Synthesis of 1,2,3-triazole and 1,2,3,4-tetrazole-fused glycosides and nucleosides by an intramolecular 1,3-dipolar cycloaddition reaction†‡

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Various 1,2,3-triazole and 1,2,3,4-tetrazole fused multi-cyclic compounds were synthesized from carbohydrate derived azido-alkyne and azido-cyanide substrates. The acid sensitive 1,2-*O*-isopropylidene group of the furanosyl sugar was utilized for diversification to glycosides and nucleosides under Fischer glycosidation and Vorbruggen's conditions, respectively.

In the post-genomic era, small molecules are anticipated to play interesting roles in elucidating and understanding biosynthetic pathways.[1] Typically, biological screening by high-throughput techniques involves testing large collections of small molecule libraries that are arrayed into micro titer plates.[2] In this regard, combinatorial ways of synthesizing small molecules facilitated the synthesis of large numbers of compounds using either solution or solid phase methods.[3] A recent chemo-informative data mining study to address lacunae in drug discovery programs showed drastic differences between compounds from natural sources, semi-synthetic, combinatorial and drug classes under various descriptors such as molecular weight, number of chiral centers, number of oxygen atoms, number of nitrogen atoms *etc.*[4] For example, several compounds from the natural products class revealed that natural products have greater numbers of oxygen atoms and chiral centers than the corresponding combinatorial products thereby highlighting the significance of synthesizing small molecules that are chiral, oxygen-rich and multi-cyclic for enhanced efficiency in the identification of hit molecules.[4]

We recently hypothesized that structurally, stereochemically and skeletally diverse small molecules[5] can be synthesized from carbohydrate precursors using various metal mediated reactions such as the Pauson–Khand reaction, enyne metathesis, cycloaddition and Au-mediated cyclization.[6] Our search for efficient and versatile reactions converged on Huisgen's 1,3-dipolar cycloaddition[7] not only due to the efficiency but also the enticing presence of 1,2,3-triazole and 1,2,3,4-tetrazole moieties in various small molecule inhibitors (Fig. 1) exhibiting a broad spectrum of biological activity[8] including anti-HIV,[8a] anti-allergic,[8b] anti-bacterial,[8c] herbicidal,[8d] fungicidal[8d] and anti-haemagglutination activity.[8e]

1,2,3-Triazoles can be conveniently synthesized from azido-alkynes as regioisomeric mixtures of 1,4- and 1,5-substituted triazoles adopting Huisgen's 1,3-dipolar cycloaddition reaction conditions.[7] Under this premise, we envisaged that triazole and tetrazole-fused oxygen-rich small molecules[9] can be synthesized by an intramolecular 1,3-dipolar cycloaddition of azido-alkyne/nitrile bearing monosaccharides.[6a] As part of a major research program on utilization of carbohydrate-based scaffolds for the synthesis of structurally diverse, chiral, oxygen-rich and polycyclic small molecules,[6] we became interested in the synthesis of 1,2,3-triazole and 1,2,3,4-tetrazole fused glycosides and nucleosides. Thus, forward synthetic analysis revealed an intramolecular Huisgen reaction[7] on carbohydrate-derived azido-alkyne and azido-nitrile as a key step that would give access to 1,2,3-triazole and 1,2,3,4-tetrazole-fused scaffolds, respectively, embedded with an acid sensitive 1,2-*O*-isopropylidene group that can be further extrapolated to corresponding glycosides and nucleosides. In this full Article [preliminary report: ref. 6*a*], we report the efficient synthesis of 1,2,3-triazole and 1,2,3,4-tetrazole fused glycosides and nucleosides *via* an intramolecular 1,3-dipolar cycloaddition of carbohydrate derivatives, which are accessible from aldopentoses.

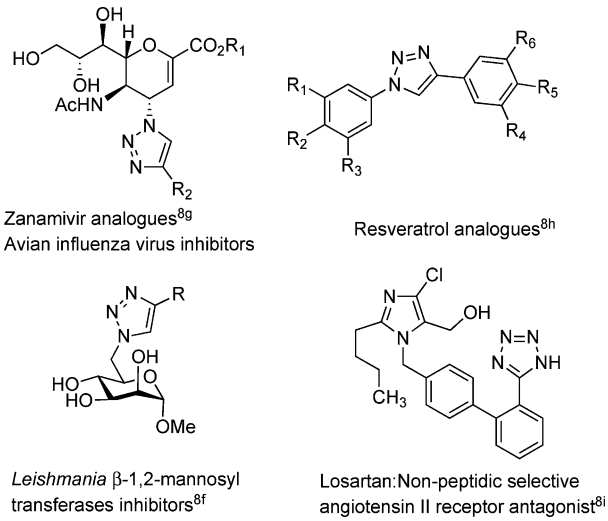

Fig. 1 Representative examples of small molecule inhibitors with a 1,2,3-triazole and 1,2,3,4-tetrazole moiety.

To commence our investigation, the carbohydrate-derived azido substrate for the intramolecular 1,3-dipolar cycloaddition was prepared by an S_N2 displacement reaction of the corresponding tosylate with NaN_3.[6a] For example, xylofuranosyl diol **1** was reacted with *p*-toluenesulfonyl chloride in the presence of pyridine

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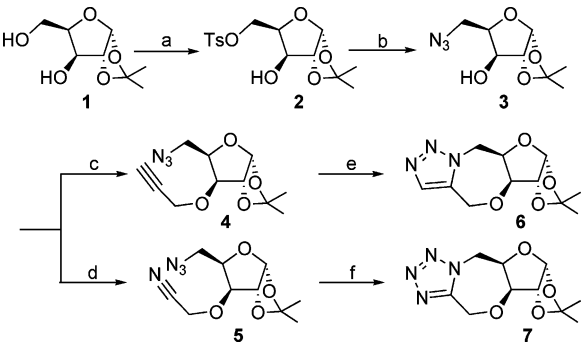
† Dedicated to Dr A. A. Natu on his 60th birthday.

