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Note

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Ring-opening Reactions of the *N*-4-Nosyl Hough-Richardson Aziridine with Nitrogen Nucleophiles

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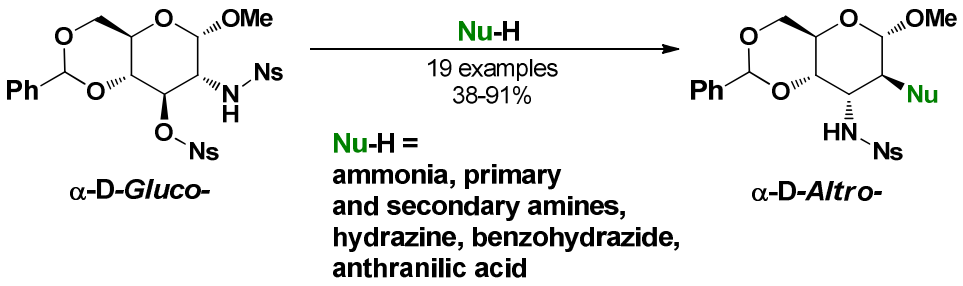
Abstract

Dinosylated α-D-glucopyranoside was directly transformed into α-D-altropyranosides *via in situ* formed *N*-4-nosyl Hough-Richardson aziridine with nitrogen nucleophiles under mild conditions in fair to excellent yields. The scope of the aziridine ring-opening reaction was substantially broadened contrary to the conventional methods introducing solely the azide anion at high temperatures. If necessary, the *N*-4-nosyl Hough-Richardson aziridine can be isolated by filtration in a very good yield and high purity.



Hexopyranosides containing the 2,3-diamino functionality are useful chiral synthetic intermediates in the synthesis of highly functionalized compounds with interesting biological or chemical properties. These intermediates were used directly as chiral ligands in half-sandwich ruthenium, rhodium and iridium complexes with antitumor activity,[1] Palladium and platinum complexes,[2] or molybdenum complexes to catalyze asymmetric allylic alkylations.[3] Further, 2,3-diaminohexopyranosides also served as a key precursor in the synthesis of the glycophospholipid ligand of lipopolysaccharide receptor,[4] chimeric scaffolds with the benzodiazepine moiety,[5] and Weinreb´s advanced intermediate for (-)-Agelastatin A formal total synthesis.[6]

One of the frequently used methods leading to the derivatives of 2,3-diaminohexapyranosides is the ring-opening reaction of the Hough-Richardson aziridine,[7] which is commonly synthesized from D-glucosamine. This valuable chiral intermediate can be transformed by regioselective ring-opening reaction of the strain-loaded three-membered ring into the corresponding diastereoisomers with α-D-*altro*- or α-D-*gluco*- configurations.

The Hough-Richardson aziridine was firstly described by Goodman[8] and, later on, the aziridine ring-formation and ring–opening reaction conditions were particularly studied by Guthrie,[9-11] Hough,[12] Meyer zu Reckendorf,[13-15] Richardson[7,16] and Baker.[17-20]

Formerly, some syntheses were based on precursors with the *altro*- configuration but these starting materials were difficult to access.[21,22] Concurrently, as expected, the syntheses starting from more readily available D-glucosamine derivatives prevailed.

The transformation sequence of aziridine into the corresponding 2,3-diaminohexapyranosides is always predominantly complicated at the ring-opening step with the azide anion by the formation of a mixture of α-D-*altro*- and α-D-*gluco*- diastereoisomers, where the *altro*-configuration is markedly preferred. A further complication can result from the formation of side oxazoline products or *N*-deacylation of aziridine leading to a relatively stable aziridine side-product with regard to the ring-opening reaction.[7,16] Then, the aziridine ring-opening reactivity must be recovered by additional *N*-benzoylation,[4] *N*-alkoxycarbonylation,[6] or methylation resulting in a reactive quaternary salt.[15]

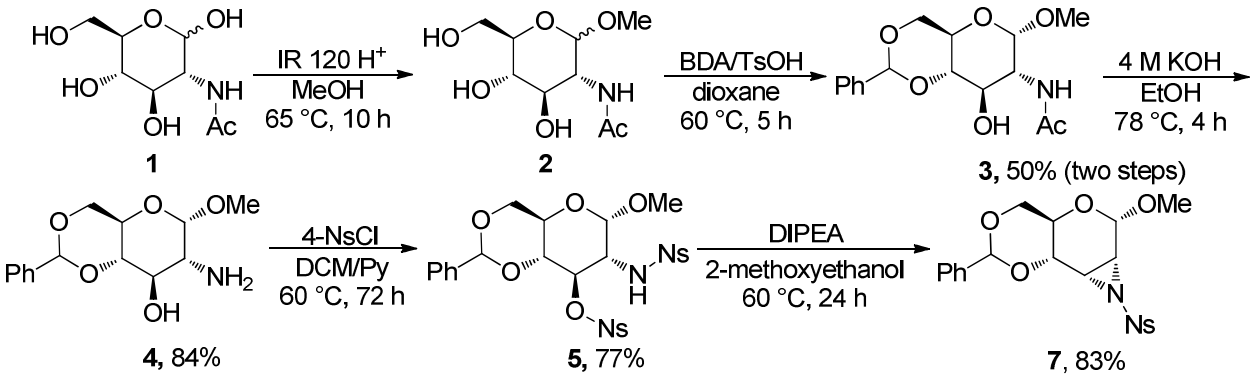
The ratio of diastereoisomers strongly depends on the *N*-substitution of the aziridine ring and the presence of ammonium chloride.[16] For example, the methoxycarbonylated aziridine undergoes the highly regioselective *trans*-diaxial ring-opening reaction with the azide anion leading to the α-D-*altro*-configuration in a very good yield.[6] Contrary, the *N*-benzoylated aziridine usually provided a significant amount of α-D-*gluco*- isomer, which was attributed to the possible formation of an oxazolinium ion intermediate.[14]

The side reactions associated with deacylation can be eliminated by utilization of mesyl or tosyl group in the sulfonamido-sulfonate system which undergoes cyclization to aziridine under mild conditions.[16] However, mesyl or tosyl group is difficult to remove from the resulting sulfonamide functionality after the ring-opening reaction.

Herein we present the first synthesis and the ring-opening reactions of *N*-4-nosyl Hough-Richardson aziridine with nitrogen nucleophiles. The electron-withdrawing effect of the nitro group in this new valuable advanced intermediate brings several significant practical advantages, especially (i) synthesis of aziridine under mild conditions and, if necessary, this intermediate can be isolated by a simple filtration in a very good yield and high purity, (ii) to perform the highly regioselective aziridine ring-opening reactions in absence of ammonium chloride resulting in products preferring the α-D-*altro*- prior to α-D-*gluco*- configuration in a ratio no less than 90:10 under mild reaction conditions utilizing more practical solvent and temperature, (iii) the scope of applicable nitrogen nucleophiles for the ring-opening reaction is substantially broadened, (iv) further modification of nosylamide functionality particularly by *N*-alkylation under classical or Fukuyama protocols,[23] and (v) potential mild deprotection conditions of nosyl group in comparison to the mesyl or tosyl group.

We chose commercially available *N*-acetyl D-glucosamine **1** as a starting compound, which was transformed according to known literature[24,25] to amino sugar **4** with small modifications in isolation process and reaction conditions (Scheme 1). Further, amine **4** on treatment with 4-nitrobenzenesulfonyl chloride provided dinosylated glucosamine 5 in 77% on a multigram scale.

