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Synthesis of *N*-Propargyl Iminosugar Scaffolds for Compound Library Generation using Click Chemistry

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We have developed an efficient synthesis of *N*-propargyl iminosugars for use in diversity-oriented library development. Through a common, crystalline intermediate both piperidine and azepane scaffolds can be prepared with an alkyne functional group, allowing for further elaboration through reaction with azides.

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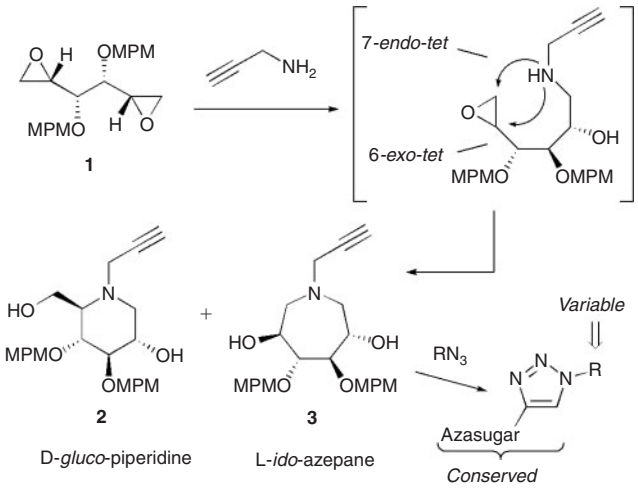
Introduction

Novel inhibitors of carbohydrate processing enzymes offer potential therapeutic intervention in several disease states and the biological activity of iminosugars can in many cases be attributed to their ability to act as competitive, reversible inhibitors of glycosidases and glycosyltransferases.[1] The preparation and evaluation of *N*-alkylated iminosugars is an active area of research, with considerable effort invested into the combinatorial and parallel synthesis of alkylated iminosugar libraries to enable discovery of glycosidase and glycosyltransferase inhibitors with improved potency and selectivity.[2] It has been shown that these compounds possess markedly different inhibition profiles than their non-alkylated parent structures, and so are valuable as tools for elucidating biochemical pathways associated with protein and lipid glycosylation.[3] The synthesis of structurally conserved iminosugar scaffolds containing one (or more) reactive functionalities to enable the conjugation of structurally diverse substituents is thus desirable. This decorative approach is a powerful means of accessing compounds for lead discovery or optimization purposes and various groups have reported the synthesis of iminosugar libraries using this 'scaffold decoration' strategy. More notable examples include the synthesis of an *N*-alkylated fuconojirimycin library in microtitre plate format by Wong et al.,[4] the solid phase synthesis of an *N*-alkylated azafagomine library containing a variable tri-peptide sequence by Bols et al.[5] and a C(2)-substituted tetrahydropyridoimidazole library reported by Vasella and coworkers.[6]

We have previously applied the azide-alkyne Cu^{I}-catalyzed azide and alkyne cycloaddition reaction (CuAAC) to carbohydrate substrates to identify isozyme-selective carbonic anhydrase inhibitors.[7] Herein we extend this methodology to prepare *N*-alkylated iminosugar libraries. The modular assembly of these libraries using click chemistry would provide both a flexible and expedient access to novel iminosugars for use as probes of discrete binding elements within the active site of carbohydrate-processing enzymes. Specifically we report the development of an efficient synthetic strategy to generate both six-membered (*N*-propargyl piperidine) and seven-membered (*N*-propargyl azepane) iminosugars from a common, crystalline intermediate and subsequent 'scaffold decoration' by employing click chemistry. Furthermore, the polyhydroxylated azepanes are a relatively unexplored class of compound, and the combinatorial or parallel synthesis of azepane libraries is thus a viable approach for promptly establishing compound libraries with novel structural attributes.



Scheme 1. Synthetic strategy to *N*-alkylated azasugar scaffolds.

Results and Discussion

Our synthetic strategy to the *N*-alkylated iminosugar scaffolds is outlined in Scheme 1. Previously, Le Merrer and colleagues examined the nucleophilic ring opening of homochiral C_2-symmetric bis-epoxides with benzyl amine as a key step in the regiospecific synthesis of deoxynojirimycin and L-*ido*-tetrahydroxyazepane.[8] By adopting a similar strategy, the installation of the required *N*-propargyl group could be

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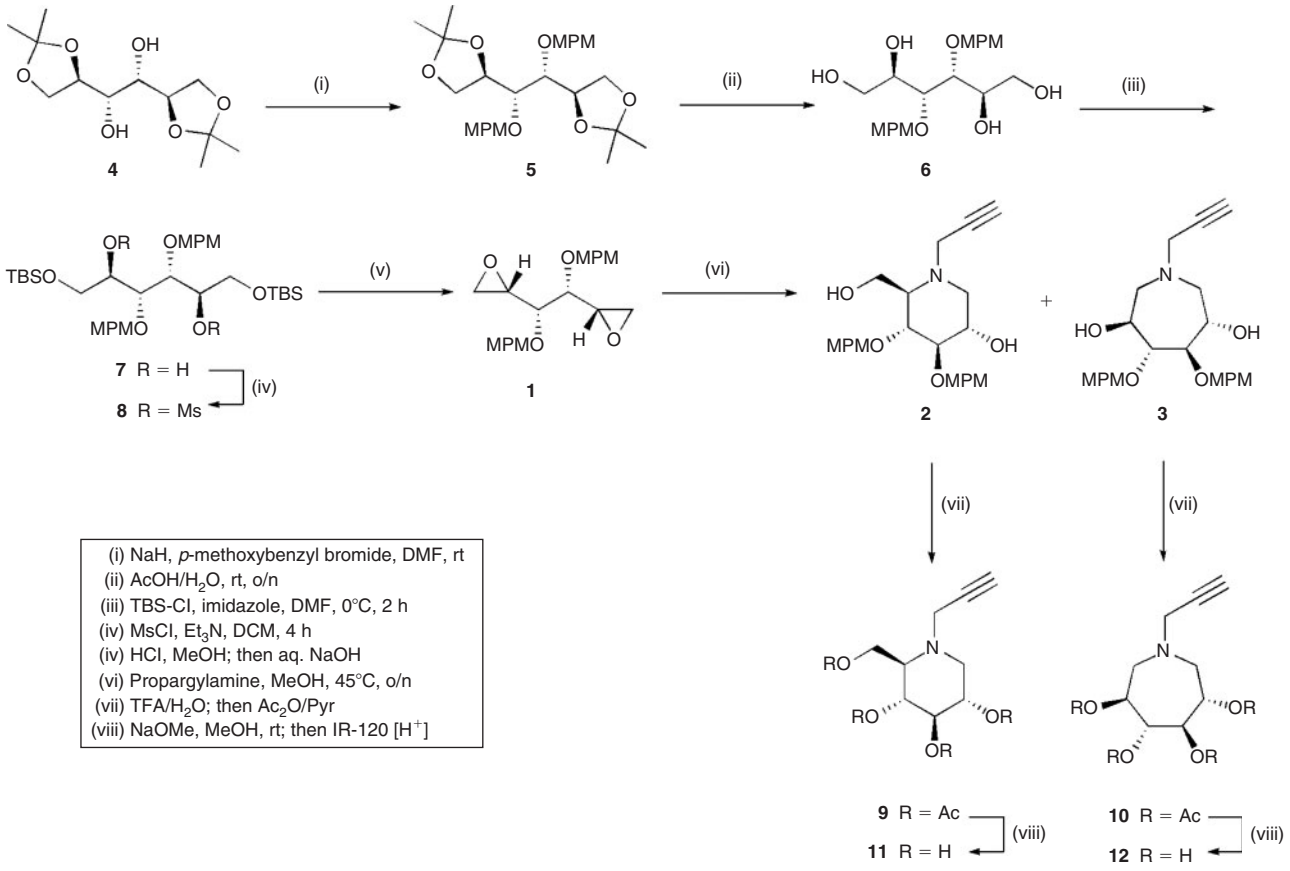


Scheme 2. Synthesis of bis-epoxide **1** and *N*-alkylated azasugar scaffolds.

achieved by the nucleophilic ring opening of the structurally rigid and crystalline C_2-symmetric bis-epoxide **1** with propargyl amine to form the *N*-propargyl D-*gluco*-piperidine **2** and the L-*ido*-azepane **3** scaffolds.

The nucleophilic ring opening and aminocyclization of diastereomeric, C_2-symmetric bis-epoxides with benzyl amine has been examined under different experimental conditions.[8] The reaction conditions as well as steric influences can be modified to favour one of the two reaction pathways: the 6-*exo*-*tet* process, which favours the formation of the D-*gluco*-piperidine; or the 7-*endo*-*tet* process, which favours the formation of the C_2-symmetric L-*ido*-azepane (Scheme 1).[8,9] In particular, the nature of the hydroxyl protecting group at C-3 and C-4 are shown to influence the relative distribution of the piperidine and azepane products. We sought a protecting group that would impart a reasonable degree of structural rigidity leading to approximately equal product distributions, but which could also be removed under mild and selective conditions. The *p*-methoxybenzyl ether protecting group was selected because it can be removed under orthogonal and mild oxidative conditions as well as providing potentially crystalline synthetic intermediates to facilitate their purification by non-chromatographic methods (Scheme 2).