‡ Electronic supplementary information (ESI) available: General experimental details and ^1H, ^{13}C and DEPT NMR spectra. See DOI: 10.1039/b716996e

at 0 °C for 10 h in order to obtain the 5-OTs derivative (**2**) in 91% yield, which was then treated with NaN_3 in DMF at 90 °C to give 1,2-*O*-isopropylidene-5-azido-5-*deoxy*-xylofuranose (**3**) in 95% yield. The lone 3-OH group of azide **3** was converted to azido-alkyne **4** and azido-cyanide **5** by reacting with propargyl bromide–NaH and chloroacetonitrile–NaH respectively (Scheme 1).[10]



Scheme 1 Synthesis of 1,2,3-triazole and 1,2,3,4-tetrazole containing tetracyclic compounds. *Reagents:* (a) *p*-TsCl, pyridine, 0 °C–rt, 10 h, 91%; (b) NaN_3, DMF, 90 °C, 8 h, 95%; (c) NaH, propargyl bromide, DMF, 0 °C–rt, 2 h, 93%; (d) NaH, $ClCH_2CN$, DMF, 0 °C–rt, 3 h, 65%; (e) toluene, 120 °C, 2 h, 95%; (f) toluene, 140 °C, 24 h, 55%.

The crucial 1,3-dipolar cycloaddition reaction was performed by heating a toluene solution of the azido-alkyne **4** to 100 °C for 2 h and the resultant 1,2,3-triazole product (**6**) precipitated out as a white solid upon cooling to room temperature. In the ^{1}H NMR spectrum of compound **6**, the olefinic proton was identified at δ 7.49 ppm as a singlet and the anomeric proton was observed at 5.77 (d, J = 3.9 Hz). Furthermore, the ^{13}C NMR spectrum of **6** revealed two olefinic carbons at δ 134.8 and 132.1 ppm and all other resonances were in complete agreement with the assigned structure.[11] During our investigation, formation of compound **6** was reported by Tripathi *et al.* starting from a similar starting material.[9d] The spectral data of Tripathi *et al.* did not correlate with our data. Meanwhile, the tetracyclic compound **6** was crystallized by slow evaporation from light petroleum (60–80 °C) and CH_2Cl_2.[9d] The single crystal X-ray structure confirmed the structural authenticity and relative stereochemistry of the 1,2,3-triazole fused tetracyclic compound **6**.[6a,11a]

Alternatively, azide **3** was treated with chloroacetonitrile–NaH to obtain azido-cyanide **5** in 65% yield. In the IR spectrum of compound **5**, the stretches corresponding to –CN and $-N_3$ were identified at 2254 and 2104 cm^{-1}, respectively, along with all other NMR spectral data in complete agreement with the assigned structure. The critical cycloaddition reaction was carried out by heating a solution of azido-cyanide **5** in toluene at 140 °C for 24 h. In the ^{1}H NMR spectrum of 1,2,3,4-tetrazole fused tetracyclic compound **7**, resonances corresponding to the anomeric proton were observed at δ 5.90 (d, J = 3.61 Hz); the ^{13}C NMR spectrum revealed an olefinic carbon at δ 154.6 ppm and the DEPT spectrum confirmed that the olefinic carbon was quaternary.[10] Tetrazole **7** was crystallized by slow evaporation of a chloroform solution and was subjected to X-ray structure determination and as evident from the ORTEP diagram, the structural as well as the relative stereochemical authenticity was confirmed (Fig. 2).[10,11b]

Furthermore, we envisioned that the 1,2-*O*-isopropylidene group of the tetracyclic compounds **6** and **7** could be utilized

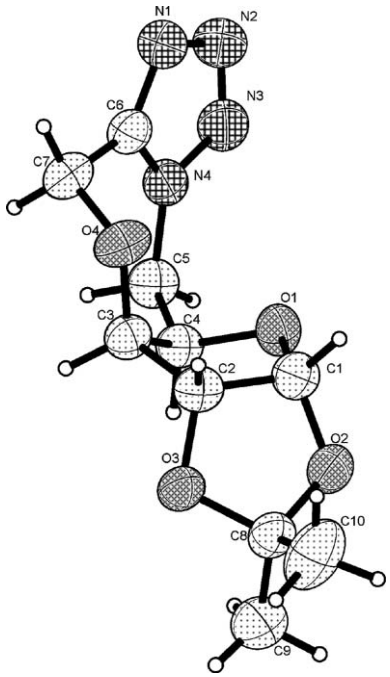
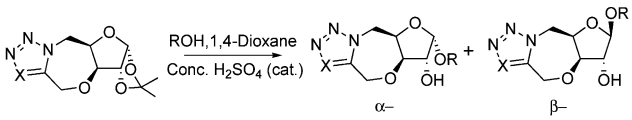


Fig. 2 ORTEP diagram of compound **7**. Ellipsoids are drawn at 50% probability. ORTEP diagram of compound **12c**. Ellipsoids are drawn at 50% probability.

for introducing diversity leading to the synthesis of glycosides and nucleosides. Glycosides can be synthesized stereoselectively yet we opted for the non-diastereoselective glycosylation in the presence of mineral acid since the diastereomeric products add to the stereochemical diversity of the resulting library.[12]

Accordingly, 1,2,3-triazole- and 1,2,3,4-tetrazole-fused tetracyclic compounds were treated with isopropyl, allyl and homopropargyl alcohols in the presence of a catalytic amount of sulfuric acid at 70–80 °C for 4–8 h to obtain α, β-glycosides (**8a**, **8b**, **8c**, **9a**, **9b** and **9c**) which were easily separated by simple column chromatography except for **9c** (Scheme 2). The ratio of α, β was



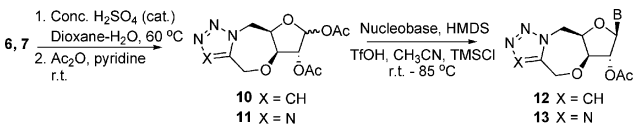
6 X = CH
7 X = N
8 X = CH
9 X = N

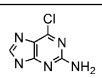
Entry	Compound Number	X	R	α:β ratio	Time (h)	Yield (%)
1	**8a**	CH		1:2	6	85
2	**8b**	CH		2:3	8	76
3	**8c**	CH		1:2	8	80
4	**9a**	N		2:3	5	90
5	**9b**	N		1:2	4	93
6	**9c**	N		1:3	4	95

