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Design and Synthesis of 1,2,3-Triazole-Fused Chiral Medium-Ring Benzo-Heterocycles, Scaffolds Mimicking Benzolactams

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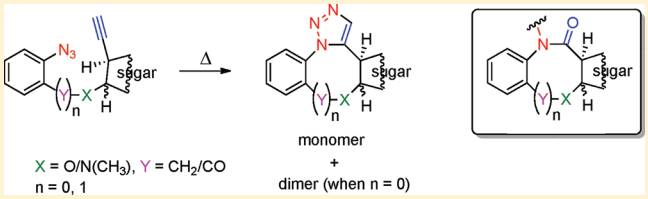
Supporting Information

ABSTRACT: Based on "amide-triazole bioequivalence" principle, 1,2,3-triazole-fused chiral medium ring benzo-heterocycles capable of mimicking benzolactams were designed. Their syntheses were accomplished by cycloaddition of different sugar-derived azidoalkynes. While triazole-fused eight-membered benzo-heterocycles were formed by exclusive intramolecuclar [3 + 2] cycloaddition, attempted preparation of seven-membered analogues led to some intermolecular cycloaddition resulting in a dimeric macrocyclic product, in addition to intramolecular cycloaddition furnishing the expected heterocycle.



1,2,3-Triazoles display a wide range of biological activities including anti-HIV activity,[1] antimicrobial activity against Gram-positive bacteria,[2] and selective β_3 adrenergic receptor agonism.[3] These heteroarenes have proved particularly valuable as genuine amide surrogates (amide−triazole bioequivalence principle) in bioactive molecules because of their physicochemical properties (peptide isosteres), in addition to their remarkable metabolic stability.[4] A number of studies reveal that the 1,4-disubstituted triazole regioisomer effectively mimics a trans amide bond,[5] while the 1,5-disubstituted analogue does it for a cis isomer (Figure 1).[6] From a synthetic point of view,

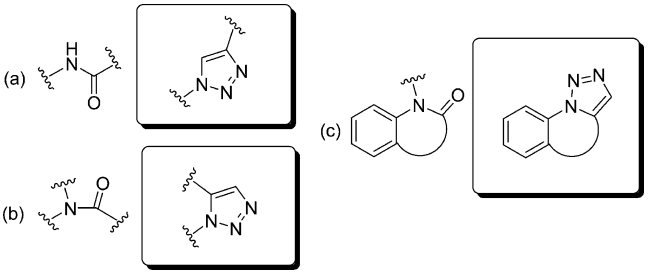


Figure 1. (a) 1,4-Disubstituted and (b) 1,5-disubstituted triazoles capable of mimicking trans and cis amides, respectively, and (c) proposed 1,5-disubstituted triazole-fused benzo-heterocycle, capable of mimicking benzolactams.

creation of a cis amide bond in a small to medium ring could be challenging, whereas 1,5-disubstituted triazole moieties are easy to access by simple azide−alkyne thermal cycloaddition (formation of 1,4-regioisomer is less favorable in this case due to strain induced in the ring). Thus, it is profitable to attempt the preparation of triazole-fused benzo-heterocycles, an alternate type of structures capable of mimicking benzolactams (Figure 1), inspired by the fact that compared to the widely applied peptidomimetics, small molecule mimetics are also known where the designed benzolactams can effectively mimic teleocidines.[7] 1,2,3-Triazoles have also found various industrial applications as dyes, corrosion inhibitors (of copper and copper alloys), photostabilizers, photographic materials, and agrochemicals.[8] On the other hand, benzofused aza-heterocycles are described as "privileged structures" due to their capacity to bind to multiple receptors with high affinity.[9] Among them, benzofused seven- and eight-membered rings are receiving a great deal of attention as these structural units are also found in numerous natural products and are components of a number of biologically interesting molecules.[10] For example, benzoxazocine[11] and benzodiazocine[12] rings are often present in pharmaceutical agents as a core structural motif. 1,5-Benzoxazepine derivatives also exhibit a wide range of bioactivity.[13] It is a small wonder therefore that fusion of 1,2,3-triazoles with medium-ring benzo-heterocycles leads to products that display an interesting range of biological properties, as in the anxiolytic agents[14] alprazolam and estazolam, and the antidepressant agent[15] triazolam.

Therefore, synthesis of 1,2,3-triazole-fused benzo-heterocycles has been of growing interest in recent times.[16] Although there are several reported procedures for the synthesis of triazole-fused five-, six-, and seven-membered benzo-heterocycles, methods for the synthesis of triazole-fused eight-membered benzo-heterocycles are scarce[17] and deal with achiral substrates only. The methodologies employing chiral substrates mainly focus on the synthesis of triazoles fused to heterocycles, not benzo-heterocycles.[18] The chiron approach to the synthesis of chiral target molecules involves the use of sugars as starting materials.[19] A key element in this strategy is the ability to form optically active heterocycles[20] and carbohydrate-based mimetics.[21] The design and synthesis of

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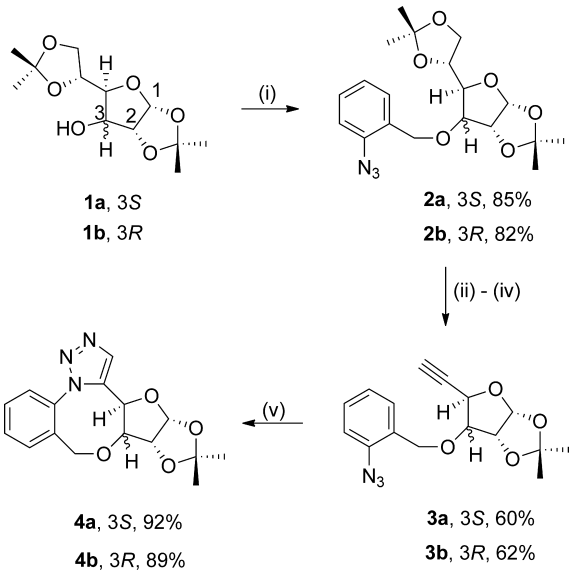
novel benzolactams possessing broad biological activities were accomplished starting from D-glucose. However, their synthesis suffers either from regioselectivity considerations[20c] or from the less favorable nature of the intramolecular S_NAr reaction employed during cyclization requiring *N*-alkylated amide[20a,b] (cis amide).[22] In continuation of our research activities related to the synthesis of benzannulated chiral medium-ring heterocycles,[11c,12,13,23] we conceptualized that an intramolecular [3 + 2] cycloaddition of sugar derived azidoalkynes would lead to highly functionalized 1,5-disubstituted 1,2,3-triazole-fused chiral benzo-heterocycles, an effective scaffold capable of mimicking sugar derived medium-ring benzolactams. Herein we report our preliminary synthetic results using different sugar derived azidoalkynes.