Synthesis of the bis-epoxide **1** and *N*-alkylated iminosugar scaffolds is presented in Scheme 2. Alkylation of the optically pure and commercially available 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**4**) with *p*-methoxy benzyl bromide in DMF afforded the 3,4-di-*O*-*p*-methoxybenzyl ether **5** in 74% yield. Cleavage of the bis-acetonide was achieved by stirring **5** in aqueous acetic acid (70% w/v) at room temperature for 20 h affording the crude tetrol **6**, which was used in the next step without further purification. Selective silylation of the hydroxyl groups at C-1 and C-6 position was achieved by immediately treating with *tert*-butyldimethylsilyl chloride (2.2 equiv.) in anhydrous DMF at 0°C, furnishing the bis-silylether **7** in good yield (68%). Treatment of **7** with methanesulfonyl chloride in anhydrous dichloromethane at 0°C facilitated the activation of C-2 and C-5 towards the ensuing intramolecular nucleophilic attack. Thus, the crude mesylate **8** (78%) was treated with an aqueous solution of 1 M HCl in methanol at 0°C for 1 h to effect cleavage of the silyl ether groups. This was promptly followed by a base-promoted (addition of 20% w/v solution of potassium hydroxide) intramolecular S_N2 reaction, leading to the inversion of stereochemistry at C-2 and C-5, thus the stereospecific formation of the L-*ido*-configured C_2-symmetric bis-epoxide **1** (55%). Pure **1** precipitated from the reaction mixture and was obtained by vacuum filtration and recrystallization from hot absolute ethanol. The molecular structure of **1** has been solved by X-ray crystallography and was in agreement with the expected stereochemical configuration (Fig. 1).[10]

With optically pure, crystalline C_2-symmetric bis-epoxide **1** in hand and available in gram quantities, we sought to optimize the experimental conditions for the aminocyclization with propargyl amine. However, adaptation of the literature method,[8] which involved treating the substrate with excess propargyl amine (5.0 equiv.) in refluxing chloroform, proved to be less effective with this particular amine. The reaction was found to be sluggish and partial decomposition of the substrate was observed by TLC after 48 h at reflux. Microwave irradiation (300 W, 150°C, up to 30 min) in the presence of 5 and 10 equiv.

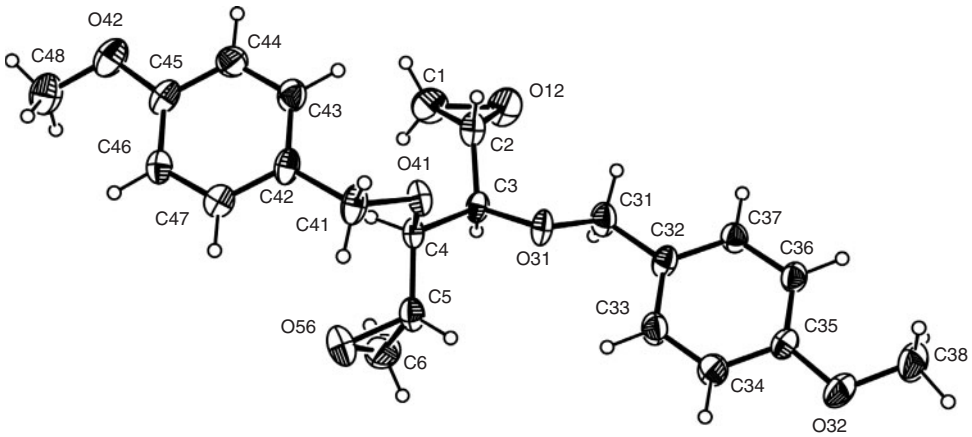


Fig. 1. The molecular structure of **1** as solved by X-ray crystallography.

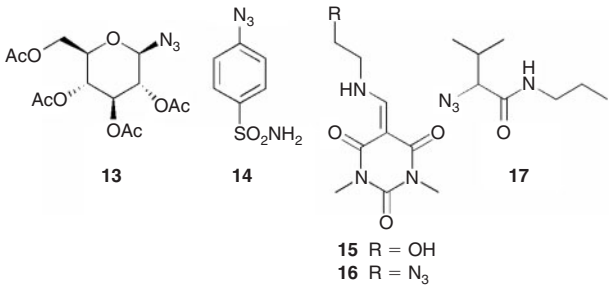


Fig. 2. Azides selected to prepare *N*-alkylated azasugar model libraries (**13** = **a**, **14** = **b**, **16** = **c**, **17** = **d**).

of propargyl amine using 1,2-DCE, DMF, or acetone as solvents did not lead to product formation by TLC. In an attempt to assist epoxide opening and subsequent cyclization, the reaction was next performed in a protic solvent at slightly elevated temperature. The bis-epoxide **1** was thus treated with excess propargyl amine (5.0 equiv.) in warm methanol (45°C). The formation of the 3,4-di-*O*-*p*-methoxybenzyl D-*gluco*-piperidine **2** and the structural isomer, C_2-symmetric L-*ido*-azepane **3** occurred overnight. The isomers were readily separated by flash chromatography and isolated in very good yields (**2**, 45%; and **3**, 41%). After surveying several deprotection methods the acetylated iminosugars **9** and **10** were obtained by treatment of **2** and **3** with aqueous TFA (1:4 TFA–H_2O) at 40°C followed by acylating the crude mixture using pyridine/Ac_2O (42% and 43% from **2** and **3**, respectively). Compounds **9** and **10** could be readily converted into free tetrol iminosugars **11** and **12**.

Having obtained both the *N*-propargyl piperidine **9** and azepane **10** scaffolds in sufficient quantities, we proceeded to prepare *N*-alkylated iminosugar model libraries containing the structurally conserved *N*-methylene 1,2,3-triazole moiety. A diverse panel of aliphatic and aryl azides were selected on the basis of previously established structure-activity relationships with respect to the selectivity and potency of the inhibition of several target glycosidases (Fig. 2).[11]

The CuAAC used to prepare iminosugar libraries were performed within capped scintillation vials in aqueous *tert*-butyl alcohol (1:1 v/v, 0.1–0.5 M) in the presence of sub-stoichiometric quantities of sodium ascorbate, $CuSO_4$ and 1.0 equiv. of the corresponding azide at 40°C. The per-*O*-acetylated triazole series **18a**–**d**, was prepared in an efficient manner from the L-*ido*-azepane scaffold **10** and azide building blocks **a**–**d** (Fig. 2, Scheme 3). The *O*-acetylated L-*ido*-azepane compounds **18a**–**d** were isolated in good yields (65–75%) following purification by flash chromatography. Deprotection of **18a**–**d** was achieved by employing anhydrous methanolic sodium methoxide followed by neutralization with acidic Amberlite IR-120 [H^+] to afford the target compounds as tetrols **19a**–**d** in near quantitative yields. Using an identical method, conjugation of the piperidine scaffold **9** with alkyl azide **17** (building block **d**) was carried out to synthesize the triazole conjugate **20d**, which could be smoothly deprotected to yield **21d**.

Conclusion

In conclusion, the bis-epoxide **1** has been successfully synthesized, its structure confirmed by X-ray crystallography and then transformed into both *N*-propargyl piperidine and azepane scaffolds. We have illustrated the utility and application of click chemistry in preparing *N*-alkylated iminosugar libraries using reaction of both scaffolds with various azide building blocks. We believe that this synthetic methodology will provide a powerful approach to accessing the structural diversity necessary for distinguishing target enzyme selectivity and tuning the physicochemical properties of the iminosugar. The scaffold decoration of the iminosugar was achieved in a single, high-yielding step using click chemistry, thus providing for flexible and expedient access to novel iminosugars for use as probes of discrete binding elements within the active site of carbohydrate-processing enzymes. An extended degree of diversity can be further achieved with the use of both a six-membered ring and seven-membered ring scaffolds and a direct comparison of biological activity with these counterparts will provide a more expansive surveillance and correlation of biological and chemical space with respect to the target enzyme.

