diethyl ether furnished **17**.[17] Proceeding from **17** and following similar reaction sequence as described in Scheme 1 afforded **18**, which upon conversion to the nucleoside afforded only **19**.

To test whether the 3-alkyl group has any role in directing α-nucleoside formation, we submitted the D-glucose derived tetraacetylated product **20** to the same nucleosidation conditions. In this case also, only the β-nucleoside **21** was formed (Scheme 6) to the exclusion of the α-nucleoside.

From mechanistic considerations, it is accepted that the involvement of the 2α-OAc substituent results in the formation of a dioxolanium ion intermediate (Fig. 1), which ensures selective formation of a β-nucleoside (*viz.* **13** or **15** from **11** or **12**). However, the 3β-OH group present in **11** or the 3β-OAc in **12** might help



Scheme 5 *Reagents*: i, dil. HOAc; ii, $NaIO_4$, aq. MeOH; iii, $NaBH_4$, MeOH; iv, 4% H_2SO_4, aq. CH_3CN; v, Ac_2O/Py/DMAP; vi, 2,4-bis(trimethylsilyloxy)pyrimidine, TMS–OTf.



Scheme 6 *Reagents and conditions*: vi, 2,4-bis(trimethylsilyloxy)-pyrimidine, TMS–OTf, CH_3CN, reflux, 4 h, N_2.

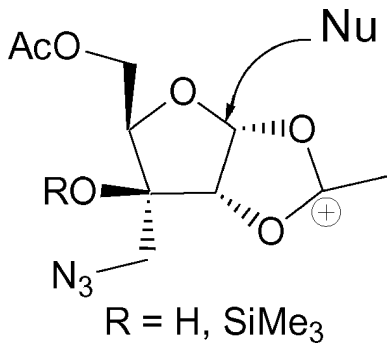


Fig. 1 β-Nucleoside formation through 2α-acetoxy participation.

to form other intermediates (Fig. 2 or 3), which could furnish the α-nucleoside **14** or **16**. With **11**, it is even possible that the 3-$OSiMe_3$ derivative is formed as the intermediate, carrying higher electron density on the oxygen atom to stabilize the carbonium ion. *N*-Glycosidation in the case of **20** must have occurred through the participation of the 2-OAc group only (Fig. 1), leading to the formation of the single product; the absence of an α-alkyl substituent at C-3 prevented the formation of a favorable sugar conformation to generate the proposed intermediate for an α-nucleoside.

In order to secure evidence to substantiate the above proposition, we carried out molecular modeling studies. This revealed that in the energy-minimized conformation[18] (using MM2 followed by MD) of the C-1 carbonium ion (or oxonium ion) intermediate,

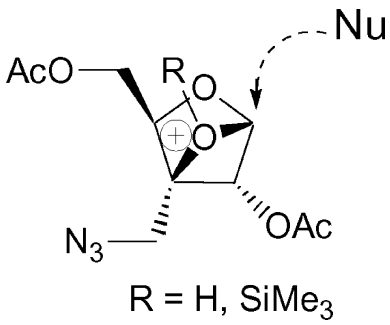


Fig. 2 α-Nucleoside formation through 3β-hydroxy/silyloxy participation.

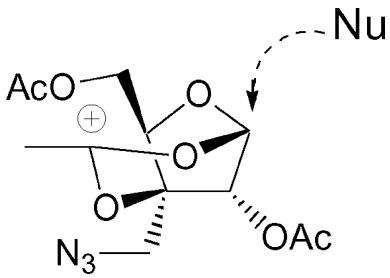


Fig. 3 Formation of α-nucleoside through 3β-acetoxy participation.

the distance between C-1 and the tertiary 3β-OH or 3β-$OSiMe_3$ or 3β-acetoxy carbonyl lies in the range of 2.6–3.0 Å, almost the same as the distance from the 2α-OAc. It is therefore considered sufficiently close for the formation of non-isolable intermediates, leading to α-nucleoside formation. However, this distance is greatly increased (to ~4.8 Å) in the case of the tertiary 3α-OAc and also the secondary 3β-OAc substituent, preventing any anchimeric assistance.

