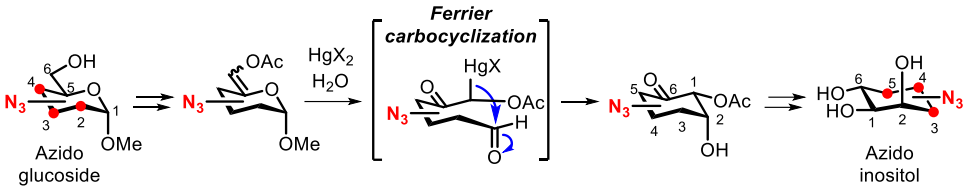
Ferrier Carbocyclization-Mediated Synthesis of Enantiopure Azido Inositol Analogues

Alex P. Ausmus, Maxwell Hogue, Justin L. Snyder, Sarah R. Rundell, Krestina M. Bednarz, Nicholas Banahene, and Benjamin M. Swarts*

Department of Chemistry and Biochemistry, Central Michigan University, Mount Pleasant, MI, USA

*Corresponding author: E-mail: ben.swarts@cmich.edu

TOC Graphic



Abstract

Azide-modified inositol (InoAz) analogues are valuable as inhibitors and have shown promise as metabolic chemical reporters (MCRs) for labeling inositol-containing glycoconjugates in eukaryotic cells and potentially in mycobacteria, but the synthesis of enantiomerically pure InoAz analogues via traditional approaches is challenging. As a complementary route, here we investigated the application of the Ferrier carbocyclization reaction to the synthesis of enantiopure InoAz analogues starting from readily available azido glucosides. Using this approach combined with a *para*-methoxybenzyl (PMB) protecting group strategy, 3-azido-3-deoxy- and 4-azido-4-deoxy-D-*myo*-inositol (3- and 4-InoAz) were efficiently synthesized. 5-Azido-5-deoxy-D-*myo*-inositol (5-InoAz) was inaccessible due to an unusual β-elimination reaction, wherein azide anion acted as the leaving group. The reported strategy is expected to facilitate continued development of synthetic InoAz analogues as inhibitors or MCRs of inositol-containing glycoconjugates in eukaryotic and mycobacterial systems.

Introduction

myo-Inositol is a non-classical carbohydrate bearing six secondary hydroxyl groups in a stereochemical arrangement that generates an internal plane of symmetry, rendering the molecule *meso*-symmetric (Fig. 1A). Inositol is an important component of many biomolecules, including phosphatidylinositol, phosphoinositides, and soluble inositol phosphates, which have important roles in membrane function and cellular signaling.[1] Inositol is also incorporated into complex glycoconjugates in many forms of life, including glycosylphosphatidylinositol (GPI) anchors found in all eukaryotes, which anchor proteins to the plasma membrane (Fig. 1B).[2] In mycobacteria, including the global pathogen *Mycobacterium tuberculosis* (*Mtb*), inositol is present in structurally related phosphatidylinositolmannosides (PIMs), which exist in free form and also as the membrane anchors of the complex glycolipids lipomannan (LM) and lipoarabinomannan (LAM) (Fig. 1C).[3] PIMs, LM, and LAM are abundant membrane-associated molecules that play important roles in the structural integrity and permeability of the mycobacterial cell envelope.[4,5] PIMs and PIM-anchored derivatives are also immune-modulating molecules that are involved in all stages of *Mtb* infection.[6] Inositol is also present in mycothiol, which is the major intracellular redox-balancing thiol in mycobacteria (Fig. 1D).[7] Proteins can undergo covalent modification by mycothiol during oxidative stress, which is likely to be an important adaptive response mechanism when *Mtb* faces the assaults of macrophages during infection.[8]

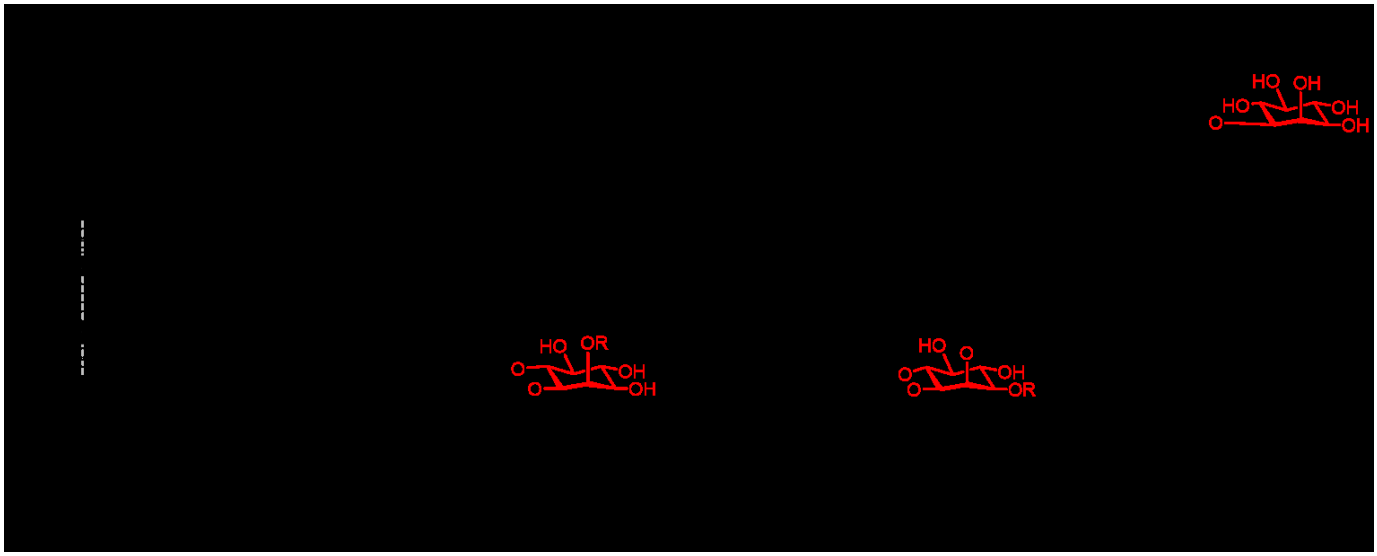


Figure 1. Structures of inositol (A) and examples of inositol-containing biomolecules, including eukaryotic GPIs (B) and mycobacterial PIMs and PIM-anchored glycans (C) and mycothiol (D). Inositol is colored in red in (B–D).

Although inositol-containing biomolecules have essential functions in diverse organisms, tools to visualize and profile these structures in their native environment are limited. In recent years, metabolic chemical reporters (MCRs), which are applied in conjunction with bioorthogonal chemistry, have emerged as valuable tools for studying various types of non-genetically encoded glycans and lipids in living systems.[9] In this regard, azide-modified inositol (InoAz) analogues have promise as MCRs for metabolic labeling and analysis of inositol-containing glycoconjugates. In the first example of such a tool, which was reported in 2015 by the Guo group, a panel of acetylated and non-acetylated inositol-based MCRs were evaluated for metabolic labeling of GPIs and GPI-anchored proteins in yeast cells and various mammalian cell lines. In Guo's report, it was found that when cells were treated with a partially acetylated 4-azidoethyl inositol analogue (**1**, Fig. 2A), the probe was taken up, deacetylated by intracellular esterases, and efficiently incorporated into GPI-anchored proteins, which enabled downstream click chemistry-mediated analysis.[10] In a similar vein, the Best group reported in 2019 that a non-acetylated 5-azidopropyl inositol analogue (**2**) labeled phosphatidylinositol lipids in yeast cells.[11] In addition to metabolic labeling applications, some azido inositol analogues have been shown to inhibit glycosidase activity and proliferation of mammalian cells.[12–14] A major focus of our research program is to create tools for probing the biosynthesis, dynamics, and post-synthetic modifications and interactions of mycobacterial glycoconjugates, and thus our interest lies in developing compounds that metabolically label, or inhibit the biosynthesis of, PIMs, LM, LAM, and mycothiol. To our knowledge, inositol-based MCRs or inhibitors for these mycobacterial structures have not yet been reported. To support this line of research, in this work we targeted three regioisomeric InoAz analogues (**3**–**5**) with minimally-sized azidodeoxy modifications at the 3-, 4-, and 5-positions of inositol (Fig. 2B). These positions are generally unmodified in mycobacterial PIMs, LM, LAM, and mycothiol (Fig. 1), and thus we expected that compounds **3**–**5** would provide an opportunity for metabolic labeling of these structures.

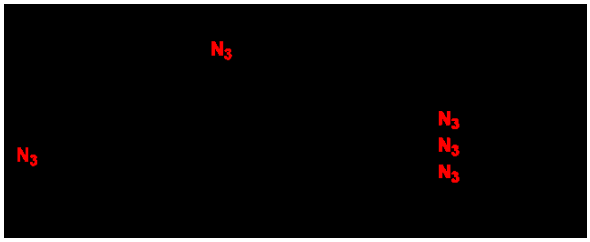


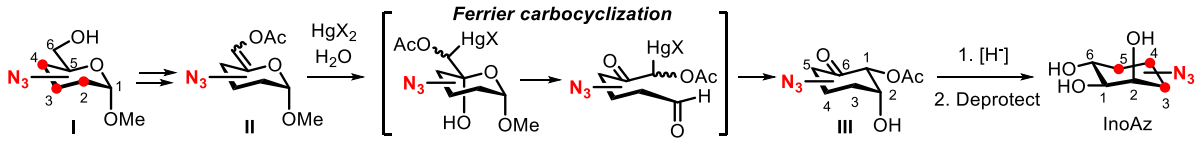
Figure 2. (A) Previously reported azidoethyl- and azidopropyl-modified inositol MCRs by the Guo (**1**) and Best (**2**) groups. (B) Azidodeoxy inositol MCRs (**3**–**5**) targeted in this work.

Despite the apparent simplicity of inositol's structure, the preparation of inositol derivatives remains a challenge. First, the selective functionalization of inositol requires the differentiation of six secondary alcohols. Second, inositol is *meso*-symmetric (as shown in Fig. 1A), so derivatization of any symmetrical position (i.e., the 1/3 and 4/6 positions) produces chirality and results in the formation of a racemic mixture that must be resolved. As a result, significant efforts have focused on the development of methods for the preparation of inositol derivatives.[15] These methods mainly involve subjecting inositol to regioselective manipulations and eventually performing chemical or enzymatic resolution of a racemic intermediate. For example, a report from 2015 described the chemical synthesis of 2-, (±)-3-, (±)-4-, and 5-InoAz (all starting from inositol) in 10, 11, 9, and 11 steps, respectively, and the racemic products (±)-3- and 4-InoAz were not resolved into enantiomers.[16] Other approaches to inositol derivatives have been reported as well, including use of chiral pool starting materials[17,18] and de novo synthesis employing enzymes[19] or ring-closing metathesis.[20] For instance, L-quebrachitol, a naturally occurring albeit expensive cyclitol, was converted to enantiopure 3-InoAz over 9–11 steps.[17] In another example, *p*-benzoquinone was elaborated via chemoenzymatic synthesis to four enantiopure InoAz regioisomers, including 1-, 3-, 4-, and 6-InoAz, over 10 steps.[19] Many of these reported synthetic routes involve late-stage S_N2 azide displacement reactions, for example on inositol sulfonates or trifluoromethanesulfonates, which can be complicated by competing elimination or S_N1 reactions.[16] Generally, it remains difficult to synthesize inositol derivatives, especially enantiopure compounds with modifications at sites off the plane of symmetry, the 1-, 3-, 4-, or 6-positions. As an alternative to prior approaches, here we report the application of the Ferrier carbocyclization reaction to the synthesis of enantiopure InoAz analogues.