The starting materials 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1a**) and 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**1b**) were separately reacted with 2-azidobenzyl bromide to give 3-*O*-(2-azidobenzyl) glucofuranoside **2a** and 3-*O*-(2-azidobenzyl) allofuranoside **2b** (Scheme 1). Selective removal

Scheme 1. Synthesis of 1,2,3-Triazole-Fused Furo-Benzoxazocine Derivatives[a]

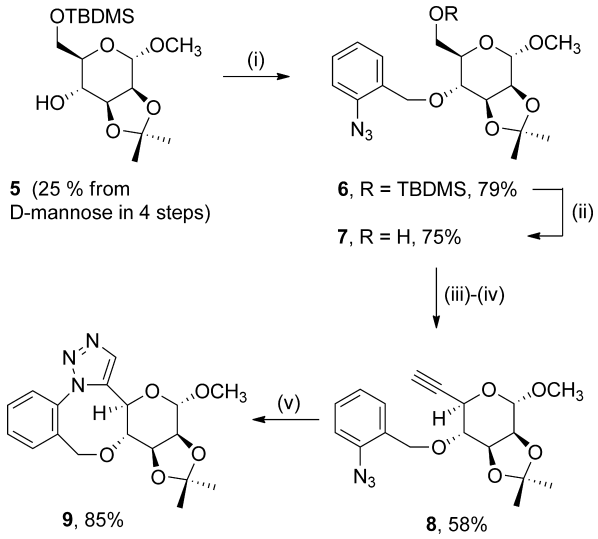


[a]Reagents and conditions: (i) NaH, dry DMF, O °C, 15 min, then 2-azidobenzyl bromide, rt, 6 h; (ii) 70% AcOH (v/v), rt, overnight; (iii) aq $NaIO_4$, MeOH, rt, 45 min; (iv) dimethyl (1-diazo-2-oxopropyl)-phosphonate [$CH_3COCN_2PO(OMe)_2$] (Bestmann's reagent), K_2CO_3, MeOH, rt, 12 h; (v) dry DMF, 120 °C, 2 h, N_2.

of the 5,6-*O*-isopropylidene moiety from **2a,b** was smoothly effected with 70% aqueous HOAc at 25 °C. Oxidation of the resulting diols with $NaIO_4$ furnished the intermediate aldehyde, which was treated with Bestmann's reagent[24] to afford the desired alkynes **3a,b** in good yields (Scheme 1). The structures of **3a,b** were supported by spectroscopic data, compared with data of similar compounds.[5a] Intramolecular azide−alkyne [3 + 2] cycloaddition strategy was utilized for the cyclization of the azidoalkynes to form 1,2,3-triazole fused furo-benzoxazocine derivatives. After screening a variety of solvents and reaction conditions (temperature, concentration) it was found that heating of azidoalkynes at 120 °C in DMF (20 mL/mmol) was most effective for the cyclization. TLC analysis showed the formation of one product only, the ^1H NMR spectrum of which lacked the peaks for alkyne protons (δ = 2.60, 2.53) but contained those for triazole protons (δ = 7.87, 7.82); formation of the desired product was supported by ESIMS analysis. Thus, compounds **3a,b** underwent exclusive intramolecular cyclization to afford triazole-fused benzoxazocines **4a,b** in excellent yields (Scheme 1).

After achieving success with 1,2,3-triazole-fused furobenzoxazocines, synthesis of fused pyranobenzoxazocine was attempted. With D-mannose as chiral precursor, conversion to alcohol **5** was done by the reported sequence of reactions (Scheme 2).[25] Reaction of **5** with 2-azidobenzyl bromide then afforded 4-

Scheme 2. Synthesis of 1,2,3-Triazole-Fused Pyranobenzoxazocine Derivative[a]



[a]Reagents and conditions: (i) NaH, dry DMF, O °C, 15 min, then 2-azidobenzyl bromide, rt, 6 h; (ii) TBAF, THF, reflux, 4 h; (iii) Dess−Martin periodinane, dry DCM, rt, 4 h; (iv) dimethyl (1-diazo-2-oxopropyl)phosphonate [$CH_3COCN_2PO(OMe)_2$] (Bestmann's reagent), K_2CO_3, MeOH, rt, 12 h; (v) dry DMF, 120 °C, 2 h, N_2.

O-(2-azidobenzyl) mannopyranoside **6**. Deprotection of the silyl ether (to **7**) with TBAF/THF followed by Dess−Martin oxidation led to the intermediate aldehyde, which was treated with Bestmann's reagent to yield the desired azidoalkyne **8**. Heating **8** at 120 °C in DMF (20 mL/mmol) gratifyingly afforded the 1,2,3-triazole-fused pyrano-benzoxazocine **9** by exclusive intramolecular [3 + 2] cycloaddition (Scheme 2).

Next, the focus was to synthesize 1,2,3-triazole-fused furobenzodiazocines and furobenzodiazocinones by similar intramolecular [3 + 2] cycloadditions. For this, the starting material 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (**10**)[12] was nosylated and the resulted nosyl amide derivative (**11**) was methylated to give 3-deoxy-3-(*N*-(4-nitrophenylsulfonyl)-*N*-methylamino)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside **12** (Scheme 3). Conversion of **12** to the nosylamido alkyne **13** was smoothly achieved following the procedure used to convert **2** to **3**. The nosyl group in **13** was then removed using thiophenol in dry acetonitrile to obtain aminoalkyne **14**, which was reacted with 2-azidobenzyl bromide or 2-azidobenzoyl chloride to give the azidoalkynes **15** and **16**, respectively. Intramolecular [3 + 2] cycloaddition of **15** and **16** gave 1,2,3-triazole fused furobenzodiazocine **17** and furobenzodiazocinone **18** derivatives exclusively and in excellent yield (Scheme 3).

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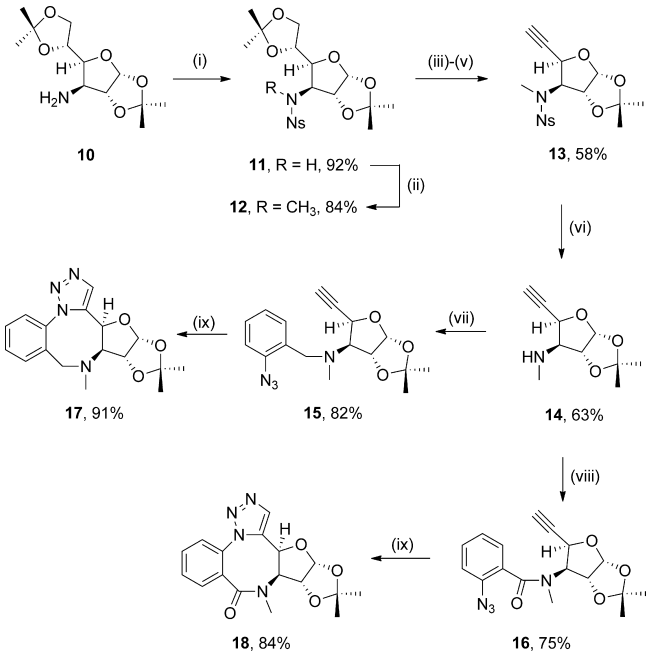
Scheme 3. Synthesis of 1,2,3-Triazole-Fused Furobenzodiazocine and Furobenzodiazocinone Derivatives[a]

