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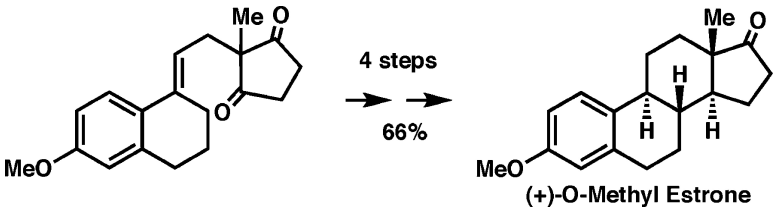

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Conversion of Torgov's Synthesis of Estrone into a Highly Enantioselective and Efficient Process

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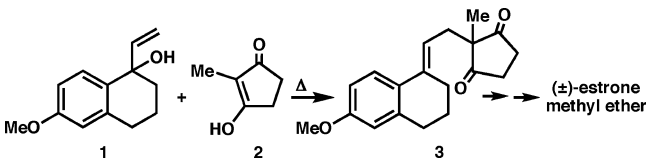
In 1963 Torgov and Ananchenko disclosed a remarkably short synthesis of (±)-estrone which was based on the high-yielding thermal coupling of the readily available components **1** and **2** to form **3** (Scheme 1).[1,2]

Although this route provides facile access to racemic estrone, its modification to a simple enantioselective version has been problematic.[3] We describe herein an effective solution to this classic unsolved problem, the key to which was the development of a new method for the enantioselective and diastereoselective reduction of the achiral Torgov diketone **3**. In addition to this route, we have recently developed a different short and highly enantioselective synthesis of estrone from 3-methoxy-8-vinyl-5,6-dihydronaphthalene (**4**), using a catalytic enantioselective Diels−Alder reaction as the key step.[4]

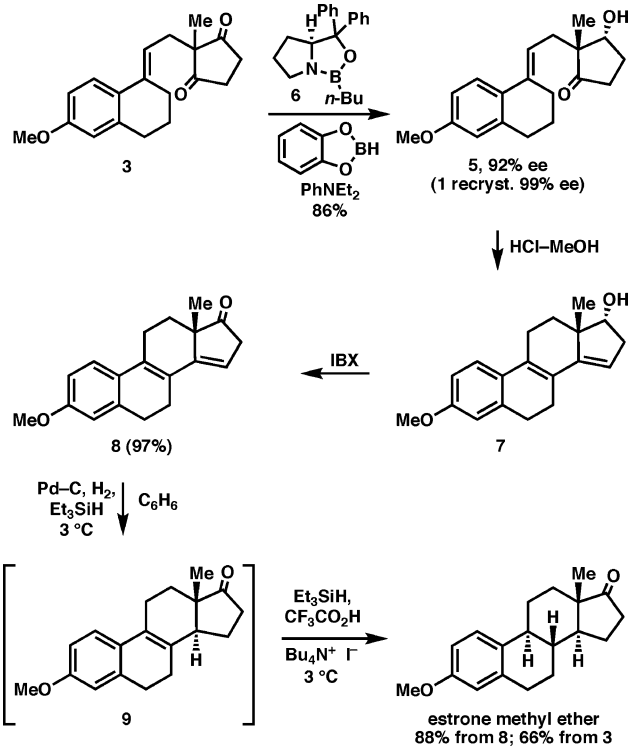
The pathway of synthesis of the natural form of estrone methyl ether from the Torgov diketone **3** is summarized in Scheme 2. The initial chirogenic step, the reduction **3** → **5**, could not be effected enantioselectively using oxazaborolidine catalysis with various boranes as reductants under any of the standard conditions.[5] Typically, the reductions were very slow and the enantiomer of **5** was obtained with an enantiomeric purity of only ca. 20−50%. However, it was possible to modify the process in such a way as to accelerate the reaction, create a new pathway, and control absolute stereochemistry. The reduction was best carried out by the slow addition of 1.8 equiv of catecholborane to a cold (−50 °C) toluene solution of diketone **3**, 0.2 equiv of catalyst **6,** and 0.4 equiv of *N*,*N*-diethylaniline. After a reaction time of 3 h at −50 °C the reaction mixture was quenched in the CH_3OH and the product **5** was isolated by extraction and flash chromatography on silica in a yield of 86% and enantiomeric purity of 92%. A single crystallization from ethyl acetate−hexane afforded **5** of 99% ee, mp 99−101 °C; the structure of **5** was confirmed by X-ray analysis. Treatment of **5** with methanolic HCl at 65 °C for 2 h generated the tetracycle **7** which was oxidized without purification by 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) in DMSO at 23 °C for 4 h to give the pure dienone **8**, mp 138−140 °C, in 97% yield overall from **5**. Exposure of dienone **8** to 20 equiv of Et_3SiH, H_2 (1 atm) and Pd−C in C_6H_6 at 3 °C generated enone **9** which, after filtration, was directly treated with CF_3CO_2H and Bu_4NI to give pure estrone methyl ether, mp 163−165 °C, $[\alpha]^{25}_D$ +155 (*c* 1.0, $CHCl_3$), in 88% overall yield from **8**. The conversion of the achiral Torgov intermediate **3** into the natural chiral form of estrone is remarkably efficient and expeditious.