Results and Discussion

Synthetic strategy. In 1991, the Prestwich and Bender groups independently reported an elegant application of the Ferrier carbocylization[21] to the synthesis of enantiomerically pure inositol derivatives.[22,23] We reasoned that this approach could be extended to the synthesis of InoAz analogues **3**–**5** as shown in Scheme 1. We hypothesized that regioisomeric azido methyl glucosides **I** could be elaborated to the enol acetate intermediates **II**, which upon treatment with Hg(II) would then undergo stereoselective Ferrier carbocyclization to give azido inososes **III**, setting up stereoselective ketone reduction and deprotection to yield the desired InoAz products. We surmised that this approach would be advantageous for several reasons, including: (i) it utilizes readily accessible azido methyl glucoside building blocks **I**, which avoids late-stage azido group installation and accompanying competing reactions; (ii) it provides enantiopure products without the need for desymmetrization; and (iii) it allows modification of the 3-, 4-, and 5-positions of inositol, which fortuitously are the positions prioritized for azide modification to allow metabolic labeling of inositol-containing biomolecules in mycobacteria and other systems (see Fig. 1). To protect hydroxyl groups at unmodified sites (i.e., positions 2–4 of azido glucosides **I**), we elected to use *para*-methoxybenzyl (PMB) groups, which are stable under Ferrier carbocyclization conditions[22] and can be deprotected under mild oxidative or acidic conditions that leave the azido group intact in the final product.[24,25]

Scheme 1. Proposed Ferrier carbocyclization-mediated synthesis of 3-, 4-, and 5-InoAz.[a]

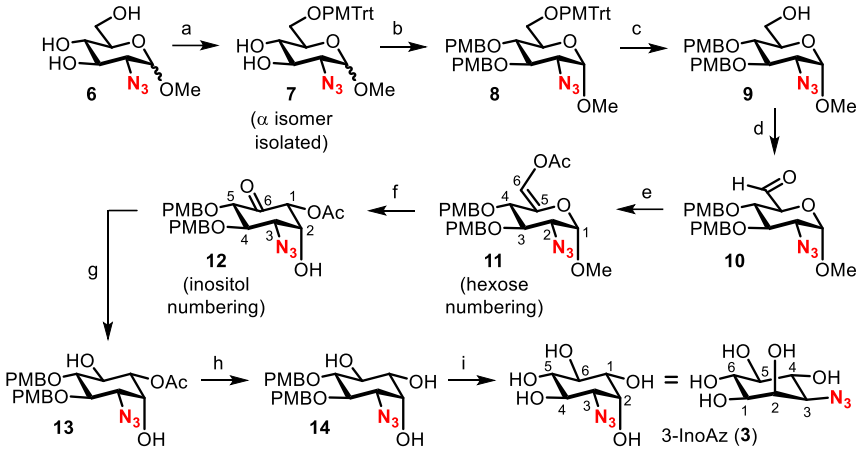


[a]Carbon numbering is based on hexose numbering for **I** and inositol numbering for **III** and InoAz. Red dots indicate sites that can, in principle, be modified using this strategy.

Synthesis of 3-InoAz (3). The preparation of 3-InoAz (**3**), depicted in Scheme 2, was initiated from an anomeric mixture of methyl 2-azido-2-deoxy-D-glucopyranoside (**6**), which was obtained from D-glucosamine via a diazo transfer procedure as previously described.[26,27] To set up for later oxidation of the 6-position, the primary alcohol of **6** was selectively protected with a bulky *para*-methoxytrityl (PMTrt) group to produce diol **7** in 57%

yield. With the anomers of **7** being separable at this stage, the α-anomer was isolated and carried forward to simplify characterization of intermediates. After the free 3-*O*- and 4-*O*-positions of **7** were *para*-methoxylbenzylated using NaH and PMBCl to give **8**, the highly acid-sensitive PMTrt group was selectively removed in the presence of acetic acid, generating primary alcohol **9** in 78% yield over two steps. Compound **9** was subjected to Swern oxidation to produce aldehyde intermediate **10**, which without purification was treated with K_2CO_3, acetic anhydride, and catalytic *N*,*N*-dimethylaminopyridine (DMAP) to produce enol acetate **11** in 52% yield over two steps.

Scheme 2. Synthesis of 3-InoAz (**3**).[a]



[a]Reagents and conditions: (a) PMTrtCl, pyridine, 0 °C → rt, 57%; (b) NaH, PMBCl, DMF, 0 °C → rt; (c) AcOH, H_2O, CH_2Cl_2, 78% over two steps; (d) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; then Et_3N, –78 °C → rt; (e) Ac_2O, DMAP, K_2CO_3, CH_3CN, 70 °C, 52% over two steps; (f) $Hg(OTFA)_2$, acetone–H_2O (4:1); then NaOAc, NaCl, 0 °C → rt, 54%; (g) $Na(OAc)_3BH$, AcOH, CH_3CN, 0 °C, 60%; (h) NaOMe, MeOH, 79%; (i) TFA, CH_2Cl_2, H_2O, 71%.

With the Ferrier precursor **11** in hand, we proceeded to test the key carbocyclization reaction using conditions previously established by Bender and Prestwich.[22,23] A solution of enol acetate **11** in aqueous acetone was treated with $Hg(OTFA)_2$, then aqueous NaOAc and NaCl were added and the reaction proceeded overnight. The major product of the reaction, inosose derivative **12**, was isolated in 54% yield, a figure consistent with literature reports on similar Ferrier carbocyclizations wherein the remainder of the mass balance was mainly attributed to minor stereoisomers.[22,23] Structural assignment of **12** was supported by NMR analysis. Using inositol

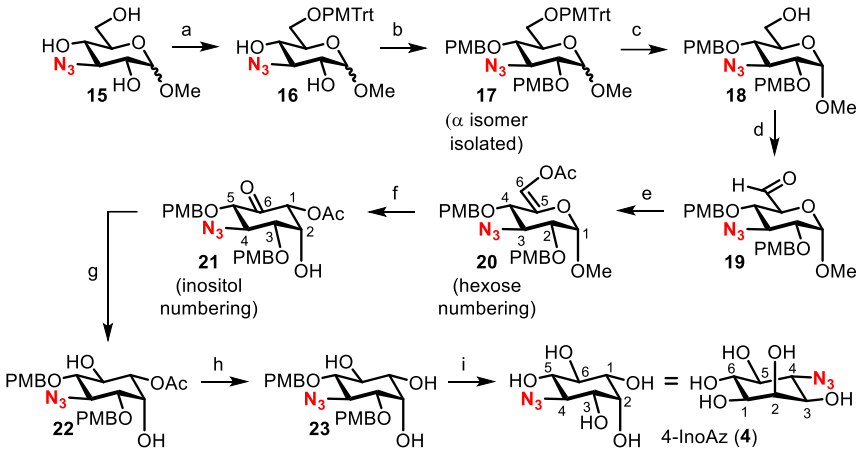
numbering for reference, the ^{1}H NMR spectrum contained a downfield-shifted H-1 absorption at 5.21 ppm, supporting the presence of an electron-withdrawing 1-*O*-acetyl group, while the ^{13}C NMR spectrum contained an absorption at 197.3 ppm, implying the presence of a ketone at C-6. The Ferrier cyclization generates two stereocenters at C-1 and C-2, and thus four diastereomeric inososе products are possible. However, the reaction typically proceeds with high diastereoselectivity to avoid transition state conformations involving twist-boat-like geometries and 1,3-diaxial interactions, ultimately favoring the desired inososе products with equatorial and axial substituents at C-1 and C-2, respectively, as shown for compound **12**.[21] We established an axial orientation of the hydroxyl group at C-2 based on the known stereochemistry of the C-3 azido group using ^{1}H NMR vicinal coupling constants ($^{3}J_{\text{H-2,H-3}}$ = 2.2 Hz). We attempted to determine the C-1 stereochemistry of **12** in a similar manner, but the $^{3}J_{\text{H-1,H-2}}$ coupling constant could not be unambiguously calculated because the H-1 splitting pattern was complicated by long-range coupling to H-5 through the *sp*^{2}-hybridized C-6. Anticipating that the C-1 configuration could be established subsequently, we proceeded to the next step, which involved stereoselective hydride reduction of the C-6 ketone to complete the inositol core structure. To achieve this transformation, $NaBH(OAc)_3$ was used as a substrate-tethering reducing reagent, which enabled C-2 hydroxyl-directed delivery of hydride to the C-6 carbonyl group, generating diol **13** in 60% yield. The stereochemistry of C-1 and C-6 were both determined at this stage by ^{1}H NMR coupling constant analysis. The equatorial orientation of the C-6 hydroxyl group was confirmed through H-6 coupling to H-5 ($^{3}J_{\text{H-5,H-6}}$ = 9.3 Hz). Finally, the stereochemistry of C-1 was established through H-1 couplings to H-6 ($^{3}J_{\text{H-1,H-6}}$ = 10.2 Hz) and H-2 ($^{3}J_{\text{H-1,H-2}}$ = 2.6 Hz). Thus, over the preceding two steps, including the key Ferrier carbocyclization reaction and ketone reduction, three contiguous tertiary stereocenters were set with good selectivity.

With the inositol core structure established in intermediate **13**, we proceeded to the deprotection sequence. Deacetylation of the 1-*O*-position was accomplished smoothly with $NaOCH_3/CH_3OH$ to give **14** in 79% yield. Lastly, the PMB protecting groups at the 4-*O*- and 5-*O*-positions were removed with 10% trifluoroacetic acid (TFA), providing 3-InoAz (**3**) in 71% yield with its azido group intact. This last step highlights the advantage of using acid-labile PMB protecting groups versus more commonly employed benzyl protecting groups, whose reductive removal would destroy the “clickable” azido group. Overall, the synthesis of the enantiomerically pure target compound **3** from azido glucoside **6** proceeded in 9 total steps and in 4.2% yield. We also tested whether the

β anomer of **11** participated in the Ferrier carbocyclization, and found that it behaved identically to the α anomer, generating the same major inososе product **12** in comparable yield. Therefore, the separation and parallel advancement of anomeric isomers can be avoided, which will significantly simplify and improve the efficiency of future syntheses.