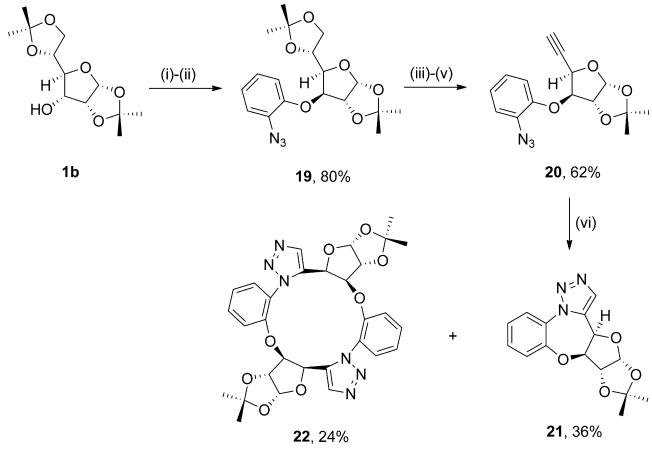


[a]Reagents and conditions: (i) NsCl (4-nitrophenylsulfonyl chloride), Et_3N, dry DCM, rt, 2 h; (ii) NaH, dry DMF, 0 °C, 15 min, then, CH_3I, rt, 6 h, N_2; (iii) 80% AcOH (v/v), rt, overnight; (iv) aq. $NaIO_4$, MeOH, rt, 45 min; (v) dimethyl (1-diazo-2-oxopropyl)phosphonate [$CH_3COCN_2PO(OMe)_2$] (Bestmann's reagent), K_2CO_3, MeOH, rt, 12 h; (vi) dry CH_3CN, PhSH, K_2CO_3, rt, 3 h, N_2; (vii) 2-azidobenzyl bromide, K_2CO_3, dry CH_3CN, rt, 6 h, N_2; (viii) 2-azidobenzoyl chloride, Et_3N, dry DCM, rt, 8 h, N_2; (ix) dry DMF, 120 °C, 2 h; N_2.

After successfully synthesizing triazole-fused eight-membered heterocycles, we next focused on extending our methodology for the synthesis of seven membered analogues. For this, the starting material 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**1b**) was converted to its triflate derivative, which was subsequently reacted with 2-azidophenol to give 3-*O*-(2-azidophenyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (**19**, Scheme 4). Usual functional group manipulation then afforded the desired alkyne **20** (Scheme 4). However, in this case, heating of **20** in DMF followed by TLC analysis showed formation of two distinct products. NMR analysis of purified products showed disappearance of the signal for the alkyne proton (δ = 2.55) and appearance of triazole proton signals instead (δ = 7.92, 8.18). ESIMS analysis identified them as momomeric and dimeric products. Thus heating of compound **20** produced both intramolecularly cyclized monomeric product **21** and intermolecularly cyclized dimeric product **22**. As use of dilute reaction condition (30 mL DMF/mmol of **20**) did not effectively suppress the formation of **22**, it was assumed that the conformational rigidity present in **20**, compared to the previous azidoalkynes, was responsible for the formation of dimeric product **22**.[26]

As a logical extension of our methodology, we next investigated the feasibility of synthesizing 1,2,3-triazole fused chiral functionalized benzo-heterocycles from the obtained annulated sugar derivatives. Thus, subjecting **4a** to a sequence of reactions involving removal of the 1,2-*O*-isopropylidene group, cleavage of the diol with $NaIO_4$, reduction of the

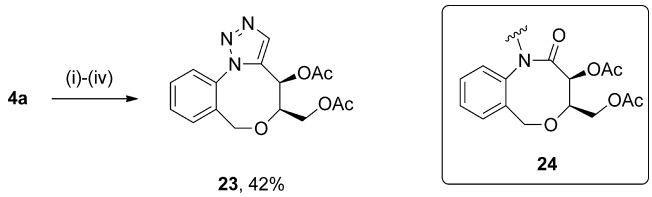
Scheme 4. Synthesis of 1,2,3-Triazole-Fused Furobenzoxazepine Derivative and Macrocycle[a]



[a]Reagents and conditions: (i) Tf_2O, Py, dry DCM, −10 °C, 1 h, N_2; (ii) 2-azidophenol, K_2CO_3, dry CH_3CN, reflux, 6 h; (iii) 70% AcOH (v/v), rt, overnight; (iv) aq. $NaIO_4$, MeOH, rt, 45 min; (v) dimethyl (1-diazo-2-oxopropyl)phosphonate [$CH_3COCN_2PO(OMe)_2$] (Bestmann's reagent), K_2CO_3, MeOH, rt, 12 h; (vi) dry DMF, 120 °C, 2 h, N_2.

generated carbonyl group with $NaBH_4$, and acetylation furnished 1,2,3-triazole fused chiral benzoxazocine derivative **23**, which may mimic the 1,5-benzoxazocinone derivative **24** (Scheme 5).

Scheme 5. Conversion of 4a to 1,2,3-Triazole-Fused Benzoxazocine Derivative[a]



[a]Reagents and conditions: (i) $CH_3CN/H_2O/H_2SO_4$ (18:5:2), rt, 24 h; (ii) aqueous $NaIO_4$, MeOH, rt, 45 min (iii) $NaBH_4$, MeOH, rt, 3 h; (iv) Ac_2O, pyridine, rt, 12 h.

In conclusion, based on the reasoning that 1,5-disubstituted 1,2,3-triazole-fused benzoheterocycles could be an alternate type of structure mimicking benzolactams ("amide-triazole bioequivalence"), we have designed 1,2,3-triazole-fused chiral medium ring benzo-heterocycles for synthesis. Cycloaddition using different sugar-derived azidoalkynes was resorted to for their synthesis. Triazole-fused eight-membered rings were generated by exclusive intramolecular cycloaddition of azidoalkynes, whereas cycloaddition in case of seven-membered rings was both intramolecular, generating the desired 1,2,3-triazole-fused heterocycle, and intermolecular, resulting in a macrocycle. The synthesized triazole-fused chiral benzoxazocine was smoothly converted to the corresponding chiral benzoxazocine derivative. We hope that the approach would be effective enough to design triazole-fused heterocycles capable of mimicking the corresponding benzolactams present in small molecule drug candidates and thus will have profound significance in drug discovery.

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EXPERIMENTAL SECTION

General Procedure for the Synthesis of Compounds 2a,b and 6. NaH (200 mg, 60% suspension in oil, 5 mmol) was added to a solution of each of **1a,b** and **5** (4 mmol) in 20 mL of DMF at 0 °C, and the solution was stirred for 15 min. Then, 2-azidobenzyl bromide (1.05 g, 5 mmol) was added, and stirring was continued for 6 h at rt. The reaction mixture was diluted with H_2O and extracted with ethyl acetate (3 × 30 mL). The ethyl acetate extract was washed with H_2O, dried, concentrated, and column chromatographed over silica gel (100−200 mesh) to afford **2a,b** and **6**.

