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Synthesis of L-*chiro*-Inositol and (-)-Conduritol F from D-Sorbitol by a Highly Stereoselective Intramolecular Pinacol Coupling Promoted by Samarium Diiodide

Jose Luis Chiara* and Nuria Valle

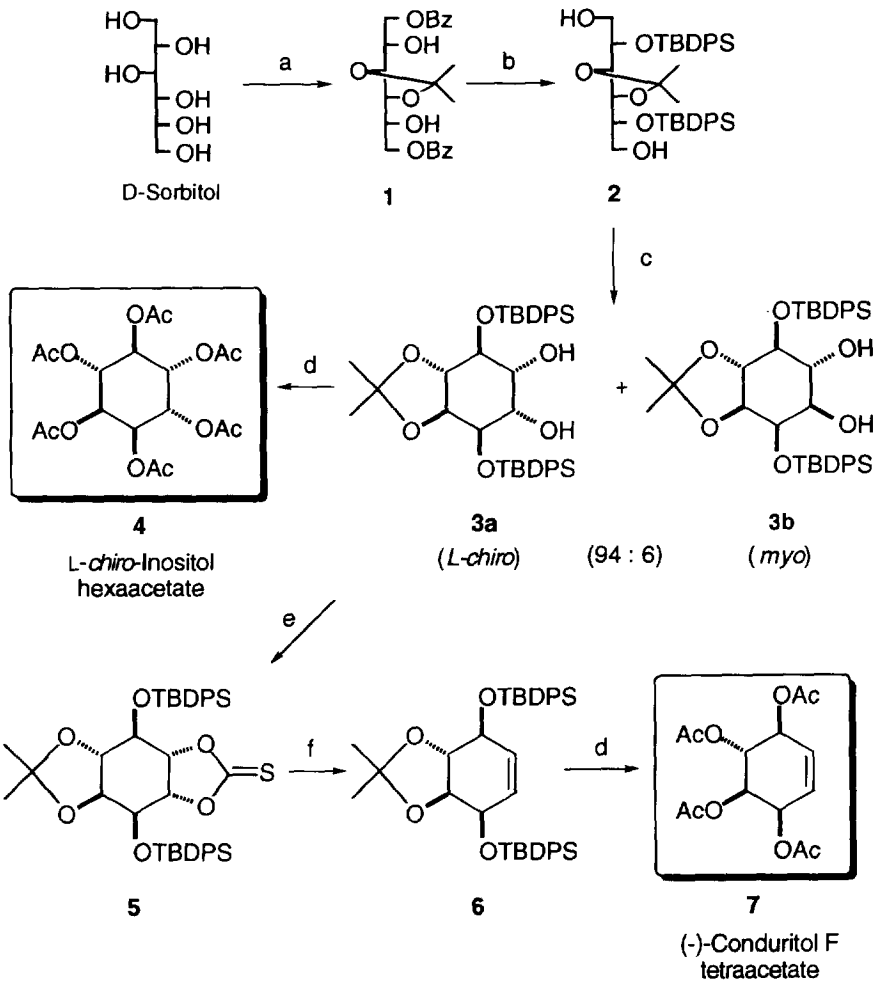
Instituto de Quimica Orgánica General, C.S.I.C., Juan de la Cierva 3, E-28006 Madrid, Spain

Abstract: A synthesis of L-*chiro*-inositol and (-)-conduritol F starting from readily available D-sorbitol is described. The route involves as a key step an efficient one-pot sequence consisting of the Swern oxidation of a 1,6-diol followed by a highly stereoselective intramolecular pinacol coupling of the resultant dialdehyde, promoted by samarium diiodide.

The pinacol coupling reaction is a very old process[1] that has seen limited application in the synthesis of complex molecules, until recently.[2] Its intramolecular version provides a direct route to cyclic 1,2-diols, which can be further transformed into alkenes, epoxides, ketones or allylic alcohols. Of the number of metal reducing agents known to promote pinacol coupling reactions,[3] samarium diiodide is proving to be superior in terms of chemical yield, chemoselectivity, stereoselectivity and mildness.[4] We have recently reported the synthesis of a chiral derivative of *myo*-inositol by a mild and high yielding intramolecular pinacol coupling of a C_2-symmetric dialdehyde derived from D-mannitol.[4h] We now report the application of this methodology to the synthesis of L-*chiro*-inositol and (-)-conduritol F using readily available D-sorbitol as starting material.

