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In situ 1,3-dipolar azide cycloaddition reaction: synthesis of functionalized D-glucose based chiral piperidine and oxazepine analogues

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Abstract—Functionalized furanose-fused piperidines **4**-**6** and oxazepines **15**-**17**, useful precursors for structurally unique bioactive nucleosides as well as for potential glycosidase inhibitors, have been synthesized by the application of 1,3-dipolar azide cycloaddition (DAC) reaction on D-glucose based substrates. The strategy works well even with the nucleoside analogue **8**, affording the bicyclic nucleoside analogues **11** and **12**.

1. Introduction

The 1,3-dipolar azide cycloaddition (DAC) reaction constitutes a simple method, which has been widely used in the synthesis of alkaloids[1] and many other heterocycles of diverse structures.[2] In recent years, effort has been made to explore cycloaddition on carbohydrate derived alkenes/alkynes. This has led to elegant methodologies for the synthesis of chiral triazoles,[3] azole-piperidinoses,[4] tetrazoles,[5] glucotriazole carboxylate,[6] and various iminosugars[7] en route to nucleoside analogues[8] and inhibitors of glycosidases,[9] glycogen phosphorylases[6] and glycosyl transferases.[10] For our project directed towards the synthesis of new carbohydrate based piperidine and oxazepine analogues, we decided to use this reaction on suitably crafted precursors. The allyl group is easy to introduce into the carbohydrate core and is particularly amenable for such cycloadditions. The precursors **1**-**3**, already used in our laboratory for other synthetic schemes, appeared as convenient starting materials.[11] The expected products could allow introduction of various nucleobases directly onto the anomeric center of a furanose ring or via easy opening of the ring. In this paper, we report the work undertaken to investigate the scope of this reaction for developing functionalized chiral piperidine and oxazepine analogues.

2. Results and discussions

The carbohydrate-derived precursors **1**-**3** on tosylation and subsequent treatment with sodium azide furnished, after column chromatography, TLC pure (in different solvent systems) products. However, these exhibited two sets of ^{1}H and ^{13}C NMR peaks for many of the protons and carbons. The formation of a mixture of enamine and imine **A** and **B** (presumably through the generation of an aziridine ring followed by its opening) was suggested by the fact that the signals at δ 1.78 (s), 2.01 (s), 1.98 (d), and 2.33 (d) in the ^{1}H NMR disappeared on D_2O exchange. In support, the ^{13}C NMR showed signals at δ 143.8 and 164.3, close to the expected shieldings for the enamine and imine carbons, respectively. In addition, the presence of three signals for methylene carbons at δ 35.5, 40.0 and 48.0 indicated formation of the mixture. Acetylation of the mixture, without further purification, furnished single *N*-acetylated products **4**-**6** in fairly good yields (Scheme 1). In the ^{13}C NMR spectrum of **5** for example, the presence of carbon signals at δ 169.4, 142.6, 108.5 and 23.7 suggested the presence of amide carbonyl, olefinic quaternary as well as methine carbons. Additionally, the methyl proton signal at δ 2.17 (d, J=0.9 Hz, allylic coupling) testified to the location of a vinylic methyl group.

When the reaction was performed on a substrate with a pre-installed nucleoside base in the furanose ring, it took an unexpectedly different course. For this study, the tosylate **7** of **1** (Scheme 2) was first treated with acid to remove the isopropylidene protecting group and then subjected to acetylation to furnish **8** as a mixture of anomers. Treatment of this mixture with bis-*O*-trimethylsilyl)uracil

Keywords: DAC reaction; Synthesis; Chiral piperidines and oxazepines; D-Glucose.
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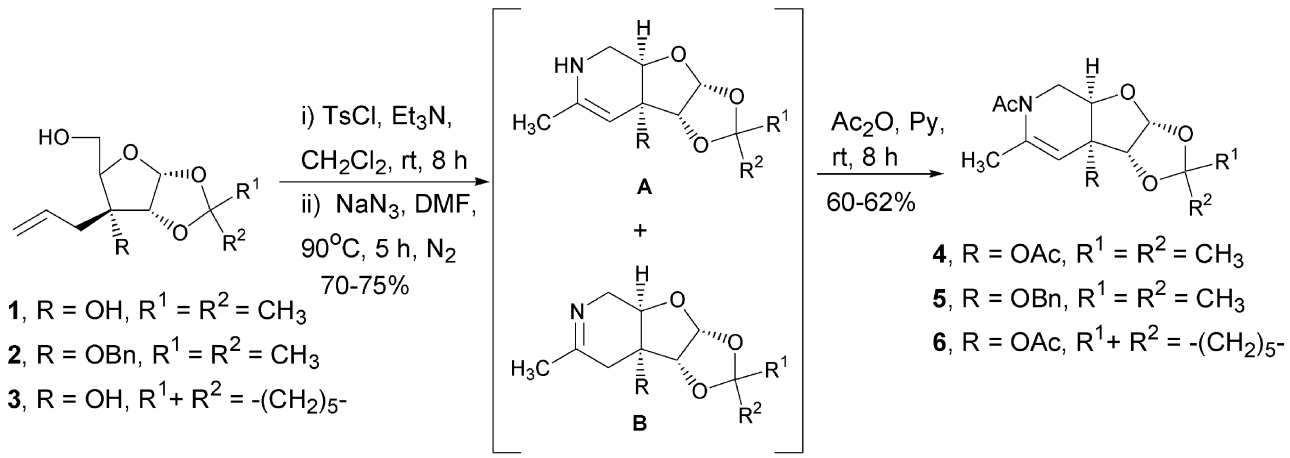
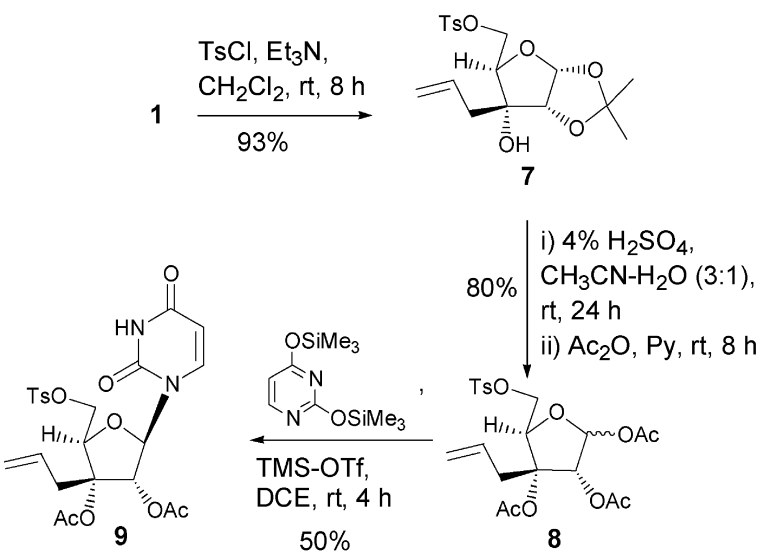