(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Azidobenzyloxy)-5-(2,2-dimethyl[1,3]-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (2a). Oil; yield 1.33 g, 85% [eluent petroleum sprit (PS) 60−80 °C/ethyl acetate (EA), 11:1]. $[\alpha]_D^{25}$ = −36.8 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.50 (s, 3H), 3.97−4.03 (m. 2H), 4.07−4.10 (m, 1H), 4.12−4.16 (m, 1H), 4.36 (dd, *J* = 13.8, 6.0 Hz, 1H), 4.56 (d, *J* = 12.3 Hz, 1H), 4.62 (d, *J* = 3.6 Hz, 1H), 4.66 (d, *J* = 12.3 Hz, 1H), 5.90 (d, *J* = 3.6 Hz, 1H), 7.11−7.44 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3, 26.2, 26.72, 26.78, 67.3, 67.5, 72.3, 81.1, 81.8, 82.4, 105.2, 108.9, 111.7, 117.9, 124.6, 128.8, 129.0, 129.6, 137.8. IR ν_{max} (film): 2985, 2934, 2123, 1587, 1488, 1455 cm^{-1}. ESIMS: *m*/*z* 414 $[M + Na]^+$. Anal. Calcd for $C_{19}H_{25}N_3O_6$: C, 58.30; H, 6.44; N, 10.74. Found: C, 58.06; H, 6.28; N, 10.58.

(3a*R*,5*R*,6*R*,6a*R*)-6-(2-Azidobenzyloxy)-5-(2,2-dimethyl[1,3]-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (2b). Oil; yield 1.285 g, 82% (eluent PS/EA, 9:1). $[\alpha]_D^{25}$ = +54.8 (*c* 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.36 (s, 3H), 1.57 (s, 3H), 1.58 (s, 3H), 3.89−3.94 (m, 1H), 3.97−4.04 (m, 2H), 4.13 (dd, *J* = 8.4, 3.0 Hz, 1H), 4.36−4.41 (m, 1H), 4.58 (d, *J* = 12.3 Hz, 1H), 4.63 (d, *J* = 4.2 Hz, 1H), 4.71 (d, *J* = 12.3 Hz, 1H), 5.78 (d, *J* = 3.6 Hz, 1H), 7.12−7.48 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.1, 25.9, 26.57, 26.77, 64.8, 67.2, 74.6, 77.4, 77.7, 77.8, 103.8, 109.5, 112.8, 118.0, 124.7, 128.7, 129.2, 130.2, 138.1. IR ν_{max} (film): 2985, 2928, 2124, 1587, 1488, 1455 cm^{-1}. ESIMS: *m*/*z* 414 $[M + Na]^+$. Anal. Calcd for $C_{19}H_{25}N_3O_6$: C, 58.30; H, 6.44; N, 10.74. Found: C, 58.02; H, 6.26; N, 10.56.

Methyl 4-*O*-(2-Azidobenzyl)-6-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-α-D-mannopyranoside (6). Oil; yield 1.515 g, 79% (eluent PS/EA, 11:1). $[\alpha]_D^{25}$ = +25.3 (*c* 0.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.36 (s, 3H), 1.52 (s, 3H), 3.37 (s, 3H), 3.47−3.56 (m, 2H), 3.74 (dd, *J* = 12.3, 4.8 Hz, 1H), 3.89 (dd, *J* = 11.1, 1.8 Hz, 1H), 4.11 (d, *J* = 5.7 Hz, 1H), 4.29 (d, *J* = 6.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.89 (s, 1H), 7.09−7.40 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.4, −5.2, 18.2, 25.8, 26.2, 26.9, 54.5, 62.6, 68.2, 69.5, 75.7, 75.9, 78.7, 97.9, 109.2, 117.9, 124.5, 128.9, 129.6, 129.9, 137.8. IR ν_{max} (film): 2932, 2858, 2435, 2122, 1586, 1458 cm^{-1}. ESIMS: *m*/*z* 502 $[M + Na]^+$. Anal. Calcd for $C_{23}H_{37}N_3O_6Si$: C, 57.59; H, 7.78; N, 8.76. Found: C, 57.37; H, 7.62; N, 8.58.

General Procedure for the Synthesis of Compounds 3a,b, 13, and 20. Each of compounds **2a,b**, **12**, and **19** (2 mmol) was dissolved in aqueous HOAc (70%, v/v, 60 mL, 80% for **12**), and the solution was stirred overnight at rt. HOAc was distilled off using toluene, and the resulting diol was dissolved in methanol (10 mL), cooled to 0 °C, and slowly treated with a solution of $NaIO_4$ (513 mg, 2.4 mmol) in water (5 mL). The reaction mixture was stirred for 45 min, filtered, evaporated, and extracted with $CHCl_3$ (4 × 30 mL). The organic layer was washed with water, dried, and evaporated to afford the crude aldehyde which was dissolved in dry methanol (10 mL) and treated with K_2CO_3 (550 mg, 4 mmol) followed by dimethyl (1-diazo-2-oxopropyl)phosphonate (660 mg, 3 mmol) at rt. After 12 h, the mixture was filtered, concentrated, extracted with ethyl acetate (30 mL), washed sequentially with saturated NH_4Cl (20 mL) and water (20 mL), dried (Na_2SO_4), concentrated, and subjected to silica gel column chromatography to afford the desired azidoalkynes **3a,b**, **13**, and **20**, respectively.

(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Azidobenzyloxy)-5-ethynyl-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (3a). Oil. Yield: 0.38 g, 60% (eluent PS/EA, 9:1). $[\alpha]_D^{25}$ = −32.7 (*c* 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.48 (s, 3H), 2.60 (d, *J* = 2.1 Hz, 1H), 4.02 (d, *J* = 3.0 Hz, 1H), 4.60−4.63 (m, 1H), 4.73 (s, 2H), 4.84−4.85 (m, 1H), 5.97 (d, *J* = 3.6 Hz, 1H), 7.12−7.53 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2, 26.7, 69.7, 70.5, 75.8, 81.1, 83.5, 84.4, 104.5, 112.0, 117.9, 125.3, 128.9, 129.2, 131.7, 143.0. IR ν_{max} (film): 3278, 2986, 2933, 2124, 1588, 1497, 1457 cm^{-1}. ESIMS: *m*/*z* 338 $[M + Na]^+$. Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.68; H, 5.27; N, 13.11.

(3a*R*,5*R*,6*R*,6a*R*)-6-(2-Azidobenzyloxy)-5-ethynyl-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (3b). Oil. Yield: 0.39 g, 62% (eluent PS/EA, 8:1). $[\alpha]_D^{25}$ = +28.7 (*c* 0.55, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.55 (s, 3H), 2.53 (d, *J* = 1.8 Hz, 1H), 4.54 (d, *J* = 4.2 Hz, 1H), 4.58 (dd, *J* = 13.2, 3.9 Hz, 1H), 4.62−4.67 (m. 1H), 4.72 (d, *J* = 4.2 Hz, 1H), 4.76 (d, *J* = 3.6 Hz, 1H), 5.78 (d, *J* = 3.6 Hz, 1H), 7.09−7.54 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3, 26.7, 67.7, 68.0, 72.2, 77.4, 82.6, 82.9, 103.8, 113.3, 118.0, 125.6, 129.2, 129.9, 132.8, 144.2. IR ν_{max} (film): 3270, 2987, 2933, 2124, 1588, 1496, 1457 cm^{-1}. ESIMS: *m*/*z* 338 $[M + Na]^+$. Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.66; H, 5.31; N, 13.17.