The selectively protected D-sorbitol derivative **1**[5,6] was prepared following a route similar to that described in the literature for the corresponding D-mannitol derivative.[7] Disilylation of **1** was followed by benzoate ester removal with DIBALH, which proceeded smoothly without silyl group migration,[8] to afford the 1,6-diol derivative **2**[5,6] in good yield. Compound **2** was subjected to our previously developed[4h] one-pot sequence of Swern oxidation and SmI_2-promoted intramolecular pinacol coupling affording a separable mixture of two inositols (**3a,b**)[5,6,9] in good overall yield and excellent stereoselectivity (94:6, respectively, from the ^1H NMR of the crude). No other diastereoisomer could be observed in the ^1H NMR of the crude reaction mixture. Noteworthy, the acid-labile *trans*-isopropylidene group in the products survives the very mild coupling conditions. The relative stereochemistry of the two new centers in **3a,b** was determined from the ^1H NMR spectra and corresponds to that in L-*chiro*- and *myo*-inositol, respectively. The diastereoselectivity observed is in accord with previous examples of intramolecular pinacol coupling of dialdehydes promoted by samarium diiodide[4b,c,h,i,k] which, for 6-membered rings, produce mainly *cis*-diols that are *trans*-aligned[4c] with respect to vicinal alkoxy substituents. The major diastereoisomer **3b** was fully deprotected to L-*chiro*-inositol,[11] characterized as its hexaacetate **4**,[5,6] whose C_2-symmetry was apparent in its ^1H and ^{13}C NMR spectra. Elimination of the *cis*-1,2-diol in **3b** provided (-)-conduritol F,[12] as follows. Treatment of **3b** with *N,N'*-thiocarbonyldiimidazole gave the cyclic thiocarbonate **5**,[5,6] which upon heating

with trimethylphosphite afforded the (-)-conduritol F derivative **6**.[5,6] Compound **6** was deprotected to (-)-conduritol F, which was characterized as its tetraacetate **7**.[6]



Reagents and conditions: (a) i. Me_2CO, cat. H_2SO_4, 22 °C (39%); ii. 70% aq HOAc, 50 °C (47%); iii. PhCOCl (2.2 equiv), py/CH_2Cl_2, -78 °C to 22 °C (80%). (b) i. TBDPSCl (2.5 equiv), imidazole (4 equiv), cat. DMAP, DMF, 22 °C (70%); ii. DIBALH (5.5 equiv), toluene, -78 °C; iii. 3% aq HCl (80%, 2 steps). (c) i. $(COCl)_2$ (3 equiv), DMSO (6 equiv), *i*-Pr_2NEt (10 equiv), THF, -60 °C to 22 °C; ii. SmI_2 (6 equiv), *t*-BuOH (3 equiv), THF, -70 °C to 22 °C (78%, 2 steps). (d) i. cat. PPTS, CH_2Cl_2/MeOH, 22 °C; ii. TBAF (4 equiv), THF, 22 °C; iii. Ac_2O, py, cat. DMAP, (75% for **4**, 85% for **7**; 3 steps). (e) thiocarbonyl diimidazole (1.3 equiv), toluene, 100 °C (85%). (f) $(MeO)_3P$, 110 °C (93%).

In conclusion, the present work further demonstrates the versatility of samarium diiodide for the stereoselective transformation of carbohydrate derivatives into densely functionalized carbocycles under very mild conditions.

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5. All new compounds gave correct microanalytical data.