Scheme 1. Synthesis of *N*-4-nosyl Hough-Richardson Aziridine 7



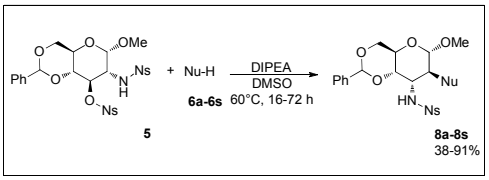
Finally, aziridine **7** was isolated via filtration in good yield and high purity after addition of DIPEA if 2-methoxyethanol was used. Poor solubility of **7** in 2-methoxyethanol obstructed the subsequent aziridine opening. However, this reaction was possible in DMSO. Glucosamine **5** on reaction with nitrogen nucleophile **6** in DIPEA/DMSO at 60°C gave 2,3-diaminoaltropyranoside **8** via in situ formation of aziridine **7** (Table 1).

The assumed mechanism of the aziridine formation involves a transition state of nosylamide **5** in the boat conformation directing the nosyl ester and nosyl amide groups in the *trans*-diaxial relationship. Formation of nosylamide anion and increased departing ability of the adjacent nosylate group was accelerated by the nitro group which led to the fast aziridine ring closure. The α-D-*allo* configuration of aziridine **7** was confirmed by NMR spectra. Subsequent aziridine ring-opening reaction with nitrogen nucleophile **6** resulted in the cleavage of C2-N bond by the Fürst-Plattner rule[26] to provide *trans*-diaxial products **8** in the preferred chair conformation with the α-D-*altro* configuration. The high ring-opening regioselectivity is enforced by the synergy of the conformation lock at C4 and C6 through the benzylidene protection and α-*O*-methyl configuration. Reckendorf observed at the similar Hough-Richardson aziridines a dominant formation of the *gluco* configuration when the C-4 and the C-6 position was acetylated and a mixture of *gluco*, *allo*, and *altro* diastereoisomers when the β-*O*-methyl configuration was introduced.[10,11] Additionally, the α-D-*altro* configuration of **8a** was unequivocally determined by a single crystal X-ray structure analysis (see Supporting Information).

To explore the aziridine ring-opening reactivity scope with regard to the structure diversity of a nitrogen nucleophile we started a set of reactions (Table 1). Since the aziridine ring closure is much faster than potential nosyl ester substitution/hydrolysis and subsequent ring-opening

reaction, we utilized the direct synthesis of α-D-altropyranosides **8** from dinosylated pyranoside **5** via *in situ* formed aziridine **7**.

Table 1. Reactions of dinosylated glucosamine 5 with nitrogen nucleophiles (6a-6s)



6a-6s **5** **8a-8s** 38-91%

Entry	Nu-H	Product	Time	Yield[a]
1	NaN_3 **6a**	**8a**	16h	72%
2	NH_3/H_2O **6b**	**8b**	16h	91%
3	$PhCH_2NH_2$ **6c**	**8c**	24h	59%
4	$MeNH_2$ **6d**	**8d**	24h	55%
5	$H_2N(CH_2)_4NH_2$ **6e**	**8e**	24h	79%
6	NH_2-cyclohexyl **6f**	**8f**	16h	68%
7	$HOCH_2CH_2NH_2$ **6g**	**8g**	16h	87%
8	$HO(CH_2)_3NH_2$ **6h**	**8h**	16h	59%
9	$HOC_2H_4OC_2H_4NH_2$ **6i**	**8i**	24h	80%
10	alaninol **6j**	**8j**	48h	51%
11	**6k**	**8k**	72h	47%
12	$N_2H_4.H_2O$ **6l**	**8l**	24h	68%
13	$H_2N(CH_2)_2NH_2$ **6m**	**8m**	24h	47%
14	piperidine **6n**	**8n**	24h	73%
15	morpholine **6o**	**8o**	24h	69%
16	prolinol **6p**	**8p**	16h	68%
17	prolinol **6q**	**8q**	16h	56%
18	anthranilic acid **6r**	**8r**	24h	56%
19	benzoylhydrazine **6s**	**8s**	72h	38%

[a] Isolated yields

Dinosylated amine **5** on treatment with sodium azide **6a** provided altropyranoside **8a** in good yield (Entry 1). In comparison to the related *N*-substituted Hough-Richardson aziridines, the ring-opening reaction was performed at 60 °C, not at conventional temperatures in the range of 120-150°C.[6,10,11,14] The increased ring-opening reactivity induced by the nosyl group directly afforded amine **8b** with aqueous ammonia in the excellent yield (Entry 2). In comparison to the classical protocols, involving the aziridine ring-opening reaction with the azide anion and essential reduction step,[6] this methodology allowed substantial simplification.

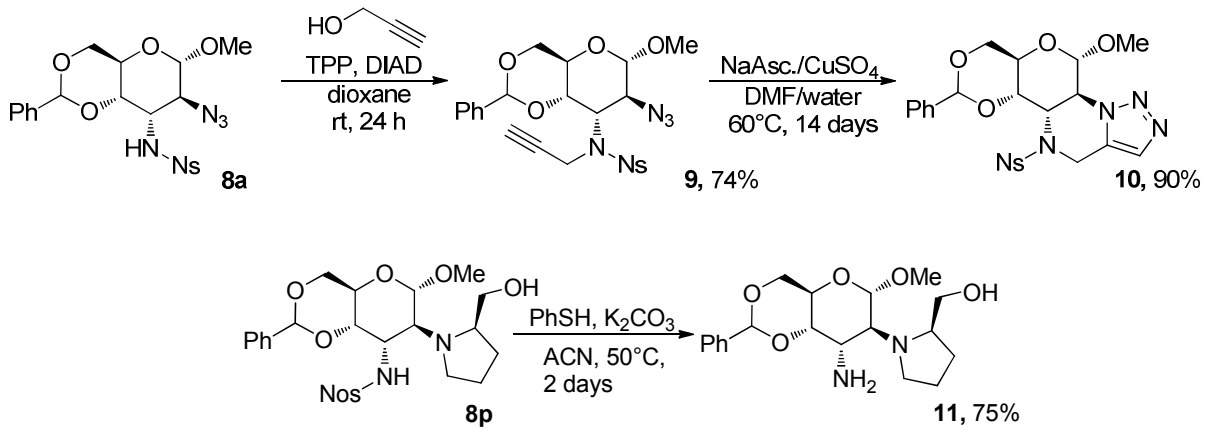
Monofunctional primary amines **6c-f** provided **8c-f** in fair to good yields (Entry 3-6). The prolonged reaction time was utilized in the reactions with **6c-e**. Later on, the method was extended to aminoalcohols **6g-j** to yield **8g-j** from fair to very good yields as well (Entry 7-10). The reaction time was necessary to extend to 48 h with amine **6j**. Further increase of steric hindrance of **6k** necessitated an extension of reaction time to 72 h to give **8k** (Entry 11). The yield was predominantly reduced by the isolation process. Preliminary attempts to cyclize nosylamides **8g-j** under Fukuyama-Mitsunobu conditions [27] failed. We assumed that prerequisite change of the altropyranoside ring from the chair to boat conformation did not occur and, consequently, both diaxially oriented reacting groups were not redirected to the equatorial conformation.

Other bifunctional nucleophiles, hydrazine **6l** and ethylenediamine **6m**, provided fair yields (Entry 12 and 13). Besides primary amines, the reactivity of secondary amines **6n-q** was also tested to give **8n-q** from fair to good yields (Entry 14-17). Preliminary attempts to carry out the ring-opening reactions with anilines afforded unsatisfactory yields particularly due to low reactivity and difficulties in the isolation process. The exception was anthranilic acid **6r** providing **8r** in fair yield (Entry 18). In connection with the good ring-opening reactivity with

hydrazine (Entry 12), we also tried benzohydrazide **6s** to obtain **8s** in a poor yield which was predominantly caused by problematic separation and decomposition during the reaction (Entry 19).