(3a*R*,5*R*,6*S*,6a*R*)-5-Ethynyl-6-(*N*-4-nitrobenzenesulfonyl-*N*-methylamino)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (13). Foamy solid. Yield: 0.445 g, 58% (eluent PS/EA 4:1). ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 3H), 1.50 (s, 3H), 2.35 (d, *J* = 2.4 Hz, 1H), 2.95 (s, 3H), 4.46 (d, *J* = 3.9 Hz, 1H), 4.64 (d, *J* = 5.1 Hz, 1H), 4.96 (dd, *J* = 5.1, 2.1 Hz, 1H), 5.88 (d, *J* = 3.9 Hz, 1H), 8.06 (d, *J* = 8.7 Hz, 2H), 8.37 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 25.9, 26.4, 32.1, 65.5, 69.6, 76.2, 77.7, 83.5, 104.3, 111.9, 124.3, 128.6, 134.4, 145.5. ESIMS: *m*/*z* 405 $[M + Na]^+$. Anal. Calcd for $C_{16}H_{18}N_2O_7S$: C, 50.26; H, 4.74; N, 7.33. Found: C, 50.12; H, 4.66; N, 7.21.

(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Azidophenoxy)-5-ethynyl-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (20). Colorless oil. Yield: 0.373 g, 62% (eluent PS/EA, 9:1). $[\alpha]_D^{25}$ = = −26.2 (*c* 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 3H), 1.53 (s, 3H), 2.55 (d, *J* = 2.4 Hz, 1H), 4.70 (d, *J* = 3.9 Hz, 1H), 4.76 (d, *J* = 3.0 Hz, 1H), 5.01−5.03 (m, 1H), 6.05 (d, *J* = 3.6 Hz, 1H), 6.91−7.44 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2, 26.5, 72.7, 75.6, 80.9, 81.7, 84.2, 104.6, 112.6, 122.1, 124.4, 124.9, 129.6, 134.7, 146.5. IR ν_{max} (film): 3279, 2986, 2936, 2120, 1598 cm^{-1}. ESIMS: *m*/*z* 324 $[M + Na]^+$. Anal. Calcd for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95. Found: C, 59.55; H, 4.88; N, 13.77.

General Procedure for the Synthesis of Compounds 4a,b, 9, 17, 18, 21, and 22. Each of compounds **3a,b**, **8**, **15**, **16**, and **20** (1 mmol) was dissolved in DMF (20 mL) and heated at 120 °C for 2 h. The solution was diluted with H_2O and extracted with Et_2O (3 × 30 mL). The combined ether extract was washed with H_2O, dried, concentrated, and column chromatographed over silica gel to afford **4a,b**, **9**, **17**, **18**, **21**, and **22**, respectively.

(10a*S*,10b*R*,13a*R*,14a*R*)-12,12-Dimethyl-10a,10b,13a,14a-tetrahydro-9*H*-[1,3]dioxolo[4′,5′:4,5]furo[3,2-*b*]benzo[*f*]-[1,2,3]triazolo[5,1-*d*][1,5]oxazocine (4a). Crystalline solid. Mp: 198−200 °C. Yield: 0.29 g, 92% (eluent PS/EA, 4:1). $[\alpha]_D^{25}$ = = −17.3 (*c* 0.25, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.47 (s, 3H), 4.09 (s, 1H), 4.50 (s, 2H), 4.62 (d, *J* = 3.3 Hz, 1H), 5.19 (s, 1H), 5.95 (s, 1H), 7.44−7.69 (m, 4H), 7.87 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0, 26.8, 68.2, 74.8, 79.1, 84.5, 104.4, 112.1, 126.7, 130.4, 130.5, 130.8, 131.3, 134.3, 136.2, 136.6. IR ν_{max} (film): 2985, 2938, 1732, 1499, 1466, 1379, 1217 cm^{-1}. ESIMS: *m*/*z* 316 $[M + H]^+$. Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.64; H, 5.31; N, 13.13.

(10a*R*,10b*R*,13a*R*,14a*R*)-12,12-Dimethyl-10a,10b,13a,14a-tetrahydro-9*H*-[1,3]dioxolo[4′,5′:4,5]furo[3,2-*b*]benzo[*f*]-[1,2,3]triazolo[5,1-*d*][1,5]oxazocine (4b). Crystalline solid. Mp: 204−208 °C. Yield: 0.28 g, 89% (eluent PS/EA, 3:1). $[\alpha]_D^{25}$ = +22.5 (*c* 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.44 (s, 3H), 3.71 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.94 (d, *J* = 13.2 Hz, 1H), 4.75 (d, *J* = 8.4 Hz, 1H), 4.86 (d, *J* = 3.9 Hz, 1H), 4.91 (d, *J* = 13.2 Hz, 1H), 5.97 (d, *J* = 3.6 Hz, 1H), 7.57−7.64 (m, 4H), 7.82 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0, 26.5, 70.3, 73.2, 79.1, 84.3, 103.3, 113.8, 126.7, 130.4, 130.6, 130.9, 132.2, 132.9, 134.5, 138.0. IR ν_{max} (film):

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2986, 2931, 1499, 1466, 1378, 1253 cm^{-1}. ESIMS: m/z 316 $[M + H]^+$. Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.58; H, 5.29; N, 13.17.

(3b*R*,5*S*,5a*S*,8a*S*,8b*S*)-5-Methoxy-7,7-dimethyl-3b,5,5a,-8a,8b,10-hexahydro-[1,3]dioxolo[4′,5′:4,5]pyrano[3,2-*b*]-benzo[*f*][1,2,3]triazolo[5,1-*d*][1,5]oxazocine (9). Crystalline solid. Mp: 235−238 °C. Yield: 0.305 g, 85% (eluent PS/EA, 3:1); $[\alpha]_D^{25}$ = +29.6 (*c* 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.54 (s, 3H), 3.29 (s, 3H), 3.45−3.51 (m, 1H), 3.85 (d, *J* = 12.3 Hz, 1H), 4.11 (d, *J* = 5.7 Hz, 1H), 4.13 (d, *J* = 4.2 Hz, 1H), 4.38 (d, *J* = 9.3 Hz, 1H), 4.80 (d, *J* = 12.9 Hz, 1H), 5.04 (s, 1H), 7.50−7.73 (m, 4H), 7.95 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0, 27.8, 55.7, 64.8, 68.4, 74.6, 76.3, 81.0, 97.9, 110.0, 126.2, 130.0, 130.6, 131.3, 132.7, 134.4, 139.3. IR ν_{max} (film): 2926, 1604, 1500, 1460, 1377 cm^{-1}. ESMS: m/z 360 $[M + H]^+$. Anal. Calcd for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 59.90; H, 5.71; N, 11.53.

