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Formal Enantioselective Synthesis of (+)-Estrone

Darunee Soorukram and Paul Knochel*

Department Chemie und Biochemie, Ludwig-Maximilians-Universität München,
Butenandtstrasse 5-13, Haus F, 81377 München, Germany

paul.knochel@cup.uni-muenchen.de

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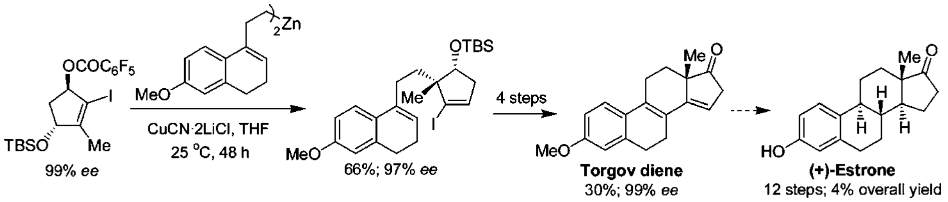
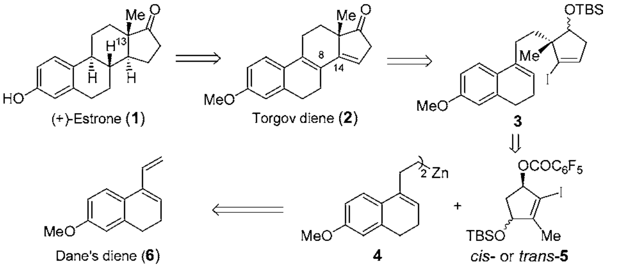
ABSTRACT



A formal total synthesis of (+)-estrone (4% overall yield; ca. 12 steps) could be achieved via the Torgov diene. An asymmetric allylic substitution is the key step for the construction of the chiral quaternary carbon center of a synthetic intermediate which was converted in four steps to the Torgov diene.

(+)-Estrone (**1**) together with estradiol and progesterone are the most important female sex hormones. (+)-Estrone is only found as trace in plants and has been isolated from the urine of pregnant women.[1] Several elegant total syntheses of **1** have been reported.[2] Our synthetic approach has focused on the presence of a chiral quaternary center at position 13 (Scheme 1) because we have recently reported a general stereoselective synthesis of chiral quaternary centers[3,4] using copper(I)-mediated *anti*-S_N2'-allylic substitutions.[5] Our retrosynthetic analysis starting from the Torgov diene (**2**)[6] disconnects the C(8)−C(14) bond leading to the key chiral intermediate **3** (Scheme 1). We expected that the alkenyl iodide **3** could be converted into the Torgov diene by using Heck methodology.[7,8] The chiral cycloalkenyl iodide **3** should be prepared using a copper(I)-mediated *anti*-S_N2'-allylic substitution[3] of the dialkylzinc **4** with the chiral cyclopentene diol derivative **5**. The zinc organometallic **4** will be readily available from Dane's diene (**6**)[9] using a hydroboration, B/Zn exchange sequence.[10]

Scheme 1



We focused first our attention on the preparation of the cyclopentene diol derivative **5**, starting from 4-hydroxy-3-