Scheme 2 Synthesis of 1,2,3-triazole and 1,2,3,4-tetrazole fused glycosides.

calculated by integrating characteristic signals in the ^{1}H NMR spectrum and thoroughly confirmed by means of ^{1}H and ^{13}C NMR spectral data. In the ^{13}C NMR spectrum, anomeric carbons were observed at δ 106–108 ppm for 1,2-*trans* (β-) glycosides and at δ 99–101 ppm for 1,2-*cis* (α-) glycosides.[10]

Further stereoselective synthesis of nucleosides from tetracyclic compounds **6** and **7** was achieved by adopting Vorbrüggen's protocol.[13] Thus, initially, the 1,2-*O*-isopropylidene group of **6** and **7** was cleaved using a catalytic amount of concentrated sulfuric acid in the presence of H_2O to obtain a diol and subsequently acetylated in the presence of acetic anhydride and pyridine to get the diacetate (**10** and **11**), which was then subjected to Vorbrüggen's conditions (HMDS–TMSCl–TfOH in CH_3CN) by treating with nucleobases such as uracil, thymine, N^6-benzoyl adenine and 6-chloro-2-amino purine to obtain β-configured nucleosides (**12a**, **12b**, **12c**, **12d** and **13a**, **13b**, **13c**, **13d**) in moderate yields (Scheme 3). The structures of all the nucleosides were thoroughly confirmed by ^{1}H, ^{13}C NMR and other spectroscopic techniques. Furthermore, an acetonitrile solution of nucleoside **12c** was subjected to slow evaporation in order to get single crystals for X-ray structure analysis. The molecular structure of **12c** was unambiguously confirmed (ORTEP diagram, Fig. 3) as well as the relative stereochemistry of the C-1 position.[9,11c]



Entry	Compound Number	X	B	Time in h	Overall % Yield
1	**12a**	CH		8	45
2	**12b**	CH		8	40
3	**12c**	CH		8	50
4	**12d**	CH		10	35
5	**13a**	N		7	35
6	**13b**	N		10	45
7	**13c**	N		8	45
8	**13d**	N		8	38

Scheme 3 Synthesis of 1,2,3-triazole and 1,2,3,4-tetrazole fused nucleosides.

In conclusion, we have investigated the 1,3-dipolar cycloaddition of azido-alkynes and azido-nitriles in an intramolecular fashion to develop routes for various 1,2,3-triazole and 1,2,3,4-tetrazole fused glycosides and nucleosides in an efficient manner. We anticipate that the heterocycle–sugar hybrid molecules will have interesting biological activities reminiscent of the existing triazole and tetrazole class of compounds.

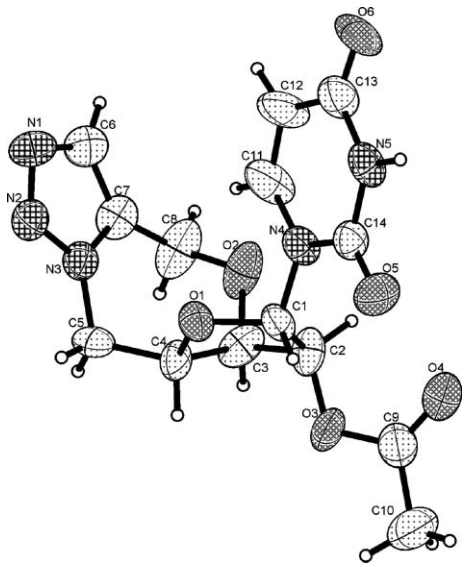


Fig. 3 ORTEP diagram of compound **12c**. Ellipsoids are drawn at 50% probability.

Experimental section

General experimental procedure for 1,3-dipolar cycloaddition

A solution of azido-alkyne or azido-nitrile (1 mmol) in 10 mL of toluene was heated to 100 °C for 1,2,3-triazole formation and 140 °C for 1,2,3,4-tetrazole formation for an appropriate length of time and cooled to room temperature. The separated solid was filtered off and crystallized by a slow evaporation technique.

General experimental procedure for the synthesis of glycosides

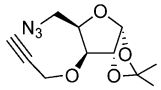
To a solution of compound **6** or **7** (2 mmol), anhydrous 1,4-dioxane (10 mL) and ROH (4 mmol) was added a catalytic amount of conc. H_2SO_4 and the solution was heated to 70 °C until TLC analysis confirmed the disappearance of starting material (typically 4–8 h). The reaction mixture was then neutralized by addition of saturated aq. $NaHCO_3$ solution, diluted with water and extracted with ethyl acetate. The organic layer was washed with water (2 × 25 mL), brine solution (1 × 25 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo* and subjected to silica gel column chromatography to afford α- and β-glycosides.

General experimental procedure for the nucleoside synthesis

To a solution of diacetate (2 mmol) and nucleobase (2 mmol) in anhydrous acetonitrile (15 mL) were added HMDS (2.4 mmol), chlorotrimethylsilane (2.8 mmol) and triflic acid (2.4 mmol) consecutively under an argon atmosphere. The reaction mixture

was stirred at room temperature for 30 min and refluxed under argon for the specified time. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (200 mL), washed with a saturated solution of aq. $NaHCO_3$ (25 mL), water (2 × 25 mL) and brine solution (25 mL). The aqueous layer was extracted with ethyl acetate (2 × 25 mL), combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain a crude residue which was purified by silica gel column chromatography using ethyl acetate and light petroleum as the mobile phase.

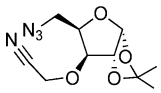
Compound characterization data of compound 4.