To demonstrate further possible modification of nosylamide group at C3 after the ring-opening reaction, azide **8a** was alkylated with propargyl alcohol under Fukuyama-Mitsunobu conditions to give **9** (Scheme 2). Subsequent intramolecular copper catalyzed 1,3-dipolar cycloaddition[28] led to novel interesting scaffold **10** containing the 1,2,3-triazolopiperazine moiety. Similar scaffolds have been reported as glycosidase inhibitors. [29] The 1,3-dipolar cycloaddition was completed in 14 days at 60 °C. Higher temperature at 80 °C immensely reduced the reaction time to 3 days. The rate of the cycloaddition step was very likely associated with the conformation change of the pyranoside ring from chair to twist-boat which redirects both reacting groups into the equatorial conformation. The evidence of the twist-boat conformation was strongly supported by the vicinal coupling constants of the hydrogen signals at C1, C2, C3, and C4. These peaks were assigned by the COSY spectrum. The observed coupling of the anomeric hydrogen was 7.3 Hz. This value is typical for an axial-axial coupling. Furthermore, the signal of the hydrogen at C2 was split into the double doublet by 7.3 and 12.2 Hz and the hydrogen at C4 showed a triplet with the coupling constant 8.9 Hz. The triplet of the hydrogen at C3 was overlapped with the hydrogen signal at C5. If we consider the chair conformation with the *altro* configuration the vicinal coupling constants should be lower because all hydrogens at C1, C2, and C3 should be equatorially oriented.

Scheme 2. Synthesis of triazolopiperazine 10 and denosylation of 8p resulting in 11



The second example illustrates denosylation conditions applied on **8p** to provide amine **11** under mild conditions.

In conclusion, the synthesis of new *N*-4-nosyl Hough-Richardson aziridine has been described. We demonstrated that this valuable advanced intermediate can be transformed by highly regioselective *trans*-diaxial ring-opening reactions with nitrogen nucleophiles into the corresponding α-D-altropyranosides. The increased ring-opening reactivity induced by the nosyl group allowed direct synthesis of the aminoaltropyranoside with aqueous ammonia in the excellent yield in comparison to the conventional methods based on the ring-opening reaction with azide anion and subsequent reduction of the azide functionality. Sodium azide, primary and secondary amines, hydrazine, and benzohydrazide provided altropyranosides in fair to very good yield.

Experimental part

General:

All starting materials are commercially available. Commercial reagents were used without any purification. Melting points were determined with a Boetius stage apparatus and are uncorrected. Flash column chromatography was performed on silica gel (pore size 60 Å, 40–63 μm particle size). Purification of compounds was performed with semi-preparative HPLC, column specifications: particle size 5 μm, inner diameter 20 mm, packing C18, Length 100 mm. Mobile phase was A=CH_3CN, B=water (gradient elution, A=60-90-90%, 0-5-10 min). Reactions were monitored by LC/MS analyses with a UHPLC-MS system consisting of a UHPLC chromatography with photodiode array detector and a triple quadrupole mass spectrometer using a C18 column at 30 °C and flow rate of 800 mL/min. The mobile phase was (A; 0.01 M ammonium acetate in water) and (B; CH_3CN), linearly programmed from 10 to 80% B over 2.5 min, kept for 1.5 min. The column was reequilibrated with 10% B for 1 min. The APCI source operated at a discharge current of 5 mA, a vaporizer temperature of 400 °C, and a capillary temperature of 200 °C. High-resolution mass spectrometer based on the orbitrap mass analyzer was equipped with Heated Electrospray Ionization (HESI). The spectrometer was tuned to obtain a maximum response for m/z 70-700. The source parameters were set to the following values: HESI temperature 30 °C, spray voltage +3.5kV, -3kV; transfer capillary temperature 270 °C, sheath gas/aux gas (nitrogen) flow rates 35/10. The HRMS spectra of target peaks allowed evaluating their elemental composition with less than 3 ppm difference between experimental and theoretically calculated value. The ^1H and ^{13}C NMR spectra were measured in DMSO-d_6, $CDCl_3$ or DMF-d_7 at 25 °C using 400 MHz spectrometer.

N-((2S,3R,4R,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)-2-methoxytetrahydro-2H-pyran-3-yl)acetamide ***2.***[24,25] *N*-acetyl D-glucosamine **1** (15.0 g, 67.8 mmol) was dissolved in dry methanol (150 mL) and ion exchange resin Amberlite IR 120 hydrogen form (IR 120 H^+) (15.0 g, dried in 130 °C for 8 h) was added. The mixture was refluxed for 10 h. Then the mixture was filtrated and the solvent was removed under reduced pressure. The residue (13.2 g) was directly used for the preparation of compound **3** without further purification.

N-((4aR,6S,7R,8R,8aS)-8-hydroxy-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)acetamide ***3***.[24,25] Pyranoside **2** (13.2 g) was dissolved in 1,4-dioxane (400 mL), then benzaldehyde dimethyl acetal (BDA) (16.8 mL, 112.0 mmol) and $TsOH.H_2O$ (2.142 g, 11.2

mmol) was added. The mixture was heated under stirring at 60 °C for 5 h. After the reaction was finished, the solvent was removed under reduced pressure and the crude product was recrystallized from ethyl acetate (900 mL) to afford **3** in overall yield 50% (9.0 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.85 (s, 3 H), 3.29 (s, 3 H), 3.48 (t, *J*=8.8 Hz, 1 H), 3.59 (dt, *J*=9.9, 4.9 Hz, 1 H), 3.65 (t, *J*=8.8 Hz, 1 H), 3.74 (t, *J*=9.9 Hz, 1 H), 3.80-3.87 (m, 1 H), 4.17 (dd, *J*=10.1, 4.9 Hz, 1 H), 4.61 (d, *J*=3.6 Hz, 1 H), 5.12 (br. s, 1H), 5.61 (s, 1 H), 7.35-7.40 (m, 3 H), 7.43-7.48 (m, 2 H), 7.90 (d, *J*=8.3 Hz, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.6, 54.1, 54.7, 62.5, 67.4, 68.0, 82.0, 98.7, 100.9, 126.4, 128.0, 128.9, 137.8, 169.5.

(4aR,6S,7R,8R,8aS)-7-amino-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-ol ***4.***[24,25] *N*-acetylated sugar **3** (9.0 g, 27.9 mmol) was added to a solution of 4 M KOH (50.4 g, 900.0 mmol) in EtOH (225 mL) in one portion and mixture was refluxed for 4 h. After starting material was consumed, one third of ethanol was removed under reduced pressure. CH_2Cl_2 (225 mL) was added and the mixture was washed with water (2x350 mL) and brine (100 mL). Organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified on silica gel chromatography ($CHCl_3$/MeOH = 10/1) to give **4** in yield 84% (6.6 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.41 (br. s, 2 H), 2.52-2.56 (m, 1 H), 3.32 (s, 3 H), 3.36-3.38 (m, 1 H), 3.38-3.40 (m, 1 H), 3.5-3.64 (m, 1 H), 3.71 (t, J=10.1 Hz, 1 H), 4.16 (dd, J=9.9, 4.7 Hz, 1 H), 4.62 (d, J=3.4 Hz, 1 H), 5.23 (br. s, 1 H), 5.58 (s, 1 H), 7.35-7.40 (m, 3 H), 7.42-7.48 (m, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 54.8, 57.1, 62.8, 68.2, 71.5, 81.6, 100.8, 100.9, 126.4, 128.0, 128.8, 137.9.

