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Synthesis of Differentially Protected *myo*- and *chiro*-Inositols from D-Xylose; Stereoselectivity in Intramolecular SmI_2-Promoted Pinacol Reactions

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Abstract

Methods for the enantioselective conversion of D-xylose to differentially protected *myo*-inositol and L-*chiro*-inositol have been developed. The key transformation is a highly diastereoselective intramolecular SmI_2-promoted pinacol coupling. The stereoselectivity was extremely dependent on the conditions, suggesting a change in mechanism. Preliminary mechanistic experiments and possible explanations for this behavior are discussed.

Keywords

Inositol; pinacol; samarium; stereoselective; carbohydrates

Natural phosphorylated and/or glycosylated inositols have been found to play central roles in a variety of cell-signaling pathways in animals,[1–9] in desiccation tolerance in plants,[10–16] and as protein anchors in all eukaryotes. [17,18] These diverse and, in some cases, medically useful activities, have stimulated great interest in the synthesis of these compounds and their analogues.[19–30] In most of the reported syntheses, the preparation of an appropriately protected inositol is prerequisite, but the availability of these key building blocks is limited by lengthy syntheses and a need for the resolution of enantiomers in the case of preparations originating with *myo*-inositol. The challenges and successes in these approaches have been extensively reviewed.[31–33]

Our approach to this problem has been to avoid the requirement for resolution of enantiomers by developing enatiospecific syntheses of the important differentially protected inositols from D-xylose. Our preliminary work in this area has been published previously[34,35] and we now report the complete details of our study. Of particular importance is the observation that the SmI_2-mediated intramolecular pinacol coupling of a pseudo-C_2-symmetric dialdehyde **6** proceeds by a different mechanism depending on the conditions, with dramatic effect on the stereoselectivity (Scheme 1).

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The preceding paper in this issue describes the conversion of 2,3,4-tribenzyl-D-xylose to dienols **3** and **4** with selectivity for either depending on the conditions. However, since **3** and **4** are not easily separable, the mixture was silylated (triisopropylsilyl chloride, DMF, pyridine, $AgNO_3$), and the silylated mixture was readily separated by silica gel chromatography to produce pure **5a** (R = TIPS) and **12** (see Scheme 5 for structure). Treatment of **5a** with ozone at −78 °C resulted in rapid (<5 min) con sumption of the starting material, producing, after reduction of the ozonide with dimethylsulfide, dialdehyde **6a** (R = TIPS). Although the aldehyde could be isolated for ^{1}H NMR characterization, it was somewhat fragile and the subsequent reaction was generally conducted without isolation of **6a**. SmI_2-promoted pinacol coupling of **6a** under standard conditions[36] (3 eq SmI_2, 3 eq *t*-BuOH, THF, −78 °C to 20 °C over 5 h) produced a disappointing 1:2.5 ratio of **7a:8a** (R = TIPS). The structures of **7a** and **8a** were established as previously described[34] and confirmed by desilylation (Bu_4NF, THF), to produce known tribenzyl-*myo*-inositols **7i**[37,38] and **8i**.[39]

Since **7a** has the correct differential protection pattern for application in the synthesis of most of the known natural *myo*-inositol glycan (IG) structures,[26,40–51] we sought to alter the stereoselectivity in the pinacol reaction to favor **7**. Accordingly, we studied the effect of the R group in **6** on the pinacol cyclization, since this group is responsible for the only difference between **7** and **8** (i.e. if R = Bn, then **6** is C_2 symmetric and **7** = **8**). Each precursor **5b–h** was prepared by desilylation of **5a** (Bu_4NF, THF) to produce pure **3**, then resilylation (**5b–f**), alkylation (**5g**), or acylation (**5h)**. The results (Table 1) show that the SmI_2-mediated pinacol reaction under standard conditions is only modestly sensitive to steric factors in the R group, and that larger R groups favor **8**. In the best case (**6f**, R = TMS) only a modest (1.5:1) selectivity for **7** was realized, clearly unacceptable for an efficient multistep synthesis of IGs.

Addition of HMPA (10% v/v in THF) resulted in drastically reduced production of **7** or **8**, with *trans*-diol becoming the major product. This is consistent with the hypothesis that the predominant formation of *cis*-diol products in SmI_2-promoted pinacol coupling reactions[52] is due to chelation of the ketyl oxygens by Sm(III) during the course of the cyclization; strongly chelating HMPA presumably competes with the oxygen atoms for the Sm(III) ion leading to an unchelated transition state predominating.

Addition of chlorotrimethylsilane, known to accelerate SmI_2-promoted pinacol reactions,[53] had no effect on the stereoselectivity (Table I).

To evaluate the effect of changes in electronic demand of the R group in **6** on the course of the cyclization, we subjected **6g** (R = PMB) and **6h** (R = Bz) to the reaction conditions. In the case of **6g**, no selectivity was observed, but in the case of **6h** the reaction took a different course (Scheme 2) producing cyclopentyl aldehyde **10**, which was revealed by ^{1}H NMR and MALDI-TOF MS to exist as a dimer. The structure was confirmed by reduction of **10** with $NaBH_4$ to produce known alcohol **11**.[54]

Surprisingly, a small change in the reaction conditions for the SmI_2-promoted pinacol cyclization of **6a** had a profound effect on the stereoselectivity. When **6a** was treated with 6 eq of SmI_2 at −78 °C for 20 min, followed by dropwise addition of sat. aq. $NaHCO_3$ at −78 °C and *then* warming to 20 °C, diol **7** was obtained in 64% yield (from **5**) with only a trace of isomeric **8** being observed.

To explore the sensitivity of the high stereoselectivity under these modified conditions to the R group in **6** we subjected **6a, 6c, 6d**, and **6g** to the reaction. The stereoselectivity under the modified conditions (Table 2) is more sensitive to the steric bulk in R than under the normal conditions and is in the opposite direction: bulkier substituents favor formation of **7**.

The dramatic change in stereoselectivity in the pinacol coupling reaction is intriguing and suggests a change in mechanism under the modified conditions. To explore the origin of this effect, we conducted a number of experiments designed to identify the important variables in the stereoselectivity (Table 3).

First, we established that the key element in the stereoselectivity is the temperature of addition of water: omission of *t*-BuOH from the standard conditions (entry 1) or omission of the $NaHCO_3$ from the aqueous quench under modified conditions (entry 3) did not affect the stereoselectivity. On the other hand, warming to −25 °C or above prior to addition of water (entries 1, 4, 8, and 14) always resulted in poor stereoselectivities favoring **8** if any selectivity was seen at all.