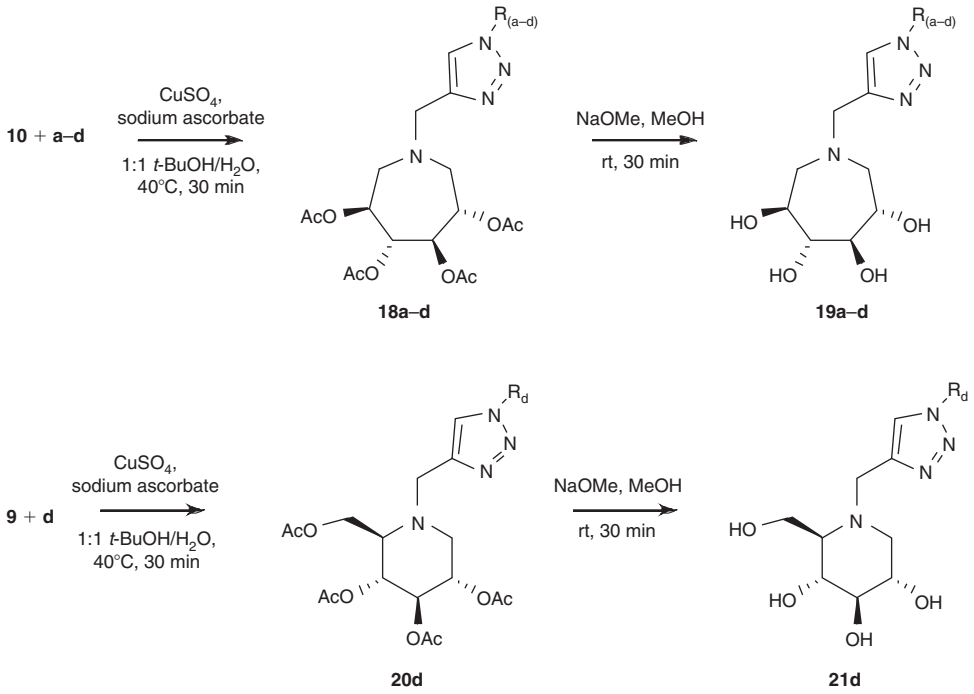
Experimental

Notes on Nomenclature

Azasugars are named according to the IUPAC-IUBMB 'Nomenclature of Carbohydrates', section from 2-CARB-34[12] and according to the literature.[8] Compound names and NMR assignments are given with preference to the triazole ring.

Preparation of N*-alkylated Iminosugar-triazoles: General Procedure 1*

A mixture of the azide (1.0 equiv.) and acetylene (1.0 equiv.) was prepared in *tert*-butyl alcohol and water (1:1, 0.2–0.5 M



Scheme 3. Synthesis and susbsequent deprotection of triazole azasugar analogues.

final concentration) and placed within a capped scintillation vial. Sodium ascorbate (0.2 equiv.) and $CuSO_4 \cdot 5H_2O$ (0.1 equiv.) was then added. The mixture was stirred vigorously at 40°C and monitored by TLC. Reactions were generally complete within 30 min at this temperature. Visualization of libraries by TLC was performed by UV fluorescence and by charring plates with a mixture of 10% ammonium molybdate (w/v) in 10% aqueous H_2SO_4 containing 0.8% cerium sulfate.[13] Conventional aqueous workup using CH_2Cl_2 or EtOAc organic phases followed by purification of the crude residue by silica filtration/flash chromatography afforded pure compound. The 1,4-regioselectivity of the reaction was verified by ^1H and ^{13}C NMR chemical shifts of the triazole moiety in products obtained using $CDCl_3$, DMSO[D6], and D_2O, and are in agreement with literature values.

Deprotection of Iminosugar Scaffolds: General Procedure 2

A solution of the benzyl ether, **2** or **3** (~0.1 M) was prepared in a mixture of TFA and distilled water (1:1 v/v) and stirred at slightly elevated temperature. The reaction was found complete after overnight stirring by TLC (C-18 reverse phase employing 1:1 CH_3CN–H_2O eluent) and electrospray ionization-mass spectrometry. Once complete, the solvent was evaporated under reduced pressure and lyophilized to dryness. Mixtures were used in the next step without further purification (see general procedure 3).

Preparation of Iminosugar Scaffolds: General Procedure 3

A solution of the crude lyophilized reaction mixture (general procedure 2) was prepared in pyridine and an equal volume of acetic anhydride was then added (~0.1 M final concentration). The reaction was stirred at room temperature until found complete by TLC. The solvent was removed under reduced pressure and the resulting residue purified by flash silica chromatography (1:2 EtOAc–CH_2Cl_2). A portion of the resulting pure material was retained for deprotection according to general method 4 to obtain tetrols **11** and **12**.

Deprotection of Iminosugars: General Procedure 4

Compounds were prepared by the treating the per-*O*-acetate precursors (final concentration of ~0.1–0.2 M) with anhydrous methanolic sodium methoxide (final pH 9–12). Full deprotection was evident by TLC within 30 min of stirring at room temperature. The solution was neutralized by the addition of acidic ion exchange resin (Amberlite IR-120 [H^+]), filtered and washed several times with methanol. Evaporation of the filtrates afforded the deprotected compounds, all of which were shown to be pure by ^1H NMR.

*1,2:5,6-Di-O-isopropylidene-3,4-di-O-p-methoxylbenzyl-D-mannitol (**5**)[10b]*

A solution of 1,2:5,6-diisopropylidene-D-mannitol (25.0 g, 95.4 mmol) in anhydrous DMF at 0°C under nitrogen was prepared and a 60% mineral oil dispersion of sodium hydride (5.0 g, 124 mmol, 2.5 equiv.) was added in three portions over 15 min. The suspension was stirred at 0°C for 30 min and then *p*-methoxybenzyl chloride (16.9 mL, 124.3 mmol, 2.5 equiv.) was added dropwise. The suspension was then brought to room temperature and stirred for 4 h. The reaction was quenched by the careful addition of methanol at 0°C. Concentration of the mixture under reduced pressure afforded a crude oil which was purified by flash chromatography to afford clear oil which slowly crystallized on standing to a white crystalline solid (**5**: 18.6 g, 36.78 mmol, 38%). R_f 0.22 (1:4 EtOAc–hexanes); mp 43–44°C (Found: C 66.77, H 7.62. $C_{28}H_{38}O_8$ requires C 66.91, H 7.62%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (6H, s, ^{i}Pr CH_3), 1.40 (6H, s, ^{i}Pr CH_3), 3.73–3.75 (2H, m, H_3), 3.78 (6H, s, $PhOCH_3$), 3.80 (2H, dd, $^2J_{1-1'}$ 8.4, $^3J_{1-2}$ 6.4, H_1), 3.97 (2H, dd, $^2J_{1'-1}$ 8.4, $^3J_{1'-2}$ 6.4, $H_{1'}$), 4.16–4.21 (2H, m, H_2), 4.60 (4H, s, OCH_2Ph), 6.80–7.20 (10H, m, ArH). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 25.5 (^{i}Pr CH_3), 26.9 (^{i}Pr CH_3), 55.5 ($PhOCH_3$), 67.1 (C_1),

74.4 (OCH_2Ph), 76.1 (C_2), 79.8 (C_3), 108.7 (^{i}Pr C), 114.0 (Ar CH), 129.7 (Ar CH), 130.7 (Ar C), 159.5 (Ar C). *m/z* (HRMS ESI) 525.2446, $[M + Na]^+$ calcd for $C_{28}H_{38}O_8Na^+$ requires 525.2459.

3,4-Di-O-p-*methoxbenzyl-1,6-di*-O-tert-*butyldimethylsilyl-D-mannitol* (***7***)

A portion of pure **5** (24 g, 47.8 mmol) was dissolved in aqueous glacial acetic acid (70% v/v, 500 mL) and stirred at room temperature for 24 h. At this time, TLC indicated full acetonide deprotection. The mixture was evaporated at room temperature under reduced pressure to afford the tetrol **6** as a pale yellow oil which, due to its highly hygroscopic nature, was used in the following step without further purification or analysis. The resulting crude **6** (12.5 g, 29.6 mmol) was azeotropically dried with 1:1 CH_3CN/toluene (3 × 50 mL) and its solution in anhydrous DMF (30 mL) was immediately prepared under an atmosphere of nitrogen. The solution was cooled to 0°C and imidazole (8.1 g, 118.3 mmol, 4.0 equiv.) was added, followed by *tert*-butyldimethylsilyl chloride (11.1 g, 73.9 mmol, 2.5 equiv.) in three equal portions. The thick suspension was stirred at 0°C for 2 h until found complete by TLC. The reaction was quenched with saturated, aqueous ammonium chloride (60 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The organic fractions were combined, washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford crude yellow oil. Flash chromatography (15% EtOAc in hexanes) afforded clear oil that slowly crystallized upon refrigeration to a white solid (**7**). R_f 0.28 (15% EtOAc in hexanes); mp 58–59°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s, Me_2Si), 0.05 (6H, s, Me_2Si), 0.89 (18H, s, *tert*-butyl CH_3), 3.57 (2H, dd, $^2J_{1–1'}$ 10, $^3J_{1–2}$ 5.2, H_1), 3.72 (2H, dd, $^2J_{1'–1}$ 10.0, $^3J_{1'–2}$ 3.2, $H_{1'}$), 3.77 (6H, s, $PhOCH_3$), 3.79–3.87 (4H, m, H_2, H_3), 4.58 (4H, AB q, $^2J_{AB}$ 11.2, OCH_2Ph), 6.82–7.25 (10H, m, ArH). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ −5.1 (Me_2Si), −5.09 (Me_2Si), 18.5 (*tert*-butyl C), 26.2 (*tert*-butyl CH_3), 55.4 ($PhOCH_3$), 64.6 (C_1), 71.0 (C_2 or C_3), 73.7 (OCH_2Ph), 77.9 (C_2 or C_3), 114.0 (Ar CH), 130.2 (Ar CH), 130.7 (Ar C), 159.5 (Ar C). *m/z* (HRMS ESI) 673.3575, $[M + Na]^+$ calcd for $C_{34}H_{58}O_8Si_2Na^+$ requires 673.3562.