Conclusion

In conclusion, this study describes a convergent approach in which α- and β-nucleosides with C-3′α-alkyl–3′β-OH substitution can be synthesized from D-glucose derived starting materials. The role of tertiary 3β-OR (R = H, Ac, $SiMe_3$) groups in the formation of α-nucleosides under Vorbrüggen conditions has been demonstrated. The results may be extended to other systems particularly those with 2-deoxy-3β-OH/OR-3α-alkyl substituents, yielding α-nucleosides in preference to the mixture of α- and β-nucleosides. These nucleosides could be potential antiviral agents and also used in the synthesis of unnatural oligonucleotides.

Experimental

General

Melting points were taken in open capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or C_5D_5N as solvents using TMS as internal standard. Mass spectra (EIMS or FABMS or ESIMS) of the compounds were taken on JEOL AX-500 and Micromass Q-Tof Micro spectrometers. Specific rotations were measured at 589 nm. HPLC was performed on a μ Bondapak C_{18} column (7.8 × 300 mm). Flash chromatography was carried

out on LiChroprep^{R} RP-18. All the solvents including petroleum ether (60–80 °C) were distilled and purified as necessary.

Syntheses

(3a*R*,5*R*,6*S*,6a*R*)-5-[(4*R*)-2,2-Dimethyl[1,3]dioxolan-4-yl]-2,2,6-trimethyl tetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (3). A solution of the epoxide **2** (1.08 g, 4.0 mmol) dissolved in dry diethyl ether (30 mL) was added drop-wise to a stirring mixture of $LiAlH_4$ (100 mg) in dry ether (20 mL) under N_2 and the mixture was heated at reflux for 1 h. It was cooled and excess $LiAlH_4$ was decomposed by the addition of NH_4Cl solution (saturated). The mixture was filtered and the ether layer was separated. It was washed with brine (2 × 5 mL), dried, and the solvent was evaporated. The crude residue was purified by column chromatography on silica gel using EtOAc–petroleum ether (1 : 19) as eluent to afford **3** (762 mg, 70%). Mp 67 °C (lit.[12] mp 66–67 °C), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.47 (s, 3H), 1.52 (s, 3H), 3.81 (d, 1H, J = 7.5 Hz), 4.00 (dd, 1H, J = 5.4, 8.7 Hz), 4.14 (dd, 1H, J = 6.6, 9.0 Hz), 4.24 (d, 1H, J = 3.3 Hz), 4.27 (m, 1H), 5.86 (d, 1H, J = 3.3 Hz). ESIMS, m/z: 297 $(M + Na)^+$.

(3a*R*,5*R*,6*S*,6a*R*)-5-Hydroxymethyl-2,2,6-trimethyl tetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (4). Compound **3** (1.10 g, 4.0 mmol) was dissolved in HOAc–H_2O (3 : 1) mixture (30 mL) and the solution was stirred at room temperature for 12 h. Evaporation of the solvent *in vacuo* followed by removal of the last traces of HOAc azeotropically furnished a gummy residue (after drying over P_2O_5). The residue (750 mg) was dissolved in CH_3OH (20 mL), the solution was cooled to 10 °C, an aqueous solution (10 mL) of $NaIO_4$ (728 mg, 3.4 mmol) was added to it drop-wise, and the mixture was stirred for 45 min. Usual work up furnished an aldehyde (IR: ν_{max} 1730 cm^{-1}). To a solution of the above aldehyde (700 mg) dissolved in MeOH (30 mL) at ice cold temperature was added $NaBH_4$ (110 mg) portionwise and the reaction mixture was stirred at room temperature for 4 h. An aqueous HOAc solution (50%, 5 mL) was added and the solvent was evaporated under reduced pressure. The residue was extracted with $CHCl_3$ (2 × 25 mL). The extract was washed with water (2 × 20 mL), dried (Na_2SO_4) and evaporated to give a crude product. Purification by column chromatography on silica gel using EtOAc–petroleum ether (3 : 7) as eluent produced **4** (342 mg, 45%). Thick liquid, $[\alpha]_D^{29}$ +13.7 (*c* 1.26, $CHCl_3$). IR (neat): ν_{max} 3402, 2986, 2937, 1457, 1378, 1217, 1167, 1078, 1007, 875 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.34 (s, 3H), 1.37 (s, 3H), 1.50 (s, 3H), 2.55 (brs, 2H, exchangeable), 3.83 (t-like, 1H, J = 2.5 Hz), 3.98 (dd, 1H, J = 2.1, 12.9 Hz), 4.12 (dd, 1H, J = 3.1, 12.9 Hz), 4.27 (d, 1H, J = 3.6 Hz), 5.96 (d, 1H, J = 3.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.7 (CH_3), 26.2 (CH_3), 27.0 (CH_3), 59.9 (CH_2), 80.6 (C), 81.0 (CH), 86.9 (CH), 104.3 (CH), 112.1 (C). ESIMS, m/z: 227 $(M + Na)^+$. Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.73, H, 7.77%.