Scheme 1. 1,3-DAC reaction on 3-*C*-allyl glucose precursors.

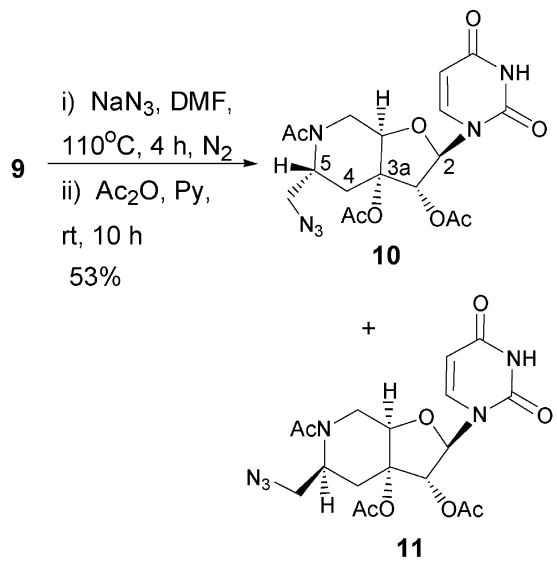


Scheme 2. Preparation of nucleoside derivative **9**.

and TMS-OTf in dichloroethane, under the conditions reported by Vorbrüggen,[12] furnished the nucleoside derivative **9**. The neighbouring acetoxy group, as is known from earlier studies,[13] guides the orientation of the nucleoside base in the product **9**.

On treatment with sodium azide, **9** underwent 1,3-DAC reaction to afford a difficult to purify product, which was therefore directly acetylated. Column chromatographic purification furnished the nucleoside analogues **10** and **11** in 3:1 ratio (Scheme 3).

The peak at $\nu_{max}\sim2106\ cm^{-1}$ in the IR spectra of the products clearly indicated the presence of azide functionality. The FABMS of both the nucleosides showed pseudo molecular ion peaks at *m*/*z* 451 ($M+H^+$) and 473 ($M+Na^+$). Among the three methylene carbon signals in the ^{13}C NMR spectrum, the one at $\delta\sim45.0$ may be assigned to the carbon carrying the azide group. In the ^1H NMR spectrum, the coupling constants $J_{2,3}$ are found to be somewhat different for **10** (6.1 Hz) and **11** (8.5 Hz). This may be due to difference in dihedral angle of the $H-C_2-C_3-H$ unit (40° in **10** and 18° in **11** in the energy-minimized structures



Scheme 3. 1,3-DAC reaction on nucleoside derivative **9**.

obtained using Chem. Office 6.0. For this, a presentation of the structure was created in Chem Draw and transferred to Chem 3D, taking care to ensure that the stereochemistry at different centers of the conformer were correct. After initial energy minimization using MM2 programme, molecular dynamics was run. The generated conformer was tested by MM2 to reach the energy minimized conformer. The piperidine ring in **11** exists in chair conformation ($J_{4a,5a}$=13.0 Hz and $J_{4a,e}$=14.7 Hz), whereas the same ring in **10** is in the twist-boat form ($J_{4a,5a}$=12.3 Hz and $J_{4a,e}$=14.0 Hz), since the chair conformation is destabilized due to 1,3-diaxial interaction between acetoxy group at C-3a and azidomethyl group at C-5.

The formation of the above products may be rationalized by assuming that the 1,3-DAC reaction proceeds through the generation of a triazoline intermediate, which after nitrogen elimination leads to an aziridine intermediate. This quickly isomerizes in case of **1**-**3** to afford imine/enamine mixture (Fig. 1), or is opened by azide attack (in case of **9**).

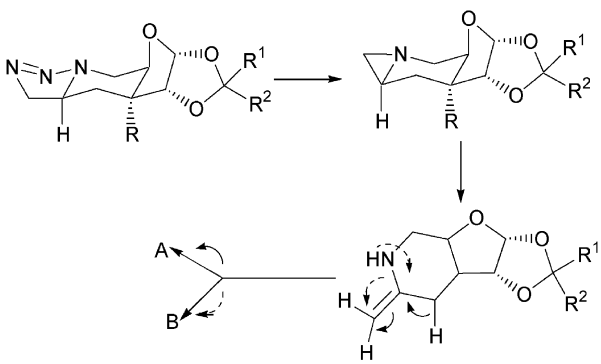


Figure 1. Proposed mechanism for the formation of imine/enamine mixture.

