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Synthesis of asymmetrically substituted *scyllo*-inositol

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ABSTRACT

scyllo-Inositol, a rare member of the inositol family, is present in axinelloside A, a marine metabolite with interesting inhibitory activity against human telomerase. Here, we present a concise synthesis of asymmetrically substituted *scyllo*-inositol starting from inexpensive D-glucose. Our synthetic approach capitalizes on Ferrier rearrangement of vinyl acetate and stereoselective reduction of the resultant ketone to establish the *scyllo*-inositol core. The protocol provides access to large quantities of *scyllo*-inositol in 10 steps from commercially available materials.

Introduction

Inositols are a class of nine distinct isomers of 1,2,3,4,5,6-cyclohexanehexol in which the configuration of the hydroxyl group is permutated giving rise to seven *meso* and two chiral isomers.[1] Among the members of this family, *myo*-inositol (**1**) and its derivatives are the most studied inositols due to their role as secondary messengers (in the form of phosphates and pyrophosphates) and their presence in glycoconjugates (e.g., glycosylphosphatidylinositol (GPI) anchors).[2] However, *scyllo*-inositol (**2**), an isomer with all hydroxyl groups in equatorial configuration, is less explored.[1] The parent compound is found at high concentrations in human brain,[3] and has been implicated in certain neurological disorders.[1] There are numerous reports describing the use of *scyllo*-inositol as a potential drug targeting Alzheimer's[4] and Parkinson's diseases,[5] and research in this area is a topic of current interest.[6] For instance, orally administered *scyllo*-inositol inhibited the aggregation of amyloid-β (Aβ)[7] and prevented the formation of insoluble amyloid fibers believed to cause neuronal dysfunction in Alzheimer's disease. Derivatives of *scyllo*-inositol (including fluorinated analogs[8]) have been investigated, among which the hexaphosphate has been identified as a promising drug candidate.

From the synthetic standpoint, the conversion of *myo*-inositol into *scyllo*-inositol by Kishi[9] is a practical route to prepare large quantities of symmetrical *scyllo*-inositol from an inexpensive starting material.[10] Other studies by Ikegami[11] and Altenbach[12] provided the parent hexols using glucose or *p*-quinone as the substrates. Similar to *myo*-inositol, phosphate esters of *scyllo*-inositols have been prepared synthetically.[13] Due to the C_3 symmetry of the orthoester derivatives, the hexol scaffold has been used in the preparation of glycodendrimers,[14] drug delivery compounds,[15] siderophore (enterobactin) analogs,[16] and hetero-bimetallic catalysts.[17]

There is only a small number of examples in which *scyllo*-inositol is present in an asymmetric form,[1] and axinelloside A (**5**) stands out due to its intriguing chemical structure and biological activity.[18] This polysulfated oligosaccharide was isolated from a marine sponge *Axinella infundibula*, and its structure was proposed based on 1D and 2D NMR studies. The unique features of this molecule are the presence of ten 1,2-*cis* glycosidic bonds, four fatty acid chains, and the eastern part terminated with *scyllo*-inositol connected through a β-glycosidic bond. Axinelloside A possesses significant inhibitory activity (2 μg/mL) against human telomerase determined in a TRAP assay. Telomerase, an enzyme overexpressed in over 85% of human tumors, is an attractive target for anticancer therapy,[19] and although a handful of small molecules (dictyodendrin A,[20] telomestatin[21]) are known to inhibit telomerase, there are no drugs utilizing telomerase inhibition as the mechanism of action. Axinelloside A and related sulfated analogs may provide a starting point for the development of small molecule candidates with a therapeutic potential.

