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A Stereoselective Route to Enantiomerically Pure *myo*-Inositol Derivatives Starting from D-Mannitol

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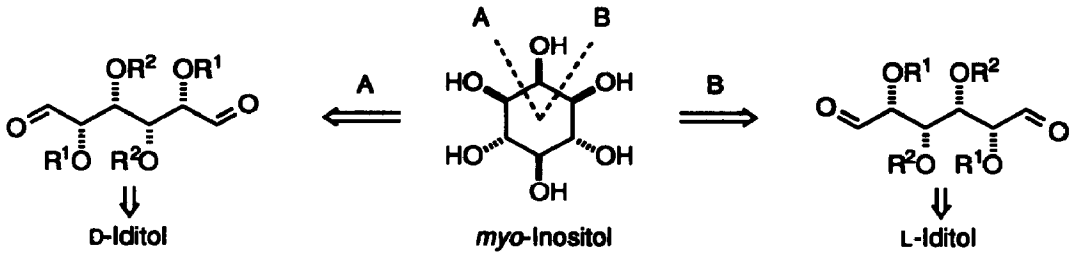
Abstract: *A carbocyclization route to inositols starting from alditols has been developed involving as a key step a stereoselective intramolecular pinacol coupling of a 1,6-dialdehyde promoted by samarium diiodide. This route has been applied to the synthesis of enantiomerically pure* myo*-inositol derivatives using readily available* D*-mannitol as starting material*

Since the discovery of the role of inositol phospholipids in cellular signalling,[1] an impressive amount of work has been devoted to the preparation of conveniently functionalized and enantiomerically pure inositol derivatives.[2] The most widely used strategy to this goal starts from cyclitols readily available from natural sources[3-5] or from bacterial oxidation of benzene derivatives.[6] When using *myo*-inositol, due to its meso character, this route requires a chemical[4] or enzymatic[5] resolution step which is generally laborious. A biomimetic approach has been developed based on the Ferrier's carbocyclization of specific sugar enol ethers promoted by mercury(II) salts, which gives a cyclohexanone or inosose that can be further transformed into a chiral inositol derivative.[7]