4

$[\alpha]_D$ ($CHCl_3$, *c* 1.04) = −44.32°; IR (cm^{-1}) = 3282, 2102; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.30, 1.48 (6 H, 2 s), 2.48 (1 H, t, *J* 2.4 Hz), 3.51 (2 H, dt, *J* 6.8, 12.6 Hz), 4.07 (1 H, d, *J* 3.3 Hz), 4.22 (2 H, t, *J* 2.7 Hz), 4.30 (1 H, m), 4.62 (1 H, d, *J* 3.8 Hz), 5.89 (1 H, d, *J* 3.8 Hz); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 26.2, 26.7, 49.2, 57.4, 75.4, 78.6, 78.7, 81.2, 82.0, 105.0, 111.9; CHN Anal. (Calcd for $C_{11}H_{15}N_3O_4$ as C, 52.17; H, 5.97; N, 16.59). Found C, 52.57; H, 6.39; N, 16.82%.

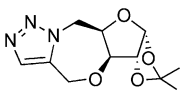
Compound characterization data of compound 5.



5

Mp 208 °C; $[\alpha]_D$ ($CHCl_3$, *c* 1.01) = −83.17°; IR (cm^{-1}) = 2254, 2104; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.33, 1.51 (6 H, 2 s), 3.54 (2 H, ddd, *J* 6.7, 12.5, 19.1 Hz), 4.05 (1 H, d, *J* 3.3), 4.30–4.41 (3 H, m), 4.65 (1 H, d, *J* 3.8), 5.93 (1 H, d, *J* 3.8); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 26.1, 26.6, 48.7, 55.5, 78.1, 81.4, 83.3, 104.9, 112.3, 127.5; CHN Anal. (Calcd for $C_{10}H_{14}N_4O_4$ as C, 47.24; H, 5.55; N, 22.04). Found C, 47.59; H, 6.04; N, 22.28%.

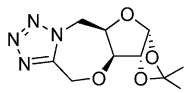
Compound characterization data of compound 6.



6

Mp 200 °C; $[\alpha]_D$ ($CHCl_3$, *c* 1.28) = −7.31°; IR (cm^{-1}): 1461, 1379; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.27, 1.46 (6 H, 2 s), 4.22 (1 H, d, *J* 2.1 Hz), 4.39 (1 H, m), 4.49 (1 H, d, *J* 3.6 Hz), 4.58 (1 H, d, *J* 14.7 Hz), 4.69 (1 H, dd, *J* 15.2, 2.4 Hz), 4.92 (1 H, d, *J* 14.7 Hz), 5.11 (1 H, dd, *J* 5.6, 15.5 Hz), 5.77 (1 H, d, *J* 3.6 Hz), 7.49 (1 H, s); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.0, 26.6, 48.00, 60.6, 74.2, 83.8, 84.4, 104.7, 111.9, 132.1, 134.8; CHN Anal. (Calcd for $C_{11}H_{15}N_3O_4$ as C, 52.17; H, 5.97; N, 16.59). Found C, 51.97; H, 5.46; N, 16.67%.

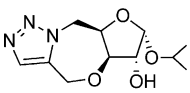
Compound characterization data of compound 7.



7

Mp 208 °C; $[\alpha]_D$ ($CHCl_3$, *c* 1.16) = −12.24°; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.33, 1.51 (6 H, 2 s), 4.28 (1 H, d, *J* 2.8 Hz), 4.61 (1 H, dd, *J* 3.2, 6.2 Hz), 4.65 (1 H, d, *J* 3.8 Hz), 4.79 (1 H, dd, *J* 3.4, 14.6 Hz), 5.03 (1 H, dd, *J* 14.8, 6.2 Hz), 5.06 (2 H, ABq, *J* 15.8 Hz), 5.90 (1 H, d, *J* 3.6 Hz); ^{13}C NMR [DMSO-d_6, 50.32 MHz): δ 26.1, 26.6, 46.4, 59.4, 72.9, 83.4, 84.0, 104.1, 111.4, 154.6; CHN Anal. (Calcd for $C_{10}H_{14}N_4O_4$ as C, 47.24; H, 5.55; N, 22.04). Found C, 47.44; H, 5.74; N, 22.38%.

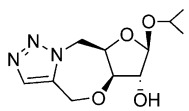
Compound characterization data of compound 8aα.



8aα

Mp = 110 °C; $[\alpha]_D$ ($CHCl_3$, *c* 1.09) = +52.84°; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.11 (3 H, d, *J* 6.3 Hz), 1.16 (3 H, d, *J* 6.3 Hz), 2.91 (1 H, bs), 3.92 (1 H, ddd, *J* 6.2, 12.4, 18.6 Hz), 4.11 (2 H, m), 4.45 (2 H, m), 4.78 (1 H, dd, *J* 3.8, 13.0 Hz), 4.92 (2 H, ABq, *J* 16.0 Hz), 5.07 (1 H, d, *J* 3.9 Hz), 7.39 (1 H, s); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 21.7, 23.3, 48.5, 64.0, 71.0, 75.1, 76.8, 86.6, 99.3, 130.6, 134.1; CHN Anal. (Calcd for $C_{11}H_{17}N_3O_4$ as C, 51.76; H, 6.71; N, 16.46). Found C, 52.09; H, 6.97; N, 16.10%.

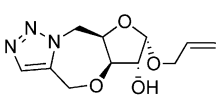
Compound characterization data of compound 8aβ.



8aβ

Mp = 92–94 °C; $[\alpha]_D$ ($CHCl_3$, *c* 1.22) = −86.39°; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.12 (3 H, d, *J* 6.3 Hz), 1.15 (3 H, d, *J* 6.3 Hz), 2.75 (1 H, bs), 3.88 (1 H, m), 4.08 (1 H, d, *J* 5.7 Hz), 4.27 (1 H, s), 4.71 (3 H, m), 4.94 (2 H, Abq, *J* 16.0 Hz), 5.02 (1 H, bs), 7.38 (1 H, s); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 21.3, 23.2, 49.6, 64.4, 70.0, 78.7, 80.8, 86.8, 106.5, 130.2, 134.1; CHN Anal. (Calcd for $C_{11}H_{17}N_3O_4$ as C, 51.76; H, 6.71; N, 16.46). Found C, 51.51; H, 6.39; N, 16.25%.

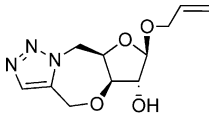
Compound characterization data of compound 8bα.