Having in mind these considerations, we embarked upon synthesis of *scyllo*-inositol suitable for further elaboration in the total synthesis of axinelloside A. The synthetic scheme toward asymmetrically substituted building block **4** capitalizes on a stereoselective Ferrier-II carbocyclization[22] of a vinyl acetate derived from D-glucose. The C2, C3, and C4 hydroxyl groups in the glucose substrate will correspond to three equatorial C2, C3, and C4 substituents in **4** (Fig. 1). Four orthogonal protective groups, which

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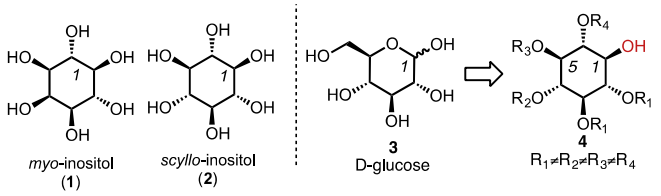


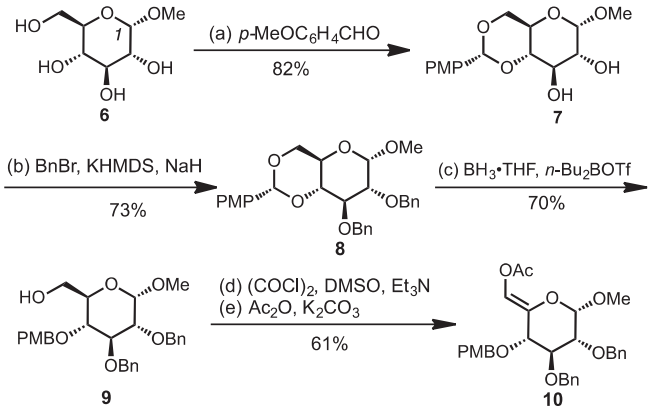
Figure 1.

will mask the sulfate monoester, fatty acid, and free hydroxyl groups in axinelloside A, and the hydroxyl group at C1 will serve as a handle to attach the galactose residue (Fig. 2).

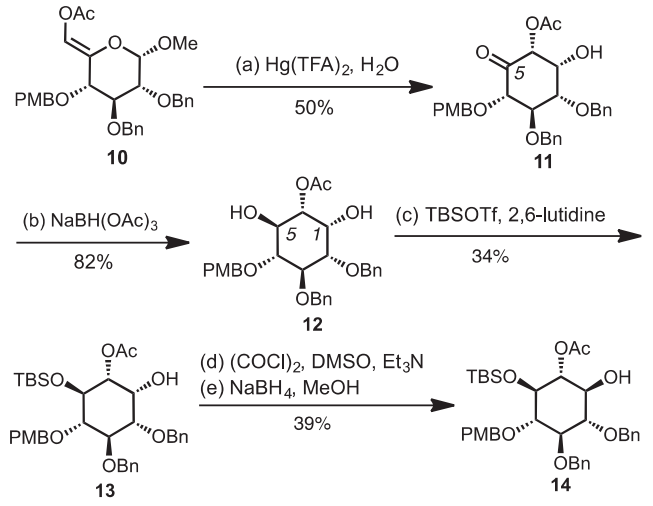
Results and discussion

The synthesis of partially protected *scyllo*-inositol **14** begun with the preparation of D-glucose derivative **10** from commercially available methyl α-D-glucopyranoside **6** (Scheme 1). First, the hydroxyl functionalities at C4 and C6 were protected as an acetal by installation of the benzylidene group with *p*-anisaldehyde in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH). The subsequent benzylation with BnBr in DMF furnished fully protected glucose **8**. The addition of KHMDS proved beneficial, as this protocol results in higher yields of O-alkylation products when multiple alcohols are simultaneously reacted with an alkylating agent. To reveal the primary hydroxyl functionality, acetal **8** was treated with three equivalents of BH_3–THF and a Lewis acid (n-Bu_2BOTf) resulting in exclusive formation of 4-O′-PMB protected glucose **9** in 70% yield. This reaction was also conducted on a multigram scale without erosion of the yield and selectivity. Next, we oxidized the resultant alcohol **9** to an aldehyde using the Swern conditions[23] and the product of this reaction was converted immediately into an enol acetate **10** in a reaction with Ac_2O and inorganic base (K_2CO_3). The formation of the enol ester proceeded in high selectivity giving exclusively the *Z* diastereoisomer **10**.