2,5-Di-O-*mesyl-3,4-di*-O-p-*methoxybenzyl-1,6-di*-O-tert-*butyldimethylsilyl-D-mannitol* (***8***)

To a solution of **7** (9.8 g, 15.1 mmol) in anhydrous CH_2Cl_2 (25 mL) at 0°C under nitrogen, was added triethylamine (8.67 mL, 61.9 mmol, 4.1 equiv.), followed by the dropwise addition of methanesulfonyl chloride (3.52 mL, 45.2 mmol, 2.0 equiv.). The thick suspension was stirred at 0°C for 15 min, at which time TLC indicated reaction completion. The reaction was quenched by the careful addition of water (20 mL) and extracted into CH_2Cl_2 (30 mL). The aqueous layer was then further extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure to afford the crude mesylate as an orange oil. Crystallization from anhydrous methanol at 0°C afforded the mesylate **8** (9.5 g, 19.4 mmol, 78%) as a white crystalline solid. R_f 0.22 (15% EtOAc in hexanes); mp 81–82°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (6H, s, Me_2Si), 0.08 (6H, s, Me_2Si), 0.90 (18H, s, *tert*-butyl CH_3), 2.97 (6H, s, OMs CH_3), 3.78 (6H, s, $PhOCH_3$), 3.90 (2H, dd, $^3J_{1–1'}$ 11.6, $^3J_{1–2}$ 6.4, H_1), 3.95–3.96 (2H, m, H_3), 3.99 (2H, dd, $^3J_{1'–1}$ 11.6, $^3J_{1'–2}$ 3.6, $H_{1'}$), 4.62 (4H, AB q, $^2J_{AB}$ 10.4, CH_2Ph), 4.77–4.80 (2H, m, H_2), 6.83–7.27 (8H, m, ArH). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ −5.2 ($SiCH_3$), −5.16 ($SiCH_3$), 18.5 (*tert*-butyl C), 26.1 (*tert*-butyl CH_3), 38.8 (OMs CH_3), 55.5 ($PhOCH_3$), 62.2 (C_1), 74.1 (CH_2Ph), 78.0 (C_3), 83.5 (C_2), 114.1 (Ar CH), 129.8 (Ar C), 130.3 (Ar CH), 159.7 (Ar CH).

1,2:5,6-Dianhydro-3,4-di-O-p-*methoxybenzyl-L-iditol* (***1***)

A solution of the mesylate **8** (13.2 g, 16.4 mmol) in methanol was cooled to 0°C and concentrated aqueous HCl (1 N, 3.47 mL, 39.2 mmol, 2.4 equiv.) was added dropwise. The solution was stirred for an additional 1 h to effect full silyl deprotection. At this time, an aqueous solution of potassium hydroxide (20% w/v, 28 mL, 98 mmol, 6.0 equiv.) was added dropwise. A thick white precipitate had formed following stirring overnight at 20°C and was collected by vacuum filtration and washed with cold methanol–H_2O (3:7, 2 × 20 mL). A final recrystallization of the crude white solid from hot absolute ethanol afforded the bis-epoxide **1** as fine colourless needles (3.52 g, 9.11 mmol, 55%). R_f 0.50 (1:1 EtOAc–hexanes); mp 108–109°C (Found: C 68.37, H 6.91. $C_{22}H_{26}O_6$ requires C 68.38, H 6.78%), $[\alpha]_D^{25}$ +25.4 (*c* 0.095, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (2H, dd, $^2J_{1–1'}$ 4.8, $^3J_{1–2}$ 2.8, H_1), 2.69 (2H, dd, $^2J_{1'–1}$ 5.2, $^3J_{1'–2}$ 4.4, $H_{1'}$), 3.15–3.17 (2H, m, H_2), 3.22–3.25 (2H, m, H_3), 3.79 (6H, s, $PhOCH_3$), 4.62 (4H, AB q, $^2J_{AB}$ 11.6, OCH_2Ph), 6.83–7.24 (8H, m, ArH). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 43.3 (C_1), 52.7 ($PhOCH_3$), 55.48 (C_2), 72.1 (OCH_2Ph), 80.3 (C_3), 113.9 (Ar CH), 129.8 (Ar CH), 130.2 (Ar C), 159.5 (Ar C). *m/z* (HRMS ESI) 409.1620, $[M + Na]^+$ calcd for $C_{22}H_{26}O_6Na^+$ requires 409.1622.

Colourless needles of **1** ($C_{22}H_{26}O_6$) suitable for X-ray crystallographic analysis were obtained by the slow evaporation of an absolute ethanol–$CHCl_3$ (1:1 v/v) solution. $M = 386.43$, monoclinic, space group $P2_1$, $a = 5.1245(5)$, $b = 10.6190(9)$, $c = 18.513(7)$ Å, $\beta = 94.320(1)°$, $V = 1004.6(4)$ Å^3, $T = 296(1)$ K, $Z = 2$, $D_x = 1.278$ Mg m^{-3}, μ(Mo-Kα) = 0.092 mm^{-1}, crystal size 0.50 × 0.40 × 0.30 mm; $2\theta_{max} = 50°$; 2080 reflections measured, 1860 unique ($R_{int} = 0.0720$). $r = 0.073$ (1219 reflections with $I > 2\sigma(I)$; $wRF^2 = 0.251$ (all data).

1,5-Dideoxy-1,5-imino-3,4-di-O-p-*methoxybenzyl*-N-*propynyl-D-glucitol* (***2***)

The bis-epoxide **1** (1.0 g, 2.6 mmol) was suspended in methanol (25 mL) and propargyl amine (3.4 mL, 5.2 mmol, 2.0 equiv.) was then added. Dissolution was achieved within 4 h by vigorous stirring at 45°C. The deep yellow solution was then stirred overnight at this temperature, at which time TLC indicated reaction completion. The mixture was concentrated under reduced pressure and the resulting orange oil purified by flash chromatography (1:1 EtOAc–CH_2Cl_2 then 100% EtOAc) to afford the piperidine **2** (520 mg, 1.2 mmol, 45%). R_f 0.21 (2:3 EtOAc–CH_2Cl_2); mp 139–140°C (Found: C 67.67, H 7.05, N 3.20. $C_{25}H_{31}NO_6$ requires C 68.01, H 7.08, N 3.17%), $[\alpha]_D^{25}$ −1.22 (*c* 0.115, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (1H, t, $^4J_{CH–CH}$ 2.4, C≡CH), 2.42–2.45 (1H, m, H_5), 2.53–2.58 (1H, m, H_1), 2.89 (1H, dd, $^2J_{1'–1}$ 11.2, $^3J_{1'–2}$ 4.8, $H_{1'}$), 3.27–3.32 (1H, m, H_3), 3.36 (1H, dd, $^2J_{CH–CH}$ 18.0, $^4J_{CH–CH}$ 2.4, NCH), 3.57–3.62 (1H, m, H_4), 3.63–3.68 (2H, m, H_2, H_6), 3.73 (1H, dd, $^2J_{CH–CH}$ 18.4, $^4J_{CH–CH}$ 2.4, NCH), 3.79 (3H, s, $PhOCH_3$), 3.80 (3H, s, $PhOCH_3$), 3.81–3.84 (1H, m, $H_{6'}$), 4.76 (2H, AB q, $^2J_{AB}$ 11.2, 10.8, CH_2OPh), 4.80 (2H, ABq, $^2J_{AB}$ 10.8, CH_2OPh), 6.86–7.30 (8H, m, ArH). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ

42.5 (NCH_2), 55.5 ($PhOCH_3$), 55.5 ($PhOCH_3$), 56.3 (C_1), 57.4 (C_6), 63.5 (C_5), 69.4 (C_2), 75.0 (OCH_2Ph), 75.1 (OCH_2Ph), 75.1 (*C*≡CH), 76.6 (C≡*C*H), 77.3 (C_4), 87.0 (C_3), 114.2 (Ar CH), 114.3 (Ar CH), 129.8 (Ar CH), 130.0 (Ar CH), 130.5 (Ar C), 130.9 (Ar C), 159.6 (Ar C), 159.6 (Ar C). *m/z* (HRMS ESI) 442.2209, $[M + H]^+$ calcd for $C_{25}H_{31}NO_6^+$ requires 442.2224.