When O_2 (air) or I_2 was admitted to the reaction mixture at −78 °C (entries 6 and 7), dialdehyde **6a** was recovered from the reaction. This suggests that the intermediate, let's call it **A**, formed from Sm(II) reduction of one or both aldehydes at low temperature is formed reversibly and can be readily reoxidized to aldehyde. However, if aq. $NaHCO_3$ is added at low temperature and *then* O_2 (air), is admitted at −78 °C (entry 5), the reaction proceeds to diol product with high selectivity for **7**. By contrast, warming to 20 °C without aq. $NaHCO_3$ addition and then recooling and admitting O_2 (air) results in diol products **7** and **8** without stereoselectivity (entry 8) showing that the act of warming also commits the reaction to products.

These results suggest that water reacts with the reversibly formed low temperature intermediate **A** to produce a more reactive intermediate **B** that proceeds to product at low temperature and with high stereoselectivity, while warming without water ultimately results in reaction of **A** to form products, but with poor stereoselectivity.

We performed a series of experiments to see if we could trap intermediates **A** or **B** by addition of hydrogen atom donors (entries 15, 20, and 21) or acids and bases of various types (entries 9, 10, 17–19), but without success. We also evaluated the temperature dependence of the stereoselectivity (entries 11–14) and found that the high selectivity for **7** is maintained up to −50 °C, and then disappears by −25 °C suggesting that the reaction of **A** to products occurs in this temperature range in the absence of water.

The identities of **A** and **B** remain unknown, but a hypothesis that is consistent with our data and literature precedent is shown in Scheme 3. According to this proposal, reduction of **6a** at −78 °C results in ketyl **A1** that rapidly proceeds via **A2** to cyclized radical anion **A3**. This cyclization is expected to proceed preferentially via a transition state in which the incipient alkoxyradical is in the equatorial position (Scheme 4), leading to the **A3** isomer in which the samarium-chelated oxygens are trans to the OTIPS group (*trans*-**A3**). A similar stereoselectivity has been reported in other 6-exo-trig radical cyclizations.[55]

Since SmI_2 reduction of aldehydes is known to be an inner sphere process requiring bonding of the Sm(II) center to the electron acceptor,[56] **A3** is stable at −78 °C, because the reducible oxygen atom is flanked by the bulky Sm(III) and TIPS centers, precluding further coordination. Intermediate **A3** would be expected to reoxidize to **6a** when treated with O_2 or I_2, as observed. If water is admitted to the reaction at low temperature, the samarium alkoxyl bond hydrolyzes leading to intermediate **B** that is now accessible to an irreversible inner sphere electron transfer by a second Sm(II) to produce products retaining the stereochemical integrity of **A3**, thus leading to **7a** with high selectivity.

By contrast, when the reaction mixture is warmed above −50 °C, the rate of the reverse sequence (i.e. **A3**→**A2**→**A1**) would increase significantly. Reversibility in the addition of ketyls to carbonyls has been previously reported. [57–59] The uncoordinated aldehyde in **A1** would then be accessible to be reduced by Sm(II) to produce diketyl **C**, which upon ligand exchange to produce **D** would cyclize very rapidly. Because of the high reactivity of **D**, the selectivity is lower, producing a 1:2.5 ratio of **7a** to **8a**.

Furthermore, the weak dependence of the stereoselectivity in the cyclization on the size of the R-group in **6** (Table 1) under the higher temperature conditions is consistent with the high reactivity of **D**, whereas the much stronger dependence of the selectivity on R under the modified conditions (Table 2) is consistent with the change in steric influence of R on the energies of the transition states shown in Scheme 4 as OTIPS is replaced with smaller groups.

A second mechanistic possibility that cannot be ruled out from our data is that **6a** does not react with SmI_2 at −78 °C at any appreciable rate. When water is added, the SmI_2 becomes a stronger reducing agent,[60] accelerating the reduction of **6a**, with the resulting ketyl proceeding on to product via any of several pathways. In the absence of water, reaction only occurs when the temperature exceeds −50 °C and the rate of reduction becomes appreciable. According to this hypothesis, the difference in stereoselectivity is due to the large difference in the temperature at which the cyclization occurs, with the lower temperature cyclization producing high selectivity for **7a**. This proposal is consistent with our inability to trap any intermediates at −78 °C, but the large magnitude of the change in stereoselectivity is surprising. This may reflect a different reduction mechanism with the more reactive H_2O-SmI_2 species, perhaps to an outer sphere process. Clearly, additional mechanistic studies are required to further clarify the origin of this remarkable change in stereoselectivity.

The conversion of the other diene isomer **12** to a cyclitol was much simpler because a single isomer was obtained, as expected based on the literature precedent[36] (Scheme 5). Accordingly, ozonolysis of **12** produced dialdehyde **13**, that was only moderately stable so was carried on without purification. Pinacol cyclization under standard conditions[36] (3 eq SmI_2, 3 eq *t*-BuOH, THF, −78 °C to 20 °C over 5 h) produced desired L-*chiro*-inositol **14** in 58% overall yield. The structure of **14** was confirmed by conversion to pentabenzyl-(-)-quebrachitol as peviously described.[35]

In conclusion, highly efficient syntheses of differentially protected *myo*- and L-*chiro*-inositols have been developed. An intriguing change in mechanism affecting stereoselectivity has been observed in the SmI_2-promoted pinacol reaction warranting further study. It should also be noted that since both enantiomers of aldehyde **2** are readily available from the very inexpensive D-xylose precursor,[61] the procedure described here also provides a straightforward preparation of the D-*chiro*-inositol skeleton.

Unless otherwise noted all commercially obtained reagents were used without purification. THF was distilled from sodium benzophenone ketyl prior to use. Dichloromethane was distilled from calcium chloride. Reactions were carried out under an argon atmosphere in oven-dried glassware using standard syringe, cannula and septa techniques. Ozonolysis was performed with a flow of O_3 in dry O_2 produced by a Welsbach ozonator operating at 0.05 CFM. Reactions were monitored by TLC (Silica Gel 60 F_{254}, 250 μm) and visualized with UV light and/or heating with a p-anisaldehyde stain (2.5% p-anisaldehyde, 3.5% sulfuric acid, 1% acetic acid, 93% ethanol) or a Haines-Isherwood stain (1 g $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 10 mL of 1M HCl, 3 mL of $HClO_4$, 90 mL H_2O). Flash chromatography was performed on silica gel (32–63 μm). Optical rotations were measured with an Autopol III automatic polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz, JEOL 300 MHz or a Varian Inova 400 MHz spectrometer.