The key enantioselective reduction **3** → **5** clearly proceeds by a different pathway from the standard CBS reduction[5] since it follows the opposite stereocourse and since the known variants of the CBS reduction are not useful with **3**, as mentioned above. We believe that the reversal caused by $PhNEt_2$ can be explained by the pre-transition-state assembly **10** in which the hydride donor is the catecholborane−$PhNEt_2$ complex and the ketone is activated by coordination to the complex of **6** with catecholborane. The success

Scheme 1



Scheme 2



of this new reduction process is due to a number of factors, including that (1) significant amounts of the catecholborane−$PhNEt_2$ complex exist in the reaction mixture, (2) there is also free catecholborane available for activation of the oxazaborolidine by coordination to the nitrogen of **6**, (3) the pre-transition state assembly **10** is of lower energy than the various alternative geometries. In the assembly **10** boron is complexed with the

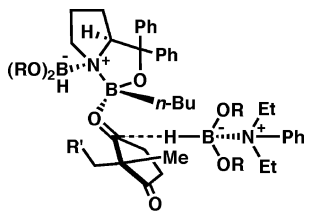


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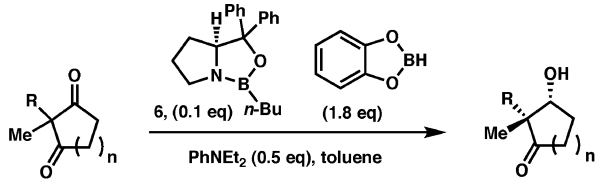
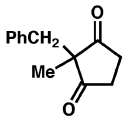
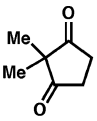
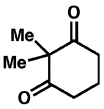
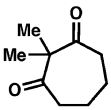
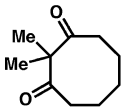
Table 1. Enantioselective Three Component Reduction of Cyclic 1,3-Diketones



entry	substrate	temp (°C)	time (h)	yield (%)	ee (%)
1		–60	5	73[a]	94
2		–60	4	72	94
3		–60	4	69	92
4		0	25	65[b,c]	76
5		0	20	91[c]	93

[a] Based on 90% conversion. [b] The B−H oxazaborolidine was used as catalyst rather than the B−*n*-Bu reagent **6**. [c] Based on 85% conversion.

sterically less screened lone electron pair of the carbonyl oxygen, steric repulsion is minimized, and the nucleophilic hydride is attached to the carbonyl carbon at the sterically more accessible face.

Our new reduction method is more broadly applicable to the enantioselective reduction of achiral 1,3-diketones, which previously had only been realized by the use of enzymic processes such as fermenting yeast reduction.[6] Five examples of the enantioselective reduction of cyclic 1,3-diketones are summarized in Table 1. Excellent enantioselectivities were observed with 5, 6, and 8-membered substrates, and yields of chiral β-hydroxyketone generally were good (entries 1−3 and 5).[7] The principal byproduct in each case was the 1,3-diol produced by further reduction of the initially formed β-hydroxyketone. The reduction of 2,2-dimethylcycloheptan-1,3-dione (entry 4) was both slower and less enantioselective than that of the other substrates in Table 1. The absolute configurations of the products of entries 2[8] and 3[9] were determined by comparison of optical rotation of each product with the value reported previously. The absolute configurations for the products of entries 1, 4, and 5 were assigned by analogy with the three examples reported (**3** → **5** and Table 1, entries 2 and 3) and from the application of mechanistic model implicit in the pre-transition-state assembly **10**.

The new methodology for the enantioselective reduction of cyclic achiral 1,3-diketones provides an alternative to the use of fermenting yeast reduction which suffers from a number of drawbacks, including the need to use large reaction volumes, troublesome foaming and copious evolution of CO_2 and, finally, difficulties in extracting water-soluble products.

We are currently exploring other applications of the new three-component process.

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Supporting Information Available: Experimental procedures and characterization data for all compounds; X-ray crystal structure of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Enantioselectivities for the reduction products of Table 1 were determined by ^{1}H NMR analysis of the Mosher MTPA esters except for entry 1 which was analyzed by HPLC using a Chiral Technologies OD column. Full details appear in the Supporting Information.
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