*1,6-Dideoxy-1,6-imino-3,4-di-*O-p-*methoxybenzyl-*N-*propynyl-L-iditol (**3**)*

Title compound was isolated using the identical procedure for **2** and was isolated as a pale yellow solid (47 mg, 41%). R_f 0.12 (1:4 EtOAc–CH_2Cl_2); mp 65–66°C (Found: C 68.01, H 7.14, N 3.02. $C_{25}H_{31}NO_6$ requires C 68.01, H 7.08, N 3.17%), $[\alpha]_D^{25}$ +1.56 (*c* 0.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (1H, t, $^3J_{CH-CH}$ 2.4, C≡CH), 2.53 (2H, dd, $^3J_{1-1'}$ 12.8, $^3J_{1-2}$ 8.0, H_1), 3.07 (2H, d, $^3J_{1'-2}$ 12.4, $H_{1'}$), 3.54 (2H, dd, $^2J_{CH-CH}$ 16.4, $^4J_{CH-C\equiv CH}$ 1.6, NCH_2), 3.61 (2H, dd, $^3J_{3-2}$ 4.8, $^3J_{3-4}$ 1.6, H_3), 3.78 (6H, s, $PhOCH_3$), 3.98–3.91 (2H, m, H_2), 4.58 (4H, ABq, $^2J_{AB}$ 11.2, OCH_2Ph), 7.03 (8H, m, *Ar*). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 49.0 (NCH_2), 55.5 ($PhOCH_3$), 56.8 (C_1), 68.1 (C_2), 73.4 (OCH_2Ph), 75.4 (*C*≡CH), 77.6 (C≡*C*H), 85.1 (C_3), 114.2 (Ar CH), 129.8 (Ar CH), 130.2 (Ar C), 159.6 (Ar C). *m/z* (HRMS ESI) 442.2211, $[M + H]^+$ calcd for $C_{25}H_{32}NO_6^+$ requires 442.2224.

*2,3,4,6-Tetra-*O-*acetyl-1,5-dideoxy-1,5-imino-*N-*propynyl-D-glucitol (**9**)*

The title compound was prepared from **2** according to general procedure 3 and was isolated as a colourless oil (85 mg, 0.23 mmol, 42%). R_f 0.43 (1:1 EtOAc–CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (3H, s, OAc), 1.99 (3H, s, OAc), 2.00 (3H, s, OAc), 2.05 (3H, s, OAc), 2.28 (1H, t, $^4J_{CH-CH}$ 2.4, C≡CH), 2.57–2.62 (1H, m, H_1), 2.71 (1H, m, H_5), 3.00 (1H, dd, $^2J_{1-1'}$ 11.2, $^3J_{1'-2}$ 5.2, $H_{1'}$), 3.39 (1H, dd, $^2J_{CH-CH}$ 18.4, $^4J_{CH-CH}$ 2.4, NCH), 3.73 (1H, dd, $^2J_{CH-CH}$ 18.4, $^4J_{CH-CH}$ 2.0, NCH), 4.10–4.20 (2H, m, H_3, H_4), 4.94–5.00 (1H, m, H_2), 5.00–5.10 (2H, m, H_6). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 20.8 (OAc), 20.8 (OAc), 20.9 (OAc), 42.58 (NCH_2), 53.9 (C_1), 58.8 (C_4), 60.0 (C_5), 69.2 (C_6 or C≡*C*H), 69.4 (C_6 or C≡*C*H), 74.5 (C_2), 75.3 (C_3), 76.1 (*C*≡CH), 169.8 (OAc), 170.1 (OAc), 170.5 (OAc), 171.1 (OAc).

*2,3,4,5-Tetra-*O-*acetyl-1,6-dideoxy-1,6-imino-*N-*propynyl-L-iditol (**10**)*

The title compound was prepared from **3** according to general procedure 3 and isolated as a colourless oil (220 mg, 0.60 mmol, 43%). R_f 0.45 (1:1 EtOAc–CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (6H, s, 2 × OAc), 2.02 (6H, s, 2 × OAc), 2.26 (1H, t, $^4J_{CH-CH}$ 2.4, C≡CH), 2.83 (1H, dd, $^2J_{1-1'}$ 14.0, $^3J_{1-2}$ 7.2, H_1), 3.00 (1H, dd, $^2J_{1'-1}$ 13.6, $^3J_{1'-2}$ 4.0, $H_{1'}$), 3.41 (1H, dd, $^2J_{CH-CH}$ 17.2, $^4J_{CH-CH}$ 2.0, NCH), 3.49 (1H, dd, $^2J_{CH-CH}$ 17.2, $^4J_{CH-CH}$ 2.4, NCH), 5.08–5.13 (2H, m, H_2), 5.26 (2H, dd, $^3J_{3-2}$ 6.0, $^3J_{3-4}$ 2.4, H_3). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 20.7 (OAc), 21.0 (OAc), 48.6 (C_1), 55.7 (NCH_2), 72.0 (C_2 and C_3), 73.9 (*C*≡CH), 78.0 (C≡*C*H), 169.5 (OAc), 169.9 (OAc).

*1,5-Dideoxy-1,5-imino-*N-*propynyl-D-glucitol (**11**)*

The title compound was prepared from **9** according to general procedure 4 and isolated as a white solid (25 mg, 100%). $[\alpha]_D^{25}$ −77.3 (*c* 0.085, MeOH). ^{1}H NMR (400 MHz, D_2O) δ 2.21–2.24 (1H, m, H_5), 2.41 (1H, m, H_1), 2.58 (1H, t, $^4J_{CH-CH}$ 2.4, C≡CH), 2.82 (1H, dd, $^2J_{1'-1}$ 11.2, $^3J_{1'-2}$ 5.2, H'_1), 3.11–3.15 (1H, m, H_3), 3.27–3.31 (1H, m, H_4), 3.35 (1H, dd, $^2J_{CH-CH}$ 18.0, $^4J_{CH-CH}$ 2.4, NCH), 3.44 (1H, ddd, $^3J_{2-1}$ 10.4, $^3J_{2-3}$ 9.2, $^3J_{2-1'}$ 4.8, H_2), 3.73 (2H, m, H_6, $H_{6'}$). $^{13}C\{^1H\}$ NMR (100 MHz, D_2O) δ 41.8 (NCH_2), 56.0 (C_1), 56.9 (C_6), 63.7 (C_5), 68.9 (C_2), 69.7 (C_4), 75.9 (C_3), 76.9 (C≡*C*H), 78.3 (*C*≡CH). *m/z* (HRMS ESI) 202.1073, $[M + H]^+$ calcd for $C_9H_{16}NO_4^+$ requires 202.1074.

*1,6-Dideoxy-1,6-imino-*N-*propynyl-L-iditol (**12**)*

The title compound was prepared from **10** (48 mg, 0.13 mmol) according to general procedure 4 and isolated as a white gum (26 mg, 0.13 mmol, 100%). $[\alpha]_D^{25}$ −2.71 (*c* 0.095, MeOH). ^{1}H NMR (400 MHz, D_2O) δ 2.58 (1H, t, $^4J_{CH-CH}$ 2.4, C≡H), 2.62 (2H, dd, $^2J_{1-1'}$ 13.2, $^3J_{1-2}$ 7.0, H_1), 2.85 (2H, dd, $^2J_{1'-1}$ 13.6, $^3J_{1'-2}$ 4.0, $H_{1'}$), 3.31 (2H, d, $^4J_{CH-CH}$ 2.4, NCH_2), 3.33 (2H, dd, $^3J_{3-2}$ 6.0, $^3J_{3-4}$ 2.4, H_3), 3.59–3.64 (2H, m, H_2). $^{13}C\{^1H\}$ NMR (100 MHz, D_2O) δ 47.8 (NCH_2), 57.9 (C_1), 71.0 (C_2), 75.0 (*C*≡CH), 75.5 (C_3), 78.4 (C≡*C*H). *m/z* (HRMS ESI) 202.1072, $[M + H]^+$ calcd for $C_9H_{16}NO_4^+$ requires 202.1074.

*5-((3-Hydroxypropylamino)methylene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**15**)*

A solution of 5-((diimethylamino)methylene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (5.62 g, 26.6 mmol) in methanol (15 mL) was cooled to 0°C, followed by the addition of 3-amino-1-propanol (2.1 mL, 26.7 mmol). A white precipitate was formed within 2 min and the suspension was stirred at 0°C for an additional 15 min. The precipitate was filtered and washed with cold methanol (~20 mL). The crude, off-white solid was recrystallized from hot, absolute ethanol to afford the title compound as colourless needles (4.6 g, 72%). R_f 0.22 (100% EtOAc); mp 129–130°C (Found: C 49.86, H 6.28, N 17.23. $C_{10}H_{15}N_3O_4$ requires C 49.79, H 6.27, N 17.42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (2H, pentet, $^3J_{CH-CH}$ 6.0, βCH_2), 2.19 (1H, br s, OH), 3.28 (3H, s, NCH_3), 3.29 (3H, s, NCH_3), 3.63 (2H, m, $NHCH_2$), 3.78 (2, t, $^3J_{CH-CH}$ 5.6, CH_2OH), 8.17 (1H, d, $^3J_{CH-NH}$ 14.4, C=CH), 10.40 (1H, br s, NH). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 27.3 (NCH_3), 28.0 (NCH_3), 32.3 (βCH_2), 48.2 (CH_2NH), 59.6 (CH_2OH), 90.8 (*C*=CH), 152.7 (C=O), 159.9 (C=*C*H), 163.9 (C=O), 165.1 (C=O).