To understand the nature of the aziridine intermediate, we carried out molecular modeling studies. This revealed that the minimium energy conformations of the two *trans*-aziridine isomers (161.3 or 173.9 kcal/mol) are far greater in steric energy than the corresponding *cis*-aziridine isomers (146.6 or 147.1 kcal/mol), which are close to each other in steric energy. The formation of the isomeric mixture of nucleoside derivatives is thus possible through the intermediacy of non-isolable *cis*-aziridines (Figs. 2 and 3).

In another variation of the reaction, the cycloaddition reaction was attempted on substrates carrying *O*-allyl rather

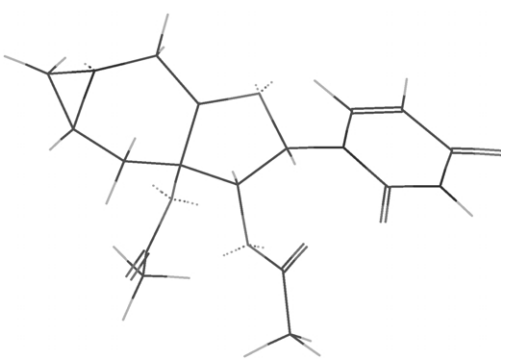


Figure 2. *cis*-Aziridine with N lone pair and ring juncture H α-oriented.

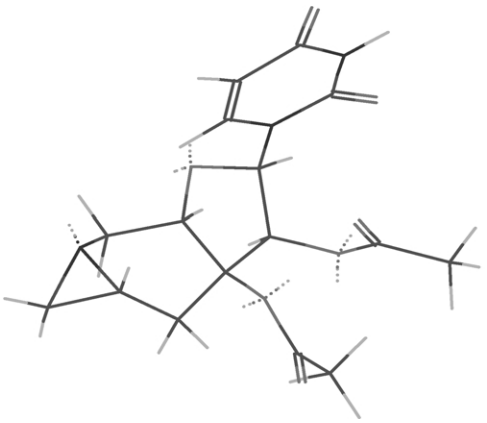


Figure 3. *cis*-Aziridine with N lone pair and ring juncture H β-oriented.

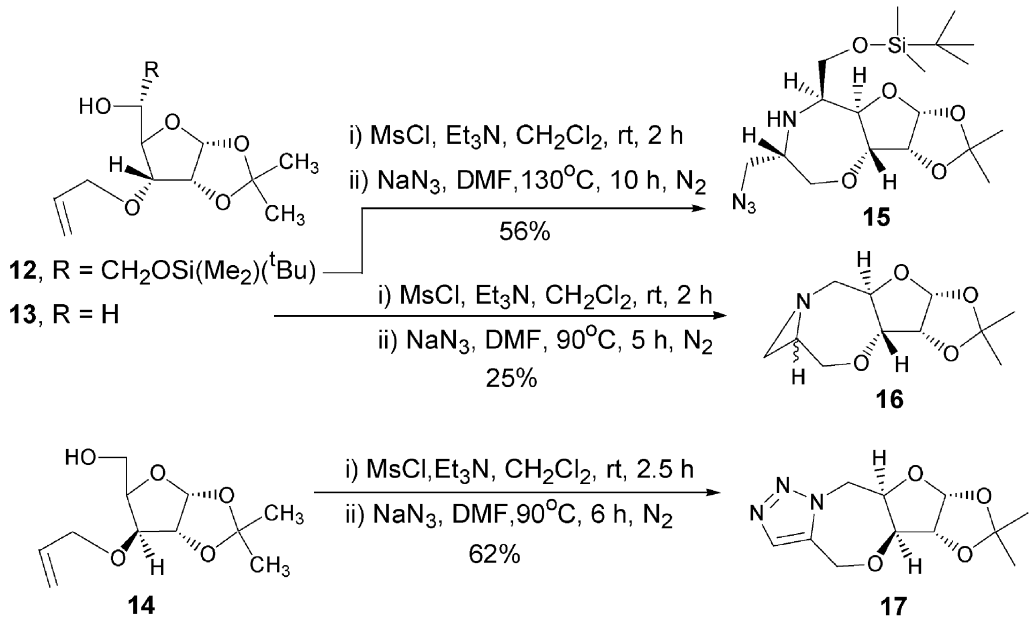
than *C*-allyl group at *C*-3 of the carbohydrate derived precursor. The substrates **12**-**14** were chosen, prepared and characterized according to our established protocols.[14] Both *cis* and *trans* substituted substrates **13** and **14** could be tested besides one (**12**) carrying a bulky group (TBDMS) in one of the substituents.

When **12** was subjected to mesylation followed by reaction with sodium azide, it afforded the oxazepine analogue **15**. However, the aziridino-oxazepine derivative **16** was obtained in low yield by DAC reaction upon **13**, while **14** afforded **17** with triazolo-oxazepine moiety (Scheme 4).

