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Preparation of azide biosynthetic surrogates of *myo*-inositol

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ABSTRACT

As a prelude to biomolecular incorporation studies, practical routes to a series of four regioisomeric azido-deoxy derivatives of inositol that mimic the natural *myo*-stereochemistry are described. Starting from commercially available *myo*-inositol, the regioselective and stereoselective introduction of azide functionality was achieved at the C-2, C-3, C-4, and C-5 positions via azide displacement of the corresponding *O*-sulfonates of suitably protected *scyllo*-, *chiro*-, *epi*-, and *neo*-inositols, respectively. Notably, a final one-pot acetolysis method conveniently allowed for rapid access to pentaacetate azido-deoxy inositols. Investigations on the metabolic incorporation of these *myo*-inositol azide surrogates in both acetate and free alcohol forms are in progress.

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Due to its putative prebiotic history and innate chemical versatility, inositol is a natural carbohydrate central to a plethora of cellular signaling processes and recognition events, both inside and outside cells, and even between different cell types.[1] Typically through initial phosphorylation events, inositol derivatives (e.g., inositol triphosphates, IP_3, and lipidated phosphatidylinositols, PIs) play key roles in modulating calcium signaling, membrane functioning, cell death, cell division, and cell-to-cell communication.[2,3] Additional glycosylation and lipidation events eventually yield higher order glycolipids, such as the glycosylphosphatidylinositols (GPIs) and poly-mannosylated lipids, including the phosphatidyl-*myo*-inositol mannosides (PIMs) and lipoarabinomannans (LAMs). These glycolipids are essential components in anchoring functional proteins on extracellular membrane surfaces and intracellular trafficking processes, and are key to host-cell recognition, immunological processes, and pathogenic infections.[4]

In this study, we have a view to prepare biosynthetic mimics of *myo*-inositol (azide-surrogates) that have the potential to be metabolically incorporated into a chosen cell type (e.g., yeast). For this purpose, the modification or introduction of bioorthogonal functional groups ('click' functionalities) was necessary. Herein, we chose to introduce azide groups to replace different hydroxyl groups of *myo*-inositol (**1**) (Fig. 1). For symmetry reasons, this would result in four regioisomeric series of *myo*-cyclohexanols **2**–**5**, of which two (the 2-series and 5-series) would be *meso* (achiral).

A few routes to the synthesis of optically active azido and amino inositols have been reported. Examples of routes start from *p*-benzoquinone[5] or conduritol-E[6] via chemo-enzymatic resolution, and also from chiral sources such as L-quebrachitol.[7] Among various synthetic protocols developed for the synthesis of *myo*-inositol intermediates and its analogues, commercially available *myo*-inositol **1** is the most commonly preferred starting material due to its low cost and pre-defined relative stereochemistry.[8] For *myo*-inositol, positions C_1, C_3 and C_4, C_6 are equivalent and unsymmetrical protection leads to racemates. The chemical synthesis of optically active inositol analogues would thus necessitate the resolution of racemic inositol intermediates (chemically, enzymatically, or via desymmetrization techniques)[9] or by starting with an alternative chiral material (e.g., via the Ferrier carbocyclization of sugars).[10] For our biological studies, the racemic azido-inositol series **3** and **4**, and the *meso* series **2** and **5**, were considered sufficient to test our hypothesis of metabolic selection and incorporation into live cells. Our synthetic routes to make **2**–**5** are described herein.

Synthesis of (±)-4-deoxy-4-azido *myo*-inositols 4

We first decided to pursue the dicyclohexylidene diketal protection approach reported by Angyal et al.[11] as a starting material

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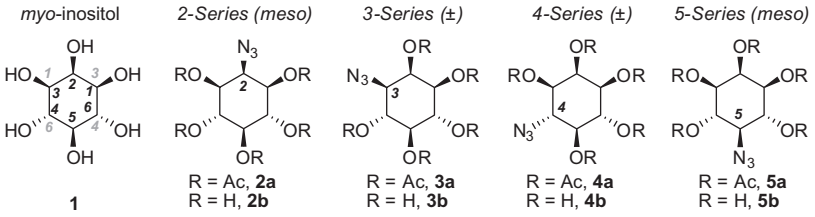


Figure 1. Azido-deoxy surrogates (2–5) of *myo*-inositol (1).