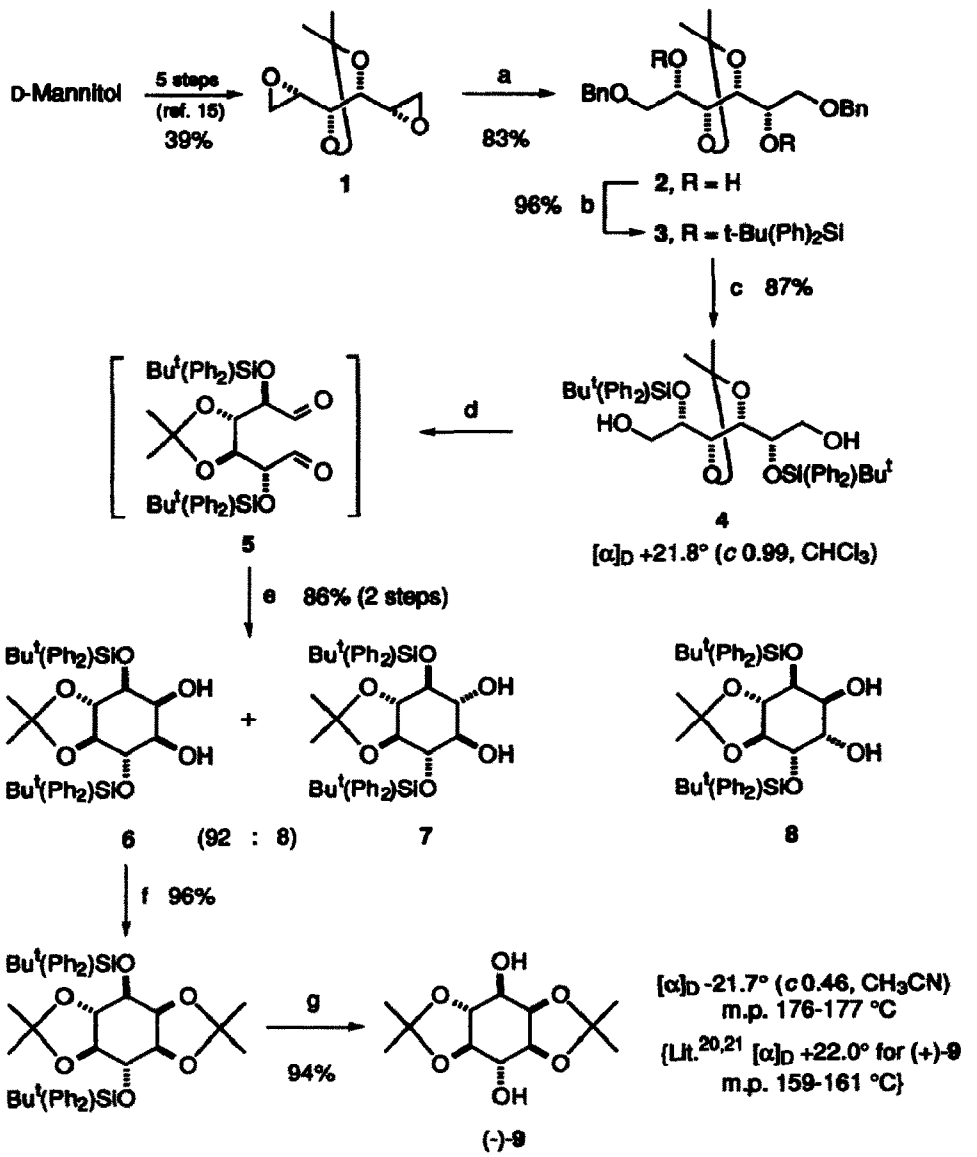
In connection with an on-going program[4c,7c,8] directed to the synthesis of glycosylinositol phosphates related to putative insulin mediators,[9] our group has developed routes to selectively protected and enantiomerically pure *myo*-inositol derivatives by chemical resolution of *myo*-inositol[4c] and by the Ferrier's approach starting from D-glucose.[7c] We now report on a different carbocyclization route based on a highly efficient reductive coupling promoted by the versatile reagent samarium diiodide and using readily available alditols as chiral starting materials.

When designing a carbocyclization approach to inositols, the most direct transform[10] of the inositol ring is the intramolecular pinacol coupling of a polyoxygenated 1,6-dialdehyde, which gives the carbocycle and a vicinal diol in a single step. Since pinacol coupling reactions produce preferentially *cis*-diols for ring size smaller than 9,[11] there are two possible disconnections for the *myo*-inositol ring (Scheme 1), each leading eventually to

Scheme 1



Scheme 2



Reagents and conditions: (a) $PhCH_2OH$, NaH, DMF, 0° → 22 °C, 24 h. (b) *t*-Bu(Ph_2)SiCl, imidazole, DMAP, DMF, 0° → 22 °C, 10 h. (c) H_2, C/Pd, *i*-PrOH-EtOAc (2:1), 22 °C, 18 h. (d) $(COCl)_2$, DMSO, Et_3N, THF, -78° → 22 °C, 3 h. (e) SmI_2 (2.5 eq), *t*-BuOH (3.0 eq), THF, -50° → 22 °C, 5 h. (f) $Me_2C(OMe)_2$, *p*-TsOH (cat), 22 °C, 1 h. (g) *n*-Bu_4NF, THF, 22 °C, 2 h

enantiomeric and C_2-symmetric iditols. There is only a single example in the literature that has followed this approach, with limited success, using a low-valent Ti reagent for the key pinacol coupling.[12]