The absence of allyl functionality in **15**-**17** was shown by the disappearance of signals for the vinyl proton(s) in the region between δ 4.84–6.34. Retention of the 1,2-*O*-isopropylidene groups in all the products and the tertiary butyl dimethyl silyl functionality in **15** was evident from their characteristic signals in the ^{1}H NMR spectra. The IR spectrum of **15**, but not those of **16** and **17**, showed a strong band at 2105 cm^{-1} for the azide group. The presence of the CH_2N_3 moiety in **15** was confirmed by the appearance of one double doublet at δ 3.16 (J=7.5, 12.0 Hz) and a doublet at δ 3.28 (J=12.0 Hz) in its ^{1}H NMR spectrum. In the ^{1}H NMR spectrum of **16**, the appearance of two upfield doublets at δ 1.49 and 2.18 clearly indicated the formation of an aziridine moiety. However, the stereochemistry at the aziridine ring juncture could not be ascertained. Mass spectrum as well as ^{13}C NMR spectrum confirmed the structures indicated.

The results of the cycloaddition reactions with *O*-allyl substituted substrates suggest that the course of the reaction remains similar to that observed with the *C*-allyl substituted substrates, that is, initial triazoline formation followed by nitrogen elimination to the aziridine, which could be isolated, albeit in low yield, in case of **13**. In case of **12** the aziridine moiety did not survive under the reaction condition and decomposed in nucleophilic attack by azide ion. The formation of a triazole product **17** from **14** may be explained by assuming that the initial triazoline possibly had a *trans* ring fusion and was therefore prone to oxidation, brought about in this case perhaps by atmospheric oxygen.

In conclusion, we have applied the 1,3-DAC reaction on D-glucose derived unactivated olefin precursors to construct



Scheme 4. 1,3-DAC reaction on glucose derived substrates **12**–**14**.

chiral piperidine and oxazepine rings, fused to ribose moiety, which may be elaborated to iminosugars, oxo-iminosugars and nucleoside analogues. The scope and limitation of the method to synthesize other such systems with different heterocycles of varied ring sizes is under study.

3. Experimental

Melting points were taken in open capillaries and are uncorrected. IR spectra were measured on a JASCO 700 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured either on a JEOL FX-100 or a Bruker AM 300 L spectrometer using TMS as internal standard. Mass spectra were obtained using a JEOL AX-500 spectrometer operating at 70 eV. Optical rotations were measured in a JASCO DIP 360 polarimeter. HPLC was performed on μ Bondapak™ C_{18} column (7.38×300 mm). Flash chromatography was carried out on LiChroprep® RP-18 (Merck).

3.1. (3a*R*,3b*R*,7a*R*,8a*R*)-Acetic acid 6-acetyl-2,2,5-trimethyl-3a,7,7a,8a-tetrahydro-6*H*-1,3,8-trioxa-6-aza-cyclopenta[*a*]inden-3b-yl ester (4)

3.1.1. Typical procedure for 4. To a stirred solution of **1** (500 mg, 2.17 mmol) in CH_2Cl_2 (30 ml) containing Et_3N (1 ml) was added TsCl (415 mg, 2.18 mmol) and the stirring was continued for 8 h at rt. The mixture was washed with brine (3×10 ml), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography using $CHCl_3$ as eluent to furnish **7** (768 mg, 93%). **7** (500 mg, 1.30 mmol) in dry DMF (5 ml) was reacted with NaN_3 (393 mg, 4.7 equiv.) at 90 °C for 5 h under N_2. The solvent was evaporated and the crude mass was extracted with $CHCl_3$ (30 ml). The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was subjected to reverse phase flash column chromatography using CH_3CN–H_2O (1:4) to furnish a mixture of enamine and imine **A** and **B** (350 mg). An aliquot of the mixture (50 mg) was then acetylated with Ac_2O/Py. The crude acetylated product was purified by chromatography on silica gel column using Pet. ether–EtOAc (13:7) to yield **4** (35 mg, 61%) as a foamy solid; [Found: C, 57.83; H, 6.73; N, 4.33. $C_{15}H_{21}NO_6$ requires C, 57.87; H, 6.80; N, 4.50%]; (α_D^{20}=−356 (*c* 0.3, $CHCl_3$); IR (KBr): ν_{max} 1733, 1670, 1401, 1380, 1237, 1210, 1067, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 3H), 1.53 (s, 3H), 2.07 (s, 3H), 2.17 (d, 3H, *J*=0.9 Hz), 2.19 (s, 3H), 3.23 (d, 1H, *J*=13.5 Hz), 4.12 (dd, 1H, *J*=2.7, 13.5 Hz), 4.32 (brs, 1H), 4.86 (d, 1H, *J*=3.6 Hz), 5.47 (s, 1H), 5.70 (d, 1H, *J*=3.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.2(q), 22.3(q), 23.7(q), 26.9(q), 27.1(q), 45.6(t), 76.6(d), 78.6(s), 81.6(d), 105.2(d), 108.5(d), 113.1(s), 142.6(s), 169.4(s), 171.3(s); FABMS: *m*/*z* at 312 (MH^+).