(2′*R*,3′*R*,4′*S*,5′*R*)-1-(5-Acetoxymethyl-3,4-diacetoxy-4-methyl-tetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (6) and (2′*S*,3′*R*,4′*S*,5′*R*)-1-(5-acetoxymethyl-3,4-diacetoxy-4-methyl-tetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (7). 1,2-*O*-Isopropylidene-3-methyl-D-xylofuranose (**4**) (270 mg, 1.32 mmol) was dissolved in 4% H_2SO_4 in CH_3CN–H_2O (3 : 1) (30 mL) and stirred at room temperature for 24 h. Evaporation of the solvent gave a residue, which was acetylated with Py/Ac_2O (2 mL/0.5 mL) in presence of DMAP (catalytic) at 100 °C for 3 h. Usual work up and purification by column chromatography over silica gel using EtOAc–petroleum ether (1 : 5) as eluent afforded an anomeric mixture of tetraacetoxy derivatives (262 mg, 60%) as a colourless thick oil. To uracil (224 mg, 2.0 mmol) taken in a dry round bottomed flask fitted with a condenser and a guard tube containing $CaCl_2$ was added hexamethyl disilazane (8 mL) and TSMCl (4 drops) under N_2. The mixture was heated at reflux for 12 h and the solvent was then evaporated *in vacuo* to give a residue. To the residue dissolved in dry CH_3CN (4 mL) was added a solution of the above tetraacetoxy derivatives (220 mg, 0.66 mmol) in CH_3CN (8 mL) followed by TMS–OTf (0.4 mL) under N_2. The mixture was heated at reflux for 4 h. TLC showed complete disappearance of the starting material. The solution was neutralized with solid $NaHCO_3$, treated with water (4 drops), and the solvent was evaporated in a rotary evaporator to give a gummy material. The material was extracted with $CHCl_3$–MeOH (97 : 3) mixture (2 × 15 mL); the extract was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by silica gel column chromatography (eluting solvent: EtOAc–petroleum ether = 3 : 7) to afford a mixture of nucleosides **6** and **7** (180 mg, 70%) as a foamy material. They were separated by HPLC on Bondapak™ C_{18} column (7.8 × 300 mm) using a mixture of H_2O–CH_3CN (3 : 1) in isocratic mode.

6: mp 94–95 °C, $[\alpha]_D^{28}$ +19.0 (*c* 0.26, $CHCl_3$). IR (KBr): ν_{max} 3223, 1751, 1697, 1455, 1375, 1221, 1095, 1041 cm^{-1}. ^{1}H NMR (C_5D_5N, 300 MHz): δ 1.90 (s, 3H), 2.00 (s, 3H), 2.06 (s, 3H), 2.09 (s, 3H), 4.04–4.16 (m, 2H), 5.40 (dd, 1H, J = 6.0, 10.0 Hz, H-4′), 5.71 (d, 1H, J = 9.4 Hz, H-2′), 5.96 (d, 1H, J = 8.0 Hz, H-5), 6.55 (d, 1H, J = 9.4 Hz, H-1′), 7.92 (d, 1H, J = 8.0 Hz, H-6), 13.59 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.1 (CH_3), 20.7 (CH_3), 21.0 (CH_3), 22.8 (CH_3), 64.1 (CH_2), 71.5 (CH), 72.6 (CH), 78.9 (CH), 82.5 (C), 103.8 (CH), 139.7 (CH), 150.7 (C), 162.8 (C), 169.3 (C), 170.3 (C), 170.3 (C). FABMS, m/z: 407 $(M + H)^+$. Anal. Calcd for $C_{16}H_{20}N_2O_9$: C, 50.00; H, 5.25; N, 7.29. Found: C, 49.83, H, 5.05, N, 7.00%.