3(S)-Triisopropylsilyloxy-4(S),5(R),6(S)-tribenzyloxy-1,7-octadiene (5a)

To the crude mixture of **3** and **4** (3:1, 2.4 g, 5.4 mmol) obtained as described in the preceding paper, in DMF (12 mL) and pyridine (1.2 mL) was added $AgNO_3$ (3.7 g, 22 mmol) followed by triisopropylsilyl chloride (2.3 mL, 10.8 mmol) at 20 °C. The reaction mixture was stirred for 2 h at 20 °C, after which it was diluted with ether (40 mL) and water (40 mL). The aqueous layer was separated and extracted with additional ether (3 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed (hexane:ether, 97:3) to give **12** (0.69 g, 18% over 3 steps) and **5a** (2.07 g, 54% over 3 steps). For **5a**:$[\alpha]^{25}_D$: +9.7 (c 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.35-7.23 (m, 15H), 6.13-6.01 (m, 1H), 5.86-5.74 (m, 1H), 5.27-5.05 (m, 4H), 4.79-4.58 (m, 5H), 4.40-4.35 (m, 2H), 4.09 (ψt, *J* = 7.7 Hz, 1H), 3.79 (dd, *J* = 3.6, 6.3 Hz, 1H), 3.65 (dd, *J* = 3.6, 5.2 Hz, 1H), 0.75-1.60 (m, 21H). ^{13}C NMR ($CDCl_3$): δ = 139.2, 138.9, 138.6, 136.1, 128.3, 128.2, 128.17, 128.13, 127.9, 127.5, 127.4, 127.3, 118.8, 115.2, 81.9, 80.2, 78.1, 74.5, 74.1, 73.8, 70.6, 18.2, 12.6. HRMS (ESI): *m/z* calcd for $C_{38}H_{52}NaO_4Si$ $(M+Na)^+$ 623.3533; found: 623.3517.

Procedure for desilylation

To **5a** or **12** (40 mg, 0.067 mmol) in THF (0.5 mL) was added TBAF (0.32 mL of 1.0 M solution in THF, 0.32 mmol) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 40 min. The solvent was evaporated and the residue was chromatographed (hexane-ethyl acetate, 6 : 1) to give pure **3** (24 mg, 82%) or **4** (26 mg, 87%).

3(S),4(R),5(R)-Tribenzyloxy-6(S)-hydroxy-1,7-octadiene (3 and 5i)

$[\alpha]^{25}_D$: +9.7 (c 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.32-7.25 (m, 15H), 6.02-5.82 (m, 2H), 5.37-5.14 (m, 4H), 4.77-4.61 (m, 5H), 4.36 (d, *J* = 11.9 Hz, 1H), 4.10 (m, 2H), 3.74 (m, 2H), 2.63 (d, *J* = 7.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 138.3, 138.2, 137.9, 135.3, 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 119.3, 116.3, 81.8, 81.4, 80.2, 74.8, 72.8, 72.0, 70.8. HRMS (ESI): *m/z* calcd for $C_{29}H_{32}NaO_4$ $(M+Na)^+$ 467.2198; found: 467.2201.

3(S),4(R),5(R)-Tribenzyloxy-6(S)-hydroxy-1,7-octadiene (4)

$[\alpha]^{25}_D$: +24.8 (c 1.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.36-7.25 (m, 15H), 5.98-5.82 (m, 2H), 5.41-5.22 (m, 4H), 4.90 (d, *J* = 11.4 Hz, 1H), 4.76-4.56 (m, 4H), 4.43 (m, 2H), 4.24 (ψt, *J* = 6.0 Hz, 1H), 3.78 (dd, *J* = 3.9, 6.0 Hz, 1H), 3.62 (ψt, *J* = 4.4 Hz, 1H), 3.20 (d, *J*= 6.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 138.7, 138.5, 138.4, 138.0, 135.4, 128.5, 128.4, 128.1, 127.9, 127.8, 119.1, 115.6, 82.1, 82.0, 80.0, 75.3, 75.1, 72.0, 70.5. HRMS (ESI): *m/z* calcd for $C_{29}H_{32}NaO_4$ $(M+Na)^+$ 467.2198; found: 467.2190.

2(R)-Triisopropylsilyloxy-3(S),4(S),5(R)-tribenzyloxy-1,6-hexadial (6a)

A solution of **5a** (1.0 g, 1.6 mmol) in pyridine (0.5 mL), CH_2Cl_2 (4.0 mL), and MeOH (20 mL) was cooled to −78 °C and subjected to a flow of O_3 in dry O_2 (0.05 CFM). When TLC indicated complete disappearance (about 5 min) of **5a** (hexane: EtOAc, 9:1, R_f (**5a**)=0.55), Me_2S (5 mL) was added. The reaction was allowed to warm to 20 °C and kept for 1 h, after which it was evaporated. The residue was dissolved in ether (40 mL), washed with aqueous 1M NH_4Cl (20 mL), water (20 mL), brine, dried ($MgSO_4$), and evaporated to produce 990 mg of crude **6a**. This residue was coevaporated with heptane (2 × 10 mL) and toluene (2 × 10 mL) and then used directly in the next reaction. ^{1}H NMR for crude **6a** (300 MHz, $CDCl_3$): δ 9.80 (s, 1H), 9.78 (s, 1H), 7.40-7.15 (m, 15H), 4.81 (d, 1H, J= 13.0 Hz), 4.63 (d, 1H, J=13.2), 4.52 (d, 1H, J=13.0 Hz), 4.42 (d, 1H, J=13.0 Hz), 4.38 (d, 1H, J=13.2 Hz), 4.29

(d, 1H, J=13.0 Hz), 4.09 (d, 1H, J=7.3 Hz), 4.05-3.94 (m, 2H), 3.75 (d, 1H, J=7.3 Hz), 1.04 (m, 21H).