3.1.2. (3a*R*,3b*R*,7a*R*,8a*R*)-1-(3b-Benzyloxy-2,2,5-trimethyl-3a,7,7a,8a-tetrahydro-3b*H*-1,3,8-trioxa-6-aza-cyclopenta[*a*]inden-6-yl) ethanone (5). *Compound* **5**. Yield 60%; sticky mass; [Found: C, 66.62; H, 7.12; N, 3.69. $C_{20}H_{25}NO_5$ requires C, 66.83; H, 7.01; N, 3.90%]; (α_D^{20}=−132 (*c* 0.84, $CHCl_3$); IR (neat): ν_{max} 1673, 1391, 1217, 1135, 1099, 1069, 1026, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 3H), 1.61 (s, 3H), 2.18 (s, 3H), 2.22 (s, 3H), 3.22 (d, 1H, *J*=13.5 Hz), 4.01 (dd, 1H, *J*=3.0, 13.5 Hz), 4.36 (brs, 1H), 4.45 (d, 1H, *J*=3.3 Hz), 4.65 (d, 1H, *J*=11.0 Hz), 4.69 (d, 1H, *J*=11.0 Hz), 5.16 (s, 1H), 5.68 (d, 1H, *J*=3.3 Hz), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.9 (q), 24.1 (q), 27.9 (q), 30.1 (q), 46.6 (t), 66.9 (t), 78.0 (d), 78.5 (s), 82.5 (d), 105.7 (d), 109.9 (d), 114.1 (s), 128.1 (d), 128.2 (d, 2C), 128.7 (d, 2C), 138.9 (s), 142.7 (s), 172.0 (s); FABMS: *m*/*z* at 360 (MH^+).

3.1.3. (3a*R*,3b*R*,7a*R*,8a*R*)-Acetic acid 6-acetyl-2,2-cyclohexylidenyl-5-methyl-3a,7,7a,8a-tetrahydro-6*H*-1,3,8-trioxa-6-aza-cyclopenta[*a*]inden-3b-yl ester (6). *Compound* **6**. Yield 62%; thick liquid; [Found: C, 61.52; H, 7.00; N, 3.83. $C_{18}H_{25}NO_6$ requires C, 61.52; H, 7.17; N,

3.99%]; ($\alpha(^{20}_{D}$=−247 (*c* 0.5, $CHCl_3$); IR (KBr): ν_{max} 1743, 1671, 1399, 1371, 1242, 1128, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (m, 2H), 1.64 (m, 6H), 1.74 (m, 2H), 2.07 (s, 3H), 2.17 (s, 3H), 2.19 (s, 3H), 3.22 (d, 1H, *J*=13.7 Hz), 4.11 (dd, 1H, *J*=3.0, 13.7 Hz), 4.31 (s, 1H), 4.83 (d, 1H, *J*=3.3 Hz), 5.48 (s, 1H), 5.71 (d, 1H, *J*=3.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.2(q), 22.3(q), 23.6 (t), 23.7(q), 24.0(t), 24.9(t), 36.4(t), 36.9(t), 45.7(t), 76.7(d), 78.8(s), 81.1(d), 104.9(d), 108.8(d), 113.8(s), 142.6(s), 169.4(s), 171.3(s); FABMS: *m*/*z* at 352(MH^+).

3.1.4. Toluene-4-sulfonic acid 6-allyl-6-hydroxy-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl ester (7). *Compound* **7**. Yield 93%; sticky mass; [Found: C, 56.18; H, 6.00. $C_{18}H_{24}O_7S$ requires C, 56.23; H, 6.29%]; ($\alpha(^{20}_{D}$=+40 (*c* 0.3, $CHCl_3$); IR (neat): ν_{max} 3397 (br), 1599, 1361, 1175, 816, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H), 1.52 (s, 3H), 2.40 (s, 3H), 2.45 (dd, 1H, *J*=7.0, 15.5 Hz), 2.52 (dd, 1H, *J*=8.0, 15.5 Hz), 4.17–4.24 (m, 3H), 4.36 (d, 1H, *J*=3.6 Hz), 5.11s, 1H), 5.20 (m, 2H), 5.68 (d, 1H, *J*=3.6 Hz), 5.86 (m, 1H), 7.28 (d, 2H, *J*=8.1 Hz), 7.76 (d, 2H, *J*=8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.0 (q), 27.0(q), 27.2(q), 35.7 (t), 67.6(t), 79.5 (d), 82.5(d), 84.1(s), 104.5(d), 113.4(s), 119.4(t), 127.9(d, 2C), 130.2(d, 2C), 132.4(d), 133.6(s), 145.0(s); FABMS: *m*/*z* at 385 (MH^+).

3.1.5. (2*R*,3*R*,4*R*,5*R*)-Acetic acid 4-acetoxy-3-allyl-5-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-2-(toluene-4-sulfonyloxymethyl)-tetrahydrofuran-3-yl ester (9). Uracil (600 mg, 5.36 mmol) was dissolved in hexamethyl disilazane (10 ml). TMSCl (2 drops) was added to it and the mixture was heated at reflux under N_2 for 12 h. The solvent was evaporated in vacuo, the residue dissolved in DCE (5 ml) and added to a stirred solution of the triacetate mixture **8** (715 mg, 1.52 mmol) in DCE (5 ml). After adding TMS–OTf (0.8 ml) the solution was stirred for 4 h at rt when tlc showed complete disappearance of the starting material. The mixture was neutralized with solid $NaHCO_3$, treated with water (2–3 drops), and the solvent was evaporated in rotary evaporator. The residue was extracted with $CHCl_3$–MeOH mixture (49:1, 20 ml), washed with brine, dried, and concentrated. The crude product was purified by silica gel column chromatography eluting with methanolic $CHCl_3$ (2%) to afford **9** (400 mg, 50%) as a foam; [Found: C, 52.58; H, 5.15; N, 5.21. $C_{23}H_{26}N_2O_{10}S$ requires C, 52.87; H, 5.02; N, 5.36%]; ($\alpha(^{20}_{D}$=−15.9 (*c* 0.49, $CHCl_3$); IR (KBr): ν_{max} 1746, 1696, 1371, 1222, 1179 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.06 (s, 3H), 2.13 (s, 3H), 2.47 (s, 3H, merged with one proton signal), 3.14 (dd, 1H, *J*=7.2, 14.5 Hz), 4.27 (dd, 1H, *J*=2.1, 11.4 Hz), 4.36 (dd, 1H, *J*=2.8, 11.4 Hz), 4.76 (brs, 1H), 5.04 (m, 2H), 5.26 (d, 1H, *J*=8.1 Hz), 5.55 (m, 1H), 5.69 (d, 1H, *J*=8.1 Hz), 6.16 (d, 1H, *J*=8.1 Hz), 7.40 (d, 2H, *J*=8.1 Hz), 7.52 (d, 1H, *J*=8.1 Hz), 7.82 (d, 2H, *J*=8.1 Hz), 7.98 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.6, 21.7 (2C), 35.6, 67.1, 76.0, 81.0, 84.0, 85.1, 103.5, 119.5, 127.9 (2C), 129.9, 130.3 (2C), 136.0, 139.1, 146.0, 150.6, 162.3, 169.7, 170.2; FABMS: *m*/*z* at 523 (MH^+).