7: mp 74–76 °C, $[\alpha]_D^{28}$ +58.7 (*c* 0.33, $CHCl_3$). IR (KBr): ν_{max} 3285, 1750, 1696, 1455, 1375, 1253, 1230, 1028 cm^{-1}. ^{1}H NMR (C_5D_5N, 300 MHz): δ 1.77 (s, 3H), 1.95 (s, 6H), 2.04 (s, 3H), 3.80 (t, 1H, J = 11.4 Hz, H-5′a), 4.16 (dd, 1H, J = 6.0, 11.4 Hz, H-5′b), 5.93 (d, 1H, J = 8.1 Hz, H-5), 6.30 (d, 1H, J = 9.5 Hz, H-2′), 6.45 (dd, 1H, J = 6.0, 10.8 Hz, H-4′), 6.57 (d, 1H, J = 9.3 Hz, H-1′), 7.74 (d, 1H, J = 8.1 Hz, H-6), 13.59 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3), 20.8 (CH_3), 21.1 (CH_3), 22.6 (CH_3), 65.0 (CH_2), 68.3 (CH), 69.9 (CH), 80.3 (CH), 83.5 (C), 104.0 (CH), 139.8 (CH), 150.9 (C), 163.0 (C), 169.6 (C), 169.8 (C), 170.7 (C). FABMS, m/z: 407 $(M + H)^+$. Anal. Calcd for $C_{16}H_{20}N_2O_9$: C, 50.00; H, 5.25; N, 7.29. Found: C, 50.15, H, 5.00, N, 7.18%.

(3′a*R*,5′*R*,6′*S*,6′a*R*)-6-Azidomethyl-5-[(4*R*)-2,2-dimethyl[1,3]dioxolan-4-yl]-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (8) and (3′a*R*,3″a*R*,5′*R*,5″*R*,6′*S*,6″S,6′a*R*,6″a*R*)-6-[6-azidomethyl-5-[(4*R*)-2,2-dimethyl[1,3]dioxolan-4-yl]-2,2-dimethyl tetrahydrofuro-[2,3-*d*][1,3]dioxol-6-yloxymethyl]-5-[(4′*R*)-2,2-dimethyl[1,3]dioxolan-4′-yl]-2,2-dimethyl tetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (9). To a solution of **2** (200 mg, 0.74 mmol) in dry DMF (5 mL) was added NaN_3 (143 mg, 2.2 mmol) and the mixture was heated

at 60 °C for 4 h. The solvent was removed *in vacuo* to yield a gummy residue, which was extracted with $CHCl_3$ (30 mL). The $CHCl_3$ solution was washed with water (2 × 10 mL), dried (Na_2SO_4) and evaporated to give a crude material. The product was purified by column chromatography on silica gel. Elution with EtOAc–petroleum ether (3 : 22) and EtOAc–petroleum ether (7 : 43) furnished **8** (67 mg, 42%) and **9** (84 mg, 28%) respectively. However, the same reaction carried out at 100 °C afforded **8** (41 mg, 30%) and **9** (120 mg, 40%).

8: liquid, $[a]_D^{28}$ +28.9 (*c* 1.1, $CHCl_3$). IR (neat): ν_{max} 3447, 2105, 1560, 1377, 1217, 1072, 1002 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (s, 6H), 1.42 (s, 3H), 1.53 (s, 3H), 2.45 (brs, 1H), 3.70 (brd, 1H, $J = 12.6$ Hz), 3.76 (brd, 1H, $J = 12.3$ Hz), 3.99 (dd, 1H, $J =$ 4.8, 8.7 Hz), 4.13 (dd, 1H, $J = 6.4$, 8.7 Hz), 4.31 (m, 1H), 4.40 (d, 1H, $J = 3.3$ Hz), 5.88 (d, 1H, $J = 3.3$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.9 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 26.9 (CH_3), 53.0 (CH_2), 67.4 (CH_2), 72.2 (CH), 81.0 (CH), 81.8 (C), 85.2 (CH), 104.4 (CH), 109.5 (C), 112.7 (C). ESIMS, *m/z*: 338 $(M + Na)^+$. Anal. Calcd for $C_{13}H_{21}N_3O_6$: C, 49.52; H, 6.71; N, 13.33. Found: C, 49.38, H, 6.52; N, 13.05%.

