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Convenient synthesis of *cis-O*-isopropylidene-3,5-cyclohexadien-1,2-diol

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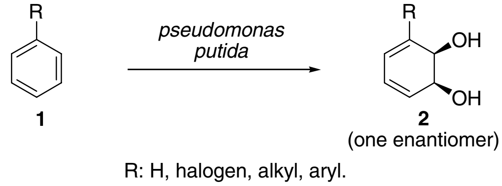
Abstract—The title compound was obtained by a convenient and scaleable three-step procedure, starting from the readily available and relatively inexpensive *myo*-inositol. The key-step of the route is an unprecedented tandem reductive elimination of two *vic*-dimesylate moieties to a conjugated diene.

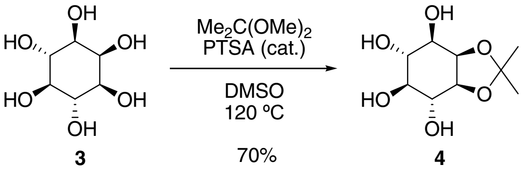
cis-3,5-Cyclohexadien-1,2-diol **2** and its protected analogues are valuable starting materials for the synthesis of a great number of biologically active substances,[1,2] unusual molecules[3] and high-performance materials.[4] The great interest in these substances arises from the presence of two easily derivatized functional groups (olefines and hydroxyls) in a specific arrangement, that allows a great number of chemical transformations.[1,5] Disappointedly, the high cost and the variable quality of commercial **2** is a serious drawback for large-scale studies and applications. Biological oxidation of benzene and its derivatives, by the use of various mutant strains of *Pseudomonas putida*[4f,6] (Scheme 1), is advantageous, but this does require large and specialist equipment, often unfamiliar to organic chemists, and only affords limited amounts of material.

A convenient four-step, 26% overall yield, procedure for the synthesis of isopropylidene or benzylidene protected *cis*-1,2-dihydrocatechol on a large scale was proposed by Yang and co-workers.[3o,p] This procedure noticeably reduces the cost for the preparation of protected *cis*-1,2-dihydrocatechols, despite the use of the relatively expensive 1,4-cyclohexadiene as starting material. A four-step, 24% overall yield, synthesis of cyclohexylidene protected 3,5-cyclohexadien-1,2-diol was also reported by Mereyala and Pannala,[7] starting from *myo*-inositol.



Scheme 1.

In this letter, we describe a convenient and scaleable three-step synthesis of *cis*-3,5-cyclohexadien-1,2-diol acetonide, that is one of the more widely used protected dihydrocatechols, starting from *myo*-inositol and other readily available and inexpensive reagents. The starting material *myo*-inositol **3** was protected with 2,2-dimethoxypropane, according to the procedure of Gigg, to afford the acetal **4** in 70% yield (Scheme 2).[8]



Scheme 2.

Keywords: 1,2-Dihydrocatechol; Inositol; Conjugated dienes; Cycloadditions; Reductions.

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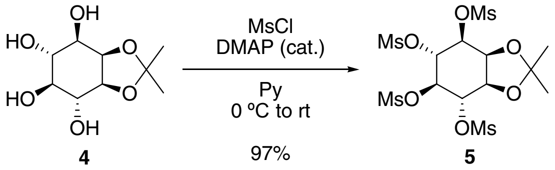
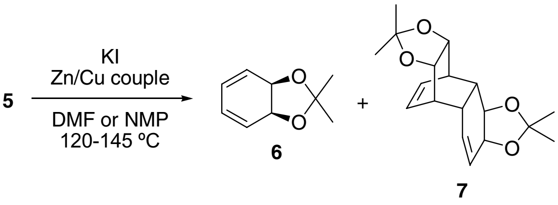
A number of methodologies were studied in order to transform *vic*-diols into olefins.[9] In early attempts we looked for direct protocols to transform the four hydroxyls into the two conjugate double bonds. Disappointedly, the use of triphenylphosphine and iodine[7,9,10] invariably led to the formation of tars. Tetrol **4** was hence transformed into tetramesyl-derivative **5**, in nearly quantitative yield, with a slight excess of methanesulfonyl chloride in pyridine (Scheme 3).[11]



Scheme 3.