3.1.6. (2*R*,3*R*,3a*R*,5*R*,7a*R*)-Acetic acid 3a-acetoxy-6-acetyl-5-azidomethyl-2-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-octahydro-furo[2,3-*c*]pyridin-3-yl ester (10) (2*R*,3*R*,3a*R*,5*S*,7a*R*)-acetic acid 3a-acetoxy-6-acetyl-5-azidomethyl-2-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-octahydro-furo[2,3-*c*]pyridin-3-yl ester (11). NaN_3 (50 mg) was added to the uridine derivative **9** (300 mg, 0.57 mmol) in DMF (8 ml) and the mixture was heated at 110 °C for 4 h under N_2. Usual work up followed by purification through reverse phase column chromatography (CH_3CN–H_2O 1:4) afforded a crude residue (175 mg). A part of the residue (60 mg) was acetylated with Ac_2O/Py and the mixture was purified by HPLC (solvent: CH_3CN–H_2O 3:7) to furnish **10** (35 mg, 40%) and **11** (11 mg, 13%).

Compound **10**. Foamy solid; [Found: C, 47.78; H, 4.88; N, 18.38. $C_{18}H_{22}N_6O_8$ requires C, 48.00; H, 4.92; N, 18.66%]; ($\alpha(^{20}_{D}$=+8 (*c* 0.5, $CHCl_3$); IR (KBr): ν_{max} 3453 (br), 2106, 1751, 1691, 1428, 1375, 1230, 1074 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.11 (s, 3H), 2.13 (s, 3H), 2.15 (s, 3H), 2.37 (dd, H, *J*=6.3, 14.0 Hz), 2.57 (t-like, 1H, *J*=12.3, 14.0 Hz), 3.31 (dd, 1H, *J*=2.5, 12.5 Hz), 3.85 (m, 3H), 4.56 (s, 1H), 4.71 (m, 1H), 5.03 (d, 1H, *J*=8.5 Hz), 5.83 (d, 1H, *J*=8.2 Hz), 6.26 (d, 1H, *J*=8.5 Hz), 6.97 (d, 1H, *J*=8.2 Hz), 8.49 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.4 (q), 21.7(q), 21.9 (q), 28.0 (t), 45.7 (t), 47.5 (d), 53.1(t), 71.9 (d), 80.0 (d), 80.9 (s), 82.6 (d), 104.8 (d), 137.8 (d), 150.4 (s), 161.8 (s) 169.8 (s), 169.9 (s), 171.7 (s); FABMS: *m*/*z* at 451 (MH^+), 473 (MNa^+).

Compound **11**. Foamy solid; [Found: C, 48.12; H, 4.90; N, 18.60. $C_{18}H_{22}N_6O_8$ requires C, 48.00; H, 4.92; N, 18.66%]; ($\alpha(^{20}_{D}$=+15 (*c* 0.54, $CHCl_3$); IR (KBr): ν_{max} 3474 (br), 2106, 1743, 1697, 1634, 1427, 1377, 1236, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.09 (s, 6H), 2.15 (s, 3H), 2.36 (t-like, 1H, *J*=13.0, 14.7 Hz), 2.70 (dd, 1H, *J*=4.8, 14.8 Hz), 3.34 (dd, 1H, *J*=2, 12.3 Hz), 3.45 (dd, 1H, *J*=10.8, 14.0 Hz), 3.91 (m, 2H), 4.27 (m, 1H), 4.43 (dd, 1H, *J*=6.4, 10.2 Hz), 5.53 (d, 1H, *J*=6.1 Hz), 5.78 (d, 1H, *J*=8.1 Hz), 5.86 (d, 1H, *J*=6.1 Hz), 7.20 (d, 1H, *J*=8.1 Hz), 9.23 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.7 (q), 21.6 (q), 22.5 (q), 33.3 (t), 45.1(t), 48.2 (d), 52.9 (t), 76.3 (d), 78.8 (d), 81.9 (s), 92.4 (d), 103.7 (d), 142.1 (d), 150.4 (s), 163.0 (s), 169.8 (s), 170.5 (s), 170.9 (s); FABMS: *m*/*z* at 451 (MH^+), 473 (MNa^+).