3,4,5-Tri-*O*-benzyl-6-*O*-triisopropylsilyl-D-*myo*-inositol (7a) and 4,5,6-tri-*O*-benzyl-3-*O*-triisopropylsilyl-D-*myo*-inositol (8a)

To 100 mL of 0.1M solution of SmI_2 in THF was added dropwise a solution of the above crude dialdehyde **6a** (990 mg) in 50 mL of THF at −78 °C. The mixture was stirred at −78 °C for 20 min, then aqueous saturated $NaHCO_3$ (40 mL) was added dropwise via syringe. The cold bath was removed and after 10 min the flask was opened to the atmosphere and allowed to warm up. Water (100 mL) was added and the white slurry was extracted with ethyl acetate (3 × 150 mL). The organic layer was washed with 10% aqueous $Na_2S_2O_3$ (100 mL), brine and dried ($MgSO_4$). The product was purified by column chromatography (CH_2Cl_2-benzene-ethyl acetate, 50 : 50 : 2) to give 632 mg of pure **7a** (64% yield over 2 steps) followed by 30 mg of pure **8a**. For **7a**: $[\alpha]_D{}^{25}$: −18.2° (c 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.15 (m, 15H), 4.95 (d, 1H, J=11.4 Hz), 4.83 (d, 1H, J=10.7 Hz), 4.74-4.64 (m, 4H), 4.17 (m, 1H), 4.11 (ψt, 1H, J=8.8 Hz), 3.94 (ψt, 1H, J=8.8 Hz), 3.53 (dd, 1H, J=8.8, 2.9 Hz), 3.42 (m, 1H), 3.33 (ψt, 1H, J=8.8 Hz), 2.54 (br s, 1H), 2.48 (br d, 1H). ^{13}C NMR ($CDCl_3$): δ = 138.9, 138.4, 137.7, 128.4, 128.2, 128.0, 127.8, 126.8, 79.0, 78.7, 78.5, 78.1, 77.9, 76.1, 75.7, 75.4, 18.2, 18.1, 13.1. FAB HRMS (NBA/NaI): *m/z* calcd for $C_{36}H_{50}NaO_6Si$ $(M+Na)^+$ 629.3276; found: 629.3272. For **8a**: $[\alpha]_D{}^{25}$: −20.4° (c 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.37-7.15 (m, 15H), 4.95 (d, 1H, J=12 Hz), 4.88 (d, 1H, J=12 Hz), 4.84 (d, 1H, J=12 Hz), 4.82 (s, 2H), 4.78 (d, 1H, J=12 Hz), 4.10 (m, 1H), 3.88-3.75 (m, 3H), 3.53 (br d, 1H, J=10 Hz), 3.46 (ψt, 1H, J=10 Hz), 2.55 (br s, 1H), 2.41 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ = 138.9, 138.6, 138.4, 128.5, 128.3, 128.1, 127.9, 127.7, 127.0, 79.1, 78.8, 78.5, 78.2, 77.9, 76.1, 75.8, 75.5, 18.1, 12.7. HRMS (ESI): *m/z* calcd for $C_{36}H_{51}O_6Si$ $(M+H)^+$ 607.3449; found: 607.3463.

3,4,5-Tri-*O*-benzyl-D-*myo*-inositol (7i)

To a solution of **7a** (4.0 mg) in 0.5 mL of THF was added 0.1 mL of 1M Bu_4NF in THF (containing 5% water) and the reaction was stirred at 20 °C for 3 h, then evaporated. The residue was dissolved in CH_2Cl_2 (10 mL), washed with water (10 mL), dried ($MgSO_4$), and evaporated. The residue was purified by preprative TLC (10% MeOH:CH_2Cl_2) to produce pure **7i** (1.5 mg, 51%), whose ^1H NMR spectrum was identical to that reported previously.[38]

4,5,6-Tri-*O*-benzyl-D-*myo*-inositol (8i)

To a solution of **8a** (8 mg, 13.2 μmol) in 0.5 mL of THF was added 0.2 mL of 1M Bu_4NF in THF (containing 5% water) and the reaction was stirred at 20 °C for 15 h, then evaporated. The residue was dissolved in CH_2Cl_2 (15 mL), washed with water (15 mL), dried ($MgSO_4$), and evaporated. The residue was purified by chromatography (10% MeOH in CH_2Cl_2) to produce pure **8i** (4.9 mg, 83%) whose ^1H NMR spectrum was identical to that reported previously.[39]

3(R)-Triisopropylsilyloxy-4(S),5(R),6(S)-tribenzyloxy-1,7-octadiene (12)

To the crude mixture of **3** and **4** (1:8.5, 0.72 g, 1.6 mmol) obtained as described in the previous paper, in DMF (3.8 mL) and pyridine (0.38mL) was added $AgNO_3$ (1.1 g, 6.5 mmol) followed by triisopropylsilyl chloride (0.7 mL, 3.3 mmol) at 20 °C. The reaction mixture was stirred for 2 h at 20 °C, after which it was diluted with ether (10 mL) and water (10 mL). The aqueous layer was separated and extracted with additional ether (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated.

The residue was chromatographed (hexane:ether, 97:3) to give **12** (0.62 g, 57% over 3 steps) and **5** (0.072 g, 7% over 3 steps). For **12**: $[\alpha]^{25}_{D}$: +18.2 (c 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.35-7.24 (m, 15H), 6.15-6.04 (m, 1H), 5.96-5.85 (m, 1H), 5.29-5.15 (m, 4H), 4.88 (d, *J* = 11.0 Hz, 1H), 4.80-4.67 (m, 4H), 4.62-4.56 (m, 2H), 4.08 (dd, *J* = 6.1, 7.2 Hz, 1H), 3.84 (dd, *J* = 2.5, 6.1 Hz, 1H), 3.59 (ψt, *J* = 5.6 Hz, 1H), 1.50-0.80 (m, 21H). $_{13}$C NMR ($CDCl^3$): δ = 139.4, 138.9, 138.6, 138.5, 135.8, 128.5, 128.3, 128.27, 128.2, 128.1, 128.0, 127.6, 127.3, 118.7, 116.0, 84.2, 82.0, 81.4, 77.4, 75.9, 75.0, 70.8, 18.3, 12.5. HRMS (ESI): *m/z* calcd for $C_{38}H_{52}NaO_4Si$ $(M+Na)^+$ 623.3533; found: 623.3522.