8bα

$[\alpha]_D$ ($CHCl_3$, *c* 1.11) = +43.24°; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 2.50 (1 H, bs), 3.72 (1 H, m), 4.03–4.35 (4 H, m), 4.35–4.94 (3 H, m), 5.07 (1 H, d, *J* 4.4 Hz), 5.15–5.36 (3 H, m), 5.91 (1 H, m), 7.45 (1 H, s); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 48.4, 63.9, 68.8, 75.1, 76.7, 86.3, 100.0, 117.8, 130.5, 133.2, 134.1; CHN Anal. (Calcd for $C_{11}H_{15}N_3O_4$ as C, 52.17; H, 5.97; N, 16.59). Found C, 52.67; H, 6.08; N, 15.98%.

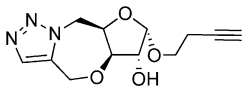
Compound characterization data of compound 8bβ.



8bβ

Mp = 110 °C; $[\alpha]_D$ ($CHCl_3$, *c* 1.17) = −79.83°; ^{1}H NMR ($CDCl_3$, 200.13 MHz): *δ* 3.29 (2 H, m), 3.92–4.28 (3 H, m), 4.40 (1 H, s), 4.52–4.96 (3 H, m), 5.06 (1 H, s), 5.10–5.45 (3 H, m), 5.90 (1 H, m), 7.43 (1 H, s); ^{13}C NMR ($CDCl_3$, 50.32 MHz): *δ* 49.5, 64.5, 68.5, 79.2, 80.8, 86.8, 107.5, 117.6, 130.3, 133.6, 134.0; CHN Anal. (Calcd for $C_{11}H_{15}N_3O_4$ as C, 52.17; H, 5.97; N, 16.59). Found C, 51.94; H, 6.30; N, 16.69%.

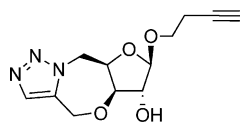
Compound characterization data of compound 8cα.



8cα

$[\alpha]_D$ ($CHCl_3$, *c* 1.02) = +43.53°; IR (cm^{-1}) = 3292; ^{1}H NMR ($CDCl_3$, 200.13 MHz): *δ* 1.95 (1 H, t, *J* 2.6 Hz), 2.31 (1 H, bs), 2.47 (2 H, dt, *J* 2.6, 6.5 Hz), 3.64 (1 H, m), 3.85 (1 H, m), 4.20 (2 H, m), 4.48–4.90 (3 H, m), 4.96 (2 H, ABq, *J* 15.7 Hz), 5.04 (1 H, d, *J* = 4.2 Hz), 7.42 (1 H, s); ^{13}C NMR ($CDCl_3$, 50.32 MHz): *δ* 19.8, 48.5, 64.1, 66.4, 69.8, 75.4, 77.0, 80.6, 86.4, 101.0, 130.7, 134.1; CHN Anal. (Calcd for $C_{12}H_{15}N_3O_4$ as C, 54.33; H, 5.70; N, 15.84). Found C, 54.57; H, 5.98; N, 15.41%.

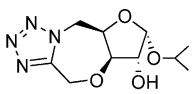
Compound characterization data of compound 8cβ.



8cβ

$[\alpha]_D$ ($CHCl_3$, *c* 1.07) = −67.85°; IR (cm^{-1}) = 3286; ^{1}H NMR ($CDCl_3$, 200.13 MHz): *δ* 1.96 (1 H, t, *J* 2.6 Hz), 2.45 (2 H, dt, *J* 2.8, 6.8 Hz), 3.52–3.90 (3 H, m), 4.01–4.25 (1 H, m), 4.37 (1 H, s), 4.50–4.91 (3 H, m), 4.98 (2 H, ABq, *J* 15.8 Hz), 5.02 (1 H, s), 7.40 (1 H, s); ^{13}C NMR ($CDCl_3$, 50.32 MHz): *δ* 19.7, 49.5, 64.6, 66.2, 69.7, 75.4, 79.4, 80.8, 86.7, 108.6, 130.4, 134.0; CHN Anal. (Calcd for $C_{12}H_{15}N_3O_4$ as C, 54.33; H, 5.70; N, 15.84). Found C, 52.98; H, 6.18; N, 16.31%.

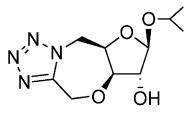
Compound characterization data of compound 9aα.



9aα

$[\alpha]_D$ ($CHCl_3$, *c* 1.05) = +86.28°; ^{1}H NMR ($CDCl_3$, 200.13 MHz): *δ* 1.20 (3 H, d, *J* 6.2 Hz), 1.23 (3 H, d, *J* 6.3 Hz), 2.31 (1 H, bs), 3.81–4.26 (3 H, m), 4.52 (2 H, m), 4.72–5.02 (1 H, m), 5.15 (1 H, d, *J* 3.9 Hz), 5.21 (2 H, ABq, *J* 16.8 Hz); ^{13}C NMR ($CDCl_3$, 50.32 MHz): *δ* 21.8, 23.4, 47.1, 65.2, 71.4, 75.2, 76.9, 87.2, 99.2, 152.7; CHN Anal. (Calcd for $C_{10}H_{16}N_4O_4$ as C, 46.87; H, 6.29; N, 21.86). Found C, 46.51; H, 5.98; N, 22.33%.

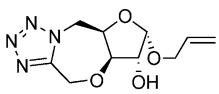
Compound characterization data of compound 9aβ.



9aβ

$[\alpha]_D$ ($CHCl_3$, *c* 1.24) = −100.00°; ^{1}H NMR ($CDCl_3$, 200.13 MHz): *δ* 1.15 (3 H, d, *J* 6.3 Hz), 1.21 (3 H, d, *J* 6.2 Hz), 3.23 (1 H, bs), 3.95 (1 H, m), 4.23 (1 H, m), 4.37 (1 H, s), 4.72 (2 H, m), 4.82 (1 H, m), 5.10 (1 H, s), 5.19 (2 H, ABq, *J* 16.7 Hz); ^{13}C NMR ($CDCl_3$, 50.32 MHz): *δ* 21.4, 23.3, 48.1, 63.4, 70.5, 78.7, 81.1, 87.5, 106.5, 152.7; CHN Anal. (Calcd for $C_{10}H_{16}N_4O_4$ as C, 46.87; H, 6.29; N, 21.86). Found C, 47.20; H, 6.50; N, 22.14%.

