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A Concise Route to (+)-Estrone

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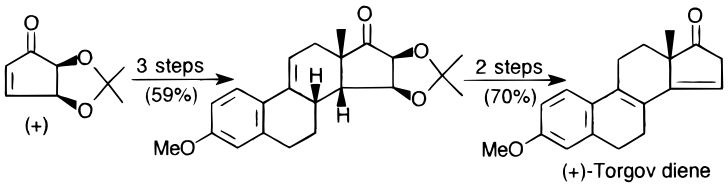
ABSTRACT



A concise route to the Torgov diene, the key intermediate of estrone, has been devised using a chiral dioxycyclopentenone as the starting material by employing a sequence of five steps of reactions involving a Lewis acid-mediated Diels–Alder reaction with Dane's diene.

We previously reported a facile six-step synthesis[1] of estrone (+)-**5**, starting from enantiopure ketodicyclopentadiene[2,3] (−)-**1**. In this synthesis, the Lewis acid-mediated Diels−Alder reaction between the chiral enone (−)-**1** and Dane's diene[4] **2** proceeded diastereoselectively in an *exo*-mode (**A**), alleviating the steric repulsion between the diene and the dienophile, to give rise to adduct **3** having *trans*-C_9-C_{14} stereochemistry (steroid numbering) matching that of (+)-estrone **5**. Moreover, the following introduction of the quaternary 18-methyl functionality occurred diastereoselectively from the convex face of adduct **3** to give the requisite *trans* C−D product **4** from which the cyclopentene blocking group on the D ring could be removed on thermolysis (Scheme 1). Since we recently developed an efficient preparation of the enantiopure bicyclic dioxycyclopentenone **6** in both enantiomeric forms,[6,7] we planned to use it as a synthetic equivalent of ketodicyclopentadiene **1** in the above estrone synthesis, making use of the 1,3-dioxolane moiety of the former enone as the cyclopentene moiety of the latter enone both in a steric and a functional sense. We wish to report here the outcome of the reaction between **6** and **2**, generating the adduct with the undesired *cis*-C_9-C_{14} stereochemistry and leading eventually to a new enantiocontrolled synthesis of Torgov diene[8,9] **13**, the key intermediate of estrone **5**, by modification on the basis of the stereochemical outcome observed.

To determine the regio- and stereochemistry of the key Diels−Alder reaction, a reaction of racemic enone (±)-**6** and Dane's diene **2** was first examined in the presence of a Lewis

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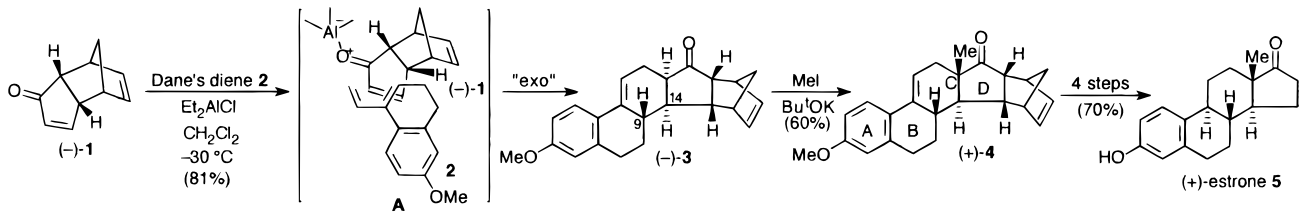
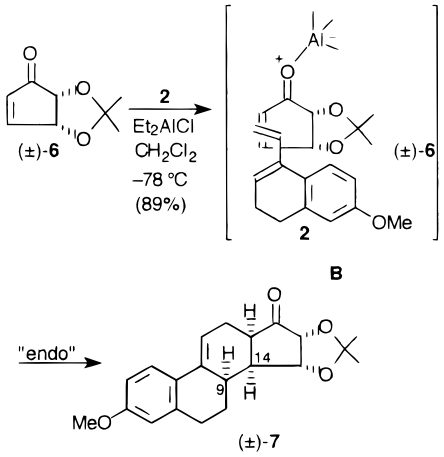
Scheme 1



acid. It was found that the reaction proceeded stereo- and regioselectively without double bond migration in the presence of diethylaluminum chloride[1,5a–c] (1.3 molar equiv) in dichloromethane at −78 °C to give the single adduct (±)-**7** in 89% yield after 2 h. As expected, the dioxolane moiety of enone (±)-**6** served as an excellent stereocontrolling element similar to the cyclopentene moiety of ketodicyclopentadiene **1** in the reaction with Dane's diene **2**. However, NOE examination revealed that the adduct **7** obtained has the undesired *cis*-C_9−C_{14} stereochemistry, indicating that the cycloaddition proceeded diastereoselectively by following the orbital-controlled *endo* rule from the opposite face of the dioxolane moiety (**B**) (Scheme 2).