2(S)-Triisopropylsilyloxy-3(S),4(S),5(R)-tribenzyloxy-1,6-hexadial (13)

A solution of **12** (65 mg, 0.11 mmol) in pyridine (20 µL), CH_2Cl_2 (2 mL) was cooled to −78 °C and subjected to a flow of O3 in dry O2 (0.05 CFM). When TLC indicated complete disappearance (about 5 min) of **5a** (hexane:EtOAc, 9:1, R_f (**12**)=0.6), Me_2S (0.2 mL) was added. The reaction was allowed to warm to 20 °C and kept for 1 h, after which it was treated with water (1.5 mL) and the layers separated. The aqueous phase was reextracted with CH_2Cl_2 (2 × 2 ML), dried ($MgSO_4$), and evaporated to produce crude **13**. This residue was used directly in the next reaction. ^{1}H NMR for crude **13** (300 MHz, $CDCl_3$): δ 9.68 (s, 1H), 9.63 (s, 1H), 7.40-7.15 (m, 15H), 4.75 (d, 2H, J= 12 Hz), 4.58 (s, 2H), 4.51 (d, 1H, J=12.0 Hz), 4.48 (d, 1H, J=12.0 Hz), 4.25 (s, 1H), 4.12-4.05 (m, 2H), 3.95 (ψt, 1H, J=5 Hz), 1.04 (m, 21H).

1-*O*-Triisopropylsilyl-2,3,4-tri-*O*-benzyl-L-*chiro*-inositol (14)

The crude dialdehyde **13** from above was diluted with t-butanol (30 µL, 0.3 mmol) in THF (6 mL) and added dropwise to a cold (− 78 °C) solution of SmI_2 (0.6 mmol) in THF (6 mL). The reaction mixture was stirred at −78 °C for 3 h and then overnight at 20 °C. Sat. $NaHCO_3$ (6 mL) was added and the white slurry was extracted with ethyl acetate (2 × 10 mL). The organic layer was washed with 10% $Na_2S_2O_3$, sat. NaCl, and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography (hexane-ethyl acetate, 8:2) afforded **14** (38 mg, 58%) followed by an unidentified isomeric diol (3 mg). For **14**: $[\alpha]_D^{25}$: −39.0° (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.26 (m, 15H), 5.01 (d, 1H, J=11.5 Hz), 4.97 (d, 1H, J=10.8 Hz), 4.81 (d, 1H, J=10.8 Hz), 4.77 (d, 1H, J=11.4 Hz), 4.70 (d, 1H, J=11.5 Hz), 4.64 (d, 1H, J=11.4 Hz), 4.31 (dd, 1H, J=3.8, 2.7 Hz), 4.02-3.89 (m, 3H), 3.80 (dd, 1H, J=9.8, 2.7 Hz), 3.63 (ψt, 1H, J=9.3 Hz), 2.3 (br s, 1H), 1.65 (br s, 1H), 1.02 (m, 21H). ^{13}C NMR ($CDCl_3$): δ = 138.45, 138.42, 138.3, 128.4, 128.1, 128.0, 127.81, 127.77, 127.73, 127.69, 127.4, 127.2, 127.1, 81.8, 81.0, 80.1, 75.2, 75.1, 73.5, 71.7, 70.9, 70.8, 17.9, 17.8, 12.2. FAB HRMS (NBA/NaI) *m/e* 629.3278, M + Na^+. Calcd for $C_{36}H_{50}O_6Si$ 629.3276.

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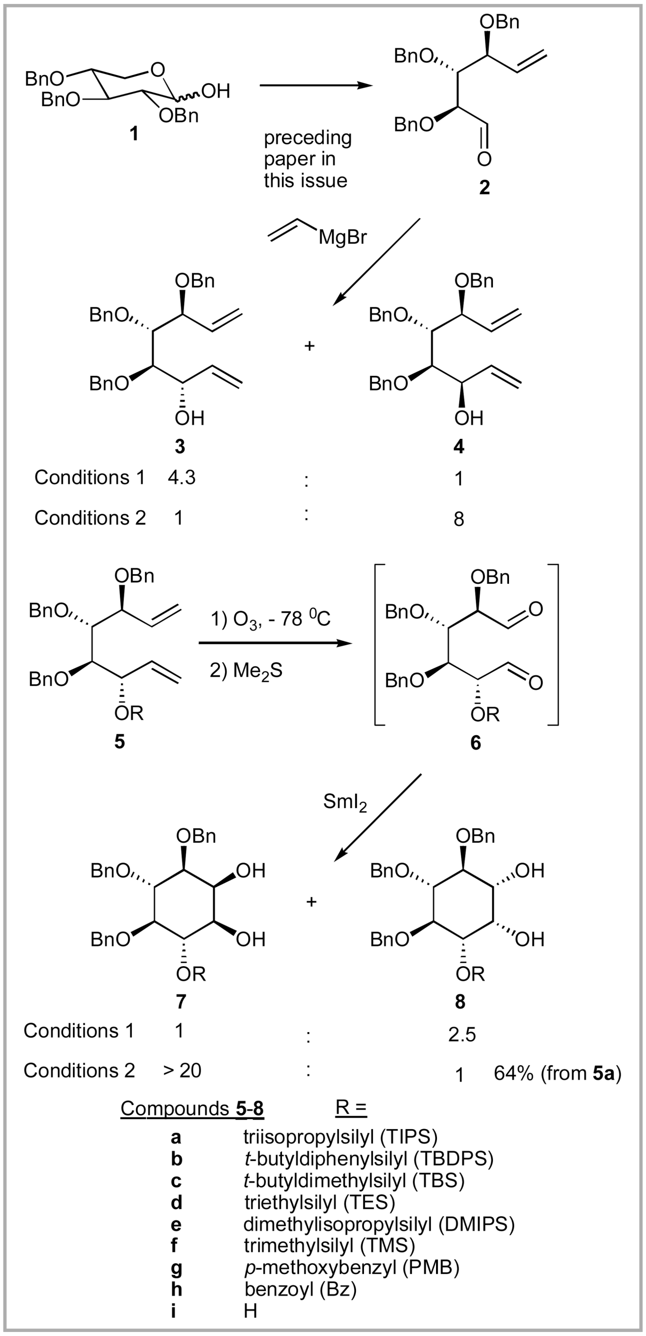