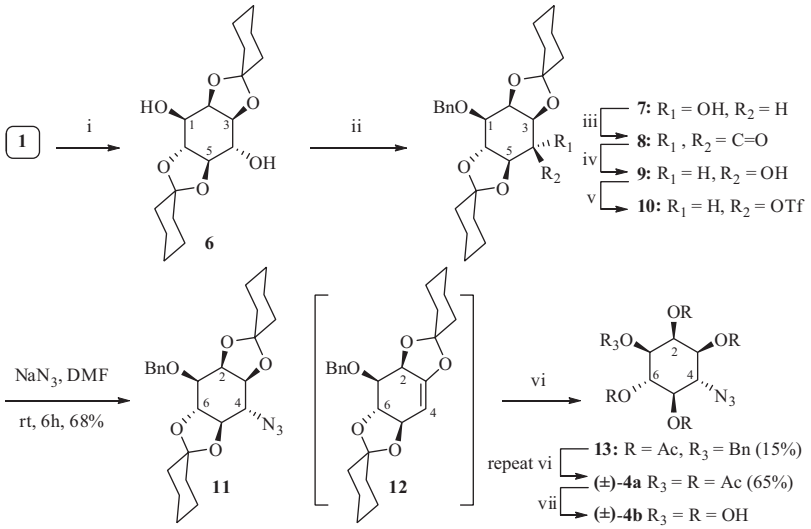
over diacetals or diisopropylidene derivatives.[12,13] This allows for the practical, differential hydroxyl protection of *myo*-inositol (**1**) as relatively stable *trans* and *cis* cyclohexylidenes that not only tolerate multi-step synthesis, but also result in reactivity differences between the two remaining hydroxyl groups. The 1,2,4,5-dicyclohexylidene *myo*-inositol **6** was isolated as a white solid in 22% yield after recrystallization from 1:9 acetone/petroleum ether.[14] The remaining two isomeric ketals (2,3,4,5- and 3,4,5,6-dicyclohexylidenes) can be converted to **6** in a sequence of partial deprotection–reprotection steps.[11b] Although yields are low, this method is scalable to multi-grams and is convenient in practice.

Barium oxide and barium hydroxide chelation-mediated benzylation of **6** produced the monobenzylated *myo*-inositol derivative **7** as the major product in 60% yield[14] (Scheme 1). The free alcohol at the C_6 position of the *myo*-inositol derivative **7** was subsequently oxidized under Dess–Martin periodinane (DMP) conditions to give the desired ketone **8** in excellent yields (93%). Stereoselective reduction of **8** by sodium borohydride produced the *epi*-alcohol **9**[15] exclusively. The free C_6 alcohol of *epi*-inositol **9** was subsequently activated as its triflate **10** using trifluoromethane sulfonic acid anhydride in pyridine.[16] In accordance with the report of Schlewer et al.,[15] azide displacement of triflate **10** gave the desired *myo*-product **11** together with trace amounts of the enol ether side-product **12** via 1,2-*anti* elimination under the basic conditions.

After several methods were explored, global deprotection of **11** in the presence of the azide group was eventually achieved in one step by acetolysis[17] using a mixture of sulfuric acid, acetic anhydride and acetic acid to afford the 4-deoxy-4-azido-*myo*-inositol pentaacetate **4a**[5,6] in 65% yield. Minor amounts of the partially acetolyzed product 3-benzyl-6-azido-*myo*-inositol tetraacetate **13** was also obtained, which could be transformed under the same conditions to yield **4a**. Further methanolysis in the presence of a catalytic amount of sodium methoxide afforded the 4-deoxy-4-azido-*myo*-inositol analogue **4b**. Single crystals of pentaacetate **4a**, from 1:1 hexane/ethyl acetate, confirmed the stereochemistry unambiguously by X-ray analysis (Fig. 2).