Synthesis of 4-InoAz (4). The synthesis of 4-InoAz (**4**), which is depicted in Scheme 3, followed the same procedures as the synthesis of 3-InoAz and yielded similar results. The starting material, an anomeric mixture of methyl 3-azido-3-deoxy-D-glucopyranoside **15**,[28] was subjected to selective 6-*O*-*para*-methoxytritylation to give **16** (77%), *para*-methoxybenzylation of the 2-*O*- and 4-*O*-positions to give **17** (77%; α and β anomers were separated at this stage), and acid-mediated removal of the PMTrt group to give **18** (88%). With the primary alcohol differentiated in compound **18**, the Swern oxidation–enol acetate formation sequence was carried out to provide compound **20** in 62% yield over two steps. Moving forward, enol acetate **20** was subjected to Ferrier conditions as described above, which produced the desired inososе derivative **21** in 47% yield. In the case of the 4-InoAz isomer, ^{1}H NMR coupling constants were successful in establishing the expected stereochemistry at C-1 and C-2 ($^{3}J_{\text{H-1,H-2}}$ = 2.5 Hz; $^{3}J_{\text{H-2,H-3}}$ = 2.4 Hz), and ^{1}H and ^{13}C NMR chemical shifts for H-1 (5.10 ppm) and C-6 (196.9 ppm), respectively, confirmed the presence of *O*-acetyl and ketone functionalities at those positions. Hydroxyl-directed stereoselective ketone reduction with $NaBH(OAc)_3$ gave diol **22** in 70% yield, then the two-step deprotection sequence of deacetylation (80%) and PMB hydrolysis (81%) provided the target 4-InoAz (**4**). This 9-step synthesis of enantiopure **4** from azido glucoside **14** proceeded in 7.8% overall yield, similar to the results of the 3-InoAz synthesis.

Scheme 3. Synthesis of 4-InoAz (**4**).[a]

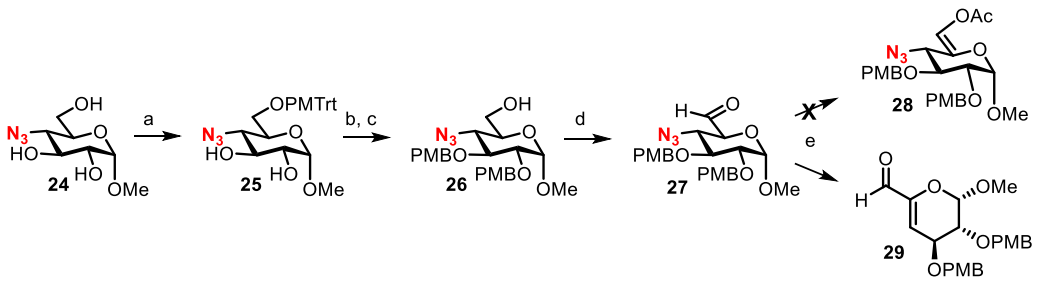


[a]Reagents and conditions: (a) PMTrtCl, pyridine, 0 °C → rt, 86%; (b) NaH, PMBCl, DMF, 0 °C → rt, 77%; (c) AcOH, H_2O, CH_2Cl_2, 88%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; then Et_3N, –78 °C → rt; (e) Ac_2O, DMAP, K_2CO_3, CH_3CN, 70 °C, 62% over two steps; (f) $Hg(OTFA)_2$, acetone–H_2O (4:1); then NaOAc, NaCl, 0 °C, 47%; (g) $Na(OAc)_3BH$, AcOH, CH_3CN, 0 °C, 70%; (h) NaOMe, MeOH, 80%; (i) TFA, CH_2Cl_2, H_2O, 82%.

Attempted synthesis of 5-InoAz (5). The final target molecule was 5-InoAz (**5**), which, like the 3- and 4-InoAz regioisomers, was predicted to be accessible from the corresponding azido glucoside (**24**) via Ferrier carbocyclization. The initial phase of the synthesis starting from **24**[29] went as expected, as 6-*O*-*para*-methoxytritylation (91%), *para*-methoxybenzylation (65%), and PMTrt removal (96%) proceeded without issue. The primary alcohol arising from this sequence **26** was successfully oxidized to aldehyde **27** by Swern oxidation. However, the major product observed when **27** was treated with K_2CO_3, acetic anhydride, and DMAP was not the desired enol acetate **28** (not observed), but rather the unanticipated β-elimination product, enal **29** (47%). Attempts to produce **28** through adjustments to temperature, stoichiometry, and base/acetylation reagents failed, as **29** was always observed as the major product. Compound **29** could have been favored due to the stability of the α,β-unsaturated carbonyl group or the entropically favorable elimination. An E2-type elimination mechanism was considered unlikely since azide anion is a poor leaving group, the azido group and the abstracted proton in **27** do not have anti-periplanar geometry, and the β-elimination proceeded even with weak bases such as Et_3N. It is possible that enal **29** was formed through an E1cB mechanism involving K_2CO_3-mediated deprotonation of the 5-position

to form a resonance-stabilized aldehyde enolate (the expected intermediate en route to the desired product **28**), which subsequently underwent elimination, ejecting the 4-position azido group. Although elimination reactions of β-azido carbonyl compounds to form the corresponding α,β-unsaturated carbonyl compounds appear to be rare, there are reports of carbohydrate-based lactones and lactams undergoing similar β-eliminations in which C-3 azido,[30] methoxy,[31] or benzyloxy[32] groups acted as leaving groups. Despite the fact that 5-InoAz was inaccessible, the need to achieve this particular target compound using the Ferrier carbocyclization is diminished in comparison to 3- and 4-InoAz, because 5-position-modified inositol analogues are achiral and do not require resolution. Indeed, Sureshan and co-workers recently reported an elegant one-pot double substitution approach that delivered achiral 2- and 5-InoAz from inositol, each in 4 steps and in 10–15% overall yield.[33]

Scheme 4. Attempted synthesis of 5-InoAz (**5**).[a]



[a]Reagents and conditions: (a) PMTrtCl, pyridine, 0 °C → rt, 91%; (b) NaH, PMBCl, DMF, 0 °C → rt, 65%; (c) AcOH, H_2O, CH_2Cl_2, 96%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; then Et_3N, –78 °C → rt; (e) Ac_2O, DMAP, K_2CO_3, CH_3CN, 70 °C, 47% of **29** over two steps (compound **28** not detected).

Conclusion

Our interest in developing MCRs and inhibitors of inositol-containing metabolites and glycoconjugates in mycobacteria (e.g., mycothiol, PIMs, LM, or LAM) motivated us to explore chemistries for accessing InoAz analogues. While a number of approaches to inositol derivative synthesis have been developed, InoAz analogues are still difficult to produce efficiently—particularly structures modified at the 1-, 3-, 4-, and 6-positions. Previous syntheses of such compounds, described in the introduction, took 9–11 steps and ranged in overall yield from approximately 1–25%; in some of those cases, racemic mixtures were not resolved. In the present work, we sought

to apply the Ferrier carbocyclization reaction to the synthesis of InoAz analogues, reasoning that it should provide access to multiple enantiomerically pure isomers relevant to our mycobacteria research program, without the need for chiral resolution or late-stage azido group installation. This approach successfully delivered 3- and 4-InoAz in 9 steps from azido glucosides in 4–8% overall yield, while 5-InoAz was inaccessible due to an unexpected β-elimination reaction. Extension of the Ferrier carbocyclization to a new class of compounds was also valuable because it further elucidated the scope and limitations of this widely used reaction. Overall, the reported approach exhibited comparable efficiency to most prior reports and it should be amenable to scale-up. To date, Altenbach's enzyme-mediated *de novo* syntheses of 1-, 3-, 4-, and 6-InoAz from *p*-benzoquinone remain the most efficient preparations of these molecules at 10 steps and about 25% overall yield.[19] However, given the ability of the Ferrier carbocyclization to tolerate a variety of functional groups and stereochemistries, as revealed in prior work[21] and herein, it is a versatile and efficient option for producing InoAz analogues and related compounds. Although Hg(II) reagents have proven successful for the Ferrier carbocyzliation, alternative conditions (e.g., use of palladium catalysts[34]) to reduce or eliminate their usage in InoAz syntheses would be beneficial. Despite the success of the prior and present approaches, the synthesis of inositol analogues remains a challenge. In the future, the development of novel synthetic approaches, for instance chemoenzymatic methods in the vein of our work on trehalose analogues,[35–38] may further improve synthetic efficiency and accelerate access to additional inositol analogues for evaluation as probes or inhibitors. We are currently evaluating 3- and 4-InoAz as MCRs for metabolic labeling of inositol-containing biomolecules in mycobacteria. As noted above, InoAz analogues have also shown inhibitory activity in various systems, so it will be of interest to test these compounds as inhibitors of inositol metabolism and bacterial growth. Whether InoAz analogues are determined to behave as MCRs or inhibitors, or both, they can be leveraged to investigate the role of inositol metabolism and inositol glycoconjugates in mycobacterial physiology and pathogenesis.

Experimental

General experimental for synthesis. Materials were obtained from commercial sources without further purification. Anhydrous solvents were obtained either commercially or from an alumina column solvent purification system. Analytical TLC was performed on glass-backed silica gel 60 Å plates (thickness 250 μm) and detected by

UV or staining (typically charring with 5% H_2SO_4 in EtOH) when appropriate. ^1H, ^{13}C, gCOSY, and HSQC NMR spectra were obtained using Varian Inova 500 or Varian Mercury 300 instruments. Coupling constants (*J*) are reported in hertz (Hz) with chemical shifts in ppm (δ) referenced to solvent peaks or an internal acetone standard, with the following splitting abbreviations: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, m = multiplet. High-resolution electrospray ionization (HR ESI) mass spectra were obtained using a Waters LCT premier XE using the following internal standards for the lock mass: reserpine for positive mode analyses, raffinose for negative mode analyses, and *myo*-inositol for 3- and 4-InoAz analyses.