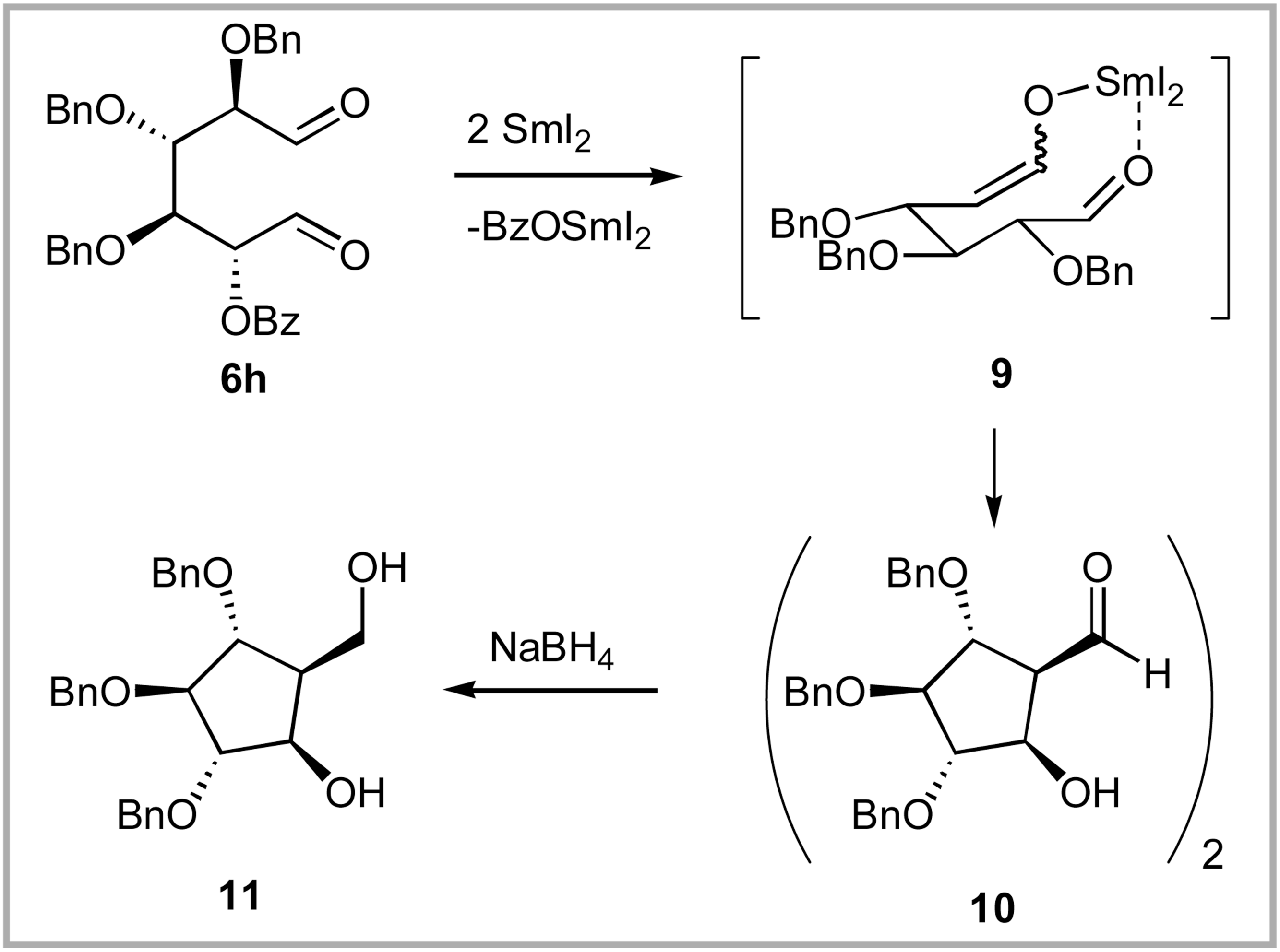
	3		4
Conditions 1	4.3	:	1
Conditions 2	1	:	8

	7		8	
Conditions 1	1	:	2.5	
Conditions 2	> 20	:	1	64% (from **5a**)

Compounds **5-8**	R =
a	triisopropylsilyl (TIPS)
b	*t*-butyldiphenylsilyl (TBDPS)
c	*t*-butyldimethylsilyl (TBS)
d	triethylsilyl (TES)
e	dimethylisopropylsilyl (DMIPS)
f	trimethylsilyl (TMS)
g	*p*-methoxybenzyl (PMB)
h	benzoyl (Bz)
i	H

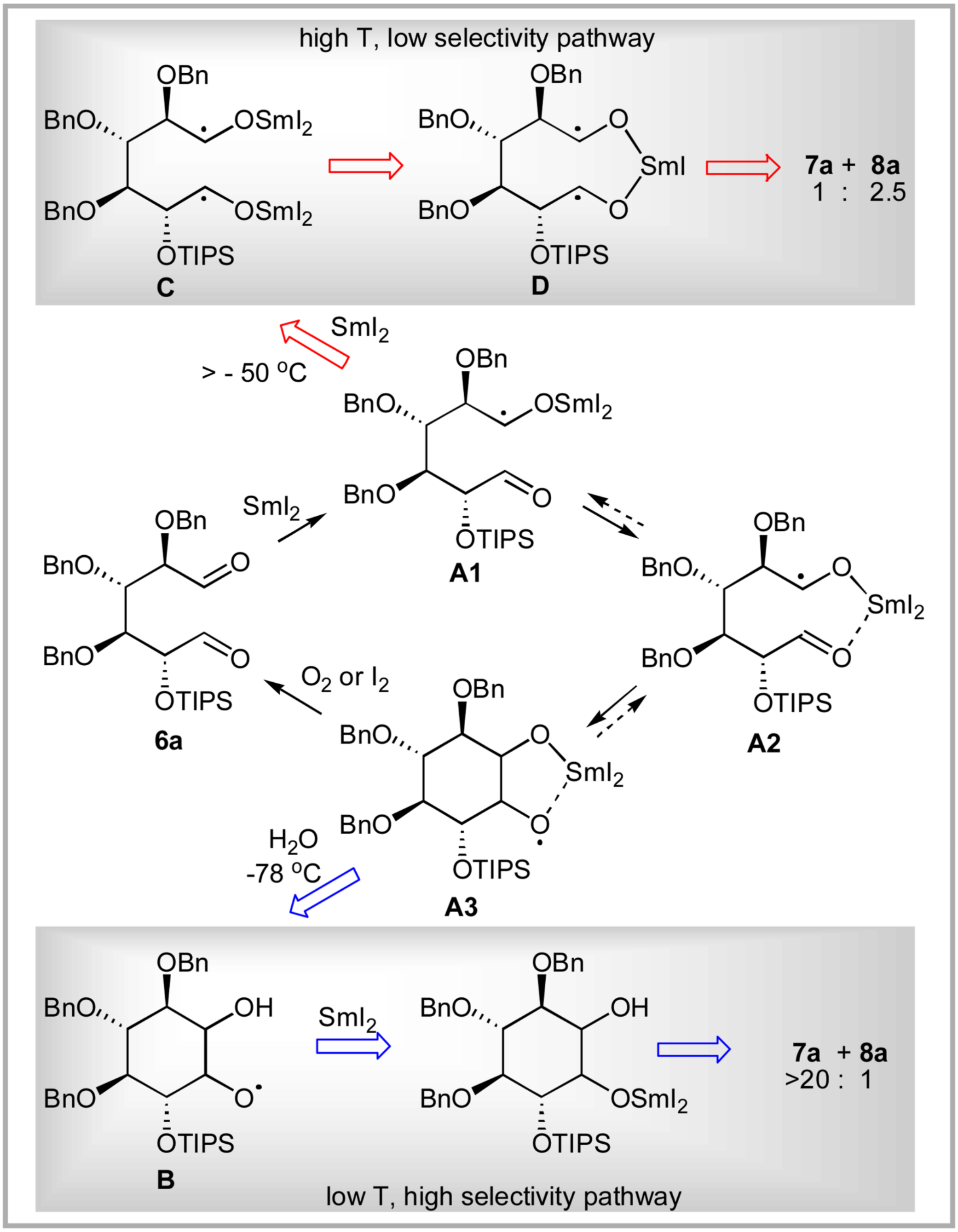
Scheme 1.