Samarium diiodide[13] has been shown to be a mild, high yielding reagent for the stereoselective reductive coupling of dialdehydes[14] and was thought to be the reagent of choice for the key reaction in our synthetic plan. Our synthesis (Scheme 2) starts with the C_2-symmetric diepoxide **1**[15] that can be readily prepared from D-mannitol on a multigram scale. Regioselective opening of the oxirane rings of **1** with benzyl alcohol,[16] followed by simple protecting group manipulations gave the 1,6-diol **4**,[17] as a syrup, in good overall yield. Swern oxidation of **4** in THF produced the C_2-symmetric dialdehyde **5**, which was not isolated. The key pinacol coupling was performed by dropwise addition of the crude reaction mixture of **5** (*ca.* 0.015 M) over a THF solution of SmI_2 (0.1 M, 2.5 eq) and *t*-BuOH (3 eq) at -50 °C, and stirring at -50° → 22 °C for 5h. The reductive carbocyclization took place in high yield and good *cis*-stereoselectivity to give the expected non-C_2-symmetric *myo*-inositol derivative **6**[17,18] as the major product, and a small amount of the C_2-symmetric *scyllo*-inositol **7**,[17,19] that were readily separated by chromatography. The other possible diastereoisomer, the D-*chiro*-inositol derivative **8** (Scheme 2) could not be detected in the ^1H nmr of the crude, in contrast to that observed for the low-valent Ti pinacol coupling of a closely related dialdehyde which produced a mixture of *cis*- and *trans*-diols in comparable amounts.[12] The structure of the major product was further confirmed by its transformation into the known 1,2;4,5-di-*O*-isopropylidene derivative (-)-**9**[17] and comparison of its physical and spectroscopic data with those reported[20] for its enantiomer (+)-**9** (Scheme 2).

In conclusion, the strategy shown in this letter takes advantage of the symmetry of *myo*-inositol for its preparation from readily available C_2-symmetric precursors. The C_2-symmetry of the starting D-mannitol has been conserved throughout the route up to the final cyclization step. This simplifies the number of synthetic operations to be performed along the route and reduces the number of possible diastereoisomers resulting from the key carbocyclization. Enantiomerically pure **6** was obtained in this way in 22% overall yield from D-mannitol. This synthesis further demonstrates the versatility of SmI_2 for the stereoselective transformation of carbohydrate derivatives into highly functionalized carbocycles under mild conditions and in excellent yields.[22] The extension of this strategy to the synthesis of other chiral inositols starting from different alditols is now in progress in our laboratory.

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17. All new compounds were fully characterized by spectroscopic and microanalytical data.
18. ^{1}H NMR (300 MHz, C_6D_6): δ 7.94-7.16 (m, 20 H, Ar*H*), 4.06 (dd, 1 H, *J* 9.8, 8.3 Hz, H-6), 3.92 (Ψt, 1 H, *J* 9.6 Hz, H-4), 3.76 (dd, 1 H, *J* 9.9, 3.3 Hz, H-3), 3.70 (t, 1 H, *J* 3.3 Hz, H-2), 3.06 (td, 1 H, *J* 8.6, 3.4 Hz, H-1), 3.04 (t, 1 H, *J* 9.5 Hz, H-5), 2.30 (bs, 1H, O*H*-2), 1.98 (d, 1 H, *J* 8.6 Hz, O*H*-1), 1.27 (s, 9 H), 1.20 (s, 3 H), 1.14 (s, 3 H), 1.13 (s, 9 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (aromatic carbons not included) 110.8, 78.4, 77.2, 75.2, 73.8, 73.3, 72.1, 27.0, 26.7, 26.6, 19.5, 19.3. $[\alpha]_D$ -24.1° (*c* 2.77, $CHCl_3$).
19. ^{1}H NMR (300 MHz, C_6D_6): δ 7.9-7.2 (m, 20 H, Ar*H*), 3.73 (m, 2 H, *J* 9.7, 8.2 Hz), 3.19 (m, 2 H, *J* 9.2, 8.2 Hz), 3.11 (m, 2 H, *J* 9.7, 9.5 Hz), 1.95 (bs, 1 H, O*H*), 1.21 (s, 18 H), 1.06 (s, 6 H). ^{13}C NMR (50 MHz, C_6D_6): δ (aromatic carbons not included) 111.0, 78.5, 77.9, 74.4, 27.3, 26.5, 19.9. $[\alpha]_D$ -21.6° (*c* 1.15, $CHCl_3$).
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