Methyl 2-azido-2-deoxy-6-*O*-(*p*-methoxytrityl)-D-glucopyranoside (7). After dissolving compound **6-(α/β)**[27] (1.02 g, 4.65 mmol) in anhydrous pyridine (20 mL), the flask was purged with argon and cooled in an ice bath. While the reaction mixture was stirring, PMTrtCl (2.94 g, 9.52 mmol) was added in portions. After stirring overnight with gradual warming to room temperature, TLC showed complete consumption of starting material. Excess methanol was added to quench unreacted PMTrtCl. The solution was transferred to a separatory funnel containing ice water, which was extracted with CH_2Cl_2 three times. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting oil was purified using silica gel chromatography (toluene/EtOAc 3:1 with 1% Et_3N) to give compound **7-(α/β)** (1.30 g, 57%) as a white solid. The anomeric mixture was separable by this method of purification. TLC (toluene/EtOAc 3:1): **7-(α)**, R_f = 0.38, **7-(β)**; R_f = 0.36. ^1H NMR of **7-(α)** (500 MHz, $CDCl_3$): δ 7.47–7.45 (m, 4 H, ArH), 7.35–7.30 (m, 6 H, ArH), 7.26–7.22 (m, 2 H, ArH), 6.86–6.85 (m, 2 H, ArH), 4.78 (d, *J* = 3.6 Hz, 1 H, H-1), 3.94 (dd, *J* = 8.9, 10.2 Hz, 1 H, H-3), 3.79 (s, 3 H, OCH_3), 3.68–3.65 (m, 1 H, H-5), 3.55 (t, *J* = 9.0 Hz, 1 H, H-4), 3.41 (s, 3 H, OCH_3), 3.40 (d, *J* = 6.2 Hz, 2 H, H-6a and H-6b), 3.25 (dd, *J* = 3.6, 10.3 Hz, 1 H, H-2), 2.96 (s, 1 H, C-3 OH), 2.85 (s, 1 H, C-4 OH). $^{13}C\{^1H\}$ NMR of **7-(α)** (125 MHz, $CDCl_3$): δ 158.7, 143.99, 143.98, 135.1, 130.3, 128.3, 128.2, 128.0, 127.1, 113.2, 98.6, 87.0, 73.0, 71.8, 69.4, 64.0, 62.8, 55.22, 55.19. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{29}N_3O_6Na$ 514.1954; Found, 514.1959. ^1H NMR of **7-(β)** (500 MHz, $CDCl_3$): δ 7.46–7.44 (m, 4 H, ArH), 7.34–7.29 (m, 6 H, ArH), 7.25–7.22 (m, 2 H, ArH), 6.86–6.84 (m, 2 H, ArH), 4.23 (d, *J* = 8.0 Hz, 1 H, H-1), 3.80 (s, 3 H, OCH_3), 3.58 (t, *J* = 7.2 Hz, 1 H, H-4), 3.58 (s, 3 H, OCH_3), 3.47–3.36 (m, 4 H, H-3, H-5, H-6), 3.30 (dd, *J* = 8.0, 10.0 Hz, 1 H, H-2) 3.04 (bs, 1 H, C_4-OH), 2.86 (bs, 1 H, C_3-OH). $^{13}C\{^1H\}$ NMR of **7-(β)** (125 MHz, $CDCl_3$): δ 158.7, 143.9, 143.8, 135.0, 130.3, 128.25,

128.24, 128.0, 127.1, 113.3, 102.8, 87.0, 74.9, 73.5, 72.5, 65.6, 64.1, 57.0, 55.2. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{29}N_3O_6Na$ 514.1954; Found 514.1974.

Methyl 2-azido-2-deoxy-3,4-di-*O*-(*p*-methoxybenzyl)-6-*O*-(*p*-methoxytrityl)-α-D-glucopyranoside (8). Compound **7-(α)** (2.42 g, 4.92 mmol) was dissolved in anhydrous DMF (100 mL) and the solution was stirred with cooling over an ice bath. After purging the flask with argon, sodium hydride (0.672 g, 28.0 mmol) was added in portions. After stirring over an ice bath for approximately 30 min, PMBCl (2.0 mL, 14.8 mmol) was added dropwise. The reaction was stirred overnight, after which TLC indicated completion. The reaction mixture was diluted with H_2O and extracted three times with CH_2Cl_2. The combined organic layer was then washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to give **8** as a yellow oil. The crude material was subjected to the next reaction without further purification. TLC (Hex/EtOAc 8:1): R_f = 0.28.

Methyl 2-azido-2-deoxy-3,4-di-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside (9). The crude yellow oil containing compound **8** was dissolved in CH_2Cl_2 (100 mL) and the solution was stirred. A solution of glacial acetic acid (18.5 mL) in water (6.0 mL) was added to the reaction mixture dropwise. The reaction was stirred overnight, after which TLC indicated completion. The reaction mixture was transferred to a separatory funnel and neutralized with saturated aqueous $NaHCO_3$. Following extraction of the mixture with CH_2Cl_2 three times, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified by silica gel chromatography (Hex/EtOAc 4:1) to give compound **9** (1.78 g, 78% over two steps) as a white solid. TLC (Hex/EtOAc 4:1): R_f = 0.25. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.23 (m, 4 H, ArH), 6.90–6.87 (m, 4 H, ArH), 4.83–4.80 (m, 3 H, PMB CH_2), 4.77 (d, J = 3.5 Hz, 1 H, H-1), 4.60 (d, J = 10.8 Hz, 1 H, PMB CH_2), 3.96 (dd, J = 8.7, 10.1 Hz, 1 H, H-4), 3.81 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.79–3.64 (m, 3 H, H-5, H-6), 3.56 (t, J = 8.7 Hz, 1 H, H-3), 3.40 (s, 3 H, OCH_3), 3.37 (dd, J = 3.6, 10.2 Hz, 1 H, H-2). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 159.42, 159.39, 130.00, 129.97, 129.8, 129.6, 113.94, 113.89, 98.7, 80.1, 77.6, 75.2, 74.7, 71.2, 63.7, 61.6, 55.28, 55.27, 55.2. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{29}N_3O_7Na$ 482.1903; Found 482.1913.

Methyl 2-azido-2-deoxy-3,4-di-*O*-(*p*-methoxybenzyl)-α-D-glucohexoaldo-1,5-pyranoside (10). Oxalyl chloride (0.72 mL, 8.4 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL) and the solution was stirred at –78 °C under argon. After approximately 15 min, DMSO (1.2 mL, 17 mmol) was added dropwise and the solution was stirred for 15 min. Next, a solution of compound **9** (0.780 g, 1.70 mmol) in anhydrous CH_2Cl_2 (15 mL) was

transferred to the reaction mixture dropwise. After stirring for 30 min, Et_3N (3.6 mL, 26 mmol) was added and the reaction was stirred for 15 min at –78 °C followed by gradual warming to room temperature. After reaching room temperature, the reaction was diluted with EtOAc and washed with brine three times. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum to give **10** an opaque yellow oil, which was subjected to the next reaction without further purification.

(*Z*)-Methyl 6-*O*-acetyl-2-azido-2-deoxy-3,4-di-*O*-(*p*-methoxybenzyl)-α-D-gluco-5-enopyranoside (11). The crude oil containing compound **10** was dissolved in anhydrous CH_3CN (20 mL). While stirring under argon, DMAP (27 mg, 0.22 mmol) and K_2CO_3 (1.88 g, 13.6 mmol) were added followed by Ac_2O (0.50 mL, 5.3 mmol), then the reaction was heated to 75 °C. After stirring overnight at 75 °C, the reaction mixture was diluted with EtOAc and washed with brine three times. After drying the organic layer over $MgSO_4$, filtration, and concentration by vacuum, the crude material was purified by silica gel chromatography (Hex/EtOAc 4:1) to give compound **11** (0.442 g, 52% over two steps) as a pale yellow oil. TLC (Hex/EtOAc 4:1): R_f = 0.24. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.26 (m, 4 H, ArH), 7.20 (d, J = 1.9 Hz, 1 H, H-6), 6.90–6.86 (m, 4 H, ArH), 4.91 (d, J = 3.4 Hz, 1 H, H-1), 4.82 (d, J = 10.4 Hz, 1 H, PMB CH_2), 4.74–4.65 (m, 3 H, PMB CH_2), 4.00 (dd, J = 2.0, 8.6 Hz, 1 H, H-4), 3.91 (t, J = 9.7 Hz, 1 H, H-3), 3.81 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 3.47 (dd, J = 3.4, 9.8 Hz, 1 H, H-2), 2.18 (s, 3 H, OAc CH_3). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.2, 159.5, 134.6, 129.9, 129.8, 129.7, 129.4, 123.4, 114.0, 113.9, 100.0, 79.1, 78.1, 77.1, 75.1, 74.1, 62.9, 56.3, 55.3, 20.6. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{29}N_3O_8Na$ 522.1852; Found 522.1856.

(1R,2R,3S,4R,5S)-3-Azido-2-hydroxy-4,5-di-O-(*p*-methoxybenzyl)-6-oxocyclohexyl acetate (12). Compound **11** (0.378 g, 0.757 mmol) was dissolved in acetone (3.7 mL) and water (0.92 mL) and placed over an ice bath. While stirring, $Hg(OTFA)_2$ (0.408 g, 0.956 mmol) was added. After 10 min, the reaction mixture was diluted with acetone (10 mL) followed by the addition of 3M aqueous NaOAc (0.32 mL) and brine (0.53 mL). After stirring overnight, TLC indicated consumption of starting material. The reaction mixture was diluted with water and extracted with CH_2Cl_2 three times. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified by silica gel chromatography (Hex/EtOAc 2:1) to give compound **12** (0.200 g, 54%) as an off-white solid. TLC (Hex/EtOAc 2:1): R_f = 0.27. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.24 (m, 4 H, ArH), 6.90–6.86 (m, 4 H, ArH), 5.21 (dd, J = 1.0, 2.7 Hz, 1 H, H-1), 4.89 (d, J = 10.1 Hz, 1

H, PMB CH_2), 4.87 (d, J = 10.9 Hz, 1 H, PMB CH_2), 4.70 (d, J = 10.1 Hz, 1 H, PMB CH_2), 4.47 (d, J = 10.8 Hz, 1 H, PMB CH_2), 4.34–4.33 (m, 1 H, H-2), 4.20 (dd, J = 1.1, 9.2 Hz, 1 H, H-5), 4.07 (t, J = 9.3 Hz, 1 H, H-4), 3.82 (dd, J = 2.2, 9.7 Hz, 1 H, H-3), 3.81 (s, 6 H, 2x OCH_3), 2.25 (s, 3 H, OAc CH_3). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 197.3, 169.5, 159.6, 159.5, 130.14, 130.06, 129.5, 129.1, 113.9, 113.8, 84.2, 80.1, 75.6, 75.4, 73.3, 70.5, 63.0, 55.3, 20.5. HRMS (ESI-TOF) m/z: $[M+K]^+$ Calcd for $C_{24}H_{27}N_3O_8K$ 524.1435; Found 524.1458.

1-*O*-Acetoxy-3-azido-3-deoxy-4,5-di-*O*-(*p*-methoxybenzyl)-*myo*-inositol (13). Compound **12** (28.7 mg, 0.059 mmol) was dissolved in anhydrous CH_3CN (2.0 mL) and cooled over an ice bath. While stirring, $Na(OAc)_3BH$ (115 mg, 0.543 mmol) was added, followed by glacial acetic acid (0.20 mL, 3.5 mmol). After approximately 1 h, TLC indicated completion. The reaction mixture was diluted with water and extracted using EtOAc. The resulting organic layer was then dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified using silica gel chromatography (Hex/EtOAc 2:3) to give compound **13** (17.4 mg, 60%) as a white solid. TLC (Hex/EtOAc 2:1): R_f = 0.46. ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.26 (m, 4 H, ArH), 6.91–6.87 (m, 4 H, ArH), 4.91–4.76 (m, 3 H, PMB CH_2), 4.71 (dd, J = 2.6, 10.2 Hz, 1 H, H-1), 4.70 (d, J = 10.6 Hz, 1 H, PMB CH_2), 4.19 (t, J = 2.4 Hz, 1 H, H-2), 4.03 (t, J = 9.7 Hz, 1 H, H-6), 3.91 (t, J = 9.7 Hz, 1 H, H-4), 3.80 (s, 6 H, 2x OCH_3), 3.48 (dd, J = 2.5, 10.1 Hz, 1 H, H-3), 3.40 (t, J = 9.3 Hz, 1 H, H-5), 2.15 (s, 3 H, OAc CH_3). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 170.4, 159.47, 159.45, 130.3, 130.0, 129.8, 129.5, 114.1, 113.9, 83.5, 79.6, 75.5, 75.3, 73.3, 70.5, 69.4, 63.9, 55.3, 29.7, 21.0. HRMS (ESI-TOF) m/z: $[M+HCO_2]^-$ Calcd for $C_{25}H_{30}N_3O_{10}$ 532.1931; Found 532.1943.