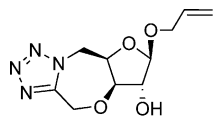
Compound characterization data of compound 9bα.



9bα

$[\alpha]_D$ (CH_3OH, *c* 1.21) = +71.24°; ^{1}H NMR ($CDCl_3$, 200.13 MHz): *δ* 2.98 (1 H, bs), 3.98 (1 H, m), 4.13–4.28 (3 H, m), 4.32–4.57 (2 H, m), 4.77–4.95 (2 H, m), 5.00 (1 H, m), 5.07–5.45 (3 H, m), 5.65–5.95 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.32 MHz): *δ* 46.9, 64.9, 68.8, 75.0, 76.7, 86.6, 99.7, 118.1, 133.1, 152.7. CHN Anal. (Calcd for $C_{10}H_{14}N_4O_4$ as C, 47.24; H, 5.55; N, 22.04). Found C, 47.78; H, 5.19; N, 21.65%.

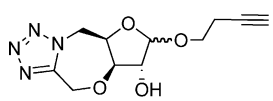
Compound characterization data of compound 9bβ.



9bβ

$[\alpha]_D$ (CH_3OH, *c* 1.05) = −86.25°; ^{1}H NMR ($CDCl_3$, 200.13 MHz): *δ* 2.63 (1 H, bs), 3.95–4.01 (1 H, m), 4.22 (2 H, m), 4.42 (1 H, s), 4.50–4.82 (2 H, m), 4.79–5.08 (2 H, m), 5.03 (1 H, s), 5.15–5.50 (3 H, m), 5.75–5.98 (1 H, m); ^{13}C NMR ($CDCl_3$, 125.76 MHz): *δ* 47.9, 65.4, 68.6, 79.2, 80.8, 87.4, 107.3, 118.0, 133.2, 152.7. CHN Anal. (Calcd for $C_{10}H_{14}N_4O_4$ as C, 47.24; H, 5.55; N, 22.04). Found C, 47.66; H, 5.94; N, 22.47%.

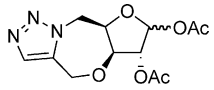
Compound characterization data of compound 9c (inseparable mixture of 9cα, 9cβ).



9cα/β

IR (cm^{-1}) = 3306, 3016, 2930; ^{1}H NMR ($CDCl_3$, 200.13 MHz): *δ* 2.01 (1 H, m), 2.43–2.58 (2 H, m), 3.01 (1 H, m), 3.55–3.96 (2 H, m), 4.20 (1 H, m), 4.41–4.95 (2 H, m), 4.70–5.15 (4 H, m), 5.38–5.52 (1 H, m); ^{13}C NMR ($CDCl_3$, 125.76 MHz): *δ* 19.6, 19.7, 46.9, 47.8, 64.8, 65.2, 66.2, 66.3, 69.7, 69.8, 75.1, 76.8, 79.1, 80.6, 80.8, 80.9, 86.4, 87.2, 100.7, 108.4, 152.7, 152.8. CHN Anal. (Calcd for $C_{11}H_{14}N_4O_4$ as C, 49.62; H, 5.30; N, 21.04). Found C, 48.96; H, 5.82; N, 21.65%.

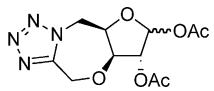
Compound characterization data of compound 10.



10

^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 2.03, 2.05, 2.08, 2.09 (6 H, 4 s), 4.39–5.02 (5 H, m), 5.21–5.34 (2 H, m), 6.10–6.49 (1 H, m), 7.42, 7.44 (1 H, 2 s); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.4, 20.7, 20.9, 21.1, 48.2, 49.0, 64.6, 64.9, 76.2, 76.4, 80.8, 81.5, 82.4, 82.4, 83.5, 93.3, 99.3, 130.7, 133.8, 169.2, 169.3, 169.4, 169.8. CHN Anal. (Calcd for $C_{12}H_{15}N_3O_6$ as C, 48.48; H, 5.09; N, 14.14). Found C, 47.95; H, 5.65; N, 13.86%.

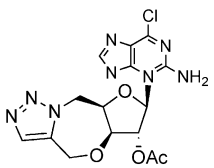
Compound characterization data for compound 11.



11

^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 2.09, 2.13, 2.14, 2.15 (6 H, 4 s), 4.39 (1 H, m), 4.48–4.75 (2 H, m), 4.78–5.10 (2 H, m), 5.20–5.63 (2 H, m), 6.21–6.52 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.3, 20.6, 20.7, 21.0, 46.6, 47.3, 65.3, 65.8, 75.8, 76.1, 80.6, 81.5, 82.6, 84.4, 92.8, 99.2, 152.1, 152.3, 168.9, 169.0, 169.3, 169.7. CHN Anal. (Calcd for $C_{11}H_{14}N_4O_6$ as C, 44.30; H, 4.73; N, 18.79). Found C, 43.86; H, 5.05; N, 19.16%.

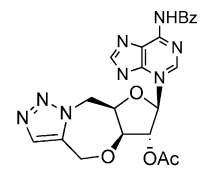
Compound characterization data of compound 12a.



12a

Mp = 200 °C; $[\alpha]_D$ ($CHCl_3$, c 1.13) = +28.14°; IR (cm^{-1}) = 1741, 1755; ^{1}H NMR (CD_3OD + $CDCl_3$ (1 : 9), 200.13 MHz): δ 2.19 (3 H, s), 4.52–4.60 (4 H, m), 4.98 (2 H, ABq, J 15.0 Hz), 4.99 (1 H, dd, J 2.0, 15.5 Hz), 5.27–5.40 (2 H, m), 6.08 (1 H, d, J 1.4 Hz), 7.47 (1 H, s), 7.69 (1 H, s); ^{13}C NMR (CD_3OD + $CDCl_3$ (1 : 9), 50.32 MHz): δ 20.6, 48.2, 60.5, 76.9, 81.2, 83.3, 87.3, 124.3, 132.7, 136.3, 140.8, 151.3, 153.7, 160.4, 170.2; CHN Anal. (Calcd for $C_{15}H_{15}ClN_8O_4$ as C, 44.29; H, 3.71; Cl, 8.72; N, 27.55). Found C, 43.88; H, 3.53; N, 26.99%.