(10a*S*,10b*R*,13a*R*,14a*S*)-10,12,12-Trimethyl-9,10,10a,10b,-13a,14a-hexahydro-[1,3]dioxolo[4′,5′:4,5]furo[2,3-*c*]benzo[*g*]-[1,2,3]triazolo[1,5-*a*][1,5]diazocine (17). Foamy solid. Yield: 0.3 g, 91% (eluent PS/EA, 4:1). $[\alpha]_D^{25}$ = −19.3 (*c* 0.32, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.55 (s, 3H), 2.26 (s, 3H), 3.53 (d, *J* = 12.6 Hz, 1H), 3.71 (d, *J* = 3.9 Hz, 1H), 3.73 (d, *J* = 12.6 Hz, 1H), 4.92 (s, 1H), 5.47 (d, *J* = 4.8 Hz, 1H), 5.86 (s, 1H), 7.42−7.58 (m, 4H), 7.77 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0, 26.6, 41.2, 55.6, 68.9, 76.1, 77.2, 104.4, 111.1, 123.9, 126.0, 128.6, 129.3, 129.4, 131.5, 136.8, 143.6. IR ν_{max} (film): 2924, 2855, 1668, 1496, 1460, 1377 cm^{-1}. ESIMS: m/z 351 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14; N, 17.06. Found: C, 61.94; H, 5.98; N, 16.92.

(10a*S*,10b*R*,13a*R*,14a*S*)-10,12,12-Trimethyl-10,10a,13a,14a-tetrahydro[1,3]dioxolo[4′,5′:4,5]furo[2,3-*c*]benzo[*g*][1,2,3]-triazolo[1,5-*a*][1,5]diazocin-9(10b*H*)-one (18). Foamy solid. Yield: 0.287 g, 84% (eluent PS/EA, 2:1). $[\alpha]_D^{25}$ = −12.5 (*c* 0.23, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.48 (s, 3H), 2.89 (s, 3H), 4.34 (d, *J* = 4.2 Hz, 1H), 5.09 (d, *J* = 3.6 Hz, 1H), 5.31 (d, *J* = 3.9 Hz, 1H), 6.15 (d, *J* = 3.6 Hz, 1H), 7.57−7.68 (m, 4H), 7.84 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7, 26.3, 30.8, 65.5, 76.4, 82.4, 104.9, 112.2, 127.2, 128.3, 131.2, 131.4, 132.6, 132.8, 132.9, 134.5, 168.0. IR ν_{max} (film): 2988, 2927, 2857, 2128, 1652, 1469, 1381 cm^{-1}. ESIMS: m/z 365 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.48; H, 5.14; N, 16.23.

(2*R*,3*R*,3a*S*,10a*R*)-2,3-(Isopropylidenedioxy)-[1,5:9,10]-1,2,3-triazolo-2,3,3a,10a-tetrahydrofuro[3,2-*c*][1,5]benzoxazepine (21). Colorless solid. Mp: 177−179 °C. Yield: 0.108 g, 36% (eluent PS/EA, 3:1). $[\alpha]_D^{25}$ = −14.8 (*c* 0.22, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.35 (s, 3H), 4.94−4.98 (m, 2H), 5.56 (d, *J* = 3.3 Hz, 1H), 5.61 (d, *J* = 3.6 Hz, 1H), 7.21−7.42 (m, 3H), 7.92 (s, 1H), 7.97−8.06 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2, 26.9, 72.8, 84.2, 89.1, 104.5, 112.4, 122.6, 123.7, 126.2, 129.7, 131.4, 131.9, 134.7, 147.3. IR ν_{max} (film): 2988, 2927, 1599, 1502, 1468, 1378 cm^{-1}. ESIMS: m/z 324 $[M + Na]^+$. Anal. Calcd for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95. Found: C, 59.47; H, 4.92; N, 13.75.

(3b*R*,4a*R*,7a*R*,7b*S*,17a*R*,20a*R*,20b*S*)-6,6,19,19-Tetramethyl-3b,4a,7a,7b,16b,17a,20a,20b-octahydro[1,3]dioxolo[4′,5′:4,5]-furo[2,3-*f*][1,3]dioxolo[4′,5′:4,5]furo[2,3-*m*]dibenzo[*b*,*i*]bis-([1,2,3]triazolo)[1,5-d:1′,5′-*k*][1,8,4,11]dioxadiaza-cyclotetradecine (22). Colorless solid. Mp: 240−244 °C. Yield: 0.145 g, 24% (eluent PS/EA, 2:1). $[\alpha]_D^{25}$ = −3.7 (*c* 0.28, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.65 (s, 3H), 4.85 (d, *J* = 3.3 Hz, 1H), 5.17 (s, 1H), 5.82 (s, 1H), 6.18 (s, 1H), 7.14−7.42 (m, 3H), 7.99 (d, *J* = 6.9 Hz, 1H), 8.18 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2, 26.5, 75.6, 80.9, 81.7, 104.6, 112.5, 112.6, 122.1, 124.4, 124.9, 126.2, 129.6, 142.1, 146.5. IR ν_{max} (film): 2979, 2930, 1597, 1503, 1378 cm^{-1}. HRMS: calcd for $[C_{30}H_{30}N_6O_8+Na]^+$ 625.2023, found 625.2051.

Methyl 4-*O*-(2-Azidobenzyl)-2,3-*O*-isopropylidene-α-D-mannopyranoside (7). A mixture of silyl ether **6** (1.438 g, 3 mmol) and TBAF (1.1 mL, 3.7 mmol) in dry THF (15 mL) was heated at reflux for 4 h. Excess THF was distilled off, and the residue was diluted with water and extracted with CH_2Cl_2 (3 × 15 mL). The organic extract was washed with H_2O, dried (Na_2SO_4), concentrated, and column chromatographed to afford alcohol **7** as oil. Yield: 0.82 g, 75% (eluent PS/EA, 6:1). $[\alpha]_D^{25}$ = +41.5 (*c* 0.45, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.55 (s, 3H), 2.09 (t-like, 1H), 3.37 (s, 3H), 3.54−3.64 (m, 2H), 3.74−3.86 (m, 2H), 4.14 (d, *J* = 5.7 Hz, 1H), 4.30 (d, *J* = 6.0 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.83 (d, *J* = 11.7 Hz, 1H), 4.92 (s, 1H), 7.10−7.41 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2, 27.9, 54.8, 62.6, 68.2, 68.4, 75.6, 76.7, 78.5, 98.1, 109.3, 118.0, 124.6, 129.1, 129.2, 130.2, 138.1. IR ν_{max} (film): 3483, 2987, 2928, 2434, 2123, 1586 cm^{-1}. ESIMS: m/z 366 $[M + H]^+$. Anal. Calcd for $C_{17}H_{23}N_3O_6$: C, 55.88; H, 6.34; N, 11.50. Found: C, 55.64; H, 6.20; N, 11.36.