Synthesis of differentially-protected *myo*-inositols from D-xylose.



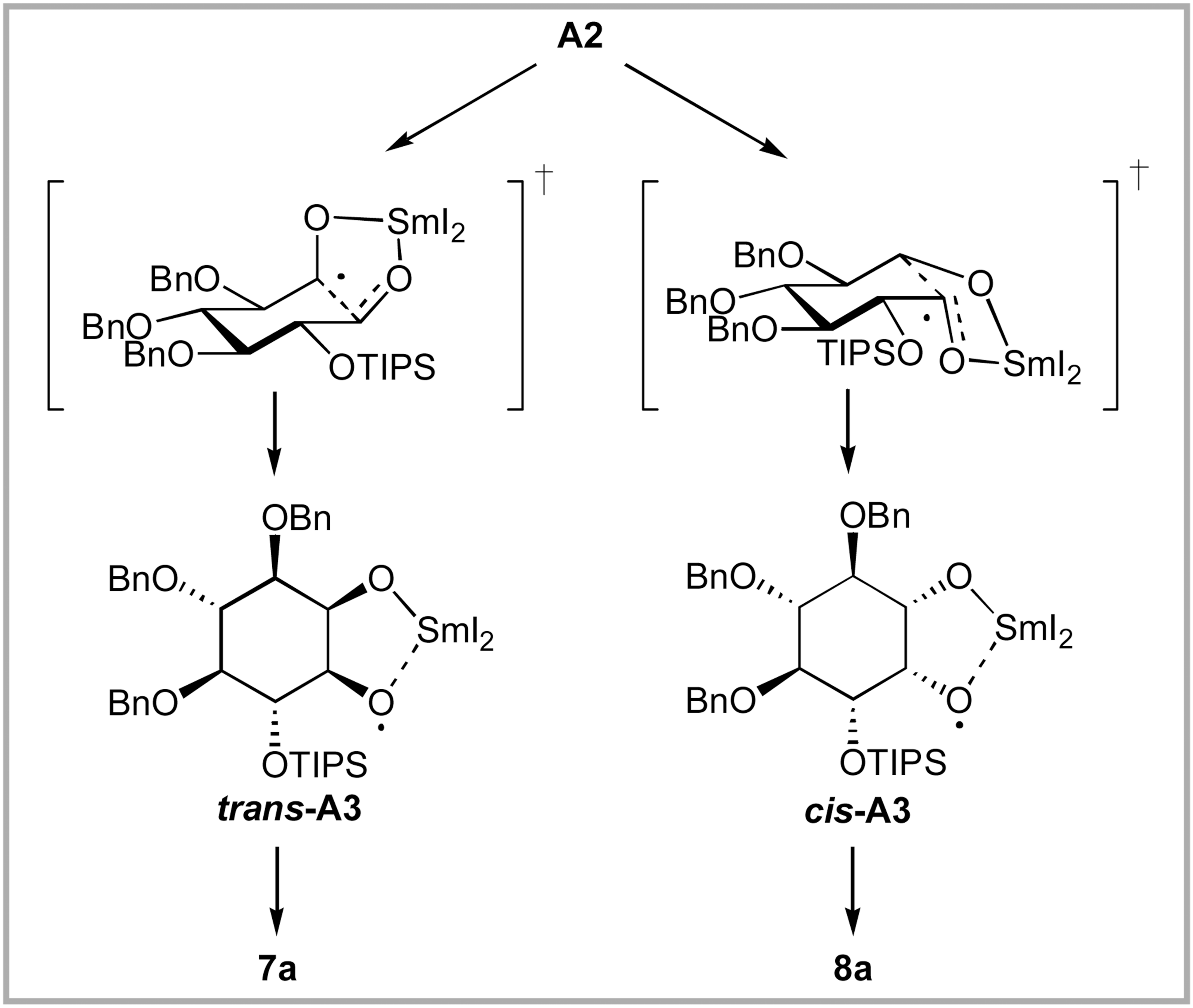
Scheme 2.

Reductive elimination of **6h** produced a polyoxygenated cyclopentane.