Synthesis of meso-5-deoxy-5-azido *myo*-inositols 5

Starting with the dicyclohexylidene diol **6**, benzylation of the two remaining hydroxyl groups afforded the fully protected inositol derivative **14** in excellent yields[18] (Scheme 2). The kinetically labile and slightly distorted *trans* ketal of the compound **14** was cleaved selectively by controlled acid hydrolysis using acetyl chloride in DCM/MeOH (3:1) to afford the diol **15** in 68% yield.[19] The diol **15** was regioselectively benzylated under phase transfer catalyst (tetrabutyl ammonium hydrogen sulfate) conditions, resulting in a separable mixture of benzylated products **16** and **17**.[20] Due to difficulties to distinguish **16** from **17**, both alcohols were converted to their corresponding methylated derivatives **18a** and **b** for identification purposes. Subsequent removal of the *cis*-ketal unit and global benzylation of **18a** and **b** provided the fully protected inositol derivatives **20a** and **b**, respectively. The ^1H and ^{13}C NMR of the derived *meso*-compound (**20b**) clearly indicated the structure to be 5-*O*-methyl-1,2,3,4,6-penta-*O*-benzyl *myo*-inositol. Thus, the corresponding starting alcohol **17** was confirmed to possess the C_5-free alcohol for the synthesis of the desired 5-series azido-analogues **5**.



Scheme 1. Synthesis of (±)-4-azido *myo*-inositol analogues **4a** and **b**. Reagents and conditions: (i) cyclohexanone, toluene/DMF (1:2), pTSA, 110 °C, 22%; (ii) BaO, $Ba(OH)_2{\cdot}8H_2O$, BnBr, DMF, 60%; (iii) DMP, DCM, rt, 93%; (iv) $NaBH_4$, EtOH, 0 °C, 76%; (v) Tf_2O, Py, DCM 0 °C to rt, 73%; (vi) **11**, AcOH, Ac_2O, 10% H_2SO_4 in Ac_2O, rt; (vii) NaOMe, MeOH, rt, 99%.

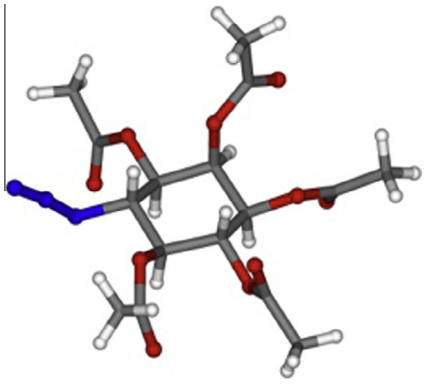


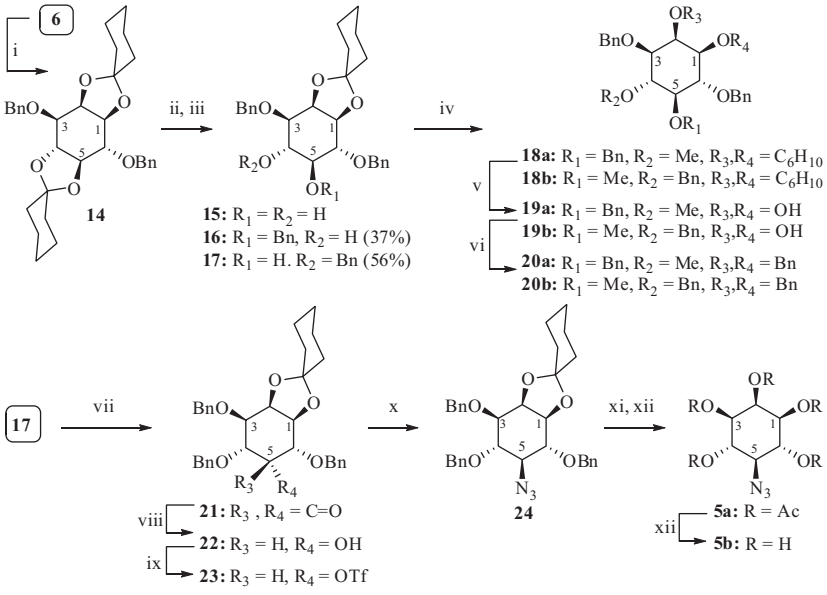
Figure 2. X-ray structure of racemic pentaacetate 4-azide analogue **4a**.