Methyl 4-*O*-(2-Azidobenzyl)-5-ethynyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (8). To a stirring solution of **7** (0.73 g, 2 mmol) in dry CH_2Cl_2 (20 mL) was added Dess−Martin periodinane (1.3 g, 3 mmol) at rt, and stirring was continued for 4 h. The reaction was quenched at 0 °C by stirring with a solution of $Na_2S_2O_3$ (4.0 g in 25 mL of water) and $NaHCO_3$ (saturated, aq, 25 mL) for 10 min and extracted with CH_2Cl_2 (3 × 30 mL). The organic extract was washed with H_2O, dried, and concentrated to give the crude aldehyde which was treated with Bestmann's reagent as earlier procedure to give alkyne **8** as oil. Yield: 0.416 g, 58% (eluent PS/EA, 11:1). $[\alpha]_D^{25}$ = +35.2 (*c* 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.48 (s, 3H), 2.47 (d, *J* = 2.1 Hz, 1H), 3.43 (s, 3H), 3.57 (dd, *J* = 9.6, 7.2 Hz, 1H), 4.09 (d, *J* = 5.7 Hz, 1H), 4.22 (d, *J* = 6.0 Hz, 1H), 4.31 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.76 (d, *J* = 12.3 Hz, 1H), 4.87 (d, *J* = 12.3 Hz, 1H), 4.91 (s, 1H), 7.10−7.52 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2, 27.7, 55.5, 60.0, 68.7, 73.8, 75.3, 77.6, 78.9, 80.6, 98.3, 109.6, 117.9, 124.6, 128.9, 129.3, 130.0, 137.8. IR ν_{max} (film): 3277, 2988, 2931, 2123, 1587, 1495, 1456 cm^{-1}. ESIMS: m/z 382 $[M + Na]^+$. Anal. Calcd for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 59.94; H, 5.73; N, 11.51.

3-Deoxy-3-(*N*-4-nitrobenzenesulfonylamino)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (11). A solution of **10** (2.075 g, 8 mmol) in anhydrous CH_2Cl_2 (25 mL) was treated at rt with Et_3N (1 mL) and NsCl (1.94 g, 8.8 mmol) and stirred for 2 h. Dilution with CH_2Cl_2 (30 mL) and evaporation of the washed (saturated aqueous $NaHCO_3$, 1 × 20 mL, and saturated aqueous NaCl, 1 × 20 mL) organic solution afforded a crude residue which was column chromatographed over silica gel to obtain **11** as a colorless solid. Mp: 143−145 °C. Yield: 3.27 g, 92% (eluent PS/EA 3:1). ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.27 (s, 3H), 1.31 (s, 3H), 1.48 (s, 3H), 3.69 (dd, *J* = 8.4, 4.8 Hz, 1H), 3.75 (dd, *J* = 6.6, 3.6 Hz, 1H), 3.99−4.11 (m, 3H), 4.80 (d, *J* = 3.9 Hz, 1H), 5.40 (d, *J* = 6.6 Hz, 1H), 5.89 (d, *J* = 3.6 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 2H), 8.36 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 26.0, 26.4, 59.2, 67.1, 72.2, 77.9, 84.7, 104.4, 109.6, 112.3, 124.1, 128.8, 145.1, 150.1. ESIMS: m/z 467 $[M + Na]^+$. Anal. Calcd for $C_{18}H_{24}N_2O_9S$: C, 48.64; H, 5.44; N, 6.30. Found: C, 48.42; H, 5.36; N, 6.18.

3-Deoxy-3-(*N*-4-nitrobenzenesulfonyl-*N*-methylamino)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (12). To a solution of **11** (2.22 g, 5 mmol) in 25 mL of DMF at 0 °C was added NaH (0.3 g, 60% suspension in oil, 7.5 mmol), and the solution was stirred for 15 min. Then, methyl iodide (0.9 mL, 2 g, 15 mmol) was added and the mixture stirred for 6 h at rt, diluted with H_2O, and extracted with ethyl acetate (3 × 30 mL). The ethyl acetate extract was washed with aqueous $Na_2S_2O_3$, H_2O, dried, concentrated, and column chromatographed over silica gel to afford **12** as a colorless solid. Mp: 168−171 °C. Yield: 1.925 g, 84% (eluent PS/EA 4:1). ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.29 (s, 3H), 1.38 (s, 3H), 1.51 (s, 3H), 2.82 (s, 3H), 3.98−4.16 (m, 4H), 4.46 (d, *J* = 3.6 Hz, 1H), 4.62 (d, *J* = 4.5 Hz, 1H), 5.82 (d, *J* = 3.6 Hz, 1H), 8.12 (d, *J* = 9 Hz, 2H), 8.36 (d, *J* = 9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3, 25.8, 26.3, 26.7, 32.5, 62.9, 67.2, 72.1, 80.3, 82.9, 104.7, 109.6, 111.7, 124.1, 129.0, 144.5, 150.1. ESIMS: m/z 481 $[M + Na]^+$. Anal. Calcd for $C_{19}H_{26}N_2O_9S$: C, 49.77; H, 5.72; N, 6.11. Found: C, 49.59; H, 5.64; N, 6.05.

(3a*R*,5*R*,6*S*,6a*R*)-5-Ethynyl-6-methylamino-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxole (14). A solution of **13** (0.382 g, 1 mmol) in anhydrous MeCN (15 mL) was treated with K_2CO_3 (0.54 g, 4 mmol, 4 equiv) in the presence of PhSH (0.3 mL, 3 mmol, 3 equiv), and the resulting reaction mixture was stirred for 3 h at rt. The

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mixture was diluted with ethyl acetate (20 mL), filtered, evaporated, and column chromatographed over silica gel to afford **14** as a colorless oil. Yield: 0.125 g, 63% (eluent PS/EA 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.50 (s, 3H), 1.68 (brs, 1H), 2.54 (s, 3H), 2.64 (d, J = 1.8 Hz, 1H), 3.14 (d, J = 3.9 Hz, 1H), 4.56 (d, J = 3.9 Hz, 1H), 4.92 (dd, J = 3.6, 2.4 Hz, 1H), 5.90 (d, J = 3.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0, 26.7, 34.6, 67.2, 70.8, 77.6, 77.9, 82.4, 104.9, 111.6. ESIMS: m/z 220 $[M + Na]^+$. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.74; H, 7.53; N, 6.98.