9: sticky material, $[a]_D^{28}$ +23.9 (*c* 0.91, $CHCl_3$). IR (Neat): ν_{max} 3471, 2105, 1465, 1376, 1216, 1164, 1072, 1000, 847 cm^{-1} ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 3H), 1.35 (s, 6H), 1.37 (s, 3H), 1.42 (s, 6H), 1.52 (s, 3H), 1.54 (s, 3H), 3.59 (d, 1 H, $J = 13.5$ Hz), 3.76 (2 × dd, 2 × 1H, $J = 3.0$, 8.1 Hz), 3.90 (d, 1H, $J = 13.5$ Hz), 3.93–3.98 (m, 2H), 4.02 (dd, 1H, $J = 4.9$, 8.8 Hz), 4.09–4.14 (m, 3H), 4.34–4.38 (m, 2H), 4.41 (d, 1H, $J = 3.2$ Hz), 4.72 (d, 1H, $J =$ 3.5 Hz), 5.86 (t-like, 2H, $J \sim 3.0$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.5 (CH_3), 25.6 (CH_3), 26.8 (CH_3), 26.9 (CH_3), 27.1 (CH_3), 27.2 (CH_3), 27.3 (CH_3), 27.7 (CH_3), 51.9 (CH_2), 64.4 (CH_2), 67.9 (CH_2), 68.4 (CH_2), 72.5 (CH), 73.0 (CH), 81.0 (CH), 81.5 (C), 83.2 (CH), 83.5 (CH), 85.6 (CH), 87.5 (C), 105.0 (CH), 105.3 (CH), 109.6 (C), 109.9 (C), 113.0 (2 × C). ESIMS, *m/z*: 610 $(M+ Na)^+$. Anal. Calcd for $C_{26}H_{41}N_3O_{12}$: C, 53.14; H, 7.03; N, 7.15. Found: C, 52.87, H, 7.05; N, 6.90%.

(3a*R*,5*S*,6*S*,6a*R*)-6-Azidomethyl-5-hydroxymethyl-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (10). Compound **8** (300 mg, 0.95 mmol) was converted to a crude aldehyde (150 mg) (IR: ν_{max} 3424, 2106, 1732, 1633, 1379, 1220, 1165, 1074, 998 cm^{-1}) following the procedure described earlier (in the preparation of **4**) using (i) HOAc–H_2O (3 : 1) mixture (10 mL) and (ii) an aqueous solution (5 mL) of $NaIO_4$ (155 mg, 0.73 mmol). The above aldehyde dissolved in MeOH (10 mL) at ice cold temperature was treated with $NaBH_4$ (25 mg) portionwise. Stirring at room temperature for 4 h followed by usual work-up and purification by column chromatography on silica gel using EtOAc–petroleum ether (3 : 7) as eluent produced **10** (97 mg, 41%). **10**: thick liquid, $[a]_D^{29}$ +52.9 (*c* 0.99, $CHCl_3$). IR (neat): ν_{max} 3413, 2105, 1438, 1378, 1218, 1073, 1000, 875 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34 (s, 3H), 1.50 (s, 3H), 3.46 (d, 1H, $J = 12.7$ Hz), 3.64 (d, 1H, $J = 12.7$ Hz), 3.90 (t, 1H, $J = 2.5$ Hz), 4.12 (m, 2H), 4.40 (d, 1H, $J = 3.6$ Hz), 5.98 (d, 1H, $J = 3.6$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.2 (CH_3), 26.8 (CH_3), 53.2 (CH_2), 60.9 (CH_2), 79.2 (CH), 82.9 (C), 85.4 (CH), 104.3 (CH), 112.7 (C). ESIMS: *m/z*: 268 $(M+ Na)^+$. Anal. Calcd for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.17; N, 17.13. Found: C, 43.95, H, 6.03; N, 16.90%.

(2′*R*,3′*R*,4′*S*,5′*R*)-1-(3-Acetoxy-5-acetoxymethyl-4-azidomethyl-4-trimethylsilanyloxy-tetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (13) and (2′*S*,3′*R*,4′*S*,5′*R*)-1-(3-acetoxy-5-acetoxymethyl-4-azidomethyl-4-trimethylsilanyloxy-tetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (14). Following the procedure described earlier (in the preparation of **6** and **7**), the compound **10** (150 mg, 0.61 mmol) was converted to the anomeric mixture of azidomethyl furanose–triacetate **11** (108 mg, 53%) through treatment with 4% H_2SO_4 in CH_3CN–H_2O (3 : 1) followed by acetylation using a mixture of pyridine (2 mL) and Ac_2O (0.5 mL) at room temperature overnight. When the above acetylation was carried out at 100 °C using a catalytic amount of DMAP, it furnished the tetraacetoxy azidomethyl furanose derivative **12** (55% yield from **8**). A solution of **11** (55 mg, 0.17 mmol) in CH_3CN (3 mL) was added to a solution of 2,4-bistrimethylsilyloxypyrimidine [prepared from uracil (56 mg, 0.5 mmol), hexamethyl disilazane (2 mL) and TMSCl (1 drop)] in CH_3CN (2 mL) in presence of TMS–OTf (0.1 mL) and the solution was heated at reflux for 4 h under N_2. Usual work up (described under the preparation of **6** and **7**) and purification by silica gel column chromatography [eluting solvent: EtOAc–petroleum ether (3 : 7)] furnished **13** (23 mg, 30%) and **14** (25 mg, 32%).