Having identified the C_5-OH derivative, the C_5-stereochemistry of **17** was inverted by DMP oxidation followed by reduction of the ketone **21** to give the alcohol **22** in the *neo*-configuration (Scheme 2). In the reduction step, the original alcohol **17** was also formed in 36% yield, presumably due to similar sterics being encountered by the hydride reagent when approaching from either the α or β face in **21**. The alcohol **22** was then converted into its trifluoromethane sulfonate **23** by treatment with Tf_2O in pyridine. Next, the azide group was installed by a clean substitution in an S_N2 fashion with sodium azide to regenerate the *myo*-configured product **24** in good yields. Interestingly, no elimination (enol) product was detected, presumably due to 1,3-diaxial sterics preventing E_2-elimination. Compound **24** was then subjected to exhaustive acetolysis to form the 5-deoxy-5-azido-*myo*-inositol pentaacetate **5a**.[17] In this case, an elevated temperature of 60 °C was required for complete conversion to the pentaacetate **5a**.[6] The isomeric, partially acetolyzed, benzyl ether products were also converted to **5a** under the same acetolysis conditions. Deacetylation of **5a** was accomplished by methanolysis in the presence of catalytic amounts of sodium methoxide to yield 5-deoxy-5-azido-*myo*-inositol **5b**. Single crystals of compound **5a** from 1:1 hexane/ether confirmed the structure unambiguously after X-ray analysis (Fig. 3).

Synthesis of (±)-3-deoxy-3-azido myo-Inositols 3

Inspired by the report of Watanabe et al.[16b] for an efficient S_N2 substitution of C_3-inositol triflates, the synthesis of the 3-series **3a** and **b** was studied by consecutive double substitution at the C_3 position of an inositol intermediate **26**, which was obtained from the previously synthesized inositol derivative **7** by subsequent methoxy methyl (MOM) ether protection to form the fully protected **25** and then Pd-C hydrogenolysis (Scheme 3).[21] The C_3-free alcohol **26** was treated with trifluoromethane sulfonic acid anhydride in pyridine to yield the corresponding triflate **27**, which was immediately reacted with potassium acetate in DMA to furnish the C_3-inverted *chiro*-acetate **28** in excellent yields (96%)[16b] without elimination, presumably due to the less basic nature of the acyl anion as compared to azide species.

Deacetylation of *chiro*-**28** in the presence of catalytic amounts of sodium methoxide gave the axial alcohol **29** (Scheme 3). After completion, acidic resin was added to the reaction mixture to remove sodium ions by ion exchange. Unexpectedly, the *trans* ketal unit of **29** rearranged into a more stable *cis* C3/C4-ketal (**30**) by ketal migration under the slightly acidic conditions. Hence, a basic aqueous work up procedure using ethylacetate–water was employed while scaling up. The free axial alcohol in **29** was subsequently treated with triflic anhydride and pyridine to form the triflate **31**. Excess pyridine led to the formation of an eliminated product (**35**) in minor amounts. Two equivalents of pyridine in dichloromethane, however, generated the trifluoromethane sulfonylated product **31** in 90% yield without elimination. On the other hand, the free axial alcohol of **29** could be smoothly mesylated in pyridine as the solvent to form **32** without elimination, presumably due to the lower leaving group aptitude of OMs as compared to OTf.[22] The isolated triflate **31** was examined first. Treatment with sodium azide in DMF generated the *myo*-configured substitution product **33** in low yields (15%) together with a minor S_N1 substitution product **34** (10%) and the elimination product **35** in 56% yield.[23] In comparison, the mesylate derivative **32**



Scheme 2. Synthesis of *meso*-5-azido *myo*-inositol analogues **5a** and **b**. Reagents and conditions: (i) NaH, DMF, BnBr 0 °C, 97%; (ii) CH_3COCl, DCM, MeOH (3:1), 68%; (iii) BnBr, Bu_4NHSO_4, DCM, 5% NaOH, reflux; (iv) NaH, DMF, MeI, 0 °C to rt, 90%; (v) DCM/MeOH (1:1), CH_3COCl, rt, 89%; (vi) (i); (vii) DMP, $NaHCO_3$, DCM, rt, 85%; (viii) $NaBH_4$, EtOH, rt, 60%; (ix) Tf_2O, Py, 0 °C, 71%; (x) NaN_3, DMF, rt, 83%; (xi) Ac_2O, AcOH, 10% H_2SO_4 in Ac_2O, 60 °C, 64%; (xii) NaOMe, MeOH, rt, 98%.