3-Azido-3-deoxy-4,5-di-*O*-(*p*-methoxybenzyl)-*myo*-inositol (14). After a solution of compound **13** (200 mg, 0.410 mmol) in 18 mL of freshly prepared 0.05 M $NaOCH_3$ in methanol was stirred for 30 min, it was neutralized to ~pH 7 using Dowex H^+ resin. The solution was filtered and concentrated under vacuum. The crude material was purified using silica gel chromatography (Hex/EtOAc 1:8) to give compound **14** (145 mg, 79%) as a white solid. TLC (Hex/EtOAc 1:8): R_f = 0.27. ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.29 (m, 4 H, ArH), 6.91–6.87 (m, 4 H, ArH), 4.90 (d, J = 11.1 Hz, 1 H, PMB CH_2), 4.86–4.78 (m, 2 H, PMB CH_2), 4.66 (d, J = 11.1 Hz, 1 H, PMB CH_2), 4.15 (t, J = 2.7 Hz, 1 H, H-2), 3.90 (t, J = 9.7 Hz, 1 H, H-6), 3.81 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.78 (t, J = 9.6 Hz, 1 H, H-4), 3.45 (dd, J = 2.9, 9.6 Hz, 1 H, H-3), 3.41 (dd, J = 2.6, 10.1 Hz, 1 H, H-1), 3.32 (t, J = 9.3 Hz, 1 H, H-5). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 159.5, 130.0, 129.5, 114.1, 113.9, 83.1, 80.0, 76.3, 75.4,

75.1, 72.8, 72.1, 70.6, 64.0, 55.3. HRMS (ESI-TOF) m/z: $[M+Cl]^-$ Calcd for $C_{22}H_{27}N_3O_7Cl$ 480.1537; Found 480.1550.

3-Azido-3-deoxy-*myo*-inositol (3). Compound **14** (129 mg, 0.290 mmol) was dissolved in CH_2Cl_2 (50 mL) to give a clear colorless solution. While stirring, trifluoroacetic acid (5.0 mL) and water (1.0 mL) were added. After 30 min of stirring, the solution was purple in color and TLC indicated complete consumption of the starting material. The reaction mixture was co-evaporated with toluene under vacuum. The resulting crude material was purified using silica gel chromatography (CH_2Cl_2/MeOH 3:1 with 1% AcOH) to give compound **3** (42.2 mg, 71%) as a white solid. TLC (CH_2Cl_2/MeOH 3:1): R_f = 0.40. ^{1}H NMR (300 MHz, D_2O): δ 4.18 (t, J = 2.7 Hz, 1 H, H-2), 3.76 (t, J = 10.0 Hz, 1 H, H-4), 3.63 (t, J = 9.7 Hz, 1 H, H-5), 3.55 (dd, J = 2.8, 9.9 Hz, 1 H, H-1), 3.45 (dd, J = 2.7, 10.6 Hz, 1 H, H-3), 3.36 (t, J = 9.1 Hz, 1 H, H-6). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, referenced to an acetone internal standard): δ 65.6, 62.9, 62.2, 62.1, 61.7, 54.0. HRMS (ESI-TOF) m/z: $[M-H]^-$ Calcd for $C_6H_{10}N_3O_5$ 204.0620; Found 204.0614.

Methyl 3-azido-3-deoxy-6-*O*-(*p*-methoxytrityl)-D-glucopyranoside (16). After dissolving compound **15-(α/β)**[28] (5.98 g, 27.3 mmol) in anhydrous pyridine (100 mL), the flask was purged with argon and cooled in an ice bath. While stirring, PMTrtCl (17.61 g, 5.703 mmol) was added in portions to the reaction mixture. After stirring overnight with gradual warming to room temperature, TLC showed complete consumption of starting material. The solution was quenched with excess methanol, transferred to a separatory funnel containing ice water, and extracted three times with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting crude oil was purified using silica gel chromatography (toluene/EtOAc 3:1 with 1% Et_3N) to compound **16-(α/β)** (11.59 g, 86%) as a white solid. TLC (toluene/EtOAc 1:1) of **16-(α/β)**: R_f = 0.60. ^{1}H NMR (500 MHz, $CDCl_3$, peaks from the major anomer **16-(α)** are listed): δ 7.46–7.44 (m, 4 H, ArH), 7.35–7.23 (m, 8 H, ArH), 6.87–6.84 (m, 2 H, ArH), 4.74 (d, J = 2.0 Hz, 1 H, H-1), 3.80 (s, 3 H, OCH_3), 3.66 (dt, J = 4.8, 9.6 Hz, 1 H, H-4), 3.54 (dd, J = 3.5, 10.4 Hz, 1 H, H-2), 3.49–3.45 (m, 2 H, H-3, H-5), 3.44 (s, 3 H, OCH_3), 3.40 (d, J = 4.9 Hz, 2 H, H-6), 2.79 (d, J = 2.9 Hz, 1 H, C4-OH), 2.28 (d, J = 9.4 Hz, 1 H, C2-OH). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, peaks from both anomers are listed): δ 158.72, 158.68, 149.5, 144.4, 144.0, 143.9, 143.7, 136.2, 135.1, 134.9, 130.33, 130.27, 129.0, 128.4, 128.3, 128.22, 128.18, 127.99, 127.96, 127.84, 127.81, 127.7, 127.12, 127.08, 126.7, 125.3, 123.8,

113.29, 113.25, 113.2, 113.0, 103.6, 98.5, 87.2, 87.1, 74.2, 72.7, 71.8, 71.3, 71.2, 69.5, 68.0, 67.1, 64.4, 64.1, 57.0, 55.3, 55.20, 51.16. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{29}N_3O_6Na$ 514.1954; Found 514.1974.

Methyl 3-azido-3-deoxy-2,4-di-*O*-(*p*-methoxybenzyl)-6-*O*-(*p*-methoxytrityl)-D-glucopyranoside (17). Compound **16-(α/β)** (11.59 g, 23.58 mmol) was dissolved in anhydrous DMF (150 mL) and the solution was stirred with cooling over an ice bath. After purging the flask with argon, sodium hydride (4.72 g, 197 mmol) was added in portions. After stirring over an ice bath for approximately 30 min, PMBCl (16.1 mL, 119 mmol) was added dropwise. The reaction was stirred overnight, after which TLC indicated completion. The reaction mixture was diluted with H_2O and extracted three times with EtOAc. The combined organic layer was then washed with brine three times, dried over $MgSO_4$, filtered, and concentrated under vacuum to give a yellow oil. The crude material was purified by silica gel chromatography (Hex/EtOAc 4:1 with 1% Et_3N) to give compound **17-(α/β)** (13.21 g, 77%) as a yellow solid. The anomeric mixture was separable by this method of purification. TLC (Hex/EtOAc 4:1): **17-(α)**, R_f = 0.31, **17-(β)**; R_f = 0.41. ^{1}H NMR of **17-(α)** (500MHz, $CDCl_3$): δ 7.49–7.46 (m, 4 H, ArH), 7.37–7.22 (m, 10 H, ArH), 6.94–6.92 (m, 2 H, ArH), 6.86–6.82 (m, 4 H, ArH), 6.75–6.73 (m, 2 H, ArH), 4.76 (d, J = 11.9 Hz, 1 H, PMB CH_2), 4.67 (d, J = 3.5 Hz, 1 H, H-1), 4.65 (d, J = 12.0 Hz, 1 H, PMB CH_2), 4.57 (d, J = 10.0 Hz, 1 H, PMB CH_2), 4.18 (d, J = 10.0 Hz, 1 H, PMB CH_2), 3.87 (t, J = 9.9 Hz, 1 H, H-3), 3.83 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.77 (ddd, J = 1.9, 5.2, 10.3 Hz, 1 H, H-5), 3.48 (dd, J = 1.8, 10.1 Hz, 1 H, H-6a or H-6b), 3.42 (s, 3 H, OCH_3), 3.41 (dd, J = 2.8, 9.7 Hz, 1 H, H-2), 3.37 (t, J = 9.8 Hz, 1 H, H-4), 3.16 (dd, J = 4.9, 10.2 Hz, 1 H, H-6a or H-6b). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 159.5, 159.3, 158.5, 144.6, 144.2, 135.4, 130.5, 130.0, 129.8, 129.7, 129.5, 128.5, 128.4, 127.79, 127.78, 126.8, 113.9, 113.6, 113.1, 97.0, 86.1, 77.7, 76.4, 74.3, 72.7, 69.9, 65.5, 62.3, 55.3, 55.2, 55.1, 54.9. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{43}H_{45}N_3O_8Na$ 754.3104; Found 754.3093. ^{1}H NMR of **17-(β)** (500MHz, $CDCl_3$): δ 7.55–7.51 (m, 4 H, ArH), 7.39–7.36 (m, 4 H, ArH), 7.32–7.29 (m, 4 H ArH), 7.26–7.23 (m, 2 H, ArH), 6.93–6.91 (m, 2 H, ArH), 6.87–6.82 (m, 4 H, ArH), 6.76–6.73 (m, 2 H, ArH), 4.87 (d, J = 10.6 Hz, 1 H, PMB CH_2), 4.70 (d, J = 10.7 Hz, 1 H, PMB CH_2), 4.57 (d, J = 9.8 Hz, 1 H, PMB CH_2), 4.34 (d, J = 7.7 Hz, 1 H, H-1), 4.25 (d, J = 9.9 Hz, 1 H, PMB CH_2), 3.82 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 3.58 (t, J = 9.6 Hz, 1 H, H-3 or H-4), 3.58 (dd, 1 H, J = 1.9, 10.2 Hz, H-6a or H-6b), 3.49 (t, J = 9.6 Hz, 1 H, H-3 or H-4), 3.38 (ddd, J = 1.9, 3.6, 9.7 Hz, 1 H, H-5), 3.31 (dd, J = 7.7, 9.8 Hz, 1 H, H-2), 3.23 (dd, J = 3.8, 10.3 Hz, 1 H, H-6a or H-6b). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 159.4, 158.6,

144.5, 144.2, 135.4, 130.6, 130.2, 130.1, 130.0, 129.5, 128.7, 128.5, 127.83, 127.82 126.91, 126.88, 113.8, 113.7, 113.1, 104.5, 86.2, 79.8, 76.2, 75.2, 74.3, 74.2, 68.4, 62.1, 56.6, 55.29, 55.25, 55.2. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{43}H_{45}N_3O_8Na$ 754.3104; Found 754.3098.