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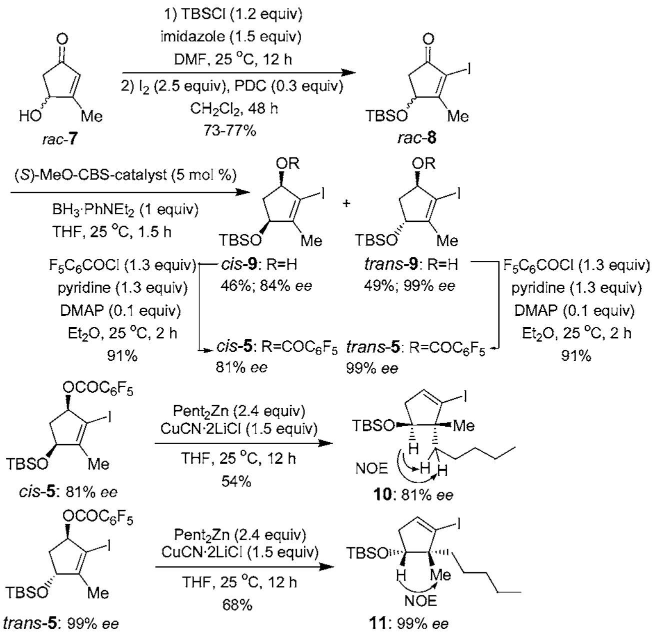
methyl-2-cyclopent-2-en-1-one (**7**) which was conveniently prepared in two steps from 2,5-dimethylfuran.[11] Treatment of the allylic alcohol **7** with TBSCl (1.2 equiv, imidazole (1.5 equiv), DMF, 25 °C) followed by an oxidative iodolysis (I_2 (2.5 equiv), PDC (0.3 equiv), CH_2Cl_2) gives the 2-iodoenone **8** in 73−77% yield. The CBS reduction[12] of *rac*-**8** with $BH_3{\cdot}PhNEt_2$ using the (*S*)-MeO CBS catalyst (25 °C, 1.5 h)[5a] affords the two readily separable diastereoisomers, *cis*-**9** (46%; 84% ee) and *trans*-**9** (49%; 99% ee). The relative configuration of *cis*-**9** and *trans*-**9** as well as an evaluation of the reactivity of the corresponding pentafluorobenzoates *cis*-**5** and *trans*-**5** were established by performing a copper(I)-mediated allylic substitution with $Pent_2Zn$ (THF, 25 °C, 12 h). As expected, the only substitution products are the *anti*-S_N2'-cyclopentenyl iodides **10** (54%; 81% ee) and **11** (68%; 99% ee). A complete transfer of the chiral information was observed for the two substrates as shown by the enantiomeric excess of the products **10** and **11**. The relative configuration of **10** and **11** was established by NOE experiments.[13] Because the configuration of the carbon attached to the TBSO substituent in *cis*- and *trans*-**5** is not important for the synthesis outcome, we decided to use for further steps the *trans*-pentafluorobenzoate (*trans*-**5**) which was available through the CBS reduction in 99% ee[14] (Scheme 2).

Scheme 2



We have prepared the required zinc reagent **4** starting from Dane's diene (**6**) which was obtained in two steps from 6-methoxytetralone.[15] Thus, the treatment of the diene **6** with Et_2BH[9] (1 equiv) for 3 h at 0 °C followed by the reaction with neat Et_2Zn (2 equiv) at 25 °C for 16 h affords the dialkylzinc **4**. The reaction was monitored by GC analysis of hydrolyzed reaction aliquots.[16] As the key step, we have

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(13) See Supporting Information.

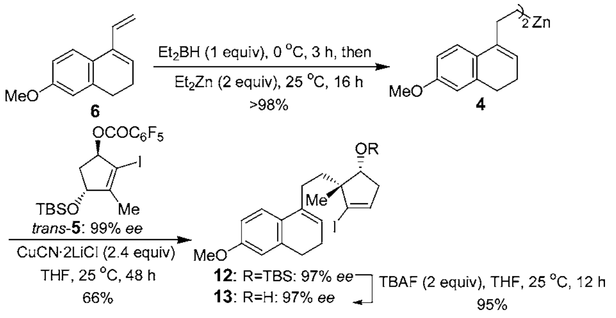
(14) The performance of the CBS reduction on the racemic mixture of **8** affords a mixture of two products, *cis*-**9** and *trans*-**9**, of which only the *trans*-isomer (*trans*-**9**) is obtained with 99% ee. To avoid the formation of *cis*-**9** (which is obtained only with 84% ee), we performed an enzymatic kinetic resolution of *rac*-**7** using porcine pancreatic lipase (PPL) and vinyl acetate at 25 °C. We have obtained both enantiomers (*R*)-**7** and (*S*)-**7** in 91% ee and in excellent yields. See Supporting Information.

(15) 6-Methoxytetralone was treated with vinylmagnesium chloride (1.2 equiv) in THF at reflux for 1 h, and then the resulting allylic alcohol was subjected to a dehydration reaction (quinoline, I_2 (cat.), benzene, reflux, 2 h) to give Dane's diene (**6**) in 83% yield.

(16) Whereas the intermediate borane is not protodeborylated under the quenching conditions of the reaction aliquots, the zinc reagent **4** produces cleanly 4-ethyl-7-methoxy-1,2-dihydronaphthalene which allows us conveniently to monitor the progress of the reaction.