3.1.7. (3a*R*,3b*R*,6*R*,8*R*,8a*S*,9a*R*)-6-Azidomethyl-8-(*tert*-butyldimethyl-silanyloxymethyl-2,2-dimethyl-octahydro-1,3,4,9-tetraoxa-7-aza-cyclopent[*a*]azulene (15). To a stirred solution of **12** (418 mg, 1.12 mmol) in CH_2Cl_2 (30 ml) containing Et_3N (0.5 ml) was added MsCl (1 equiv.) and the mixture was stirred for 2 h under N_2. The solution was thoroughly washed with brine (3×10 ml), dried (Na_2SO_4), and concentrated to furnish a mesyl derivative. Without further purification this was dissolved in DMF (10 ml) and treated with NaN_3 (300 mg). The reaction mixture was heated at 130 °C under N_2 for 10 h. Usual work up followed by column chromatography using $CHCl_3$–MeOH (99:1) afforded **15** (250 mg, 56%) as a thick liquid; [Found: C, 52.00; H, 8.20; N, 13.21. $C_{18}H_{34}N_4O_5Si$ requires C, 52.15; H, 8.27; N, 13.51%]; ($\alpha(^{20}_{D}$=−9.4 (*c* 0.54, $CHCl_3$); IR (neat): ν_{max} 2100, 1470, 1373, 1255, 1098, 1037, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.063 (s, 3H), 0.076 (s, 3H), 0.91 (s, 9H), 1.35 (s, 3H), 1.60 (s, 3H), 2.99 (m, 1H), 3.16 (dd, 1H, *J*=7.5, 12.0 Hz), 3.27 (d, 1H,

J=12.0 Hz), 3.31(dd, 1H, *J*=4.5, 11.5 Hz), 3.42 (m, 1H), 3.75 (d, 2H, *J*=4.8 Hz), 4.00 (dd, 1H, *J*=1.5, 11.7 Hz), 4.21 (dd, 1H, *J*=4.5, 9.3 Hz), 4.41 (t-like, 1H, *J*=8.1 Hz), 4.58 (t-like, 1H, *J*=3.9 Hz), 5.72 (d, 1H, *J*=3.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.50 (q), −5.54 (q), 18.1(s), 25.8 (q), 26.1 (q, 3C), 26.7 (q), 53.2 (t), 56.2 (d), 57.9 (d), 62.0 (t), 75.3 (t), 78.4 (d), 79.6 (d), 79.7(d), 103.0 (d), 113.0 (d); FABMS: *m/z* at 415 (MH^+).

3.1.8. (3a*R*,3b*R*,7a*R*,8a*R*)-2,2-Dimethyl-3a,5,6,7,7a,8a-hexahydro-3b*H*,5a*H*-1,3,4,8-tetraoxa-6a-aza-cyclopropan[*f*]cyclopent[*a*]azulene (16). MsCl (0.35 ml) and Et_3N (0.5 ml) were added to a solution of **13** (750 mg, 3.26 mmol) in CH_2Cl_2 (30 ml) and the mixture was stirred at rt for 2 h. The solvent was evaporated and the crude mesyl derivative was dissolved in DMF (10 ml). NaN_3 (800 mg) was added to it and the mixture was heated at 90 °C for 5 h. Usual work up and purification afforded **16** (185 mg, 25%) as a gum; [Found: C, 57.86; H, 7.34; N, 5.88. $C_{11}H_{17}NO_4$ requires C, 58.14; H, 7.54; N, 6.17%]; ($\alpha(^{20}_{D}$=−8.8 (*c* 1.17, $CHCl_3$). IR (neat): ν_{max} 1455, 1377, 1216, 1164, 1023, 873 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (s, 3H), 1.49 (d, 1H, *J*=3.3 Hz), 1.64 (s, 3H), 2.18 (d, 1H, *J*=5.1 Hz), 2.34 (t, 1H, *J*=10.8 Hz), 2.44 (m, 1H), 3.21 (dd, 1H, *J*=4.2, 9.0 Hz), 3.27 (dd, 1H, *J*=11.1, 13.2 Hz), 3.83 (d, 1H, *J*=11.1 Hz), 4.23 (t-like, 1H, *J*=9.0 Hz), 4.50 (dd, 1H, *J*=4.5, 13.5 Hz), 4.67 (t-like, 1H, *J*=3.9 Hz), 5.75 (d, 1H, *J*=3.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.2 (q), 26.3 (q), 35.4 (d), 35.5 (t), 56.7(t), 72.1(t), 75.3 (d), 78.4 (d), 88.6 (d), 104.0 (d), 113.5 (s); FABMS: *m/z* at 228 (MH^+).

3.1.9. (3a*R*,3b*S*,9a*R*,10a*R*)-2,2-Dimethyl-3a,9,9a,10a-tetrahydro-3b*H*,5*H*-1,3,4,10-tetraoxa-7,8,8a-triaza-cyclopent[*f*]cyclopent[*a*]azulene (17). Compound **17** was prepared from **14** using procedure as adopted in the preparation of **16**.

Yield 62%; gum; [Found: C, 52.08; H, 5.88; N, 16.32. $C_{11}H_{15}N_3O_4$ requires C, 52.17; H, 5.97; N, 16.59%]; ($\alpha(^{20}_{D}$=+9.7 (*c* 0.2, $CHCl_3$); IR (neat): ν_{max} 1644, 1574, 1379, 1218, 1082, 1021, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (s, 3H), 1.47 (s, 3H), 3.78 (d, 1H, *J*=2.6 Hz), 4.51 (dd, 1H, *J*=9.5, 13.0 Hz), 4.54 (d, 1H, *J*=3.7 Hz), 4.64 (m, 1H), 4.77 (dd, 1H, *J*=4.7, 13.0 Hz), 4.84 (d, 1H, *J*=6.8 Hz), 5.54 (d, 1H, *J*=6.8 Hz), 5.97 (d, 1H, *J*=3.6 Hz), 7.31(s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.2, 26.7, 44.4, 79.2, 84.1, 86.8, 88.6, 105.4, 112.6, 121.3, 149.8; FABMS: *m/z* at 254 (MH^+).