Many attempts to react mesylate **5** with sodium naphthalenide in dry THF at low temperature,[9,12] led invariably to a complex mixture of products. Mesylate **5** was refluxed 24 h in DMF with potassium iodide and zinc–copper couple,[9,13] to afford the diene **6** in 20–46% concomitantly with variable amounts of cycloadduct **7** (Scheme 4).[14]



Scheme 4.

The quality of the zinc–copper couple[15] was found to be crucial for the success of the reaction, in fact freshly activated metal afforded the higher yields of **6**. A further improvement in the synthesis was the use of NMP (*N*-methylpyrrolidinone) as solvent; this allowed the co-distillation at reduced pressure. This procedure allowed improved yields (48–60%); possibly because of the more efficient activation of the de-mesylation at the higher temperatures (145 °C), and the removal of the product from the reaction mixture. The absence of zinc salts in the crude mixture and the higher purity of **6** after extractions are other significant advantages of this procedure (dimer **7** was not observed in the product).

To conclude, in this letter we describe a new, more convenient, effective, three-step synthesis of 1,2-dihydrocatechol acetonide **6**, with an overall 36% yield. The key-step of the procedure is the unprecedented reductive elimination of a *vic*-tetramesylate to a conjugate diene.

Experimental

Synthesis of 1,2-*O*-isopropylidene-3,4,5,6-tetra-(methanesulfonyl)-*myo*-inositol (5)

Mesyl chloride (57.0 mL, 84.9 g, 741 mmol) was added via syringe to a solution of **4** (32.6 g, 148 mmol) and DMAP (1.0 g, 8.2 mmol) in pyridine (250 mL) maintained at 0 °C under argon. The mixture was left to rise to rt overnight and was poured onto crushed ice (800 g). The resulting white-off solid was filtered, washed with cold water (3 × 100 mL), *i*-PrOH (2 × 100 mL) and dried in vacuum over P_2O_5 to obtain 76.4 g (97% yield) of **5**, pure enough for the next step. An analytical sample was obtained by recrystallisation from DMF/Et_2O, mp 210 °C. IR (KBr) ν_{max} 3037, 2983, 2957, 1362, 1181, 973, 875, 818, 518 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 5.37–5.28 (1H, m), 5.21–5.08 (2H, m), 4.87–4.76 (1H, m), 4.68–4.60 (1H, m), 4.51–4.43 (1H, m), 3.35 (3H, m), 3.32 (3H, m), 3.29 (3H, m), 3.28 (3H, m), 1.56 (3H, m), 1.35 (3H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 110.9, 80.7, 75.7, 74.8, 74.5, 73.8, 73.6, 39.2, 39.0, 38.7, 38.1, 27.0, 25.6. Anal. Calcd for $C_{13}H_{24}O_{14}S_4$: C, 29.32; H, 4.54. Found: C, 29.35; H, 4.51.

Synthesis of *cis-O*-isopropylidene-3,5-cyclohexadien-1,2-diol (6)

In a 500 mL two necked round-bottomed flask equipped with a mechanical stirrer and distillation apparatus, a mixture of **5** (10.0 g, 18.78 mmol) and KI (24.0 g, 144.6 mmol) in NMP (200 mL) was heated at 120 °C with an oil bath. Approx. 30 mL of volatile materials were distilled off in vacuum (10 Torr) in 1 h.[16] Freshly prepared Zn/Cu couple[15] (from 15 g of Zn dust, 225 mmol) was added to the solution and the resulting mixture was heated at 120 °C for 24 h. Vacuum (20 Torr) was applied to the apparatus, the oil bath was heated at 145 °C and the volatile materials were distilled (bp 90–100 °C). The distillate was poured into a 3:2 satd aq NaCl/H_2O mixture (500 mL) and extracted with AcOEt (3 × 50 mL). The combined organic extracts were washed with water (5 × 50 mL), saturated NaCl (3 × 50 mL), dried over $MgSO_4$ and carefully concentrated at reduced pressure to afford 1.37–1.70 g (48–60% yield) of **6**, identical to authentic sample.

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