13: sticky material, $[a]_D^{29}$ +14.1 (*c* 0.56 $CHCl_3$). IR (neat): ν_{max} 3368, 1748, 1694, 1456, 1222, 1053, 846, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.20 (s, 9H), 2.13 (s, 3H), 2.19 (s, 3H), 3.62 (d, 1H, $J = 13.0$ Hz), 3.73 (d, 1H, $J = 13.0$ Hz), 4.24 (dd, 1H, $J = 3.8$, 6.5 Hz), 4.32 (dd, 1H, $J = 6.5$, 11.9 Hz), 4.41 (dd, 1H, $J = 3.8$, 11.9 Hz), 5.19 (d, 1H, $J = 2.4$ Hz), 5.76 (brd, 1H, $J =$ 7.9 Hz), 5.88 (d, 1H, $J = 2.4$ Hz), 7.64 (d, 1H, $J = 8.1$ Hz), 8.40 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 2.32 (3 × CH_3), 21.09 (CH_3), 21.22 (CH_3), 53.4 (CH_2), 62.8 (CH_2), 81.8 (CH), 82.5 (C), 83.0 (CH), 89.2 (CH), 102.9 (CH), 140.1 (CH), 150.5 (C), 163.4 (C), 169.3 (C), 170.9 (C). ESIMS (*m/z*): 478 $(M + Na)^+$. Anal. Calcd for $C_{17}H_{25}N_5O_8Si$: C, 44.83; H, 5.53; N, 15.38. Found: C, 44.95, H, 5.38; N, 15.09%.

14: sticky material, $[a]_D^{29}$ +23.6 (*c* 0.49, $CHCl_3$). IR (KBr): ν_{max} 3362, 1752, 1696, 1455, 1375, 1218, 1081, 844 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.12 (s, 9H), 2.10 (s, 3H), 2.18 (s, 3H), 3.75–3.87 (m, 3H), 4.14 (dd, 1H, $J = 6.0$, 11.0 Hz), 5.06 (partially merged signal, 1H), 5.10 (d, 1H, $J = 9.7$ Hz), 5.79 (brd, 1H, $J =$ 7.7 Hz), 6.18 (d, 1H, $J = 9.7$ Hz), 7.35 (d, 1H, $J = 8.1$ Hz), 8.44 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 2.31 (3 × CH_3), 20.9 (CH_3), 21.3 (CH_3), 51.4 (CH_2), 64.6 (CH_2), 73.6 (CH), 74.7 (CH), 77.3 (C, merged under solvent peak), 79.7 (CH), 103.7 (CH), 139.7 (CH), 150.7 (C), 163.1 (C), 169.7 (C), 170.0 (C). ESIMS, *m/z*: 478 $(M + Na)^+$. Anal. Calcd for $C_{17}H_{25}N_5O_8Si$: C, 44.83; H, 5.53; N, 15.38. Found: C, 44.55, H, 5.47; N, 15.15%.

(2′*R*,3′*R*,4′*S*,5′*R*)-1-(5-Acetoxymethyl-4-azidomethyl-3,4-diacetoxy-tetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (15) and (2′*S*,3′*R*,4′*S*,5′*R*)-1-(5-acetoxymethyl-4-azidomethyl-3,4-diacetoxy-tetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (16). Compound **12** (60 mg, 0.16 mmol)) furnished the nucleosides **15** (11 mg, 15%) and **16** (35 mg, 48%) as foamy solids adopting the procedure described above.