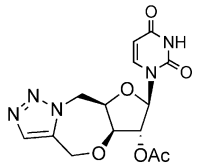
Compound characterization data of compound 12b.



12b

Mp = 130 °C; $[\alpha]_D$ (CH_3OH, c 1.315) = −3.05°; ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 2.20 (3 H, s), 4.45 (1 H, dd, J 0.9, 2.5 Hz), 4.56 (2 H, m), 4.89 (1 H, dd, J 2.6, 14.9 Hz), 4.95 (2 H, ABq, J 14.9 Hz), 5.30 (1 H, dd, J 5.8, 15.2 Hz), 5.48 (1 H, t, J 1.3 Hz), 6.34 (1 H, d, J 1.4 Hz), 7.45–7.62 (3 H, m), 7.65 (1 H, s), 7.80 (1 H, s), 7.96–8.08 (2 H, m), 8.77 (1 H, s); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.7, 47.8, 60.9, 76.8, 80.9, 83.0, 87.0, 122.8, 127.9–128.8, 132.5, 132.8, 133.5, 134.6, 141.0, 149.6, 151.5, 152.7, 165.1, 169.2. CHN Anal. (Calcd for $C_{22}H_{20}N_8O_5$ as C, 55.46; H, 4.23; N, 23.52). Found C, 55.96; H, 4.70; N, 23.45%.

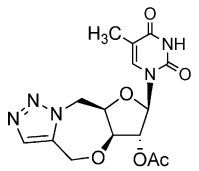
Compound characterization data of compound 12c.



12c

Mp = 225 °C; $[\alpha]_D$ (CH_3OH, c 1.18) = +72.88°; ^{1}H NMR ($CDCl_3$ + DMSO-d_6 (9 : 1), 200.13 MHz): δ 2.50 (3 H, s), 4.76 (2 H, s), 5.24 (2 H, ABq, J 14.9 Hz), 5.27 (1 H, dd, J 1.0, 14.9 Hz), 5.44 (1 H, s), 5.68 (1 H, m), 5.80 (1 H, d), 6.31 (1 H, d, J 1.3 Hz), 7.04 (1 H, d, J 8.2 Hz), 8.01 (1 H, s), 11.02 (1 H, s); ^{13}C NMR ($CDCl_3$ + DMSO-d_6 (9 : 1), 50.32 MHz): δ 19.4, 46.2, 58.3, 74.5, 79.4, 81.1, 86.5, 100.8, 131.2, 135.0, 137.7, 149.1, 162.1, 167.7. CHN Anal. (Calcd for $C_{14}H_{15}N_5O_6$ as C, 48.14; H, 4.33; N, 20.05). Found C, 48.05; H, 4.38; N, 19.79%.

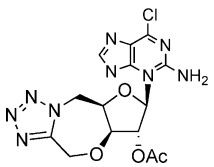
Compound characterization data of compound 12d.



12d

Mp = 180 °C; $[\alpha]_D$ (CH_3OH, c 1.68) = +6.19°; ^{1}H NMR [DMSO-d_6, 200.13 MHz): δ 1.53 (3 H, s), 2.07 (3 H, s), 4.28–4.52 (1 H, m), 4.65–4.82 (1 H, m), 4.87–5.05 (3 H, m), 5.24 (1 H, dd, J 4.7, 15.9 Hz), 5.75 (1 H, d, J 0.9 Hz), 6.29 (1 H, d, J 1.0 Hz), 7.61 (1 H, s), 7.85 (1H, s), 11.17 (1 H, s); ^{13}C NMR ($CDCl_3$ + DMSO-d_6 (9 : 1), 50.32 MHz): δ 12.5, 20.8, 47.4, 59.0, 75.9, 80.7, 82.0, 87.6, 109.2, 132.7, 134.9, 136.6, 150.4, 163.9, 169.5. CHN Anal. (Calcd for $C_{15}H_{17}N_5O_6$ as C, 49.59; H, 4.72; N, 19.28). Found C, 48.97; H, 4.87; N, 18.97%.

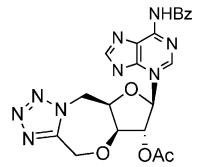
Compound characterization data of compound 13a.



13a

Mp = 170 °C (decomposed); $[\alpha]_D$ (CH_3OH, c 1.60) = −11.00°; ^{1}H NMR (CD_3OD + $CDCl_3$ (1 : 9), 200.13 MHz): δ 2.17 (3 H, s), 4.72 (4 H, m), 5.00 (1 H, m), 5.25 (1 H, dd, J 6.1, 14.5 Hz), 5.28 (2 H, ABq, J 15.8 Hz), 5.80 (1 H, m), 6.08 (1 H, d, J 3.5 Hz), 7.82 (1 H, s); ^{13}C NMR (CD_3OD + $CDCl_3$ (1 : 9), 50.32 MHz): δ 20.4, 46.3, 63.0, 75.4, 78.2, 82.3, 85.2, 120.0, 127.4, 150.1, 153.6, 159.8, 159.9, 169.2; CHN Anal. (Calcd for $C_{14}H_{14}ClN_9O_4$ as C, 41.24; H, 3.46; Cl, 8.69; N, 30.91). Found C, 41.15; H, 3.52; Cl, 7.99; N, 30.94%.

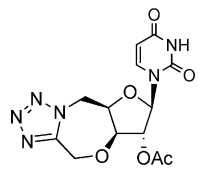
Compound characterization data for compound 13b.