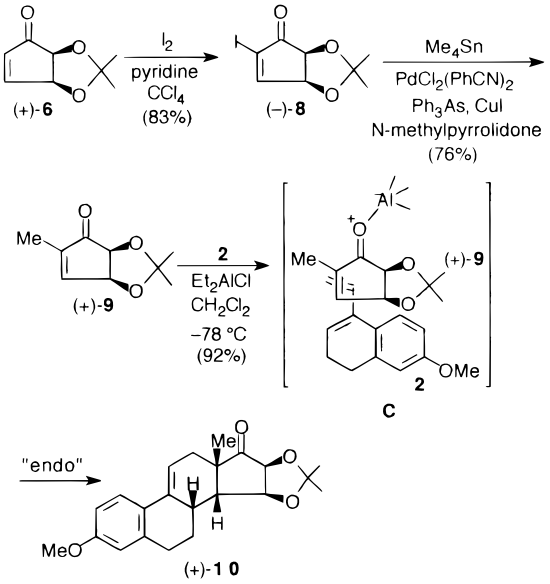
Scheme 2



Moreover, as adduct **7** was found to be unstable under the strongly basic conditions required for the introduction of the quaternary 18-methyl functionality,[1] we chose an alternative route to reach (+)-estrone[10] **5**. Thus, to avoid diastereoselective construction of the *trans*-C_9−C_{14} stereochemistry in the cycloaddition stage as well as to avoid introduction of the quaternary stereogenic center in the later stage, we changed our target to the Torgov diene[8] (+)-**13**, having a single chiral quaternary stereogenic center, which has been used as the key intermediate in industrial synthesis of estrone **5**.

Thus, enantiopure enone[6] (+)-**6** was first transformed into the α-iodide (−)-**8**, mp 85.5 °C, $[\alpha]^{28}_D$ −10.4 (*c* 0.74, $CHCl_3$), in 83% yield on exposure to iodine in a pyridine−carbon tetrachloride (1:1) solution at 0 °C to room temperature for 2 h.[11] To replace the iodine with a methyl functionality, (−)-**8** was treated with tetramethylstannane (3 equiv) in the presence of dichlorobis(benzonitrile)palladium-(II) (5 mol %), copper(I) iodide (10 mol %), and triphenylarsine (10 mol %) in *N*-methylpyrrolidinone[12] to give the α-methyl enone (+)-**9**, $[\alpha]^{24}_D$ +17.0 (*c* 0.44, $CHCl_3$), in 76% yield after 2 h at 75 °C. Reaction of **9** with Dane's diene **2** (1.3 equiv) in the presence of diethylaluminum chloride[1] (1.2 equiv) in dichloromethane at −78 °C for 2 h furnished the single adduct (+)-**10**, $[\alpha]^{28}_D$ +142.8 (*c* 0.88, $CHCl_3$), diastereoselectively, in 92% yield. The product was found to have *cis*-C_9−C_{14} stereochemistry by NOE experiment, indicating that the cycloaddition occurred in an *endo*-mode (**C**) as the nonmethylated enone **6** (Scheme 3).

Scheme 3



To obtain the Torgov diene (+)-**13**, adduct (+)-**10** was first treated with an aluminum amalgam[7i,13] in aqueous

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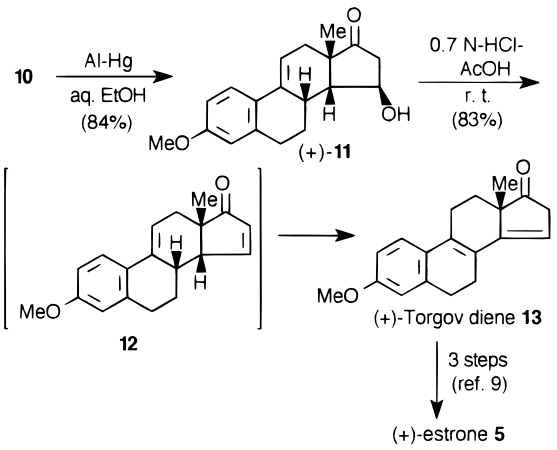
Scheme 4



ethanol (75%) to give β-ketol (+)-**11**, mp 135−137 °C, $[\alpha]^{27}_D$ +241.6 (*c* 0.36, $CHCl_3$), in 84% yield. Upon stirring in HCl−AcOH (0.7 N) at room temperature for 3 h, ketol **11** afforded in one step the Torgov diene (+)-**13**, mp 142−143 °C, $[\alpha]^{25}_D$ −96.5 (*c* 0.20, $CHCl_3$) [lit. mp 145−146 °C, $[\alpha]^{20}_D$ −102.6 (*c* 0.904, $CHCl_3$);[9a] mp 141−144 °C, $[\alpha]^{24}_D$ −98.46 (*c* 0.9, $CHCl_3$)],[9b] in 83% yield presumably via transient diene **12**. Conversion of the Torgov diene (+)-**13** into estrone (+)-**5** has been carried out in three steps without difficulty[9] (Scheme 4).

In short, we have devised a concise route to (+)-estrone **5** via the Torgov diene **13** starting from chiral dioxycyclopentenone building block (+)-**6** which exhibited *endo*-selectivity in the convex-face selective Diels−Alder reaction with Dane's diene **2** in the presence of a Lewis acid.

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