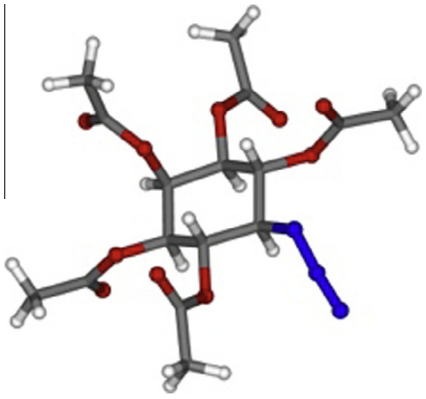


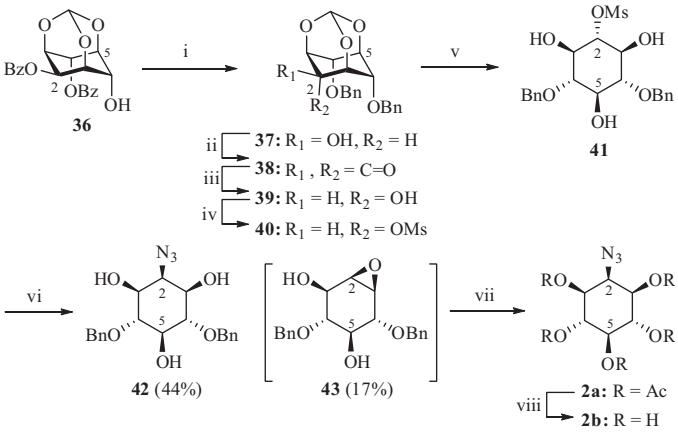
Figure 3. X-ray structure of meso pentaacetate 5-azide analogue **5a**.

failed to undergo azide displacement with sodium azide in DMF, even upon heating at 70 °C. Also, Mitsunobu reaction of the alcohol **29** in order to achieve direct azide displacement was unsuccessful.

We thus opted to optimize the azide displacement of triflate **31** by screening differing azide reagents and solvents: NaN_3/DMA, $NaN_3/Me_2CO/H_2O$, $^nBu_4NN_3$/DCM, $TMSN_3$/TBAF/THF. Eventually, the combination of excess $TMSN_3$ (8 equiv) in the presence of (0.5 equiv) of TBAF in THF medium provided *myo*-azide **33** in a 43% optimal yield.[24] To complete the 3-series, global acetolysis of compound **33** formed the desired 3-deoxy-3-azido *myo*-inositol pentaacetate **3a**[5] in moderate yields (Scheme 3) under mildly acidic conditions (2% H_2SO_4 in acetic anhydride). Treatment of **33** in dry, ethereal HCl further allowed all acid labile protecting groups to be cleaved in one step and 3-deoxy-3-azido-*myo*-inositol **3b** could be isolated cleanly as a white solid after an ether wash.

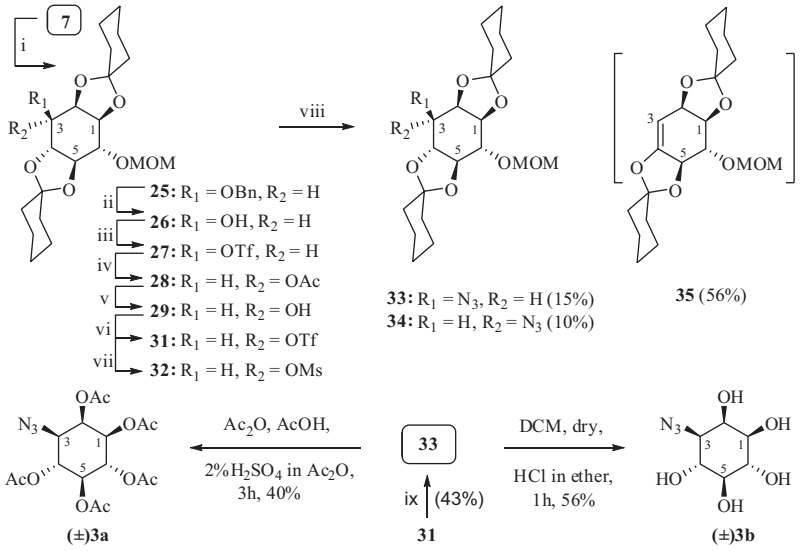
Synthesis of meso-2-deoxy-2-azido myo-inositols 2