With compound **10** in hand, we explored the feasibility of the Ferrier rearrangement (Scheme 2). Mercury salts are known as efficient promoters of this reaction,[22b] and $Hg(TFA)_2$ facilitated the conversion of **10** into the desired diastereoisomer **11** in 50% yield (including 7% of C1 epimer). The configuration of the major product was confirmed by NMR spectroscopy where the diagnostic coupling constant revealed an axial configuration of the C1 alcohol (^{1}H NMR: 4.31 ppm, t, ^3J = 2.8 Hz). This compound was stable to chromatographic purifications, and no elimination to α,β-unsaturated ketone was observed. The subsequent reduction of **11** with borohydride afforded **12** (^{1}H NMR: 4.11 ppm, ^3J = 9.8 Hz), in which the new stereocenter (C5) was formed through a hydroxyl directed delivery of a hydride nucleophile.



Scheme 1. Reagents and conditions: (a) *p*-anisaldehyde (1.0 equiv), *p*-TsOH (0.025 equiv), $(MeO)_3CH$ (1.2 equiv), DMF, 50 °C, 82%; (b) BnBr (3.0 equiv), NaH (10 equiv), KHMDS (0.5 equiv), DMF, rt, 73%; (c) BH_3–THF (10 equiv), n-Bu_2BOTf (1.95 equiv), 0 °C, 70%; (d) $(COCl)_2$ (1.2 equiv), DMSO (2.5 equiv), Et_3N (3.5 equiv), CH_2Cl_2, −78 to −40 °C; (e) Ac_2O (12 equiv), K_2CO_3 (8 equiv), MeCN, reflux, 61% (over 2 steps).



Scheme 2. Reagents and conditions: (a) $Hg(TFA)_2$ (1.2 equiv), H_2O/AcONa, rt, 50%, (b) $NaBH(OAc)_3$ (10 equiv), AcOH (16 equiv), MeCN, rt, 82%; (c) TBSOTf (1.5 equiv), 2,6-lutidine (2 equiv), CH_2Cl_2, rt, 34%; (d) $(COCl)_2$ (1.2 equiv), DMSO (2.5 equiv), Et_3N (3.5 equiv), CH_2Cl_2, −78 to −40 °C; (e) $NaBH_4$ (4.5 equiv), MeOH, rt, 39% (over 2 steps).

At this point, two hydroxyl groups in **12** were distinguished via selective silyl protection. We found that the yield of this reaction was critically dependent on the temperature and silylating agent. When the diol **12** was treated with TBSOTf at a low temperature (−78 °C) a mixture of **13** (25%) and doubly protected ether (18%) was formed. We found that the yield of this reaction could be

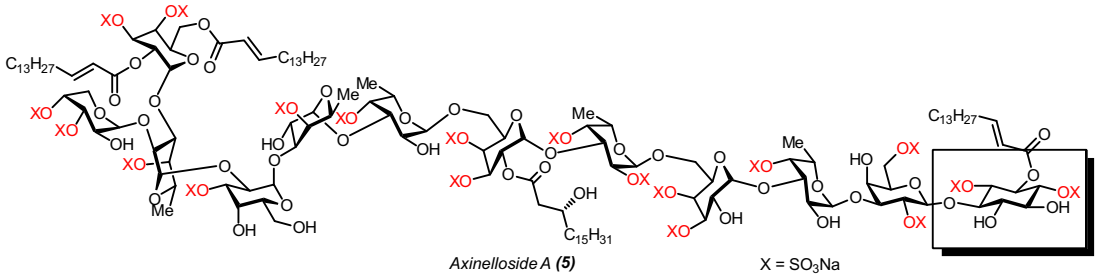


Figure 2.