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11. Commercially available diacetone glucose was converted[15] to the diol **1** through oxidation of C-3 OH group followed by Grignard reaction with allyl magnesium bromide, selective deprotection of 5,6-ketal, vicinal diol cleavage and sodium borohydride reduction of the aldehyde. Compound **2** was, however, prepared[15] by benzylation of the above Grignard product and thereafter following a sequence of reactions similar to that in case of **1**. 1,2:5,6-Di-*O*-cyclohexylidene-3-*C*-allyl-α-D-allofura-nose was obtained from D-glucose via conventional steps and converted to **3** following a sequence of reactions similar to that in case of **1**. Characteristic data for 1,2:5,6-di-*O*-cyclohexylidene-3-*C*-allyl-α-D allofuranose: mp 106–108 °C; $[\alpha]^{20}_{D}$=+44.8 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41–1.68 (m, 20H), 2.18 (dd, 1H, *J*=6.0, 14.4 Hz), 2.65 (dd, 1H, *J*=5.4, 14.4 Hz), 2.78 (s, 1H), 3.79 (d, 1H, *J*=7.8 Hz), 3.90 (m, 1H), 4.13 (m, 2H), 4.33 (d,1H, *J*=3.6 Hz), 5.15 (d,1H, *J*=17.3 Hz), 5.19 (d, 1H, *J*=10.2 Hz), 5.77 (d, 1H, *J*=3.6 Hz), 5.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.9, 24.26, 24.30, 24.5, 25.3, 25.5, 35.2, 36.4, 36.66, 36.70, 37.3, 68.2, 73.3, 79.1, 81.3, 82.8, 103.7, 110.6, 113.6, 119.1, 133.2. For **3**: mp 155–156 °C; $[\alpha]^{20}_{D}$=+56.6° (*c* 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (t, 2H, *J*=5.0 Hz), 1.56 (m, 4H), 1.69 (m, 2H), 1.79 (t, 1H, *J*=5.4 Hz), 1.95 (brs, 1H), 2.14 (dd, 1H, *J*=8.2, 14.6 Hz), 2.42 (dd, 1H, *J*=5.9, 14.6 Hz), 2.77 (d, 1H, *J*=1.1 Hz), 3.81 (m, 2H), 3.93 (dd, 1H, *J*=3.8, 7.2 Hz), 4.29

(d, 1H, *J*=3.9 Hz), 5.15 (m, 2H), 5.75 (d, 1H, *J*=3.9 Hz), 5.91 (m, 1H).

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14. The 3-*O*-allylated substrates **12**-**14** were prepared from diacetone D-glucose. The compound **12** was obtained through the oxidation of the hydroxyl group, reduction of the carbonyl group to 3-*epi* alcohol, allylation of the generated hydroxyl group, removal of 5,6-*O*- isopropylidene group, and finally, selective protection of primary hydroxyl group at *C*-6 with *tert*. butyl dimethylsilyl group. The precursors **13** and **14** were generated through allylation of the corresponding hydroxyl groups of diacetone D-glucose/D-allose followed by selective cleavage of 5,6-ketal, vicinal diol cleavage and reduction of the formed aldehyde. **12**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.079 (s, 3H), 0.088 (s, 3H), 0.90, 0.91(2×s, 9H), 1.36 (s, 3H), 1.58 (s, 3H), 2.52 (d, 1H, *J*=2.7 Hz), 3.66 (dd, 1H, *J*=7.5, 10.3 Hz), 3.72 (dd, 1H, *J*=3.8, 10.3 Hz), 3.94 (m, 2H), 4.02 (dd, 1H, *J*=3.8, 8.7 Hz), 4.09 (tdd, 1H, *J*=1.2, 5.9, 12.6 Hz), 4.22 (tdd, 1H, *J*=1.2, 5.9, 12.6 Hz), 4.62 (t, 1H, *J*=3.9 Hz), 5.29 (m, 2H), 5.75 (d, 1H, *J*=3.6 Hz), 5.97 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.4 (2C), 18.4, 25.9 (3C), 26.6, 26.8, 63.8, 71.5, 72.0, 77.8, 77.9, 104.0, 112.9, 117.9, 118.0, 134.5. **13**: ^{1}H NMR ($CDCl_3$+D_2O, 300 MHz): δ 1.32 (s, 3H), 1.47 (s, 3H), 3.75 (dd, 1H, *J*=3.6, 6.0 Hz), 3.82 (dd, 1H, *J*=2.7, 6.0 Hz), 3.87 (m, 1H), 4.03 (dd, 1H, *J*=3.6, 7.5 Hz), 4.08–4.15 (m, 2H), 4.55 (d, 1H, *J*=3.6 Hz), 5.19–5.35 (m, 2H), 5.85–5.98 (m, 2H). **14**: ^{1}H NMR ($CDCl_3$+D_2O, 300 MHz): δ 1.36 (s, 3H), 1.58 (s, 3H), 3.73 (dd, 1H, *J*=3.5, 5.8 Hz), 3.75 (dd, 1H, *J*=2.8, 5.8 Hz), 3.92 (dd, 1H, *J*=4.0, 6.0 Hz), 4.01–4.24 (m, 2H), 4.63 (t-like, 1H, *J*=3.9 Hz), 5.24–5.36 (m, 2H), 5.78 (d, 1H, *J*=3.6 Hz), 5.85–6.01 (m, 1H).
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