(4aR,6S,7R,8R,8aR)-6-methoxy-7-(4-nitrophenylsulfonamido)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl 4-nitrobenzenesulfonate ***5.*** *N*-deacylated sugar **4** (6.8 g, 24.2 mmol) was

dissolved in a mixture of CH_2Cl_2/pyridine (320/160 mL) and the reaction flask was cooled at 0°C with an ice bath. Subsequently, 4-nosyl chloride (4-NsCl) (4.2 equiv, 22.5 g, 101.6 mmol) was added and the mixture was heated at 60 °C. After 3 days, the solvents were removed under reduced pressure; the residue was dissolved in EtOAc (700 mL) and washed with water (3x700 mL). The organic layer was washed with brine (300 mL) and dried with $MgSO_4$. The crude product was purified on silica gel chromatography ($CHCl_3$/MeOH = 100/1) to give **5** in yield 77% (12.0 g) as a pale yellow solid, mp. 149-151 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.17 (s, 3 H), 3.56-3.6 (m, 1 H), 3.62-3.69 (m, 1 H), 3.82-3.86 (m, 1 H), 3.87-3.91 (m, 1 H), 4.15 (dd, *J*=4.2, 1.0 Hz, 1 H), 4.37 (d, *J*=3.6 Hz, 1 H), 4.78 (t, *J*=9.9 Hz, 1 H), 5.32 (s, 1 H), 7.10-7,16 (m, 2 H), 7.20-7.32 (m, 3 H), 7.87-7.97 (m, 4 H), 8.09 (dt, *J*=8.8, 2.6 Hz, 2 H), 8.35 (dt, *J*=8.8, 2.1 Hz, 2 H), 8.94 (d, *J*=9.9 Hz, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 55.2, 55.9, 62.3, 67.5, 77.9, 79.4, 99.1, 100.8, 124.0, 124.5, 126.1, 127.8, 127.9, 128.7, 129.1, 136.6, 142.2, 147.4, 149.5, 149.6; HRMS (Orbitrap) *m/z* [M - H]$^-$ calcd for $C_{26}H_{25}N_3O_{13}S_2$ did not found; we found m/z [M – -SO_2-C_6H_4-NO_2 - H]$^-$ calcd for $C_{20}H_{21}N_2O_9S$ 465.0962, found 465.0967; $[\alpha]_D^{23}$ + 18 (c 1.41, CH_2Cl_2).

(4aR,6S,6aR,7aS,7bS)-6-methoxy-7-((4-nitrophenyl)sulfonyl)-2-phenylhexahydro-4H-[1,3]dioxino[4',5':5,6]pyrano[3,4-b]azirine ***7.*** Compound **5** (400.0 mg, 0.62 mmol) was suspended in 2-methoxyethanol (12 mL) and DIPEA (0.332 mL, 1.91 mmol) was added. The mixture was heated to 60 °C and stirred for 24 h. Then the precipitate was filtered off and washed with a small portion of 2-methoxy ethanol. Compound **7** was obtained in 83% yield (229.0 mg) as a yellow solid, mp. 260-262 °C. ^{1}H NMR (400 MHz, DMF-d_7) δ 3.37 (s, 3 H), 3.59 (dd, *J*=7.3, 2.6 Hz, 1 H), 3.75 (dd, *J*=10.9, 9.3 Hz, 1 H), 3.77-3.84 (m, 1 H), 3.86 (dd, *J*=7.3, 4.2 Hz, 1 H),

4.08 (dd, *J*=8.8, 2.6 Hz, 1 H), 4.15 (dd, *J*=9.6, 4.4 Hz, 1 H), 5.15 (d, *J*=4.2 Hz, 1 H), 5.70 (s, 1 H), 7.24-7.42 (m, 5 H), 8.33-8.39 (m, 2 H), 8.50-8.56 (m, 2 H); ^{13}C NMR (DMF-d_7) δ 40.1, 42.3, 55.3, 60.9, 68.5, 74.7, 94.2, 101.9, 124.9, 126.5, 128.2, 129.3, 129.9, 138.2, 143.9, 151.1; HRMS (Orbitrap) *m/z* $[M + NH_4]^+$ calcd for $C_{20}H_{24}N_3O_8S$ 466.1279, found 466.1279; $[\alpha]_D^{23}$ + 108 (c 0.56, CH_2Cl_2).

General Procedure. Direct synthesis of altropyranosides **8** from **5** via *in situ* formed aziridine **7**

The reaction was carried out at a 0.15 mmol scale unless otherwise noted. Compound **5** (0.15 mmol, 100.0 mg) was dissolved in DMSO (3 mL) and DIPEA (0.083 mL, 0.48 mmol) was added. The mixture was stirred for 5 minutes, then nucleophile **6** (2.1 equiv) was added and the mixture was heated to 60 °C. After the reaction was finished, CH_2Cl_2 (10 mL) and water (10 mL) was added and the organic layer was washed with water (3x10 mL), brine (10 mL), and dried with $MgSO_4$. The crude product was purified by silica gel chromatography using chloroform/methanol as solvents.

N-((4aR,6S,7S,8S,8aS)-7-azido-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8a.*** Following the general procedure on a 0.6 mmol scale, the reaction was heated with sodium azide **6a** for 16 h to afford **8a** in 72% yield (212.0 mg) as a pale yellow solid (purification on silica gel chromatography was not necessary), mp. 190-191 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.35 (s, 3 H), 3.62 (t, J=10.1 Hz, 1 H), 3.81 (br. s., 1 H), 3.86 (dd, J=9.9, 4.7 Hz, 1 H), 3.99 (dd, J=2.6, 1.0 Hz, 1 H), 4.03 - 4.13 (m, 1 H), 4.17 (dd, J=9.9, 5.2 Hz, 1 H), 4.74 (s, 1 H), 5.50 (s, 1 H), 7.04 - 7.13 (m, 2 H), 7.17 - 7.30 (m, 3 H), 7.89 - 8.01 (m, 4 H), 8.40 (br. s., 1 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 51.8, 54.9, 58.2, 62.5, 68.1, 72.5, 97.9, 100.8,

123.7, 126.1, 127.6, 128.0, 128.7, 137.1, 146.8, 148.8; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{20}H_{22}N_5O_8S$ 492.1184, found 492.1182; $[\alpha]_D^{23}$ + 96 (c 0.67, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-7-amino-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8b.*** Following the general procedure, the reaction was heated with concentrated aqueous ammonia **6b** (25% in water) for 16 h to afford **8b** in 91% yield (65.0 mg) as a pale yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =30/1), mp. 132-134 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.95 (br. s., 2 H), 3.00 (d, J=1.6 Hz, 1 H), 3.29 (s, 3 H), 3.64 (t, J=9.9 Hz, 1 H), 3.67 - 3.73 (m, 1 H), 3.92 - 4.09 (m, 2 H), 4.15 (dd, J=10.1, 4.9 Hz, 1 H), 4.45 (s, 1 H), 5.44 (s, 1 H), 7.09 (dd, J=8.3, 1.6 Hz, 2 H), 7.16 - 7.32 (m, 3 H), 7.95 (s, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 54.6, 54.6, 55.6, 58.5, 68.4, 72.8, 100.8, 102.1, 123.6, 126.0, 127.5, 128.0, 128.6, 137.3, 147.4, 148.7; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{20}H_{24}N_3O_8S$ 466.1279, found 466.1280; $[\alpha]_D^{23}$ + 56 (c 0.75, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-7-(benzylamino)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8c.*** Following the general procedure on a 0.3 mmol scale, the reaction was heated with benzylamine **6c** for 24 h to afford **8c** in 59% yield (100.0 mg) as a pale yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =100/1), mp. 175-177 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.56 (q, J=6.1 Hz, 1 H,), 2.73 (d, J=4.2 Hz, 1 H), 3.26 (s, 3 H), 3.64 (t, J=10.1 Hz, 1 H), 3.76 (qd, J=14.4, 5.7 Hz, 2 H), 3.89 (br. s., 1 H), 3.97 - 4.05 (m, 1 H), 4.08 (dd, J=9.9, 4.7 Hz, 1 H), 4.16 (dd, J=10.1, 4.9 Hz, 1 H), 4.59 (s, 1 H), 5.47 (s, 1 H), 7.09 - 7.15 (m, 2 H), 7.19 - 7.28 (m, 3 H), 7.28 - 7.36 (m, 5 H), 7.86 (br. s, 1 H), 7.90 - 7.96 (m, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 50.7, 51.6, 54.5, 58.5, 60.5, 68.4, 73.2, 100.1, 100.9, 123.6, 126.1, 126.7, 127.6, 128.0, 128.1, 128.6, 137.4, 140.3, 140.3, 147.4, 148.7; HRMS

(Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{27}H_{30}N_3O_8S$ 556.1748, found 556.1750; $[\alpha]_D^{23}$ + 47 (c 0.4, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-6-methoxy-7-(methylamino)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8d.*** Following the general procedure, the reaction was heated with methylamine **6d** for 24 h to afford **8d** in 55% yield (41.0 mg) as a pale yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =50/1), mp. 187-189 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.23 (br. s., 1 H), 2.32 (s, 3 H), 2.65 (d, J=2.1 Hz, 1 H), 3.30 (s, 3 H), 3.60 (t, J=9.6 Hz, 1 H), 3.82 (br. s., 1 H), 3.92 - 4.06 (m, 2 H), 4.14 (dd, J=10.1, 4.4 Hz, 1 H), 4.57 (s, 1 H), 5.43 (s, 1 H), 7.04 - 7.14 (m, 2 H), 7.16 - 7.29 (m, 3 H), 7.89 (br. d, J=7.8 Hz, 1 H), 7.94 - 7.98 (m, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 34.6, 51.1, 54.6, 58.5, 64.1, 68.4, 73.2, 99.8, 100.9, 123.7, 126.1, 127.6, 128.0, 128.6, 137.3, 147.3, 148.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3 H) 3.06 (d, J=2.1 Hz, 1 H), 3.48 (s, 3 H), 3.73 (t, J=10.4 Hz, 1 H), 3.87 (td, J=9.9, 4.7 Hz, 1 H), 3.94 (dd, J=9.9, 4.2 Hz, 1 H), 4.11 (m, 1 H), 4.26 (dd, J=10.4, 4.7 Hz, 1 H), 4.72 (s, 1 H), 5.43 (s, 1 H), 6.05 (d, J=9.3 Hz, 1 H), 7.12 (m, 2 H), 7.25 (m, 2 H), 7.33 (m, 1 H), 7.79 (m, 2 H), 7.89 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 34.7, 55.9, 59.6, 63.0, 68.9, 74.1, 77.2, 100.8, 101.8, 123.5, 125.8, 128.0, 128.2, 129.3, 136.6, 146.6, 149.3; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{21}H_{26}N_3O_8S$ 480.1435, found 480.1436; $[\alpha]_D^{23}$ + 70 (c 0.69, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-6-methoxy-7-(pentylamino)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8e.*** Following the general procedure, the reaction was heated with pentylamine **6e** for 24 h to afford **8e** in 79% yield (65.0 mg) as an amorphous yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =80/1). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 0.87 (t, J=6.7 Hz, 3 H), 1.20 - 1.33 (m, 5 H), 1.33 - 1.42 (m, 2 H), 1.88 (br. s., 1 H), 2.53 - 2.59 (m, 1 H), 2.73 (br. s, 1 H), 3.30 (s, 3 H), 3.62 (t, J=9.6 Hz, 1 H), 3.78 (br. d, J=8.3 Hz,

1 H), 3.95 - 4.03 (m, 2 H), 4.14 (dd, J=9.3, 3.6 Hz, 1 H), 4.57 (s, 1 H), 5.45 (s, 1 H), 7.06 - 7.15 (m, 2 H), 7.18 - 7.29 (m, 3 H), 7.89 (d, J=9.3 Hz, 1 H), 7.96 (s, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 14.0, 22.1, 28.9, 29.2, 47.7, 51.7, 54.5, 58.4, 62.0, 68.4, 73.1, 100.2, 100.8, 123.6, 126.1, 127.6, 128.0, 128.6, 137.3, 147.3, 148.7; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{25}H_{34}N_3O_8S$ 536.2061, found 536.2064; $[\alpha]_D^{23}$ + 59 (c 0.73, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-7-(cyclohexylamino)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8f.*** Following the general procedure, the reaction was heated with cyclohexylamine **6f** for 16 h to afford **8f** in 68% yield (57.0 mg) as a pale yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =80/1), mp. 176-178 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 0.87 - 1.04 (m, 2 H), 1.06 - 1.24 (m, 3 H), 1.49 - 1.59 (m, 1 H), 1.60 - 1.69 (m, 3 H), 1.69 - 1.82 (m, 2 H), 2.35 - 2.46 (m, 1 H), 2.84 (d, J=2.6 Hz, 1 H), 3.29 (s, 3 H), 3.64 (t, J=9.6 Hz, 1 H), 3.67 - 3.72 (m, 1 H), 3.92 - 4.05 (m, 2 H), 4.14 (dd, J=9.9, 4.2 Hz, 1 H), 4.52 (s, 1 H), 5.47 (s, 1 H), 7.05 - 7.18 (m, 2 H), 7.18 - 7.31 (m, 3 H), 7.89 (br. d, J=8.3 Hz, 1 H), 7.93-8.01 (m, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 24.3, 25.7, 29.7, 32.5, 33.2, 52.6, 54.4, 54.5, 58.4, 58.4, 68.3, 73.1, 100.8, 101.0, 123.7, 126.1, 127.6, 128.1, 128.6, 137.4, 147.3, 148.7; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{26}H_{34}N_3O_8S$ 548.2061, found 548.2065; $[\alpha]_D^{23}$ + 57 (c 0.4, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-7-((2-hydroxyethyl)amino)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8g.*** Following the general procedure on a 0.6 mmol scale, the reaction was heated with 2-aminoethanol **6g** for 16 h to afford **8g** in 87% yield (272.0 mg) as a pale yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =30/1), mp. 203-204 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.93 (br. s., 1 H), 2.57 - 2.72 (m, 2 H), 2.78 (d, J=1.6 Hz, 1 H), 3.30 (s, 3 H), 3.39 - 3.47 (m, 2 H), 3.62 (t, J=9.9 Hz, 1 H), 3.75 -

3.84 (m, 1 H), 3.92 - 4.07 (m, 2 H), 4.15 (dd, J=10.1, 4.9 Hz, 1 H), 4.52 (t, J=5.2 Hz, 1 H), 4.59 (s, 1 H), 5.45 (s, 1 H), 7.10 (dd, J=8.0, 1.3 Hz, 2 H), 7.15 - 7.31 (m, 3 H), 7.92 (s, 1 H), 7.94 - 7.97 (m, 4 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 50.2, 51.8, 54.6, 58.4, 60.4, 62.1, 68.4, 73.2, 100.3, 100.8, 123.6, 126.1, 127.5, 128.0, 128.6, 137.3, 147.3, 148.7; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{22}H_{28}N_3O_9S$ 510.1541, found 510.1543; $[\alpha]_D^{23}$ + 56 (c 0.62, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-7-((3-hydroxypropyl)amino)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8h.*** Following the general procedure on a 0.6 mmol scale, the reaction was heated with 3-aminopropanol **6h** for 16 h affording **8h** in 59% yield (188.0 mg) as a pale yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =40/1), mp. 171-173 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.54 (quin, J=6.6 Hz, 2 H), 1.84 - 1.98 (m, 1 H), 2.53 - 2.70 (m, 2 H), 2.74 (br. s., 1 H), 3.30 (s, 3 H), 3.45 (dd, J=6.2, 4.7 Hz, 2 H), 3.62 (t, J=9.6 Hz, 1 H), 3.75 - 3.84 (m, 1 H), 3.93 - 4.06 (m, 2 H), 4.15 (dd, J=9.6, 4.4 Hz, 1 H), 4.41 (t, J=4.9 Hz, 1 H), 4.57 (s, 1 H), 5.45 (s, 1 H), 7.10 (dd, J=8.0, 1.3 Hz, 2 H), 7.17 - 7.28 (m, 3 H), 7.89 (d, J=8.8 Hz, 1 H), 7.96 (s, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 33.3, 45.6, 52.2, 55.1, 58.9, 59.6, 62.7, 68.9, 73.7, 100.8, 101.4, 124.2, 126.6, 128.1, 128.5, 129.1, 137.9, 147.9, 149.3; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{23}H_{30}N_3O_9S$ 524.1697, found 524.1699; $[\alpha]_D^{23}$ + 60 (c 0.59, CH_2Cl_2).