13b

$[a]_D$ (CH_3OH, *c* 1.06) = −12.45°; ^1H NMR (CD_3OD + $CDCl_3$ (1 : 9), 200.13 MHz): δ 2.18 (3 H, s), 4.70 (2 H, m), 5.05 (1 H, dd, *J* 3.0, 15.0 Hz), 5.28 (2 H, ABq, *J* 15.7 Hz), 5.29 (1 H, dd, *J* 6.3, 14.9 Hz), 5.74 (1 H, t, *J* 2.5 Hz), 6.33 (1 H, d, *J* 2.7 Hz), 7.50–7.75 (4 H, m), 8.07 (2 H, m), 8.12 (1 H, s), 8.73 (1 H, s); ^{13}C NMR (CD_3OD + $CDCl_3$ (1 : 9), 50.32 MHz): δ 18.8, 45.6, 60.9, 75.6, 79.3, 82.4, 85.9, 127.3–127.8, 131.9, 141.2, 151.0, 151.5, 153.2, 169.0. CHN Anal. (Calcd for $C_{21}H_{19}N_9O_5$ as C, 52.83; H, 4.01; N, 26.40). Found C, 52.76; H, 4.10; N, 26.35%.

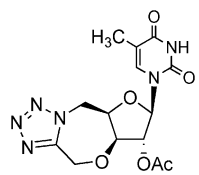
Compound characterization data of compound 13c.



13c

Mp = 126 °C; $[a]_D$ (CH_3OH, *c* 1.10) = +13.27°; ^1H NMR (CD_3OD, 200.13 MHz): δ 2.13 (3 H, s), 4.53 (1 H, m), 4.61 (1 H, m), 4.96–5.08 (2 H, m), 5.14–5.40 (3 H, m), 5.58 (1 H, d, *J* 8.1 Hz), 5.95 (1 H, d, *J* 2.8 Hz), 7.10 (1 H, d, *J* 8.2 Hz); ^{13}C NMR (CD_3OD + $CDCl_3$ (1 : 9), 50.32 MHz): δ 18.7, 45.3, 60.3, 74.5, 79.4, 82.1, 87.0, 101.43, 139.2, 149.7, 153.3, 163.4, 169.0; CHN Anal. (Calcd for $C_{13}H_{14}N_6O_6$ as C, 44.68; H, 4.18; N, 23.99). Found C, 44.68; H, 4.18; N, 23.85%.

Compound characterization data of compound 13d.



13d

Mp = 123 °C; $[a]_D$ (CH_3OH, *c* 1.14) = +4.38°; ^1H NMR ($CDCl_3$ + DMSO-d_6 (9 : 1), 200.13 MHz): δ 1.73 (3 H, s), 2.14 (3 H, s), 4.30–4.65 (2 H, m), 4.82–5.45 (5 H, m), 5.97 (1 H, d, *J* 3.0 Hz), 6.72 (1 H, d, *J* 1.1 Hz), 11.16 (1 H, m); ^{13}C NMR (CD_3OD + $CDCl_3$ (1 : 9), 50.32 MHz): δ 12.6, 20.7, 47.4, 61.9, 76.6, 81.4, 84.1, 89.1, 111.8, 136.5, 151.9, 155.5, 165.9, 171.0. CHN Anal. (Calcd for $C_{14}H_{16}N_6O_6$ as C, 46.16; H, 4.43; N, 23.07). Found C, 46.10; H, 4.33; N, 23.15%.

Acknowledgements

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11 (*a*) Crystallographic data of compound **6** was reported by us[6a] and is in the CSD [REFCODE DAQJOV]; (*b*) crystal data of **7**: single crystals of the complex were grown by slow evaporation of the solution in chloroform. A colourless needle, of approximate size 0.54 × 0.08 × 0.07 mm, was used for data collection. Crystal to detector distance 6.05 cm, 512 × 512 pixels per frame, hemisphere data acquisition. Total scans = 3, total frames = 1271, oscillation per frame −0.3°, exposure per frame = 10.0 sec per frame, maximum detector swing angle = −30.0°, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 1.92 to 25.0°, completeness to θ of 25.0° is 100.0%. SADABS correction applied, $C_{10}H_{14}N_4O_4$, M = 254.25. Crystals belong to orthorhombic, space group $P2_12_12_1$, a = 5.6672(5),

$b = 9.8214(9)$, $c = 21.2188(19)$ Å, $V = 1181.03(18)$ Å^3, $Z = 4$, $D_c = 1.430$ mg m^{-3}, μ(Mo–K$_a$) = 0.112 mm^{-1}, 5801 reflections measured, 2080 unique [$I > 2\sigma(I)$], R value 0.0406, $wR2 = 0.0900$. Largest diff. peak and hole 0.144 and −0.148 eÅ^{-3}. Crystallographic data has been deposited for compound **7** with the Cambridge Crystallographic Data Centre [CCDC 637450]; (*c*) crystal data of **12c**: single crystals of the complex were grown by slow evaporation of the solution mixture in acetonitrile. A colourless needle, of approximate size 0.20 × 0.07 × 0.06 mm, was used for data collection. Crystal to detector distance 6.05 cm, 512 × 512 pixels per frame, hemisphere data acquisition. Total scans = 3, total frames = 1271, oscillation per frame −0.3°, exposure per frame = 20.0 sec per frame, maximum detector swing angle = −30.0°, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 1.77 to 25.00°, completeness to θ of 25.0° is 99.9%. SADABS correction applied, $C_{14}H_{15}N_5O_6$, $M = 351.98$. Crystals belong to orthorhombic, space group $P2_12_12_1$, $a = 5.9329(8)$, $b = 14.5318(19)$, $c = 18.898(3)$ Å, $V = 1629.3(4)$ Å^3, $Z = 4$, $D_c = 1.434$ mg m^{-3}, μ(Mo–K$_a$) = 0.114 mm^{-1}, 8097 reflections measured, 2861 unique [$I > 2\sigma(I)$], R value 0.0607, $wR2 = 0.1060$. Largest diff. peak and hole 0.189 and −0.179 eÅ^{-3}. Crystallographic data has been deposited for compound **12c** with the Cambridge Crystallographic Data Centre [CCDC 637451]§.

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