6. Characterization data for compounds **1-7**:

1. Colorless oil; $[\alpha]_D^{22}$ +1.3 (*c* 3.7, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ (aromatic protons not included) 4.67 (dd, *J* = 11.9, 2.6 Hz, 1 H), 4.51-4.39 (m, 3 H), 4.23-4.00 (m, 4 H), 3.25 (br s, 1 H), 2.92 (br d, *J* = 8.6 Hz, 1 H), 1.45 (s, 3 H), 1.42 (s, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (aromatic carbons not included) 167.30 (s), 166.77 (s), 110.02 (s), 80.11 (d), 76.12 (d), 72.40 (d), 68.84 (d), 67.19 (t), 66.71 (t), 27.07 (q), 26.92 (q).

2. Colorless oil; $[\alpha]_D^{22}$ +13.6 (*c* 0.6, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ (aromatic protons not included) 4.31 (t, *J* = 6.5 Hz, 1 H), 4.14 (dd, *J* = 6.4, 2.5 Hz, 1 H), 3.85-3.76 (m, 2 H), 3.56-3.30 (m, 4 H), 1.9 (br s 2 H), 1.44 (s, 3 H), 1.23 (s, 3 H), 1.08 (s, 9 H), 0.98 (s, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ aromatic carbons not included) 110.02 (s), 80.54 (d), 78.45 (d), 74.50 (d), 73.29 (d), 64.48 (t), 64.34 (t), 27.58 (q), 27.03 (q), 19.49 (s), 19.29 (s).

3a. Colorless oil; $[\alpha]_D^{22}$ -28.7 (*c* 2.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ (aromatic protons not included) 4.28 (t, *J* = 2.9 Hz, 1 H), 4.10 (t, *J* = 9.5 Hz, 1 H), 3.94 (t, *J* = 9.5 Hz), 1 H), 3.86 (dt, *J* = 8.5, 3.1 Hz, 1 H), 3.62 (t, *J* = 2.9 Hz, 1 H), 3.61 (dd, *J* = 9.5, 2.5 Hz), 2.09 (br s, 1 H), 2.03 (d, *J* = 2.6 Hz, 1 H), 1.31 (s, 3 H), 1.28 (s, 3 H), 1.12 (s, 9 H), 1.10 (s, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (aromatic carbons not included) 110.75 (s), 76.75 (d), 75.78 (d), 75.35 (d), 74.26 (d), 73.25 (d), 69.06 (d), 27.09 (q), 26.96 (q), 26.60 (q), 19.54 (s), 19.32 (s).

3b. White crystalline solid, m.p. 129-130 °C; $[\alpha]_D^{22}$ +66.4 (*c* 0.25, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ (aromatic protons not included) 4.42 (t, *J* = 2.3 Hz, 1 H), 4.20 (t, *J* = 9.5 Hz, 1 H), 3.84 (ddd, *J* = 9.2, 7.8, 2.2 Hz, 1 H), 3.69 (dd, *J* = 9.5, 9.2 Hz, 1 H), 3.25 (ddd, *J* = 9.2, 7.1, 2.3 Hz, 1 H), 3.18 (dd, *J* = 9.6, 2.1 Hz, 1 H), 2.16 (d, *J* = 2.4 Hz, 1 H), 1.67 (d, *J* = 7.1 Hz, 1 H), 1.27 (s, 3 H), 1.23 (s, 3 H), 1.16 (s, 9 H), 1.14 (s, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (aromatic carbons not included) 111.24 (s), 76.99 (d), 76.72 (d), 76.10 (d), 75.50 (d), 74.19 (d), 69.83 (d), 27.12 (q), 26.89 (q), 26.48 (q), 19.66 (s), 19.60 (s).

4. Colorless oil; $[\alpha]_D^{22}$ -3.1 (*c* 0.6, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 5.46-5.26 (m, 6 H), 2.19 (s, 6 H), 2.03 (s, 6 H), 2.00 (s, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.80 (s), 169.72 (s), 169.04 (s), 69.74 (d), 68.90 (d), 67.25 (d), 20.74 (q), 20.57 (q).