(3a*R*,5*R*,6*S*,6a*R*)-6-(*N*-(2-Azidobenzyl)-*N*-methylamino)-5-ethynyl-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (15). A solution of **14** (0.099 g, 0.5 mmol) in anhydrous CH_3CN (8 mL) at rt was treated with K_2CO_3 (0.27 g, 2 mmol, 4 equiv) and 2-azidobenzyl bromide (0.12 g, 0.6 mmol), and the mixture was stirred for 6 h under N_2 atmosphere. The mixture was filtered, concentrated and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with H_2O, dried (Na_2SO_4), evaporated, and column chromatographed over silica gel to afford **15** as oil. Yield: 0.134 g, 82% (eluent PS/EA, 12:1). $[\alpha]_D^{25}$ = −23.5 (c 0.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.49 (s, 3H), 2.37 (s, 3H), 2.66 (d, J = 2.1 Hz, 1H), 3.43 (d, J = 5.4 Hz, 1H), 3.68 (d, J = 14.1 Hz, 1H), 3.84 (d, J = 14.1 Hz, 1H), 4.79 (d, J = 3.9 Hz, 1H), 4.97 (dd, J = 5.4, 2.1 Hz, 1H), 5.92 (d, J = 3.9 Hz, 1H), 7.10−7.58 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0, 26.7, 38.9, 53.3, 70.6, 71.4, 76.5, 78.3, 81.0, 104.6, 111.1, 118.0, 124.7, 128.2, 129.9, 130.4, 138.2. IR ν_{max} (film): 3286, 2986, 2931, 2857, 2122, 1587 cm^{-1}. ESIMS: m/z 351 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14; N, 17.06. Found: C, 61.98; H, 5.96; N, 16.88.

(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Azidobenzoyl)methylamino-5-ethynyl-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (16). A solution of **14** (0.099 g, 0.5 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated at rt with Et_3N (0.2 mL) and cooled to 0 °C. To it was added dropwise a solution of 2-azidobezoyl chloride (0.11 g, 0.6 mmol) in CH_2Cl_2 (5 mL), and the resulting solution was stirred for 8 h under N_2 atmosphere. The reaction mixture was cooled to 0 °C and diluted with CH_2Cl_2 (10 mL) and washed successively with 2 N HCl (20 mL), H_2O (20 mL), and saturated $NaHCO_3$ (20 mL), dried, evaporated, and column chromatographed over silica gel to afford **16** as a gummy material. Yield: 0.128 g, 75% (eluent PS/EA, 9:1). $[\alpha]_D^{25}$ = −18.6 (c 0.32, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.48 (s, 3H), 2.79 (d-like, 1H), 2.89 (s, 3H), 4.34 (d, J = 3.9 Hz, 1H), 5.08 (d, J = 3.9 Hz, 1H), 5.31 (d, J = 4.2 Hz, 1H), 6.04 (d, J = 3.6 Hz, 1H), 7.06−7.68 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.8, 26.4, 30.9, 65.5, 76.5, 77.9, 82.4, 84.8, 104.9, 112.3, 127.9, 128.4, 129.3, 131.2, 132.6, 132.9, 168.0. IR ν_{max} (film): 3278, 2988, 2936, 2128, 1644, 1478, 1380 cm^{-1}. ESIMS: m/z 365 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.42; H, 5.16; N, 16.19.

(3a*R*,5*R*,6*S*,6a*R*)-6-[(2-azidophenoxy)-5-(2,2-dimethyl[1,3]-dioxolan-4-yl)]-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (19). To a magnetically stirred solution of **1b** (1.04 g, 4 mmol) in dry CH_2Cl_2 (20 mL) at −10 °C was added pyridine (2 mL) followed by trifluoromethanesulfonic anhydride (1.7 g, 1 mL, 6 mmol), and stirring was continued for 1 h under N_2 atmosphere. The mixture was poured into crushed ice and extracted with CH_2Cl_2 (3 × 30 mL). The CH_2Cl_2 extract was washed with H_2O, dried, and concentrated to afford a gummy material which was dissolved in 25 mL of dry CH_3CN. Anhydrous K_2CO_3 (2.8 g, 20 mmol) and 2-azidophenol (1.08 g, 4.8 mmol) were added. The mixture was refluxed for 6 h, filtered, concentrated, diluted with H_2O, and extracted with CH_2Cl_2 (3 × 30 mL). The CH_2Cl_2 extract was washed with H_2O, dried, concentrated, and column chrotographed over silica gel to yield **19** as syrup. Yield: 1.207 g, 80% (eluent PS/EA, 11:1). $[\alpha]_D^{25}$ = −26.3 (c 0.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.33 (s, 3H), 1.44 (s, 3H), 1.54 (s, 3H), 4.11 (dd, J = 11.7, 5.1 Hz, 1H), 4.20 (dd, J = 8.7, 6.3 Hz, 1H), 4.30 (dd, J = 7.8, 3.0 Hz, 1H), 4.47−4.54 (m, 1H), 4.60 (d, J = 3.6 Hz, 1H), 4.76 (d, J = 3.0 Hz, 1H), 5.97 (d, J = 3.6 Hz, 1H), 6.99−7.14 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2, 26.2, 26.6, 26.8, 67.2, 72.1, 80.5, 81.2, 82.1, 105.2, 109.2, 112.1, 114.9, 120.9, 122.5, 125.7, 129.5, 149.3. IR ν_{max} (film): 2987, 2108, 1589, 1496, 1377, 1233, 1162 cm^{-1}. ESIMS: m/z 400 $[M + Na]^+$. Anal. Calcd for $C_{18}H_{23}N_3O_6$: C, 57.29; H, 6.14; N, 11.13. Found: C, 57.05; H, 5.98; N, 11.01.

(3*R*,4*R*)-3-Acetoxy-4-(acetoxymethyl)-[1,5:1,2]-[1,2,3-triazolo]-3,4,6-trihydrobenzo[*c*][1,5]oxazocine (23). Compound **4a** (0.5 mmol) was dissolved in 25 mL of CH_3CN/H_2O (18:5) containing 8% H_2SO_4 and stirred at rt for 24 h. The acidic solution was neutralized with solid $NaHCO_3$ and filtered, and the filtrate was evaporated in vacuo. The residue was dissolved in a minimum volume of MeOH and treated dropwise at 0 °C with an aqueous solution of $NaIO_4$ (128 mg, 0.6 mmol) with stirring for 1 h. Usual workup followed by $NaBH_4$ reduction in MeOH afforded the diol. This was acetylated with Ac_2O (0.3 mL) and pyridine (2 mL) at rt for 12 h to furnish a crude product, which was purified by silica gel flash chromatography to afford **23** as a gummy material. Yield: 0.07 g, 42% (eluent PS/EA, 2:1). $[\alpha]_D^{25}$: +37.8 (c 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (s, 3H), 2.12 (s, 3H), 3.97 (d, J = 6.0 Hz, 1H), 4.08−4.30 (m, 3H), 4.79 (d, J = 11.7 Hz, 1H), 6.12 (s, 1H), 7.57−7.69 (m, 4H), 7.80 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9, 20.7, 62.6, 64.0, 68.1, 77.2, 125.5, 129.9, 130.4, 131.5, 132.3, 133.3, 135.5, 135.8, 168.9, 170.4. IR ν_{max} (film): 2924, 2855, 1742, 1530, 1460, 1372 cm^{-1}. ESI: m/z 354 $[M + Na]^+$. Anal. Calcd for $C_{16}H_{17}N_3O_5$: C, 58.00; H, 5.17; N, 12.68. Found: C, 57.72; H, 5.03; N, 12.36.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **2a**, **4a**, **6**, **8**, **9**, **11**−**15**, **17**−**19**, and **21**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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