*5-((3-Azidopropylamino)methylene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**16**)*

A solution of **15** (1.0 g, 4.2 mmol) and triethylamine (690 μL, 5.0 mmol, 1.2 equiv.) in anhydrous CH_2Cl_2 (10 mL) was prepared under an atmosphere of nitrogen and cooled to 0°C. Methanesulfonyl chloride (390 μL, 5.0 mmol, 1.2 equiv.) was then added dropwise. The solution was gradually brought to room temperature and the solution was stirred for 30 min until TLC had indicated reaction completion. The solution was then diluted with CH_2Cl_2 (10 mL) and washed with distilled H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to afford a crude orange oil, which was used in the following step without further purification. The crude mesylate was immediately dissolved in anhydrous DMF (15 mL) and sodium azide (810 mg, 12.5 mmol, 3.0 equiv.) was added in a single portion. The resulting deep pink solution was stirred overnight at room temperature. At this time, TLC analysis indicated reaction completion. The solvent was concentrated under vacuum and CH_2Cl_2 (20 mL) was added. The organic layer was washed with distilled H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash chromatography (2:3 hexanes–EtOAc) and

recrystallization from hot absolute ethanol to afford the azide as a white solid (830 mg, 3.1 mmol, 74%). R_f 0.67 (100% EtOAc); mp 114–115°C (Found: C 45.17, H 5.38, N 31.42. $C_{10}H_{14}N_6O_3$ requires C 45.11, H 5.30, N 31.56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (2H, pentet, $^3J_{CH–CH}$ 6.5, βCH_2), 3.29 (3H, s, NCH_3), 3.30 (3H, s, NCH_3), 3.43 (2H, t, $^3J_{CH–CH}$ 6.4, N_3CH_2), 3.56 (2H, m, $NHCH_2$), 8.16 (1H, d, $^3J_{CH–NH}$ 14.4, C=C*H*NH), 10.28 (1H, br s, NH). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 27.4 (NCH_3), 28.1 (NCH_3), 29.7 (βCH_2), 47.8 (CH_2N_3), 48.4 (CH_2NH), 91.3 (*C*=CH), 152.3 (C=O), 159.9 (C=*C*H), 163.1 (C=O), 165.3 (C=O).

*1-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosyl)-4-(N-methylene-2,3,4,5-tetra-O-acetyl-1,6-dideoxy-1,6-imino-L-iditol)-1,2,3-triazole (**18a**)*

The title compound was prepared from **10** and **13** according to the general procedure 1 and isolated as a colourless oil (87 mg, 0.11 mmol, 78%). R_f 0.32 (1:1 EtOAc–hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (3H, s, OAc), 1.99 (3H, s, OAc), 2.00 (3H, s, OAc), 2.01 (3H, s, OAc), 2.03 (3H, s, OAc), 2.04 (3H, s, OAc), 2.06 (3H, s, OAc), 2.07 (3H, s, OAc), 2.81 (2H, br s, azepane H_1), 3.00–3.03 (2H, m, azepane $H_{1'}$), 3.90–4.01 (2H, br s, NCH_2), 3.98 (1H, ddd, $^3J_{5'–4'}$ 10.0, $^3J_{5'–6'}$ 5.2, $^3J_{5'–6''}$ 2.0, Glc $H_{5'}$), 4.14 (1H, dd, $^2J_{6''–6'}$ 12.8, $^3J_{6''–5'}$ 2.0, Glc $H_{6''}$), 4.29 (1H, dd, $^2J_{6'–6''}$ 12.4, $^3J_{6'–5'}$ 5.2, Glc $H_{6'}$), 5.10 (2H, br s, azepane H_2), 5.20–5.27 (3H, m, Glc $H_{4'}$, azepane H_3), 5.37–5.43 (2H, m, Glc $H_{2'}$, Glc $H_{3'}$), 5.81–5.83 (1H, m, Glc $H_{1'}$), 7.79 (1H, br s, triazole CH). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 20.3 (OAc), 20.69 (OAc), 20.72 (OAc), 20.8 (OAc), 20.9 (2 × OAc), 21.0 (2 × OAc), 53.5 (NCH_2), 55.5 (azepane $C_{1'}$), 61.8 (Glc $C_{6'}$), 67.9 (Glc $C_{4'}$), 70.6 (Glc $C_{2'}$ or Glc $C_{3'}$), 72.0 (azepane C_2), 72.3 (azepane C_3), 72.7 (Glc $C_{2'}$ or Glc $C_{3'}$), 75.4 (Glc $C_{5'}$), 86.0 (Glc $C_{1'}$), 121.0 (triazole CH), 143.5 (triazole C), 169.0 (OAc), 169.45 (2 × OAc), 169.54 (OAc), 169.8 (2 × OAc), 170.1 (OAc), 170.7 (OAc).

*1-(β-D-Glucopyranosyl)-4-(1,6-dideoxy-1,6-imino-L-iditol)-1,2,3-triazole (**19a**)*

The title compound was prepared from **18a** according to general procedure 4 and isolated as a white foam (28 mg, 0.07 mmol, 100%). ^{1}H NMR (400 MHz, D_2O) δ 2.51 (2H, dd, $^2J_{1–1'}$ 13.6, $^3J_{1–2}$ 7.6, azepane H_1), 2.76 (2H, dd, $^2J_{1'–1}$ 13.2, $^3J_{1'–1}$ 4.0, azepane $H_{1'}$), 3.30 (2H, dd, $^3J_{3'–2'}$ 5.6, $^3J_{3'–4'}$ 2.0, azepane $H_{3'}$), 3.47–3.67 (7H, m, Glc $H_{3'}$, Glc $H_{4'}$, Glc $H_{5'}$, Glc $H_{6'}$, Glc $H_{6''}$ and azepane H_2), 3.76 (2H, s, NCH_2), 3.84–3.89 (1H, m, Glc $H_{2'}$), 5.61 (1H, d, $^3J_{1'–2'}$ 9.2, Glc $H_{1'}$), 8.10 (1H, s, triazole CH). $^{13}C\{^1H\}$ NMR (100 MHz, D_2O) δ 52.8 (NCH_2), 58.4 (azepane C_1), 60.6 (Glc $C_{6'}$), 69.1 (Glc $C_{4'}$), 71.3 (azepane C_2), 72.5 (Glc $H_{2'}$), 76.0 (azepane C_3), 76.5 (Glc $C_{3'}$), 79.1 (Glc $C_{5'}$), 87.7 (Glc H_1), 123.5 (triazole CH), 145.8 (triazole C). *m/z* (HRMS ESI) 407.1765, $[M + H]^+$ calcd for $C_{15}H_{27}N_4O_9^+$ requires 407.1773.

*1-(p-Sulfamoylphenyl)-4-(N-methylene-2,3,4,5-tetra-O-acetyl-1,6-imino-L-iditol)-1,2,3-triazole (**18b**)*

The title compound was prepared from **10** and **14** according to the general procedure 1 and isolated as a pale yellow foam (88 mg, 0.16 mmol, 74%). R_f 0.18 (1:4 CH_2Cl_2–EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (6H, s, 2 × OAc), 2.02 (6H, s, OAc), 2.92 (2H, br s, azepane H_1), 3.10 (2H, br s, azepane $H_{1'}$), 4.03 (2H, br s, NCH_2), 5.12 (2H, br s, azepane H_2), 5.30 (2H, dd, $^3J_{3–2}$ 6.0, $^3J_{3–4}$ 2.0, azepane H_3), 7.90–8.06 (4H, m, *Ar*) 8.21 (1H, br s, triazole CH). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 20.8 (OAc), 21.1 (OAc), 53.6 (azepane C_1), 60.1 (NCH_2), 72.0 (azepane C_2 and C_3), 120.7 (Ar CH), 121.8 (triazole CH), 128.5 (Ar CH), 139.7 (Ar C), 142.6 (Ar C), 145.2 (triazole C), 169.6 (OAc), 170.1 (OAc).