N-(8-((2-(2-hydroxyethoxy)ethyl)amino)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)-4-nitrobenzenesulfonamide ***8i****.* Following the general procedure, the reaction was heated with aminoalcohol **6i** for 24 h to afford **8i** in 80% yield (68.0 mg) as a pale yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =20/1), mp. 68-70 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) d ppm 1.98 (br. s., 1 H), 2.74 (d, J=4.7 Hz, 2 H), 2.79 (br. s., 1 H), 3.30 (s, 3 H), 3.43 (m, 4 H), 3.50 (q, J=5.2 Hz, 2 H), 3.62 (t, J=9.9 Hz, 1 H), 3.80 (m, 1 H), 4.00

(m, 2 H), 4.15 (dd, J=10.1, 4.4 Hz, 1 H), 4.57 (t, J=5.2 Hz, 1 H), 4.59 (s, 1 H), 5.46 (s, 1 H), 7.10 (m, 2 H), 7.24 (m, 3 H), 7.90 (d, J=9.3 Hz, 1 H), 7.96 (s, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) d ppm 47.2, 51.8, 54.5, 58.4, 60.2, 62.1, 68.3, 69.8, 72.1, 73.1, 100.2, 100.8, 123.6, 126.1, 127.5, 128.0, 128.5, 137.3, 147.3, 148.7; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{24}H_{32}N_3O_{10}S$ 554.1803, found 554.1806; $[\alpha]_D^{23}$ + 50 (c 0.56, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-7-(((S)-1-hydroxypropan-2-yl)amino)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8j.*** Following the general procedure, the reaction was heated with *S*-alaninol **6j** for 48 h to afford **8j** in 51% yield (41.3 mg) as a pale yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =40/1), mp. 195-197 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 0.91 (d, J=6.2 Hz, 3 H), 1.73 - 1.81 (m, 1 H), 2.69 - 2.78 (m, 1 H), 2.91 (br. d, J=6.2 Hz, 1 H), 3.19 - 3.27 (m, 2 H), 3.31 (s, 3 H), 3.62 (t, J=10.1 Hz, 1 H), 3.77 (br. s., 1 H), 3.88 - 3.95 (m, 1 H), 3.99 - 4.07 (m, 1 H), 4.15 (dd, J=10.1, 4.9 Hz, 1 H), 4.54 (s, 1 H), 4.60 (t, J=5.7 Hz, 1 H), 5.45 (s, 1 H), 7.09 - 7.15 (m, 2 H), 7.19 - 7.30 (m, 3 H), 7.94 - 7.95 (m, 1 H), 7.96 (s, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 16.9, 51.2, 52.3, 54.5, 58.4, 58.6, 65.6, 68.4, 73.1, 100.9, 101.5, 123.6, 126.1, 127.6, 128.0, 128.6, 137.3, 147.3, 148.7; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{23}H_{30}N_3O_9S$ 524.1697, found 524.1700; $[\alpha]_D^{23}$ + 79 (c 0.55, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-7-(((4aS,6R,7S,8S,8aR)-8-hydroxy-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)amino)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8k.*** Following the general procedure on a 0.6 mmol scale, the reaction was heated with glucosamine **6k** for 72 h to afford **8k** in 47% yield (212.0 mg) as a pale yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =80/1), mp. 130-132 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.77

(t, J=6.7 Hz, 1 H), 2.56 - 2.64 (m, 1 H), 2.98 (dd, J=6.0, 2.3 Hz, 1 H), 3.32 (s, 3 H), 3.33 (s, 3 H), 3.44 - 3.52 (m, 2 H), 3.53 - 3.68 (m, 2 H), 3.74 (t, J=9.9 Hz, 1 H), 3.95 (br. s., 1 H), 3.97 - 4.10 (m, 2 H), 4.12 - 4.22 (m, 2 H), 4.59 (s, 1 H), 4.73 (d, J=3.6 Hz, 1 H), 5.28 (d, J=4.7 Hz, 1 H), 5.44 (s, 1 H), 5.63 (s, 1 H), 7.07 - 7.13 (m, 2 H), 7.18 - 7.27 (m, 3 H), 7.35 - 7.40 (m, 3 H), 7.43 - 7.48 (m, 2 H), 7.83 (br. s., 1 H), 7.99 (s, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 51.6, 54.6, 54.9, 58.5, 59.6, 61.3, 62.4, 68.1, 68.4, 68.6, 73.0, 79.2, 81.7, 98.9, 100.8, 100.9, 101.2, 123.6, 126.1, 126.4, 127.5, 128.0, 128.6, 128.8, 137.4, 137.8, 147.4, 148.7; HRMS (Orbitrap) *m/z* [M + H]$^+$ calcd for $C_{34}H_{40}N_3O_{13}S$ 730.2276, found 730.2276; $[\alpha]_D^{23}$ + 83 (c 0.79, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-7-hydrazinyl-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8l.*** Following the general procedure, the reaction was heated with hydrazine hydrate **6l** for 24 h to afford **8l** in 68% yield (50.0 mg) as a pale yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =40/1), mp. 168-170 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.81 (d, J=2.1 Hz, 1 H), 3.30 (s, 3 H), 3.59 (t, J=9.9 Hz, 1 H), 3.90 (dd, J=4.7 Hz, 2 H), 3.96 - 4.04 (m, 1 H), 4.05 - 4.11 (m, 1 H), 4.14 (dd, J=10.1, 4.9 Hz, 1 H), 4.66 (s, 1 H), 5.43 (s, 1 H), 7.00 - 7.15 (m, 2 H), 7.16 - 7.29 (m, 3 H), 7.74 (br. s., 1 H), 7.96 (s, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 50.8, 55.2, 59.0, 67.0, 69.0, 74.0, 99.0, 101.3, 124.1, 126.6, 128.1, 128.5, 129.1, 137.9, 148.0, 149.2; HRMS (Orbitrap) *m/z* [M + H]$^+$ calcd for $C_{20}H_{25}N_4O_8S$ 481.1388, found 481.1389; $[\alpha]_D^{23}$ + 65 (c 0.72, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-7-((2-aminoethyl)amino)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8m.*** Following the general procedure except using semipreparative HPLC for purification, the reaction was heated with ethylene diamine **6m** for 24 h to afford **8m** in 47% yield (37.0 mg) as a pale yellow solid, mp. 152-154 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.59 - 2.74 (m, 4 H), 2.75 (d, J=1.6 Hz, 1 H), 3.30 (s, 3 H), 3.62 (t, J=9.9 Hz,