Following the orthoformate protection approach of Kishi et al.,[25] which allows for large differences in reactivity between equatorial and axial hydroxyl groups of inositol in terms of sterics and electronics,[26] a route to the 2-series of azide analogues was developed (Scheme 4). The symmetric dibenzyl *myo*-inositol orthoformate **37**[27] was prepared from the dibenzoate derivative **36** through a



Scheme 4. Synthesis of 2-azido *myo*-inositol analogues **2a** and **b**. Reagents and conditions: (i) (a) Ag_2O, BnBr, DMF, rt, (b) $(CH_3)_2CHCH_2NH_2$, MeOH, reflux, 70%; (ii) DMP, DCM, rt, 95%; (iii) MeOH, THF, $NaBH_4$, 87%; (iv) CH_3SO_2Cl, py, 92%; (v) *p*TSA, MeOH, 97%; (vi) NaN_3, DMF, 80 °C; (vii) **42**, Ac_2O, AcOH, 15% H_2SO_4 in Ac_2O, 50 °C, 64%; (viii) NaOMe, MeOH, 99%.

prolonged silver(I) oxide chelation mediated bis-benzylation[28] and aminolysis sequence. The equatorial free hydroxyl group of **37** was oxidized under DMP condition to give the ketone **38** in excellent yields. Next, stereoselective reduction of ketone **38** produced the inverted axial alcohol **39** in the *scyllo*-configuration exclusively.[25] The rigidity of the orthoformate unit presumably accounts for this highly stereoselective reduction step. The axially positioned free alcohol of **39** was then sulfonylated[22] by treatment with methane sulfonyl chloride in pyridine to give **40** in excellent yields. At this stage, an S_N2 attack at C_2 of compound **40** was presumed to be sterically challenging. Hence, orthoformate cleavage of compound **40** was performed first, and the triol **41** was formed by mild methanolysis with pTSA.[29] Next, the mesylate derivative **41** was heated with sodium azide in DMF, which formed the *myo*-configured azide substituted product **42** in moderate yields, along with minor amounts of the epoxide **43** and some unreacted starting material **41**. No elimination product was identified in this case; however, the reaction required heating at 80 °C, which led to decomposition of some material. Final exhaustive acetolysis of **42**



Scheme 3. Synthesis of (±)-3-azido *myo*-inositol analogues **3a** and **b**. Reagents and conditions: (i) MOMCl, DIPEA, 0 °C to rt, 87%; (ii) EtOAc, THF, 20% Pd-C, H_2, 60%; (iii) Tf_2O, Py, DCM, 0 °C, 78%; (iv) KOAc, DMA, 70 °C, 96%; (v) NaOMe, MeOH, rt, 97%; (vi) (iii), 90%; (vii) $MeSO_2Cl$, py, 94%; (viii) NaN_3, DMF, rt; (ix) **31**, $TMSN_3$, TBAF, THF, 43%.

completed the synthesis of the desired 2-deoxy-2-azido-*myo*-inositol pentaacetate **2a** in good yields. Clean methanolysis under basic conditions regenerated the free hydroxyl groups to produce *meso* 2-deoxy-2-azido-*myo*-inositol **2b**.

Summary

In this letter, we have described straightforward routes to various azido-deoxy inositol analogues through azide installation. As a common strategy, we adopted a consecutive S_N2 double-inversion approach on suitably protected inositol derivatives, which were derived via convenient oxidation-reduction sequences from *myo*-inositol. A final, global acetolysis step in the presence of the azide group (2–15% sulfuric acid in acetic anhydride/acid) enabled the direct and convenient synthesis of azido-inositol pentaacetate analogues **2a**–**5a**. Methanolysis by treatment with catalytic sodium methoxide subsequently provided the fully unprotected azido *myo*-inositol surrogates **2b**–**5b** cleanly. The routes are convenient and provide sufficient material for biological study. Having genuine azide-surrogates of *myo*-inositol in hand, a more concise and diversified strategy is under investigation. In the meantime, the metabolic incorporation of these modified azido inositol analogues into various inositol lipids of yeast cells is in progress, and lipid profiling and biosynthetic cell compatabilities will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.04.009. These data include MOL files and InChiKeys of the most important compounds described in this article.

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