5. White amorphous solid; m.p. 58-60 °C; $[\alpha]_D^{22}$ -1.2 (*c* 1.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ (aromatic protons not included) 4.91 (dd, *J* = 6.9, 6.3 Hz, 1 H), 4.61 (t, *J* = 2.4 Hz, 1 H), 4.42 (dd, *J* = 7.1, 2.2 Hz, 1 H), 4,19 (t, *J* = 10.0 Hz, 1 H), 3.88 (dd, *J* = 10.0, 6.0 Hz, 1 H), 3.33 (dd, *J* = 9.8, 2.7 Hz, 1 H), 1.39 (s, 3 H), 1.24 (s, 3 H), 1.14 (s, 9 H), 1.135 (s, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (aromatic carbons not included) 189.09 (s), 111.90 (s), 87.28 (d), 83.78 (d), 77.07 (d), 75.89 (d), 73.73 (d), 66.11 (d), 27.06 (q), 28.84 (q), 26.54 (q), 19.50 (s), 19.30 (s).

6. Colorless oil; $[\alpha]_D^{22}$ -64.5 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ (aromatic protons not included) 5.41 (dd, *J* = 10.0, 1.8 Hz, 1 H), 5.15 (ddd, *J* = 10.0, 5.0, 1.9 Hz, 1 H), 4.61 (dd, *J* = 9.8, 8.0 Hz, 1 H), 4.44 (dtd, *J* = 8.1, 1.9, 0.6 Hz, 1 H), 4.38 (dd, *J* = 5.4, 3.4 Hz, 1 H), 3.01 (dd, *J* = 9.7, 3.5 Hz, 1 H), 1.55 (s, 3 H), 1.37 (s, 3 H), 1.23 (s, 9 H), 1.20 (s, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 136.24 (d), 136.16 (d), 135.98 (d), 134.55 (s), 134.39 (s), 133.64 (s), 133.45 (s), 133.08 (d), 129.59 (d), 127.69 (d), 127.50 (d), 127.33 (d), 110.04 (s), 77.03 (d), 76.72 (d), 73.67 (d), 65.86 (d), 27.31 (q), 26.96 (q), 28.90 (q), 19.39 (s), 19.32 (s).

7. Colorless oil; $[\alpha]_D^{22}$ -46.5 (*c* 1.13, $CHCl_3$) [lit.[10c] for (+)-conduritol F tetraacetate: $[\alpha]_D^{25}$ +45.6 (*c* 1.12, $CHCl_3$)]; ^1H NMR (200 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 9.9, 4.9, 1.3 Hz, 1 H), 5.83 (dd, *J* = 10.1, 1.7 Hz, 1 H), 5.64-5.48 (m, 3 H), 5.17-5.09 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.20 (s), 170.00 (s), 169.77 (s), 130.77 (d), 125.29 (d), 71.73 (d), 69.07 (d), 68.48 (d), 65.81 (d) 20.82 (q), 20.72 (q), 20.52 (q).

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8. Methanolysis of the benzoate esters with NaOMe/MeOH produced a mixture of products due to partial silyl group migration.

9. **Typical procedure**: To a solution of oxalyl chloride (152 μL, 1.74 mmol) in THF (4 mL) at -60 °C under argon was added DMSO (270 μL, 3.48 mmol) dropwise. The mixture was stirred at -60 °C for 10 min and a solution of **2** (405 mg, 0.58 mmol) in THF (8.5 mL + 2.5 mL rinse) was added dropwise via cannula. After stirring at -60 °C for 30 min, *i*-Pr_2NEt (1.0 mL, 5.79 mmol) was added dropwise and the mixture was stirred at -60 °C for 30 min and then at room temperature for 2 h. The mixture was diluted with THF (30 mL) and added via cannula over 1 h to a freshly prepared[10] solution of SmI_2 (3.5 mmol) in THF (35 mL) and *t*-BuOH (165 μL, 1.75 mmol) at -70 °C. After stirring for 6 h at -70 °C to room temperature, aqueous sat. $NaHCO_3$ (50 mL) was added and the mixture was extracted with EtOAc (3 x 120 mL). The combined organic extracts were washed with 10% aqueous $Na_2S_2O_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated at reduced pressure. The crude was purified by flash column chromatography (hexane/EtOAc 4:1) affording 288 mg (71 %) of **3b** (R_f = 0.28, hexane/EtOAc 4:1) and 28 mg (7%) of **3a** (R_f = 0.18, hexane/EtOAc 4:1).

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