1 H), 3.80 (br. s., 1 H), 3.96 - 4.06 (m, 2 H), 4.12 - 4.19 (m, 1 H), 4.59 (s, 1 H), 5.44 (s, 1 H), 7.02 - 7.17 (m, 2 H), 7.18 - 7.31 (m, 3 H), 7.96 (s, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 40.6, 48.9, 52.1, 55.1, 58.9, 62.5, 68.9, 73.6, 100.9, 101.4, 124.2, 126.6, 128.1, 128.5, 129.1, 137.9, 147.9, 149.2; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{22}H_{29}N_4O_8S$ 509.1701, found 509.1703; $[\alpha]_D^{23}$ + 59 (c 0.58, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-6-methoxy-2-phenyl-7-(piperidin-1-yl)hexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8n.*** Following the general procedure, the reaction was heated with piperidine **6n** for 24 h to afford **8n** in 73% yield (60.0 mg) as a pale yellow solid (purification on silica gel chromatography was not necessary), mp. 188-190 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.34 - 1.44 (m, 2 H), 1.44 - 1.54 (m, 4 H), 2.44 - 2.49 (m, 2 H), 2.62 - 2.69 (m, 2 H), 2.70 (d, J=1.0 Hz, 1 H), 3.30 (s, 3 H), 3.59 (t, J=10.1 Hz, 1 H), 3.78 - 3.90 (m, 2 H), 3.95 - 4.07 (m, 1 H), 4.16 (dd, J=9.9, 5.2 Hz, 1 H), 4.74 (s, 1 H), 5.49 (s, 1 H), 7.12 (dd, J=8.0, 1.3 Hz, 2 H), 7.17 - 7.31 (m, 3 H), 7.93 (d, J=2.1 Hz, 4 H), 8.07 (br. s., 1 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 23.9, 26.2, 49.6, 51.2, 54.4, 57.7, 68.5, 69.0, 74.3, 99.7, 100.9, 123.6, 126.2, 127.6, 128.0, 128.6, 137.4, 147.2, 148.7; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{25}H_{32}N_3O_8S$ 534.1905, found 534.1906; $[\alpha]_D^{23}$ + 72 (c 0.81, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-6-methoxy-7-morpholino-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8o.*** Following the general procedure, the reaction was heated with morpholine **6o** for 24 h to afford **8o** in 69% yield (57.0 mg) as a pale yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =60/1), mp. 203-205 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.49 - 2.53 (m, 2 H), 2.56 - 2.66 (m, 3 H), 3.27 (s, 3 H), 3.50 - 3.60 (m, 5 H), 3.76 - 3.83 (m, 1 H), 3.83 - 3.91 (m, 1 H), 3.92 - 4.03 (m, 1 H), 4.12 (dd, J=9.9, 5.2 Hz, 1 H), 4.77 (s, 1 H), 5.46 (s, 1 H), 7.02 - 7.11 (m, 2 H), 7.13 - 7.26 (m, 3 H), 7.84 - 7.96 (m, 4 H), 8.02

(d, J=7.8 Hz, 1 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 50.1, 50.7, 54.5, 57.9, 66.6, 68.2, 68.4, 73.9, 98.4, 100.8, 123.6, 126.2, 127.6, 128.0, 128.6, 137.3, 147.2, 148.7; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{24}H_{30}N_3O_9S$ 536.1697, found 536.1699; $[\alpha]_D^{23}$ + 71 (c 0.77, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-7-((R)-2-(hydroxymethyl)pyrrolidin-1-yl)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8p.*** Following the general procedure on a 0.6 mmol scale, the reaction was heated with (*R*)-pyrrolidin-2-ylmethanol **6p** for 16 h to afford **8p** in 68% yield (230.0 mg) as a pale yellow solid(after purification on silica gel chromatography, $CHCl_3$/MeOH =50/1), mp. 106-108 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.56 - 1.81 (m, 4 H), 2.52 - 2.58 (m, 1 H), 2.83 - 2.95 (m, 2 H), 2.96 - 3.11 (m, 2 H), 3.21 - 3.31 (m, 1 H), 3.33 (s, 3 H), 3.61 (t, J=10.1 Hz, 1 H), 3.86 - 4.05 (m, 3 H), 4.16 (dd, J=10.1, 4.9 Hz, 1 H), 4.35 (t, J=5.4 Hz, 1 H), 4.76 (s, 1 H), 5.50 (s, 1 H), 7.08 (dd, J=8.0, 1.3 Hz, 2 H), 7.15 - 7.28 (m, 3 H), 7.88 (d, J=8.8 Hz, 1 H), 7.95 (s, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 23.8, 28.1, 51.3, 52.4, 55.2, 58.7, 61.9, 64.2, 67.1, 69.0, 74.0, 100.7, 101.4, 124.2, 126.7, 128.1, 128.5, 129.1, 137.9, 147.9, 149.2; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{25}H_{32}N_3O_9S$ 550.1854, found 550.1853; $[\alpha]_D^{23}$ + 43 (c 0.69, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-7-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8q.*** Following the general procedure on a 0.6 mmol scale, the reaction was heated with (*S*)-pyrrolidin-2-ylmethanol **6q** for 16 h to afford **8q** in 56% yield (186.0 mg) as a pale yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =50/1), mp. 67-69 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.58 - 1.74 (m, 4 H), 2.56 - 2.65 (m, 1 H), 2.83 - 2.95 (m, 3 H), 3.07 - 3.17 (m, 1 H), 3.31 (s, 3 H), 3.32 - 3.37 (m, 1 H), 3.63 (t, J=9.6 Hz, 1 H), 3.85 (br. d, J=8.8 Hz, 1 H), 3.91 - 4.06 (m, 2 H), 4.15 (dd, J=10.1, 4.4 Hz, 1 H), 4.57 (t, J=5.2 Hz, 1 H), 4.82 (s, 1 H), 5.49 (s, 1 H), 7.09 (dd,

J=8.0, 1.8 Hz, 2 H), 7.16 - 7.30 (m, 3 H), 7.95 (br. s., 1 H), 7.96 (s, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 23.6, 27.4, 50.9, 53.7, 54.6, 58.0, 64.2, 64.2, 66.2, 68.4, 73.4, 98.4, 100.8, 123.6, 126.1, 127.5, 128.0, 128.6, 137.4, 147.2, 148.7; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{25}H_{32}N_3O_9S$ 550.1854, found 550.1856; $[\alpha]_D^{23}$ + 49 (c 0.61, CH_2Cl_2).

2-(((4aR,6S,7S,8S,8aS)-6-methoxy-8-(4-nitrophenylsulfonamido)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)amino)benzoic acid ***8r***. Following the general procedure on a 0.6 mmol scale, the reaction was heated with anthranilic acid **6r** for 24 h to afford **8r** in 56% yield (200.0 mg) as a yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =100/1), mp. 119-121 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.37 (s, 3 H), 3.71 (t, J=9.6 Hz, 1 H), 3.93 (m, 1 H), 4.06 (dd, J=9.7, 4.8 Hz, 1 H), 4.20 (m, 2 H), 4.71 (s, 1 H), 5.00 (dd, J=2.6, 1.0 Hz, 1 H), 5.59 (s, 1 H), 6.56 (ddd, J=8.0, 7.0, 1.0 Hz, 1 H), 6.72 (br. s, 2 H), 6.80 (dd, J=8.6, 0.8 Hz, 1 H), 7.13 (m, 2 H), 7.26 (m, 4 H), 7.80 (dd, J=8.0, 1.6 Hz, 1 H), 7.96 (dt, J=9.6, 2.3 Hz, 4 H), 8.42 (d, J=8.8 Hz, 1 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 51.4, 54.9, 58.2, 68.2, 71.4, 73.1, 97.9, 100.8, 107.5, 114.8, 116.6, 123.6, 126.2, 127.6, 128.2, 128.7, 131.0, 134.7, 137.2, 146.8, 148.8, 151.9, 165.6; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{27}H_{28}N_3O_{10}S$ 586.1490, found 586.1491; $[\alpha]_D^{23}$ + 56 (c 1.08, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-7-(2-benzoylhydrazinyl)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitrobenzenesulfonamide ***8s.*** Following the general procedure, the reaction was heated with benzohydrazide **6s** for 72 h to afford **8s** in 38% yield (34.0 mg) as an amorphous yellow solid (after purification on silica gel chromatography, $CHCl_3$/MeOH =70/1). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.20 (t, J=2.3 Hz, 1 H), 3.31 - 3.32 (s, 3 H), 3.67 (t, J=9.9 Hz, 1 H), 4.01 - 4.16 (m, 3 H), 4.20 (dd, J=10.1, 4.9 Hz, 1 H), 4.74 (s, 1 H), 5.44 (dd, J=5.4, 3.4 Hz, 1 H), 5.52 (s, 1 H), 7.16 (dd, J=7.8, 1.6 Hz, 2 H), 7.21 - 7.32 (m, 3 H), 7.45 - 7.61 (m, 3 H), 7.79 - 7.86 (m,

2 H), 7.90 - 7.93 (m, 5 H), 10.12 (d, J=5.7 Hz, 1 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 50.3, 54.6, 58.5, 63.3, 68.4, 73.2, 98.4, 100.9, 123.6, 126.1, 127.2, 127.6, 127.9, 128.4, 128.6, 131.5, 133.1, 137.4, 147.3, 148.7, 166.3; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{27}H_{29}N_4O_9S$ 585.1650, found 585.1651; $[\alpha]_D^{23}$ + 55 (c 0.79, CH_2Cl_2).