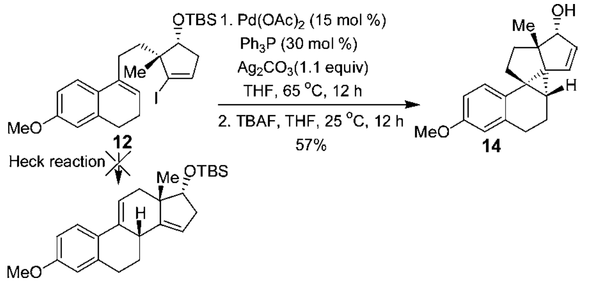
now reacted the zinc organometallic **4** (2.4 equiv)[17] with the allylic pentafluorobenzoate *trans*-**5** in the presence of CuCN·2LiCl (2.4 equiv) in THF (25 °C, 48 h) leading to the *anti*-S_N2'-substitution product **12** in 66% yield. Removal of the TBS group provides the alcohol **13** which has allowed us to determine its enantiopurity by HPLC analysis as well as to confirm the relative stereochemistry of the adjacent methyl and hydroxyl groups by NMR analysis (NOE experiments; Scheme 3).

Scheme 3



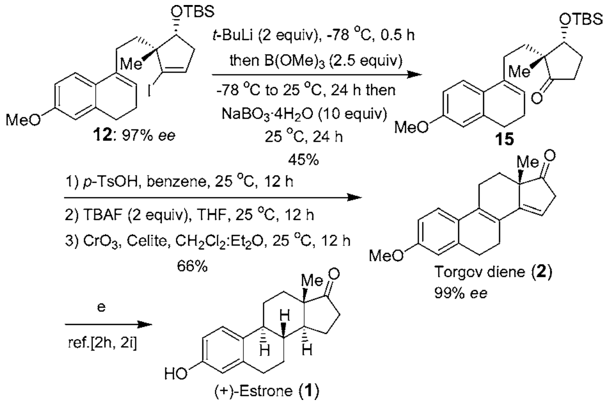
We had planned to complete the synthesis of the Torgov diene (**2**) by performing a Heck ring-closure reaction.[8] However, the reaction of the unsaturated iodide **12** with Pd(OAc)$_2$ (15 mol %), PPh$_3$ (30 mol %), and Ag$_2$CO$_3$ (1.1 equiv) in THF at 65 °C for 12 h[18] leads only to the unexpected pentacyclic product **14** in 57% yield (Scheme 4).[7i,j]

Scheme 4



However, we achieved the desired ring closure by converting the cyclopentenyl iodide **12** to the corresponding ketone **15** by a method previously developed in our laboratory.[3c] Thus, in a one-pot procedure, the iodide **12** was reacted with *t*-BuLi (2 equiv, −78 °C, 0.5 h) in THF followed by the addition of B(OMe)$_3$ (2.5 equiv, −78 °C to 25 °C, 24 h) and oxidation with sodium perborate (NaBO$_3$·4H$_2$O, 10 equiv, 25 °C, 24 h) affording the ketone **15** in 45% yield. An acid-mediated ring closure[19] (*p*-TsOH, benzene, 25 °C, 12 h) followed by the removal of the TBS group by using TBAF (2 equiv, THF, 25 °C, 12 h) and subsequent oxidation with CrO$_3$ on Celite[20] furnished Torgov diene (**2**) in 61% overall yield and 99% ee, mp = 141−144 °C (lit. mp = 144−145 °C),[2h,i] $[\alpha]_D^{20} = -95.6$ (*c* 0.5, CHCl$_3$) (lit. $[\alpha]_D^{20} = -102.6$ (*c* 0.904, CHCl$_3$)[2h,i] (Scheme 5).[21] The conversion of the diene **2** into (+)-estrone (**1**) has been previously reported by Quinkert and Ogasawara in three steps and 32−37% yield.[2h,i]

Scheme 5



Thus, we have performed, using a Cu(I)-mediated *anti*-S_N2'-substitution, an enantioselective synthesis of the Torgov diene (**2**) in nine steps and 12% yield starting from 4-hydroxy-3-methylcyclopent-2-en-1-one (**7**). This represents a formal total synthesis of (+)-estrone (**1**) in 12 steps and 4% overall yield. It demonstrates the utility of the Cu-catalyzed S_N2'-substitution for constructing quaternary centers with high enantioselectivity.

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Supporting Information Available: Experimental procedures and characterization of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The zinc organometallic **4** was used as an excess to obtain the product **12** with a short reaction time under mild reaction conditions.

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