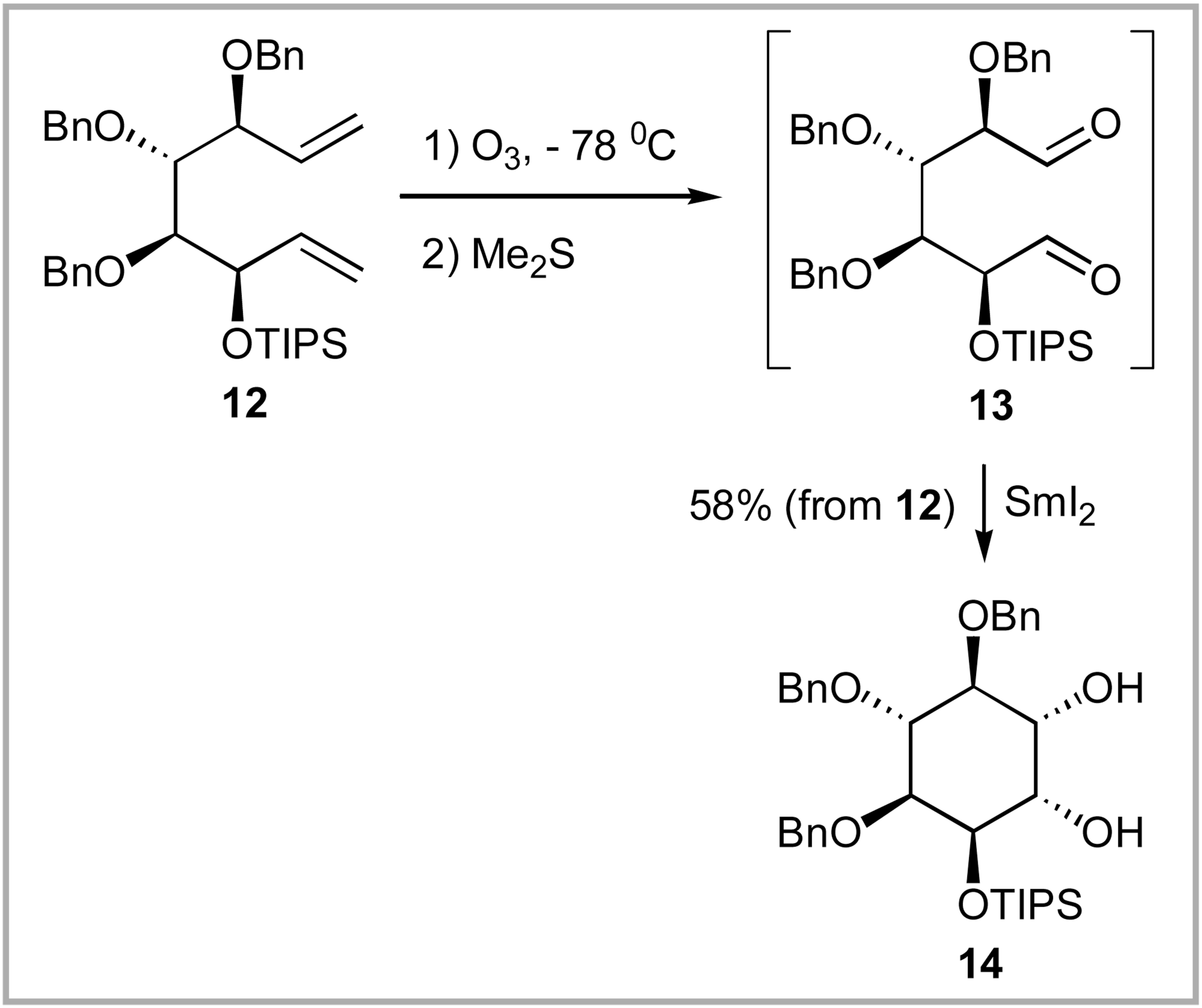
Scheme 3.

A hypothesis for the origin of the observed change in stereoselectivity in the SmI_2-promoted cyclization of **6a** as a function of temperature of quenching.



Scheme 4.

Stereoselective formation of **7a**.



Scheme 5.

Synthesis of a differentially protected *chiro*-inositol via SmI_2-promoted pinacol coupling.

Table 1

Stereoselectivity in pinacol cyclization of **6** under standard conditions: 3 eq SmI_2, 3 eq *t*-BuOH, THF, −78 °C to 20 °C.

Compound	R	Additive	Ratio 7:8
6a	TIPS	None	1:2.5
6b	TBDPS	None	1:2.5
6b	TBDPS	6 eq TMSCl	1:2.5
6b	TBDPS	HMPA (10%)	trans-diol
6c	TBS	None	1:2
6d	TES	None	1:1
6d	TES	6 eq TMSCl	1:1
6d	TES	HMPA (10%)	trans-diol
6e	DMIPS	None	1:1
6f	TMS	None	1.5:1
6g	PMB	None	1:1

Table 2

Stereoselectivity in pinacol cyclization of **6** under modified conditions: 6 eq SmI_2, THF, −78 °C; sat. aq. $NaHCO_3$, −78 °C; warm to 20 °C.

Compound	**R**	**Ratio 7 : 8**
6a	TIPS	>20:1
6c	TBS	2.9:1
6d	TES	2.7:1
6g	PMB	1:1

Table 3

The effect of reaction conditions on the stereoselectivty of SmI_2-promoted pinacol cyclization of **6a**. Reactions were performed with 6 eq SmI_2 in THF under the conditions listed.

Entry	Reaction Conditions	Quench Conditions	Ratio 7: 8
1	−78 °C, 10 min, then 20 °C, 5h	$NaHCO_3$ at 20 °C	1:2.5
2	−78 °C, 10 min	$NaHCO_3$ at −78 °C	>20:1
3	−78 °C, 10 min	H_2O at −78 °C	>20:1
4	−78 °C, 10 min, then 20 °C, 10 min	O_2 (air)	1:1
5	−78 °C, 10 min	$NaHCO_3$ at −78 °C, then O_2 (air) at −78 °C	>20:1
6	−78 °C, 10 min	O_2 (air) at −78 °C	**6a** recov.
7	−78 °C, 10 min	I_2 at −78 °C	**6a** recov.
8	−78 °C, 10 min, then 20 °C, 10 min, then −78 °C, 10 min	$NaHCO_3$ at −78 °C	1:1
9	−78 °C, 10 min	1M NH_4OH at −78 °C	>20:1
10	−78 °C, 10 min	2M HCl at −78 °C	>20:1
11	−72 °C, 10 min	$NaHCO_3$ at −72 °C	>20:1
12	−61 °C, 30 min	NaHCO3 at −72 °C	>20:1
13	−50 °C, 10 min	$NaHCO_3$ at −50 °C	>20:1
14	−25 °C, 10 min	$NaHCO_3$ at −25 °C	1:1.5
15	−78 °C, 10 min	Bu_3SnH, then $NaHCO_3$ at −78 °C	>20:1
16	−78 °C, 10 min	CuBr, then $NaHCO_3$ at −78 °C	>20:1
17	−78 °C, 10 min	MeOH, then $NaHCO_3$ at −78 °C	>20:1
18	−78 °C, 10 min	$PhCO_2H$, then $NaHCO_3$ at −78 °C	>20:1
19	−78 °C, 10 min	CF_3CO_2H, then $NaHCO_3$ at −78 °C	>20:1
20	−78 °C, 10 min	Bu_3SnH, then O_2 (air) at−78 °C	**6a** recov.
21	−78 °C, 10 min	PhSH, then O_2 (air) at−78 °C	**6a** recov.