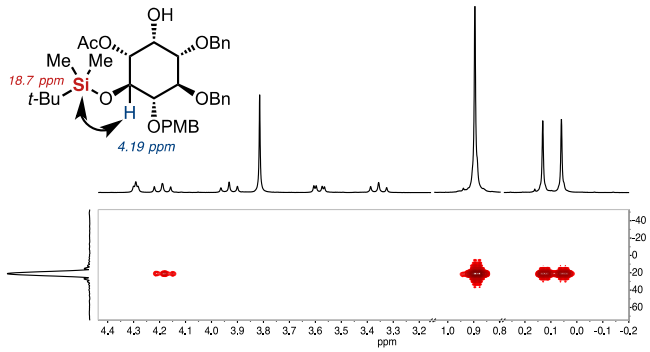


Figure 3. ^{29}Si–^{1}H HMBC NMR correlation for **13**.

improved when 1.5 equiv of the silylating agent was added to **12** at 0 °C in the presence of 2,6-lutidine. Although the silyl ether **13** was formed in 39% (the remainder of the material being **12**), no doubly protected side product was detected and exclusive selectivity for the equatorial OH was observed. To confirm the structural assignment of **13**, ^{29}Si–^{1}H HMBC experiments,[24] which allow for ^{29}Si–^{1}H shift correlations over two and/or three bonds, were performed (Fig. 3). This structural method is particularly useful in systems where the long-range C–H couplings cannot be detected. The ^{29}Si NMR signal (18.7 ppm) showed three cross peaks—two of the *t*-BuMe_2 group and a weaker one with a signal at 4.19 ppm (dd, ^{3}J = 9.9, 8.9 Hz) assigned to the axial proton at C5.

To complete the synthesis of *scyllo*-inositol **14**, the configuration of the alcohol group at C1 in **13** needed to be corrected to provide the all-equatorial product. This transformation turned out to be challenging as the hindered C1 hydroxyl group in the axial configuration was resistant to the Mitsunobu conditions (2,2-bis (diphenylphosphino)ethane (dppe) or PPh_3, diethyl azodicarboxylate (DEAD), $PhCO_2H$).[25] Although we were able to form the expected phosphonium salt by mixing DEAD and Ph_3P, this intermediate was reluctant to undergo substitution with a nucleophile, and the only product observed after extended heating was the benzoate ester derived from activation of benzoic acid with a phosphonium salt followed by O-acylation. Approaches to convert the alcohol into a triflate ester under standard conditions (Tf_2O, pyridine, CH_2Cl_2, 0 °C) followed by a substitution with sodium benzoate were equally unsuccessful. However, we found that the desired configuration of the C1 alcohol could be established in a two-step oxidation–reduction sequence. Thus, the hydroxyl group in **13** was oxidized under the Swern conditions and the resultant ketone was reduced with $NaBH(OAc)_3$/AcOH to provide **14** in 58% yield (*dr* 1.5:1.0). A more reactive (and smaller) reducing reagent ($NaBH_4$) provided *scyllo*-inositol in an improved yield (62%) and higher diastereoselectivity (1.7:1.0). The configuration of the product was established using 1D and 2D NMR techniques—the diagnostic coupling constant of H1 (t, ^{3}J = 9.6 Hz) indicated that the newly established alcohols was formed in an equatorial configuration. We also isolated protected *myo*-inositol **13**, which can be recycled and reduced to *scyllo*-inositol **14** via the sequence of reactions described above. The axial delivery of the hydride to **13** is contrasting with the previously reported addition of hydride or Grignard nucleophiles to per-*O*-benzylated *scyllo*-inose, in which the *myo*-inositol was the major diastereoisomer.[26] We rationalize the reversal of selectivity by a weakly coordinating ability of the acetate group to direct the delivery of a hydride.

Conclusions

To summarize, we described a practical synthesis of asymmetrically protected *scyllo*-inositol starting from a readily available α-methyl D-glucoside. The key features of the synthetic scheme include a rearrangement of vinyl acetate under the Ferrier conditions to establish the cyclohexane ring and a stereoselective reduction of the ketone group to install the equatorial hydroxyl group. This protocol provides an entry into the synthesis of axinelloside A and relevant sulfated analogs containing *scyllo*-inositol groups. Studies focused on the synthesis of axinelloside A and its analogs will be published 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.2016.06.038.

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