Methyl 3-azido-3-deoxy-2,4-di-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside (18). To a stirring solution of **17-(α)** (3.30 g, 4.51 mmol) in CH_2Cl_2 (3.3 mL), a solution of glacial acetic acid (16.8 mL) and water (1.0 mL) was added dropwise over 5 minutes. After stirring overnight, TLC indicated completion. The reaction was diluted with CH_2Cl_2, transferred to a separatory funnel, and neutralized with saturated aqueous $NaHCO_3$. The aqueous layer was extracted using CH_2Cl_2 twice, and the combined organic layers were washed once with water, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified by silica gel chromatography (toluene/EtOAc 2:1) to give **18** (1.83 g, 88%) as a colorless oil. TLC (toluene/EtOAc 2:1): R_f = 0.20. ^{1}H NMR (500MHz, $CDCl_3$): δ 7.33–7.28 (m, 4 H, ArH), 6.91–6.88 (m, 4 H, ArH), 4.80 (d, J = 10.6 Hz, 1 H, PMB CH_2), 4.73 (d, J = 12.0 Hz, 1 H, PMB CH_2), 4.59 (d, J = 12.8 Hz, 1 H, PMB CH_2), 4.56 (d, J = 10.9 Hz, 1 H, PMB CH_2), 4.48 (d, J = 3.5 Hz, 1 H, H-1), 3.90 (t, J = 9.9 Hz, 1 H, H-3), 3.81 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.76–3.66 (m, 2 H, H-6), 3.59 (dt, J = 3.2, 9.9 Hz, 1 H, H-5), 3.33 (s, 3 H, OCH_3) 3.31 (t, J = 10.0 Hz, 1 H, H-4), 3.30 (dd, J = 3.3, 10.0 Hz, 1 H, H-2). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 159.51, 159.48, 130.0, 129.8, 129.7, 129.6, 129.0, 128.2, 113.91, 113.88, 97.3, 77.6, 75.4, 74.4, 72.8, 70.3, 65.2, 61.5, 55.24, 55.23, 55.2. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{29}N_3O_7Na$ 482.1903; Found 482.1885.

Methyl 3-azido-3-deoxy-2,4-di-*O*-(*p*-methoxybenzyl)-α-D-glucohexoaldo-1,5-pyranoside (19). Oxalyl chloride (0.04 mL, 0.47 mmol) was dissolved in anhydrous CH_2Cl_2 (3.0 mL) and the solution was stirred at –78 °C under argon. After approximately 5 min, DMSO (0.05 mL, 0.7 mmol) was added dropwise and the solution was stirred for 15 min. Next, a solution of compound **18** (0.105 g, 0.229 mmol) in anhydrous CH_2Cl_2 (3 mL) was transferred to the reaction mixture dropwise. After stirring for 30 min, Et_3N (0.19 mL, 1.4 mmol) was added and the reaction was stirred for 15 min at –78 °C followed by gradual warming to room temperature. After stirring overnight, the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O three times. The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum to give **19** as an opaque yellow oil, which was subjected to the next reaction without further purification.

(*Z*)-Methyl 6-*O*-acetyl-3-azido-3-deoxy-2,4-di-*O*-(*p*-methoxybenzyl)-α-D-gluco-5-enopyranoside (20). The crude oil containing compound **19** was dissolved in anhydrous CH_3CN (2.0 mL). While stirring under argon, DMAP (2.8 mg, 0.023 mmol) and K_2CO_3 (0.159 g, 1.15 mmol) were added followed by Ac_2O (0.065 mL, 0.69 mmol), then the reaction was heated to 70 ˚C. After stirring for 3 h at 70 ˚C, TLC indicated completion and the reaction was diluted with CH_2Cl_2 and washed three times with H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated by vacuum. The crude material was purified by silica gel chromatography (Hex/EtOAc 4:1) to give compound **20** (0.071 g, 62% over two steps) as a yellow oil. TLC (Hex/EtOAc 4:1): R_f = 0.30. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.28 (m, 4 H, ArH), 7.16 (d, *J* = 2.0 Hz, 1 H, H-6), 6.92–6.89 (m, 4 H, ArH), 4.75 (d, *J* = 11.9 Hz, 1 H, PMB CH_2), 4.70–4.65 (m, 2 H, PMB CH_2), 4.58 (d, *J* = 3.5 Hz, 1 H, H-1), 4.56 (d, *J* = 12.0 Hz, 1 H, PMB CH_2), 3.86 (t, *J* = 9.9 Hz, 1 H, H-3), 3.81 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.73 (dd, *J* = 1.9, 9.7 Hz, 1 H, H-4), 3.43 (s, 3 H, OCH_3), 3.37 (dd, *J* = 3.4, 10.1 Hz, 1 H, H-2), 2.15 (s, 3 H, OAc). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.2, 159.6, 134.0, 130.0, 129.8, 129.4, 129.0, 123.5, 113.93, 113.91, 99.1, 77.5, 77.0, 75.5, 74.1, 73.1, 64.6, 56.3, 55.3, 20.6. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{29}N_3O_8Na$ 522.1852; Found 522.1873.

(1R,2R,3S,4R,5S)-4-Azido-2-hydroxy-3,5-di-O-(*p*-methoxybenzyl)-6-oxocyclohexyl acetate (21). Compound **20** (40 mg, 0.082 mmol) was dissolved in acetone (1.6 mL) and water (0.40 mL) and placed over an ice bath. While stirring, $Hg(OTFA)_2$ (50 mg, 0.12 mmol) was added. After 10 min, 3M aqueous NaOAc (0.034 mL) and brine (0.090 mL) were added. After stirring overnight, TLC indicated consumption of starting material. The reaction mixture was diluted with water and extracted with CH_2Cl_2 three times. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified by silica gel chromatography (Hex/EtOAc 3:2) to give compound **21** (19.3 mg, 47%) as an off-white solid. TLC (Hex/EtOAc 3:2): R_f = 0.20. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.30 (m, 4 H, ArH), 6.92–6.88 (m, 4 H, ArH), 5.10 (dd, *J* = 1.0, 2.5 Hz, 1 H, H-1), 4.83 (d, *J* = 11.1 Hz, 1 H, PMB CH_2), 4.71 (d, *J* = 11.4 Hz, 1 H, PMB CH_2), 4.66 (d, *J* = 11.4 Hz, 1 H, PMB CH_2), 4.50 (d, *J* = 11.0 Hz, 1 H, PMB CH_2), 4.31 (t, *J* = 2.4 Hz, 1 H, H-2), 4.03 (t, *J* = 10.1 Hz, 1 H, H-4), 3.86 (d, *J* = 10.3 Hz, 1 H, H-5), 3.82 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.62 (dd, *J* = 2.3, 9.8 Hz, 1 H, H-3), 2.60 (bs, 1 H, C2-OH), 2.23 (s, 3 H, OAc CH_3). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 196.9, 169.8, 159.8, 159.6, 130.1, 129.9, 128.7, 128.6, 114.1, 113.9, 80.0, 76.7, 74.6, 73.0, 72.8, 69.6, 65.2, 55.29, 55.26, 20.5. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{27}N_3O_8Na$ 508.1696; Found 508.1720.

1-*O*-Acetoxy-4-azido-4-deoxy-3,5-di-*O*-(*p*-methoxybenzyl)-*myo*-inositol (22). Compound **21** (36 mg, 0.074 mmol) was dissolved in anhydrous CH_3CN (2.6 mL) and cooled over an ice bath. While stirring, $Na(OAc)_3BH$ (124 mg, 0.585 mmol) was added, followed by glacial acetic acid (0.20 mL, 3.5 mmol). After approximately 2 h, TLC analysis showed complete consumption of starting material. The reaction mixture was diluted with water and extracted with EtOAc. The resulting organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified using silica gel chromatography (Hex/EtOAc 1:2) to give compound **22** (25 mg, 69%) as a white solid. TLC (Hex/EtOAc 1:2): R_f = 0.32. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.30 (m, 4 H, ArH), 6.92–6.89 (m, 4 H, ArH), 4.87 (d, J = 10.8 Hz, 1 H, PMB CH_2), 4.68 (d, J = 11.0 Hz, 1 H, PMB CH_2), 4.65 (dd, J = 2.7, 10.1 Hz, 1 H, H-1), 4.64–4.59 (m, 2 H, PMB CH_2), 4.25 (t, J = 2.6 Hz, 1 H, H-2), 4.07 (t, J = 9.8 Hz, 1 H, H-6), 3.84–3.80 (m, 7 H, 2x OCH_3, H-4), 3.34 (dd, J = 2.6, 10.0 Hz, 1 H, H-3), 3.13 (t, J = 9.6 Hz, 1 H, H-5), 2.38 (s, 1 H, C-6 OH), 2.22 (s, 1 H, C-2 OH), 2.15 (s, 3 H, OAc CH_3). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 170.7, 159.7, 159.5, 129.9, 129.8, 128.8, 114.07, 114.06, 80.8, 77.9, 75.2, 72.7, 72.4, 70.4, 67.4, 64.3, 55.29, 55.27, 21.0. HRMS (ESI-TOF) m/z: $[M+HCO_2]^-$ Calcd for $C_{25}H_{30}N_3O_{10}$ 532.1931; Found 532.1906.

4-Azido-4-deoxy-3,5-di-*O*-(*p*-methoxybenzyl)-*myo*-inositol (23). After a solution of compound **22** (34 mg, 0.070 mmol) in a 4 mL of freshly prepared 0.05 M $NaOCH_3$ in methanol was stirred for 30 min, it was neutralized to ~pH 7 using Dowex H^+ resin. The solution was filtered and concentrated under vacuum. The crude material was purified using silica gel chromatography (Hex/EtOAc 1:8) to give compound **23** (25 mg, 80%) as a white solid. TLC (Hex/EtOAc 1:8): R_f = 0.35. ^{1}H NMR (500 MHz, CD_3OD): δ 7.36–7.33 (m, 4 H, ArH), 6.91–6.86 (m, 4 H, ArH), 4.81 (d, J = 10.5 Hz, 1 H, PMB CH_2), 4.70 (d, J = 10.5 Hz, 1 H, PMB CH_2), 4.66 (d, J =11.4 Hz, 1 H, PMB CH_2), 4.54 (d, J = 11.4 Hz, 1 H, PMB CH_2), 4.11 (t, J = 2.7 Hz, 1 H, H-2), 3.79 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.77 (t, J = 9.5 Hz, 1 H, H-6), 3.71 (t, J = 10.1 Hz, 1 H, H-4), 3.28 (dd, J = 2.6, 10.8 Hz, 1 H, H-3), 3.26 (dd, J = 2.8, 10.0 Hz, 1 H, H-1), 3.09 (t, J = 9.4 Hz, 1 H, H-5). $^{13}C\{^1H\}$ NMR (125 MHz, CD_3OD): δ 160.9, 160.8, 132.0, 131.3, 130.9, 130.8, 114.7, 114.6, 82.8, 79.3, 75.9, 74.4, 73.0, 72.5, 70.2, 66.5, 55.67, 55.65. HRMS (ESI-TOF) m/z: $[M+HCO_2]^-$ Calcd for $C_{23}H_{28}N_3O_9$ 490.1862; Found 490.1845.