15: mp 105–106 °C (decomp.), $[a]_D^{29}$ +19.7 (*c* 0.37, $CHCl_3$). IR (Neat): ν_{max} 3352, 2112, 1747, 1695, 1456, 1374, 1223, 1050, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.13 (s, 6H), 2.18 (s, 3H), 3.77 (d, 1H, $J = 13.5$ Hz), 4.12 (d, 1H, $J = 13.5$ Hz), 4.35–4.47 (m, 2H), 4.52 (dd, 1H, $J = 2.4$, 12.0 Hz), 5.58 (d, 1H, $J =$ 5.5 Hz), 5.82 (d, 1H, $J = 8.2$ Hz), 5.89 (d, 1H, $J = 5.5$ Hz), 7.46

(d, 1H, $J = 8.2$ Hz), 8.28 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.8 (CH_3), 21.2 (CH_3), 21.7 (CH_3), 51.2 (CH_2), 62.8 (CH_2), 78.6 (CH), 82.1 (CH), 85.7 (C), 87.2 (CH), 103.9 (CH), 139.1 (CH), 150.4 (C), 162.8 (C), 169.3 (C), 170.2 (C), 170.8 (C). ESI MS, *m/z*: 448 $(M + Na)^+$. Anal. Calcd for $C_{16}H_{19}N_5O_9$: C, 45.18; H, 4.50; N, 16.46. Found: C, 44.90, H, 4.39; N, 16.18%.

16: mp 73–74 °C, $[\alpha]_D^{29}$ +41.8 (*c* 0.79, $CHCl_3$). IR (KBr): ν_{max} 3485, 2113, 1754, 1697, 1375, 1218, 1090 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.00 (s, 3H), 2.10 (s, 3H), 2.17 (s, 3H), 3.87 (d, 1H, $J = 12.8$ Hz), 3.94 (d, 1H, $J = 12.8$ Hz), 3.94 (dd-like, 1H, $J = 10.4$, 11.4 Hz), 4.10 (dd, 1H, $J = 6.5$, 11.5 Hz), 5.80 (dd, 1H, $J = 2.0$, 8.2 Hz), 6.07 (d, 1H, $J = 9.6$ Hz), 6.08 (dd, 1H, $J = 6.5$, 10.2 Hz), 6.17 (d, 1H, $J = 9.6$ Hz), 7.38 (d, 1H, $J = 8.2$), 8.23 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.3 (CH_3), 20.6 (CH_3), 21.9 (CH_3), 49.5 (CH_2), 64.7 (CH_2), 67.5 (CH), 69.4 (CH), 79.5 (CH), 82.6 (C), 103.7 (CH), 139.0 (CH), 150.3 (C), 162.7 (C), 169.2 (C), 169.3 (C), 169.9 (C). ESIMS, *m/z*: 448 $(M + Na)^+$. Anal. Calcd for $C_{16}H_{19}N_5O_9$: C, 45.18; H, 4.50; N, 16.46. Found: C, 45.02, H, 4.52; N, 16.32%.

(3a*R*,5*R*,6*R*,6a*R*)-5-[(4*R*)-2,2-Dimethyl[1,3]dioxolan-4-yl]-2,2,6-trimethyl tetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (17). A solution of 1,2:5,6-di-*O*-isopropylidene-α-D-ribo-hexofuran-3-ulose **1** (1.03 g, 4 mmol) [dried by heating at 100 °C under vacuum] in dry diethyl ether (30 mL) was added to a solution (50 mL) of CH_3MgI (prepared from 200 mg of Mg, 1.42 g of CH_3I and cat. amount of I_2) and the mixture was stirred at room temperature for 2 h. Usual work up followed by purification on silica gel using EtOAc–petroleum ether (1 : 19) as eluent afforded **17** (710 mg, 65%). Mp 106–107 °C (lit.[16] mp 105–106 °C), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (s, 3H), 1.35 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 1.59 (s, 3H), 2.67 (brs, 1H), 3.78 (d, 1H, $J = 7.0$ Hz), 3.92 (dd, 1H, $J = 8.3$, 11.1 Hz), 4.07–4.13 (m, 2H), 4.17 (d, 1H, $J = 3.6$ Hz), 5.70 (d, 1H, $J = 3.6$ Hz). ESIMS, *m/z*: 297 $(M + Na)^+$.