N-((4aR,6S,7S,8S,8aS)-7-azido-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl)-4-nitro-N-(prop-2-yn-1-yl)benzenesulfonamide ***9.*** To a solution of triphenylphosphine (TPP) (0.40 mmol, 104 mg) and DIAD (0.40 mmol, 79 μL) in dry dioxane (4 mL) compound **8a** (0.20 mmol, 100 mg) was added. After 5 minutes, propargyl alcohol (0.40 mmol, 24 μL) was added in one portion. The reaction mixture was stirred at room temperature for 18 h, then the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using $CHCl_3$/MeOH (50/1) as a mobile phase to afford **9** in 74% yield (80 mg) as a yellow solid, mp. 99-102 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.36 (t, J=2.3 Hz, 1 H), 3.43 (s, 3 H), 3.49 (m, 1 H), 3.86 (t, J=9.9 Hz, 1 H), 4.16 (m, 3 H), 4.32 (dd, J=19.2, 2.1 Hz, 1 H), 4.42 (dd, J=10.4, 6.7 Hz, 1 H), 4.51 (t, J=9.9 Hz, 1 H), 4.77 (d, J=6.7 Hz, 1 H), 5.15 (s, 1 H), 6.99 (d, J=7.3 Hz, 2 H), 7.18 (t, J=7.5 Hz, 2 H), 7.26 (m, 1 H), 7.97 (m, 4 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 54.2, 55.3, 60.0, 62.7, 66.3, 68.8, 73.7, 74.8, 80.5, 100.9, 101.2, 123.7, 125.9, 127.7, 128.6, 128.8, 136.6, 144.5, 149.0; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{23}H_{24}N_5O_8S$ 530.1340, found 530.1341; $[\alpha]_D^{23}$ + 1 (c 1.85, CH_2Cl_2).

(4aS,5S,6aR,10aS,10bS)-5-methoxy-11-((4-nitrophenyl)sulfonyl)-9-phenyl-4a,5,6a,7,10a,10b,11,12-octahydro-[1,3]dioxino[4',5':5,6]pyrano[4,3-e][1,2,3]triazolo[1,5-a]pyrazine ***10.*** Method A: Azide **9** (0.08 mmol, 40 mg) was dissolved in 1 mL of DMF and 0.3 mL of water. Then a freshly prepared aqueous solution of sodium ascorbate (NaAsc.) (1 M in water, 16 μL) and $CuSO_4.5H_2O$ (0.1 M, 16 μL) was added and the reaction mixture was heated

under stirring at 60 °C for 14 days. Caution: Sodium ascorbate must be properly stored and its solution freshly prepared. When the reaction was completed, water (5 mL) was added and the mixture was extracted with chloroform (3x5 mL). Collected organic layers were dried with brine and $MgSO_4$, evaporated under reduced pressure, and the residue was purified by silica gel chromatography using chloroform as a mobile phase to afford **10** in 90% yield (36 mg) as a yellow solid, mp. 89-91 °C. Method B: The reaction was carried out at 80°C for 3 days in 20 mg scale. Isolation process followed Method A and afforded **10** in 70% yield (14 mg) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.51 (s, 3 H, OCH_3), 3.95 (t, J=9.6 Hz, 1 H, $HC6_{ax}$), 4.02-4.11 (m, 2 H, HC3+HC5), 4.16 (t, J=8.9 Hz, 1 H, HC4), 4.38 (dd, J=9.3, 3.9 Hz, 1 H, $HC6_{eq}$), 4.52 (d, J=16.6 Hz, 1 H, CH_2-piperazine), 5.05 (d, J=16.6 Hz, 1 H, CH_2-piperazine), 5.24 (dd, J=12.2, 7.3 Hz, 1 H, HC2), 5.60 (d, J=7.3 Hz, 1 H, HC1), 5.72 (s, 1 H, CH-Ph), 7.34 (s, 1 H, CH-triazole), 7.36-7.41 (m, 3 H, Ph), 7.41-7.47 (m, 2H, Ph), 8.05 (d, J=9.1 Hz, 2 H, Ns), 8.11 (d, J=9.1 Hz, 2H, Ns); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 40.3, 54.3, 56.0, 56.0, 65.7, 69.5, 76.8, 99.9, 102.3, 124.7, 126.8, 128.5, 129.4, 129.5, 129.6, 133.0, 137.8, 143.1, 150.3; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{23}H_{24}N_5O_8S$ 530.1340, found 530.1341; $[\alpha]_D^{26}$ -60 (c 0.6, CH_2Cl_2).

((2R)-1-((4aR,6S,7S,8S,8aS)-8-amino-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)pyrrolidin-2-yl)methanol ***11***. Sugar derivate **8p** (0.09mmol, 50mg) was dissolved in acetonitrile (2mL), then K_2CO_3 (0.36mmol, 50mg) and thiophenol (0.27mmol, 28μL) was added. The suspension was heated at 50°C for 2 days and the solvent was evaporated. The residue was dissolved in $CHCl_3$ (15mL). The organic layer was washed with water (3x15mL) and brine (15mL), dried with $MgSO_4$, and concentrated under reduced pressure. The purification on silica gel chromatography afforded **11** in 75% yield (25mg) as a yellow solid, mp. 52-54 °C. ^{1}H NMR

(400 MHz, DMSO-*d6*) δ 7.50 - 7.43 (m, 2 H), 7.40 - 7.33 (m, 3 H), 7.29 - 7.12 (m, 1 H), 5.73 (s, 1 H), 4.73 (s, 1 H), 4.40 (br. s., 1 H), 4.22 (dd, *J* = 4.7, 9.9 Hz, 1 H), 4.00 - 3.82 (m, 2 H), 3.74 (t, *J* = 9.6 Hz, 1 H), 3.31 (s, 3 H), 3.29 (br. s., 2 H), 3.05 (t, *J* = 8.3 Hz, 1 H), 2.94 (t, *J* = 6.7 Hz, 1 H), 2.88 - 2.79 (m, 2 H), 1.87 (br. s., 2 H), 1.76 - 1.53 (m, 4 H); ^{13}C NMR (101MHz ,DMSO-d_6) δ = 128.8, 128.0, 126.4, 119.5, 101.3, 100.8, 76.7, 68.5, 65.6, 64.0, 61.8, 57.2, 54.7, 51.7, 48.3, 27.6, 23.3; HRMS (Orbitrap) *m/z* $[M + H]^+$ calcd for $C_{19}H_{28}N_2O_5$ 365.2071, found 365.2071; $[\alpha]_D^{26}$ + 40 (c 0.77, CH_2Cl_2).

Associated content

^{1}H and ^{13}C NMR spectra for all compounds; crystallographic information file (CIF) for compound **8a**.

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