4-Azido-4-deoxy-*myo*-inositol (4). Compound **23** (24 mg, 0.054 mmol) was dissolved in CH_2Cl_2 (10 mL) to give a clear colorless solution. While stirring, trifluoroacetic acid (1.1 mL) and five drops of water were added. After 30 min of stirring, the solution was purple in color and TLC indicated complete consumption of the starting

material. The reaction mixture was co-evaporated with toluene under vacuum. The resulting solid was purified using silica gel chromatography (CH_2Cl_2/MeOH 2:1) which was further purified by silica gel chromatography (*n*-butanol/EtOH/H_2O 5:3:2) to give compound **4** (9 mg, 81%) as a white solid. TLC (*n*-butanol/EtOH/H_2O 5:3:2): R_f = 0.64. ^{1}H NMR (500 MHz, D_2O): δ 4.06 (t, *J* = 2.6 Hz, 1 H, H-2), 3.66 (t, *J* = 9.7 Hz, 1 H, H-5), 3.61–3.55 (m, 2 H, H-4, H-1), 3.49 (dd, *J* = 3.0, 10.0 Hz, 1 H, H-3), 3.31 (dt, *J* = 2.0, 9.6 Hz, 1 H, H-6). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, referenced to an acetone internal standard): δ 64.0, 63.2, 62.9, 61.6, 60.9, 56.5. HRMS (ESI-TOF) m/z: [M-H]$^-$ Calcd for $C_6H_{10}N_3O_5$ 204.0620; Found 204.0626.

Methyl 4-azido-4-deoxy-6-*O*-(*p*-methoxytrityl)-α-D-glucopyranoside (25). After dissolving compound **24**[29] (4.68 g, 21.4 mmol) in anhydrous pyridine (200 mL), the flask was purged with argon and cooled in an ice bath. While stirring, PMTrtCl (13.85 g, 44.85 mmol) was added in portions to the reaction mixture. After stirring overnight with gradual warming to room temperature, TLC showed complete consumption of starting material. The solution was quenched with excess methanol, transferred to a separatory funnel containing ice water, and extracted three times with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting crude oil was purified using silica gel chromatography (toluene/EtOAc 1:1 with 1% Et_3N) to give compound **25** (9.55 g, 91%) as a white solid. TLC (toluene/EtOAc 1:1) of **25**: R_f = 0.42. ^{1}H NMR of **25** (300 MHz, $CDCl_3$): δ 7.51–7.47 (m, 4 H, ArH), 7.39–7.28 (m, 6 H, ArH), 7.26–7.22 (m, 2 H, ArH), 6.88–6.83 (m, 2 H, ArH), 4.87 (d, *J* = 3.8 Hz, 1 H, H-1), 3.80 (s, 3 H, OCH_3), 3.76 (t, *J* = 9.1 Hz, 1 H, H-3), 3.63 (dd, *J* = 3.7, 8.3 Hz, 1 H, H-2), 3.58 (d, *J* = 7.0 Hz, 2 H, H-6), 3.44 (s, 3 H, OCH_3), 3.41 (t, *J* = 10.9 Hz, 1 H, H-4), 3.19 (dd, *J* = 4.0, 10.4 Hz, 1 H, H-5). ^{13}C{^{1}H} NMR of **25** (75 MHz, $CDCl_3$): δ 158.5, 144.5, 144.2, 135.4, 130.4, 128.43, 128.37, 127.78, 128.77, 126.9, 113.1, 99.0, 86.2, 73.9, 72.6, 69.7, 62.7, 62.0, 55.3, 55.2. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{27}H_{29}N_3O_6Na$ 514.1954; Found 514.1948.

Methyl 4-azido-4-deoxy-2,3-di-*O*-(*p*-methoxybenzyl)-6-*O*-(*p*-methoxytrityl)-D-α-glucopyranoside (30). Compound **25-(α)** (9.47 g, 19.3 mmol) was dissolved in anhydrous DMF (150 mL) and the solution was stirred with cooling over an ice bath. After purging the flask with argon, sodium hydride (2.32 g, 96.7 mmol) was added in portions. After stirring over an ice bath for approximately 30 min, PMBCl (7.85 mL, 57.9 mmol) was added dropwise. After overnight stirring at room temperature, TLC indicated starting material remained so additional sodium hydride (3.23 g, 135 mmol) and PMBCl (10.2 mL, 75.4 mmol) were added and the reaction stirred for four

days. The reaction mixture was quenched with excess methanol, diluted with H_2O, and transferred to a separatory funnel. The mixture was extracted with EtOAc three times. The organic layer was then washed with brine three times, dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude material was purified using silica gel chromatography (toluene/EtOAc 4:1 with 1% Et_3N) to give compound **30** (9.16 g, 65%) as an orange oil. TLC (toluene/EtOAc 2:1): R_f = 0.81. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.45 (m, 4 H, ArH), 7.36–7.27 (m, 12 H, ArH), 6.93–6.83 (m, 6 H, ArH), 4.88 (d, *J* = 10.0 Hz, 1 H, PMB CH_2), 4.78 (d, *J* = 11.8 Hz, 1 H, PMB CH_2), 4.73 (d, *J* = 10.1 Hz, 1 H, PMB CH_2), 4.67 (d, *J* = 4.9 Hz, 1 H, H-1), 4.65 (d, *J* = 12.0 Hz, 1 H, PMB CH_2), 3.83 (s, 3 H, OCH_3), 3.82–3.79 (m, 7 H, 2x OCH_3, H-4), 3.64 (t, *J* = 10.4 Hz, 1 H, H-3), 3.60 (dd, *J* = 3.5, 9.5 Hz, 1 H, H-2), 3.53–3.48 (m, 1 H, H-5), 3.40 (s, 3 H, OCH_3), 3.38 (dd, *J* = 1.8, 10.9 Hz, 1 H, H-6a or H-6b), 3.15 (dd, *J* = 4.3, 10.3 Hz, 1 H, H-6a or H-6b). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 159.44, 159.39, 158.5, 144.5, 144.2, 135.4, 130.4, 130.2, 129.6, 128.4, 128.3, 127.77, 127.75, 126.8, 113.90, 113.85, 113.1, 98.1, 86.1, 80.0, 79.6, 75.5, 72.9, 69.3, 62.6, 62.1, 55.3, 55.23, 55.17. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{43}H_{45}N_3O_8Na$ 754.3104; Found 754.3105.

Methyl 4-azido-4-deoxy-2,3-di-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside (26). Compound **30** (8.86 g, 12.1 mmol) was dissolved in CH_2Cl_2 (8.4 mL) and the solution was stirred. A solution of glacial acetic acid (31.4 mL) and water (2.1 mL) was added to the reaction mixture dropwise. After stirring for 72 h, TLC indicated the reaction was complete. The reaction mixture was transferred to a separatory funnel and neutralized with saturated aqueous $NaHCO_3$. Following extraction of the mixture with CH_2Cl_2 three times, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified by silica gel chromatography (toluene/EtOAc 2:1) to give compound **26** (5.37 g, 96%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.27 (m, 4 H, ArH), 6.90–6.86 (m, 4 H, ArH), 4.88 (d, *J* = 10.1 Hz, 1 H, PMB CH_2), 4.76–4.72 (m, 2 H, PMB CH_2), 4.58 (d, *J* = 11.8 Hz, 1 H, PMB CH_2), 4.52 (d, *J* = 3.5 Hz, 1 H, H-1), 3.89–3.71 (m, 9 H, 2x OCH_3, H-3, H-6), 3.52–3.45 (m, 3 H, H-2, H-4, H-5), 3.35 (s, 3 H, OCH_3), 1.85 (bt, *J* = 6.7 Hz, 1 H, C6-OH). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 159.5, 159.3, 130.1, 130.0, 129.9, 129.7, 113.9, 113.8, 98.3, 79.6, 79.4, 75.3, 73.0, 69.8, 62.0, 61.4, 55.4, 55.2. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{29}N_3O_7Na$ 482.1903; Found 482.1910.

Methyl 4-azido-4-deoxy-2,3-di-*O*-(*p*-methoxybenzyl)-α-D-glucohexoaldo-1,5-pyranoside (27). Oxalyl chloride (1.1 mL, 12.8 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL) and the solution was stirred at –78 °C under argon. After approximately 15 min, DMSO (2.20 mL, 31.0 mmol) was added dropwise and the solution was

stirred for 15 min. Next, a solution of compound **26** (1.44 g, 3.13 mmol) in anhydrous CH_2Cl_2 (15 mL) was transferred to the reaction mixture dropwise. After stirring for 30 min, Et_3N (6.5 mL, 46.6 mmol) was added and the reaction was stirred for 15 min at –78 °C followed by gradual warming to room temperature. After reaching room temperature, the reaction mixture was diluted with EtOAc and washed with brine three times. The organic solution was dried over $MgSO_4$ and concentrated under vacuum to give an opaque yellow oil. The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum to give **27**, which was subjected to the next reaction without further purification.

Methyl (6S)-3-deoxy-4,5-di-*O*-(*p*-methoxybenzyl)-D-threo-hex-2-enodialdo-6,2-pyranoside (29). The oil containing compound **27** was dissolved in anhydrous CH_3CN (40 mL). While stirring under argon, DMAP (41 mg, 0.34 mmol) and K_2CO_3 (3.22 g, 23.3 mmol) were added followed by Ac_2O (1.2 mL, 12.7 mmol), then the reaction was heated to 65 °C. After stirring overnight at 65 °C, TLC indicated completion and the reaction mixture was diluted with EtOAc and washed with brine three times. The organic layer was dried over Na_2SO_4, filtered, and concentrated by vacuum. The crude material was purified by silica gel chromatography (toluene:EtOAc 10:1) to give compound **29** (0.61 g, 47% over two steps) as a yellow oil. TLC (toluene/EtOAc 10:1): R_f = 0.24. ^{1}H NMR (300 MHz, $CDCl_3$, D-glucose numbering used for peak assignments): δ 9.17 (s, 1 H, CHO), 7.30–7.25 (m, 4 H, ArH), 6.90–6.86 (m, 4 H, ArH), 5.84 (d, J = 2.7 Hz, 1 H, =CH), 4.87 (d, J = 2.6 Hz, 1 H, H-1), 4.76 (d, J = 11.8 Hz, 1 H, PMB CH_2), 4.68–4.61 (m, 3 H, PMB CH_2), 4.44 (dd, J = 2.7, 8.1 Hz, 1 H, H-3), 3.81 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.76 (dd, J = 2.6, 8.1 Hz, 1 H, H-2), 3.45 (s, 3 H, OCH_3). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 186.0, 159.5, 159.4, 148.2, 129.9, 129.8, 129.7, 129.5, 120.8, 113.9, 99.8, 75.8, 73.1, 72.8, 72.3, 56.9, 52.23, 55.22. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{26}O_7Na$ 437.1576; Found 437.1571.

Supporting Information: ^{1}H and ^{13}C NMR spectra.

Acknowledgements

This work was supported by a National Science Foundation CAREER Award (1654408) and a Henry Dreyfus Teacher-Scholar Award from The Camille & Henry Dreyfus Foundation (TH-17-034). Dr. Robin J. Hood is thanked for assistance with NMR and MS instrumentation.

References

(1) Best, M. D.; Zhang, H.; Prestwich, G. D. Inositol Polyphosphates, Diphosphoinositol Polyphosphates and Phosphatidylinositol Polyphosphate Lipids: Structure, Synthesis, and Development of Probes for Studying Biological Activity. *Nat. Prod. Rep.* **2010**, *27*, 1403–1430.