*1-(p-Sulfamoylphenyl)-4-(N-methylene-1,6-imino-L-iditol)-1,2,3-triazole (**19b**)*

The title compound was prepared from **18b** according to general procedure 4 and isolated as a pale yellow oil (38 mg, 100%). ^{1}H NMR (400 MHz, D_2O) δ 2.54 (2H, dd, $^2J_{1–1'}$ 13.6, $^3J_{1–2}$ 7.6, H_1), 2.79 (2H, dd, $^2J_{1'–1}$ 13.6, $^3J_{1'–2}$ 4.4, $H_{1'}$), 3.32 (2H, dd, $^3J_{3–2}$ 5.6, $^3J_{3–4}$ 2.0, azepane H_3), 3.54–3.58 (2H, m, azepane H_2), 3.77 (2H, s, NCH_2), 7.71–7.86 (4H, m, *Ar* CH), 8.34 (1H, s, triazole CH). $^{13}C\{^1H\}$ NMR (100 MHz, 1:9 DMSO[D6]D_2O) δ 52.8 (NCH_2), 58.3 (azepane C_1), 71.3 (azepane C_2), 75.7 (azepane C_3), 121.3 (*Ar* CH), 123.6 (triazole CH), 128.0 (*Ar* CH), 139.4 (*Ar* C), 142.1 (*Ar* C or triazole C), 144.2 (*Ar* C or triazole C). *m/z* (HRMS ESI) 400.1269, $[M + H]^+$ calcd for $C_{15}H_{22}N_5O_6S^+$ requires 400.1285.

*1-(1,3-Dimethyl-5-((propylamino)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione)-4-(N-methylene-1,6-dideoxy-1,6-imino-2,3,4,5-tetra-O-acetyl-L-iditol)-1,2,3-triazole (**18c**)*

The title compound was from **10** and **16** prepared according to general procedure 1 and isolated as a colourless oil (98 mg, 0.15 mmol, 84%). R_f 0.28 (2:3 CH_2Cl_2–EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) 2.01 (6H, s, 2 × OAc), 2.02 (6H, s, 2 × OAc), 2.30 (2H, pentet, $^3J_{CH–CH}$ 7.2, βCH_2), 2.83 (2H, s, azepane H_1), 3.02 (2H, s, azepane $H_{1'}$), 3.23 (2H, s, NCH_3), 3.24 (3H, s, NCH_3), 3.46–3.51 (2H, m, αCH_2), 3.87 (2H, s, NCH_2), 4.38–4.51 (2H, m, γCH_2), 4.98–5.03 (2H, m, azepane H_2), 5.24 (2H, dd, $^3J_{2–3}$ 5.6, $^3J_{3–4}$ 1.6, azepane H_3), 7.66 (1H, s, triazole CH), 8.14 (1H, d, $^3J_{CH–NH}$ 14.0, C=C*H*), 10.24–10.30 (1H, m, NH). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 20.8 (OAc), 21.0 (OAc), 27.3 (NCH_3), 28.0 (NCH_3), 31.0 (βCH_2), 47.2 (αCH_2), 47.3 (γCH_2), 53.7 (azepane C_1), 55.3 (NCH_2), 71.8 (C_2 or C_3), 72.0 (C_2 or C_3), 91.4 (*C*=CH), 123.4 (triazole CH), 152.3 (C=*C*H), 160.0 (C=O), 163.0 (C=O), 165.1 (C=O), 169.5 (OAc), 170.0 (OAc).

*1-(1,3-Dimethyl-5-((propylamino)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione)-4-(N-methylene-1,6-dideoxy-1,6-imino-L-iditol)-1,2,3-triazole (**19c**)*

The title compound was prepared from **18c** according to method 4 and isolated as a colourless gum (28 mg, 0.06 mmol, 100%). ^{1}H NMR (400 MHz, D_2O) δ 2.21 (2H, pentet, $^3J_{CH–CH}$ 6.4, βCH_2), 2.46 (2H, dd, $^2J_{1–1'}$ 13.6, $^3J_{1–2}$ 8.0, azepane H_1), 2.71 (2H, dd, $^2J_{1'–1}$ 13.6, $^3J_{1'–2}$ 4.0, azepane $H_{1'}$), 3.03 (6H, s, 2 × NCH_3), 3.28 (2H, dd, $^3J_{2–3}$ 6.0, $^3J_{3–4}$ 2.8, azepane H_3), 3.46–3.53 (4H, m, azepane H_2, γCH_2), 3.63 (2H, br s, NCH_2), 4.43 (2H, t, $^3J_{CH–CH}$ 6.0, αCH_2), 7.90 (1H, s, C=C*H*), 7.95 (1H, s, triazole CH). $^{13}C\{^1H\}$ NMR (100 MHz, D_2O) δ 27.3 (βCH_2), 29.4 (NCH_3), 48.04 (αCH_2), 48.3 (γCH_2), 52.7 (NCH_2), 58.2 (azepane C_1), 71.3 (azepane C_2), 75.6 (azepane C_3), 90.2 (*C*=CH), 125.2 (triazole CH), 143.5 (triazole C), 153.2 (C=*C*H), 160.3 (2 × C=O), 164.7 (C=O). *m/z* (HRMS ESI) 468.2219, $[M + H]^+$ calcd for $C_{19}H_{30}N_7O_7^+$ requires 468.2201.

*1-(2,3-Dimethyl-*N*-propylbutanamide)-4-(*N*-methylene-2,3,4,5-tetra-*O*-acetyl-1,6-dideoxy-1,6-imino-L-iditol)-1,2,3-triazole (**18d**)*

The title compound was prepared from **10** and **17** according to the general procedure 1 and isolated as a colourless oil (89 mg, 0.16 mmol, 100%). R_f 0.31 (2:3 EtOAc–hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (6H, s, OAc × 2), 2.00 (6H, s, OAc, 2 × CH_3), 2.97 (2H, pentet, $^3J_{CH–CH}$ 6.8, CH_2), 2.78 (2H, br s, H_1), 2.97–3.00 (2H, m, $H_{1'}$), 3.23 (3H, s, NCH_3), 3.24 (3H, s, NCH_3), 3.48 (2H, dt, $^3J_{CH–CH}$ 13.6, $^3J_{CH–CH}$ 6.8, γCH_2), 3.86 (2H, br s, NCH_2), 4.38–5.11 (2H, m, αCH_2), 4.96–5.03 (2H, m, azepane H_2), 5.22–5.27 (2H, m, azepane H_3), 7.66 (1H, br s, triazole CH), 8.14 (1H, d, $^3J_{CH–NH}$ 14.0, C=C*H*), 10.24–10.28 (1H, m, C=CHN*H*).

*1-(2,3-Dimethyl-*N*-propylbutanamide)-4-(*N*-methylene-1,6-dideoxy-1,6-imino-L-iditol)-1,2,3-triazole (**19d**)*

The title compound was prepared from **18d** according to general procedure 4 and isolated as an off-white foam (22 mg, 0.06 mmol, 100%). ^{1}H NMR (400 MHz, D_2O) δ 0.64 (3H, d, $^3J_{CH–CH}$ 6.4, *sec*-butyl CH_3), 0.70 (3H, t, $^3J_{CH–CH}$ 7.6, *n*-Pr CH_3), 0.91 (3H, d, $^3J_{CH–CH}$ 6.8, *sec*-butyl CH_3), 1.37 (2H, sextet, $^3J_{CH–CH}$ 7.2, *n*-Pr CH_2), 2.37–2.46 (2H, m, *sec*-butyl CH), 2.57 (2H, dd, $^2J_{1–1'}$ 13.2, $^3J_{1–2}$ 7.6, azepane H_1), 2.80 (2H, dd, $^2J_{1'–1}$ 13.6, $^3J_{1'–2}$ 3.6, azepane $H_{1'}$), 2.98–3.12 (2H, m, *n*-Pr CH_2), 3.33 (2H, dd, $^3J_{2–3}$ 5.6, $^3J_{3–4}$ 1.6, azepane H_3), 3.54–3.60 (2H, m, azepane H_2), 3.82 (2H, br s, NCH_2), 4.78 (1H, d, $^3J_{CH–CH}$ 10.8, *sec*-butyl CH), 8.09 (1H, s, triazole CH). $^{13}C\{^1H\}$ NMR (100 MHz, D_2O) δ 10.7 (*n*-Pr CH_3), 18.0 (*sec*-butyl CH_3), 18.4 (*sec*-butyl CH_3), 21.8 (*n*-Pr CH_2), 31.0 (*sec*-butyl CH), 41.5 (*n*-Pr CH_2), 52.7 (NCH_2), 57.9 (azepane C_1), 70.7 (*sec*-butyl CH), 70.9 (azepane C_2), 75.7 (azepane C_3), 124.7 (triazole CH), 142.6 (triazole C), 169.5 (C=O). *m/z* (HRMS ESI) 386.2392, $[M + H]^+$ calcd for $C_{17}H_{32}N_5O_5^+$ requires 386.2398.