(3a*R*,5*R*,6*R*,6a*R*)-5-Hydroxymethyl-2,2,6-trimethyl tetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (18). The compound **18** was prepared (in 48% yield) from **17** using the same procedure and protocol as described for the preparation of **4**. Liquid, $[\alpha]_D^{29}$ +21.5 (*c* 0.71, $CHCl_3$). IR (neat): ν_{max} 3404, 1457, 1378, 1167, 1078, 1007, 875 cm^1. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.17 (s, 3H), 1.36 (s, 3H), 1.59 (s, 3H), 2.65 (brs, 2H, exchangeable with D_2O), 3.75 (dd, 1H, $J = 7.2$, 11.7 Hz), 3.82 (dd, 1H, $J = 3.3$, 11.7 Hz), 3.89 (dd, 1H, $J = 3.6$, 6.9 Hz), 4.12 (d, 1H, $J = 3.6$ Hz), 5.78 (d, 1H, $J = 3.6$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.1 (CH_3), 26.2 (2 × CH_3), 60.3 (CH_2), 76.6 (C), 81.7 (CH), 84.1 (CH), 103.1 (CH), 112.3 (C). ESIMS, *m/z*: 227 $(M + Na)^+$. Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.66, H, 7.83%.

(2′*R*,3′*R*,4′*R*,5′*R*)-1-(5-Acetoxymethyl-3,4-diacetoxy-4-methyl-tetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (19). The compound **18** (300 mg, 1.47 mmol) was converted to a mixture of 1,2,3,5-tetraacetoxy-3-methyl allofuranose (302 mg, 62%) as a colourless liquid using a procedure similar to that described earlier (under the preparation of **4**). The material was used for the introduction of uracil base using the procedure as described in the preparation of **6** and **7** and the following reactants: (i) tetraacetoxy allofuranose derivative (200 mg), (ii) TMS–OTf (0.4 mL), (iii) CH_3CN (10 mL), and (iv) 2,4-bistrimethylsilyloxypyrimidine [prepared from uracil (202 mg, 1.80 mmol), hexamethyl disilazane (8 mL), and TMSCl (4 drops)]. Usual work up followed by silica gel column chromatography [eluting solvent: EtOAc–petroleum ether = 8 : 17] furnished **19** (265 mg, 76%). Foamy solid, mp 65–66 °C. IR (KBr): ν_{max} 3300, 1750, 1697, 1633, 1456, 1375, 1228, 1095, 1042 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.71 (s, 3H), 2.07 (s, 3H), 2.13 (3H), 2.19 (s, 3H), 3.85 (m, 2H), 4.94 (d, 1H, $J = 9.6$ Hz), 4.96 (dd, 1H, $J = 6.0$, 10.2 Hz), 5.76 (dd, 1H, $J = 1.5$, 8.1 Hz), 6.04 (d, 1H, $J = 9.6$ Hz), 7.30 (d, 1H, $J = 8.1$ Hz), 8.64 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.5 (CH_3), 20.1 (CH_3), 20.4 (CH_3), 22.2 (CH_3), 63.4 (CH_2), 70.8 (CH), 71.9 (CH), 78.2 (CH), 81.9 (C), 103.2 (CH), 139.3 (CH), 150.5 (C), 163.0 (C), 168.8 (C), 169.7 (C), 169.9 (C). ESIMS, *m/z*: 407 $(M+ Na)^+$. Anal. Calcd for $C_{16}H_{20}N_2O_9$: C, 50.00; H, 5.25; N, 7.29. Found: C, 50.11, H, 5.23; N, 7.00%.

(2′*R*,3′*R*,4′*S*,5′*R*)-1-(5-Acetoxymethyl-3,4-diacetoxy-tetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (21). The anomeric mixture of tetraacetoxy derivatives **20** (318 mg, 1.0 mmol) (derived from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose in 30% overall yield, following the procedure used in the preparation of **11**) was transformed into the nucleoside analogue **21** (260 mg, 70%) adopting the method similar to that described in Scheme 1 (for the generation of **6** and **7**). Foamy solid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.01 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 3.53 (t, 1H, $J = 11.0$ Hz), 4.22 (dd, 1H, $J = 5.7$, 11.5 Hz), 5.04 (m, 1H), 5.10 (t, 1H, $J = 9.5$ Hz), 5.43 (t, 1H, $J = 9.5$ Hz), 5.78 (d, 1H, $J = 9.5$ Hz), 5.81 (merged dd, 1H, $J = 2.0$, 8.4 Hz), 7.32 (d, 1H, $J = 8.1$Hz), 8.84 (s, 1H). FABMS, *m/z*: 371 $(M + H)^+$.

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