(2) Paulick, M. G.; Bertozzi, C. R. The Glycosylphosphatidylinositol Anchor: A Complex Membrane-Anchoring Structure for Proteins. *Biochemistry* **2008**, *47*, 6991–7000.

(3) Morita, Y. S.; Fukuda, T.; Sena, C. B.; Yamaryo-Botte, Y.; McConville, M. J.; Kinoshita, T. Inositol Lipid Metabolism in Mycobacteria: Biosynthesis and Regulatory Mechanisms. *Biochim. Biophys. Acta* **2011**, *1810*, 630–641.

(4) Morita, Y. S.; Velasquez, R.; Taig, E.; Waller, R. F.; Patterson, J. H.; Tull, D.; Williams, S. J.; Billman-Jacobe, H.; McConville, M. J. Compartmentalization of Lipid Biosynthesis in Mycobacteria. *J. Biol. Chem.* **2005**, *280*, 21645–21652.

(5) Fukuda, T.; Matsumura, T.; Ato, M.; Hamasaki, M.; Nishiuchi, Y.; Murakami, Y.; Maeda, Y.; Yoshimori, T.; Matsumoto, S.; Kobayashi, K.; et al. Critical Roles for Lipomannan and Lipoarabinomannan in Cell Wall Integrity of Mycobacteria and Pathogenesis of Tuberculosis. *MBio* **2013**, *4*, e00472-12.

(6) Mishra, A. K.; Driessen, N. N.; Appelmelk, B. J.; Besra, G. S. Lipoarabinomannan and Related Glycoconjugates: Structure, Biogenesis and Role in Mycobacterium Tuberculosis Physiology and Host-Pathogen Interaction. *FEMS Microbiol Rev* **2011**, *35*, 1126–1157.

(7) Newton, G. L.; Fahey, R. C. Mycothiol Biochemistry. *Arch. Microbiol.* **2002**, *178*, 388–394.

(8) Chi, B. K.; Busche, T.; Van Laer, K.; Basell, K.; Becher, D.; Clermont, L.; Seibold, G. M.; Persicke, M.; Kalinowski, J.; Messens, J.; et al. Protein S-Mycothiolation Functions as Redox-Switch and Thiol Protection Mechanism in Corynebacterium Glutamicum under Hypochlorite Stress. *Antioxid Redox Signal* **2014**, *20*, 589–605.

(9) Sletten, E. M.; Bertozzi, C. R. Bioorthogonal Chemistry: Fishing for Selectivity in a Sea of Functionality. *Angew. Chem. Int. Ed.* **2009**, *48*, 6974–6998.

(10) Lu, L.; Gao, J.; Guo, Z. Labeling Cell Surface GPIs and GPI-Anchored Proteins through Metabolic Engineering with Artificial Inositol Derivatives. *Angew. Chem. Int. Ed.* **2015**, *54*, 9679–9682.

(11) Ricks, T. J.; Cassilly, C. D.; Carr, A. J.; Alves, D. S.; Alam, S.; Tscherch, K.; Yokley, T. W.; Workman, C. E.; Morrell-falvey, J. L.; Barrera, F. N.; et al. Labeling of Phosphatidylinositol Lipid Products in Cells through Metabolic Engineering by Using a Clickable Myo-Inositol Probe. *ChemBioChem* **2019**, *20*, 172–180.

(12) Brunn, G.; Fauq, A. H.; Chow, S.; Kozikowski, A. P.; Gallegos, A.; Powis, G. Cellular Pharmacology of D-3-Azido-3-Deoxy-Myo-Inositol, an Inhibitor of Phosphatidylinositol Signaling Having Antiproliferative Activity. *Cancer Chemother. Pharmacol.* **1994**, *35*, 71–79.

(13) Sureshan, K. M.; Ikeda, K.; Watanabe, Y. Efficient Routes to Optically Active Azido- , Amino- , Di-Azido- and Di-Amino-Cyclitols with Chiro - and Allo -Configuration from Myo -Inositol. *Tetrahdron Lett.* **2004**, *45*, 8367–8370.

(14) Sureshan, K. M.; Ikeda, K.; Asano, N.; Watanabe, Y. Efficient Syntheses of Optically Pure Chiro - and Allo -Inositol Derivatives , Azidocyclitols and Aminocyclitols from Myo -Inositol. *Tetrahdron* **2008**, *64*, 4072–4080.

(15) Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Das, T. Regioselective Protection and Deprotection of Inositol Hydroxyl Groups. *Chem. Rev.* **2003**, *103*, 4477–4504.

(16) Pasari, S.; Ismail, S. M.; Wenk, M. R.; Lear, M. J. Preparation of Azide Biosynthetic Surrogates of Myo-Inositol. *Tetrahdron Lett.* **2015**, *56*, 2597–2601.

(17) Powis, G.; Aksoy, I. A.; Melder, D. C.; Aksoy, S.; Eichinger, H.; Fauq, A. H.; Kozikowski, A. P. D-3-Deoxy-3-Substituted Myo-Inositol Analogues as Inhibitors of Cell Growth. *Cancer Chemother. Pharmacol.* **1991**, *29*, 95–104.

(18) Sanfilippo, C.; Patti, A.; Piattelli, M.; Nicolosi, G. Convenient Access to Both Enantiomers of New Azido- and Aminoinositols via a Chemoenzymatic Route. *Tetrahedron Asymmetry* **1998**, *9*, 2809–2817.

(19) Podeschwa, M. A. L.; Plettenburg, O.; Altenbach, H. Stereoselective Synthesis of Several Azido / Amino- and Diazido / Diamino- Myo -Inositols and Their Phosphates from p -Benzoquinone. *Org. Biomol. Chem.* **2003**, *1*, 1919–1929.

(20) Conrad, R. M.; Grogan, J. M.; Bertozzi, C. R. Stereoselective Synthesis of Myo-Inositol via Ring-Closing Metathesis: A Building Block for Glycosylphosphatidylinositol (GPI) Anchor Synthesis. *Org. Lett.* **2002**, *4*, 1359–1361.

(21) Ferrier, R. J.; Middleton, S. The Conversion of Carbohydrate Derivatives into Functionalized Cyclohexanes and Cyclopentanes. *Chem. Rev.* **1993**, *93*, 2779–2831.

(22) Estevez, V. A.; Prestwich, G. D. Synthesis of Enantiomerically Pure, P-1-Tethered Inositol Tetrakis(Phosphate) Affinity Labels via a Ferrier Rearrangement. *J. Am. Chem. Soc.* **1991**, *113*, 9885–9887.

(23) Bender, S. L.; Budhu, R. J. Biomimetic Synthesis of Enantiomerically Pure D-Myo-Inositol Derivatives. *J. Am. Chem. Soc.* **1991**, *113*, 9883–9885.

(24) Swarts, B. M.; Guo, Z. Synthesis of a Glycosylphosphatidylinositol Anchor Bearing Unsaturated Lipid Chains. *J. Am. Chem. Soc.* **2010**, *132*, 6648–6650.

(25) Swarts, B. M.; Guo, Z. Chemical Synthesis and Functionalization of Clickable Glycosylphosphatidylinositol Anchors. *Chem. Sci.* **2011**, *2*, 2342–2352.

(26) Alper, P. B.; Hung, S.-C.; Wong, C.-H. Metal Catalyzed Diazo Transfer for the Synthesis of Azides from Amines. *Tetrahedron Lett.* **1996**, *37*, 6029–6032.

(27) Li, Y.; Zhou, Y.; Ma, Y.; Li, X. Design and Synthesis of Novel Cell Wall Inhibitors of Mycobacterium Tuberculosis GlmM and GlmU. *Carbohydr. Res.* **2011**, *346*, 1714–1720.

(28) Bozó, É.; Boros, S. Synthesis of 4-Cyanophenyl and 4-Nitrophenyl 2,6-Anhydro-1,2-Dithio-D-Manno-Andaltropyranosides and Their DerivativesPossessing Antithrombotic Activity. *Pol. J. Chem.* **1999**, *73*, 989–1002.

(29) Sinha, S. K.; Brew, K. Synthesis of 4-Deoxy-d-Xylo-Hexose and 4-Azido-4-Deoxy-d-Glucose and Their Effects on Lactose Synthase. *Carbohydr. Res.* **1980**, *81*, 239–247.

(30) García-Martín, M. de G.; Báñez, M. V. de P.; Galbis, J. A. Preparation and Reactivity of Some 3-Deoxy-D- Altronic Acid Derivatives. *J. Carbohydr. Chem.* **2001**, *20*, 145–157.

(31) Zamora, F.; Galbis, J. A. Synthesis of 3-Deoxy-2,4-Di-O-Methyl-D-Erythro- Pentono-1,5-1actone and of Its L Enantiomer by Stereoselective Hydrogenation. *Carbohydr. Res.* **1996**, *293*, 251–258.

(32) Hoos, R.; Naughton, A. B.; Vasella, A. A Convenient Procedure for the Synthesis of 2,3,4,6-Tetra-O-Benzyl-D- Gluconolactam and D-Nojirilactam. *Helv. Chim. Acta* **1992**, *75*, 1802–1807.

(33) Ravi, A.; Hassan, S. Z.; Vanikrishna, A. N.; Sureshan, K. M. Regioselective SN2 Reactions for Rapid Syntheses of Azido-Inositols by One-Pot Sequence-Specific Nucleophilysis. *Chem. Commun.* **2017**, *53*, 3971–3973.

(34) Takahashi, H.; Kittaka, H.; Ikegami, S. Novel Synthesis of Enantiomerically Pure Natural Inositols and Their Diastereoisomers. *J. Org. Chem.* **2001**, *66*, 2705–2716.

(35) Urbanek, B. L.; Wing, D. C.; Haislop, K. S.; Hamel, C. J.; Kalscheuer, R.; Woodruff, P. J.; Swarts, B. M. Chemoenzymatic Synthesis of Trehalose Analogues: Rapid Access to Chemical Probes for Investigating Mycobacteria. *ChemBioChem* **2014**, *15*, 2066–2070.

(36) Meints, L. M.; Poston, A. W.; Piligian, B. F.; Olson, C. D.; Badger, K. S.; Woodruff, P. J.; Swarts, B. M. Rapid One-Step Enzymatic Synthesis and All-Aqueous Purification of Trehalose Analogues. *J. Vis. Exp.* **2017**, e54485.

(37) Rundell, S. R.; Wagar, Z. L.; Meints, L. M.; Olson, C. D.; O'Neill, M. K.; Piligian, B. F.; Poston, A. W.; Hood, R. J.; Woodruff, P. J.; Swarts, B. M. Deoxyfluoro-D-Trehalose (FDTre) Analogues as Potential PET Probes for Imaging Mycobacterial Infection. *Org. Biomol. Chem.* **2016**, *14*, 8598–8609.

(38) O'Neill, M. K.; Piligian, B. F.; Olson, C. D.; Woodruff, P. J.; Swarts, B. M. Tailoring Trehalose for Biomedical and Biotechnological Applications. *Pure Appl. Chem.* **2017**, *89*, 1223–1249.