*1-(2,3-Methyl-*N*-propylbutanamide)-4-(*N*-methylene-1,6-dideoxy-1,6-imino-D-glucitol)-1,2,3-triazole (**21d**)*

The title compound was prepared from **20d** according to general method 4 and isolated as a pale yellow oil (12 mg, 0.03 mmol, 100%). ^{1}H NMR (400 MHz, D_2O) δ 0.64 (3H, d, $^3J_{CH–CH}$ 6.4, *sec*-butyl CH_3), 0.70 (3H, t, $^3J_{CH–CH}$ 7.2, *n*-Pr CH_3), 0.92 (3H, d, $^3J_{CH–CH}$ 6.4, *sec*-butyl CH_3), 1.33–1.42 (2H, m, *n*-Pr CH_2), 2.06–2.16 (3H, m, piperidine H_1 and H_5), 2.37–2.47 (1H, m, *sec*-butyl CH), 2.93 (1H, dd, $^2J_{1'–1}$ 11.6, $^3J_{1'–2}$ 4.8, piperidine $H_{1'}$), 3.02–3.12 (3H, m, *n*-pr CH_2, piperidine H_3), 3.32–3.37 (1H, m, piperidine H_4), 3.42–3.48 (1H, m, piperidine H_2), 3.82–3.87 (1H, m, piperidine H_6), 3.96–4.07 (3H, m, NCH_2, piperidine $H_{6'}$), 4.43 (1H, d, $^3J_{CH–CH}$ 10.4, *sec*-butyl CH), 8.09 (1H, s, triazole CH). $^{13}C\{^1H\}$ NMR (100 MHz, D_2O) δ 10.7 (*n*-Pr CH_3), 18.0 (*sec*-butyl CH_3), 18.4 (*sec*-butyl CH_3), 21.8 (*n*-Pr CH_2), 30.9 (*sec*-butyl CH), 41.5 (*n*-Pr CH_2), 46.2 (NCH_2), 55.3 (piperidine C_1), 56.7 (piperidine C_6), 64.4 (piperidine C_5), 68.5 (piperidine C_2), 69.5 (piperidine C_4), 70.8 (*sec*-butyl CH), 77.9 (piperidine C_3), 125.2 (triazole CH), 140.6 (triazole C), 169.5 (C=O). *m/z* (HRMS ESI) 386.2415, $[M + H]^+$ calcd for $C_{17}H_{32}N_5O_5^+$ requires 386.2398.

Accessory Publication

^{1}H and ^{13}C NMR spectra of compounds **1**, **2**, **5**, **8**–**10**, **19a**, **19b** (^{1}H only), **19c**, **19d**, and **21d** are provided. A cif file for compound **1** is also provided on the Journal's website.

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References

[1] (a) M. L. Sinnott, *Chem. Rev.* **1990**, *90*, 1171. doi:10.1021/CR00105A006
(b) V. L. Y. Yip, S. G. Withers, *Org. Biomol. Chem.* **2004**, *2*, 2707. doi:10.1039/B408880H

[2] (a) L. Cipolla, B. La Ferla, M. Gregori, *Comb. Chem. High T. Scr.* **2006**, *9*, 571.
(b) I. Velter, B. La Ferla, F. Nicotra, *J. Carbohydr. Chem.* **2006**, *25*, 97. doi:10.1080/07328300600733020

[3] (a) V. H. Lillelund, H. H. Jensen, X. Liang, M. Bols, *Chem. Rev.* **2002**, *102*, 515 and references cited therein. doi:10.1021/CR000433K
(b) N. Asano, *Glycobiology* **2003**, *13*, 93R. doi:10.1093/GLYCOB/CWG090
(c) A. Ossor, A. D. Elbein, *Carbohydrates in Chemistry and Biology* (Eds B. Ernst, G. W. Hart, P. Sinaÿ) **2000**, Vol. 3, pp. 513–531 (Wiley-VCH Verlag GmbH: Weinheim).
(d) T. A. Houston, J. T. Blanchfield, *Mini Rev. Med. Chem.* **2003**, *3*, 669. doi:10.2174/1389557033487827
(e) L. L. Johnson, Jr, T. A. Houston, *Tetrahedron Lett.* **2002**, *43*, 8905. doi:10.1016/S0040-4039(02)02196-2
(f) R. A. Dwek, T. D. Butters, F. M. Platt, N. Zitzmann, *Nat. Rev. Drug Discov.* **2002**, *1*, 65. doi:10.1038/NRD708
(g) P. Compain, O. R. Martin, *Curr. Top. Med. Chem.* **2003**, *3*, 541. doi:10.2174/1568026033452474
(h) L. L. Rossi, A. Basu, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3596. doi:10.1016/J.BMCL.2005.05.081
(i) Y. Zhao, Y. Zhou, K. M. O'Boyle, P. V. Murphy, *Bioorg. Med. Chem.* **2008**, *16*, 6333. doi:10.1016/J.BMC.2008.05.012

[4] C.-Y. Wu, C.-F. Chang, J. S.-Y. Chan, C.-H. Wong, C.-H. Lin, *Angew. Chem. Int. Ed.* **2003**, *42*, 4661. doi:10.1002/ANIE.200351823

[5] (a) A. Lohse, J. K. Jensen, M. Bols, *Tetrahedron Lett.* **1999**, *40*, 3033. doi:10.1016/S0040-4039(99)00317-2
(b) A. Lohse, J. K. Jensen, K. Lundgren, M. Bols, *Bioorg. Med. Chem.* **1999**, *7*, 1965. doi:10.1016/S0968-0896(99)00116-9

[6] N. Panday, Y. Canac, A. Vasella, *Helv. Chim. Acta* **2000**, *83*, 58. doi:10.1002/(SICI)1522-2675(20000119)83:1<58::AID-HLCA58>3.0.CO;2-K

[7] (a) M. Meldal, C. T. Tornoe, *Chem. Rev.* **2008**, *108*, 2952. doi:10.1021/CR0783479
(b) B. L. Wilkinson, A. Innocenti, D. Vullo, C. T. Supuran, S.-A. Poulsen, *J. Med. Chem.* **2008**, *51*, 1945. doi:10.1021/JM701426T
(c) S.-A. Poulsen, B. L. Wilkinson, A. Innocenti, D. Vullo, C. T. Supuran, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4624. doi:10.1016/J.BMCL.2008.07.010
(d) M. Singer, M. Lopez, L. F. Bornaghi, A. Innocenti, D. Vullo, C. T. Supuran, S.-A. Poulsen, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2273. doi:10.1016/J.BMCL.2009.02.086
(e) A. J. Salmon, M. L. Williams, A. Innocenti, D. Vullo, C. T. Supuran, S.-A. Poulsen, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5032. doi:10.1016/J.BMCL.2007.07.024

[8] (a) L. Poitout, Y. Le Merrer, J.-C. Depezay, *Tetrahedron Lett.* **1994**, *35*, 3293. doi:10.1016/S0040-4039(00)76888-2
(b) Y. Le Merrer, L. Poitout, J.-C. Depezay, I. Dosbaa, S. Geoffroy, M.-J. Foglietti, *Bioorg. Med. Chem.* **1997**, *5*, 519. doi:10.1016/S0968-0896(96)00266-0

[9] (a) J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* **1976**, 734. doi:10.1039/C39760000734
(b) J. E. Baldwin, R. C. Thomas, L. I. Kruse, L. Silberman, *J. Org. Chem.* **1977**, *42*, 3846. doi:10.1021/JO00444A011

[10] (a) Crystallographic data (excluding structure factors) for compound **1** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 699227. Copies of the data

can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0) 1223–336033 or email: deposit@ccdc.cam.ac.uk).
(b) For a related stereoisomer see: E. Bozo, A. Medgyes, S. Boros, J. Kuszmann, *Carbohydrate Res.* **2000**, *329*, 25.

[11] (a) T. D. Butters, L. A. G. M. van den Broek, G. W. J. Fleet, T. M. Krulle, M. W. Wormald, R. A. Dwek, F. M. Platt, *Tetrahedron Asymmetry* **2000**, *11*, 113. doi:10.1016/S0957-4166(99)00468-1
(b) T. D. Butters, R. A. Dwek, F. M. Platt, *Chem. Rev.* **2000**, *100*, 4683. doi:10.1021/CR990292Q
(c) T. D. Butters, R. A. Dwek, F. M. Platt, *Glycobiology* **2005**, *15*, 43R. doi:10.1093/GLYCOB/CWI076
(d) R. Inmaculada, A. J. Moreno-Vargas, A. T. Carmona, P. Vogel, *Curr. Drug. Metabol.* **2004**, *5*, 329. doi:10.2174/1389200043335513
(e) Y. C. Zeng, Y. T. Pan, N. Asano, R. J. Nash, A. D. Elbein, *Glycobiology* **1997**, *7*, 297.
(f) P. B. Fischer, G. B. Karlsson, T. D. Butters, R. A. Dwek, F. M. Platt, *J. Virol.* **1996**, *70*, 7143.

[12] (a) O. Berteau, R. Stenutz, *Carbohydr. Res.* **2004**, *339*, 929. doi:10.1016/J.CARRES.2003.11.008 (http://www.chem.qmul.ac.uk/iupac/2carb/34.html)
(b) A. D. McNaught, *Carbohydr. Res.* **1997**, *297*, 1. doi:10.1016/S0008-6215(97)83449-0
(c) A. D. McNaught, *Pure Appl. Chem.* **1996**, *68*, 1919. doi:10.1351/PAC199668101919

[13] J. Spreitz, A. E. Stütz, T. M. Wrodnigg, *Carbohydr. Res.* **2002**, *337*, 183. doi:10.1016/S0008-6215(01)00291-9