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Enantioconvergent Synthesis of (+)-Estrone from Racemic 4-*tert*-Butoxy-2-cyclopentenone

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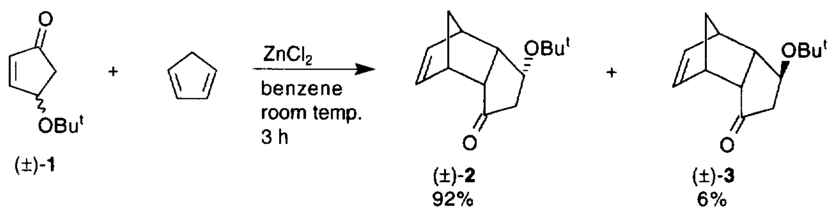
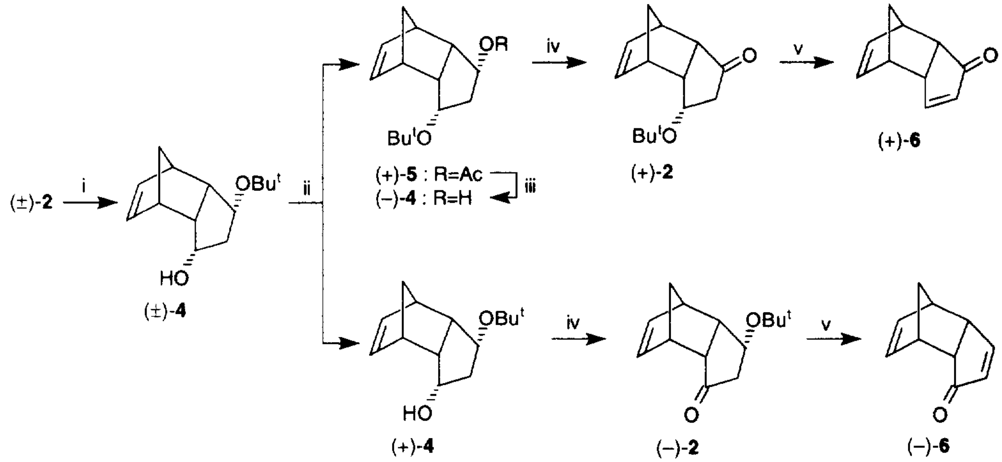
Abstract: (+)-Estrone has been synthesized in an enantioconvergent manner from racemic 4-*tert*-butoxy-2-cyclopentenone *via* contrasteric Diels-Alder reaction and lipase-mediated kinetic transesterification as the key steps. Copyright © 1996 Elsevier Science Ltd

Quite recently, we found[1] that the Lewis acid-mediated Diels-Alder reaction between racemic 4-*tert*-butoxy-2-cyclopentenone[2] **1** and cyclopentadiene occurred in a contrasteric way to give the *endo*-adduct (±)-**2** bearing an *endo*-alkoxy group in 92% yield after separation of a minor amount (6%) of the *exo*-alkoxy diastereomer (±)-**3** (**Scheme 1**). We report here lipase-mediated kinetic resolution of the major adduct (±)-**2** and enantioconvergent transformation of the resolved enantiomers to the representative estrogenic steroid hormone (+)-estrone[3,4] **18**.



Scheme 1

Reduction of (±)-**2** with sodium borohydride took place stereoselectively from the convex face of the molecule to give the single *endo*-alcohol (±)-**4**. Stirring (±)-**4** and vinyl acetate in *tert*-butyl methyl ether in the presence of lipase LIP[5] (*Pseudomonas* sp., Toyobo) furnished the (+)-acetate **5**, $[\alpha]_D^{28}$ +5.6 (*c* 1.1, $CHCl_3$), in 48% yield with recovery (51%) of the unchanged (+)-alcohol **4**, mp 95 °C, $[\alpha]_D^{28}$ +75.4 (*c* 1.2, $CHCl_3$). Methanolysis of (+)-**5** yielded the enantiomeric (−)-alcohol (−)-**4**, mp 94.5 °C, $[\alpha]_D^{28}$ −73.8 (*c* 0.45, $CHCl_3$), excellently. Oxidation of (−)-**4** with sulfur trioxide-pyridine complex in the presence of dimethyl sulfoxide and triethylamine[6] gave the ketone (+)-**2**, $[\alpha]_D^{29}$ +176.8 (*c* 0.4, $CHCl_3$), in 94% yield. On the same treatment, (+)-**4** gave the enantiomeric ketone (−)-**2**, $[\alpha]_D^{26}$ −186.6 (*c* 1.0, $CHCl_3$), in 98% yield. The absolute configuration and optical purities of the resolved products were determined by hplc using a chiral column (CHIRALCEL OD, *i*-PrOH/hexane, 1:9) after transformation into the known ketodicyclopentadiene[1,7] **6** though direct elimination of the β-*tert*-butoxy group of **2** was unexpectedly difficult. Thus, the *tert*-butyl group was first removed by separate treatment of both (+)- and (−)-**2** with titanium(IV) chloride[8] in dichloromethane to give the correspond-

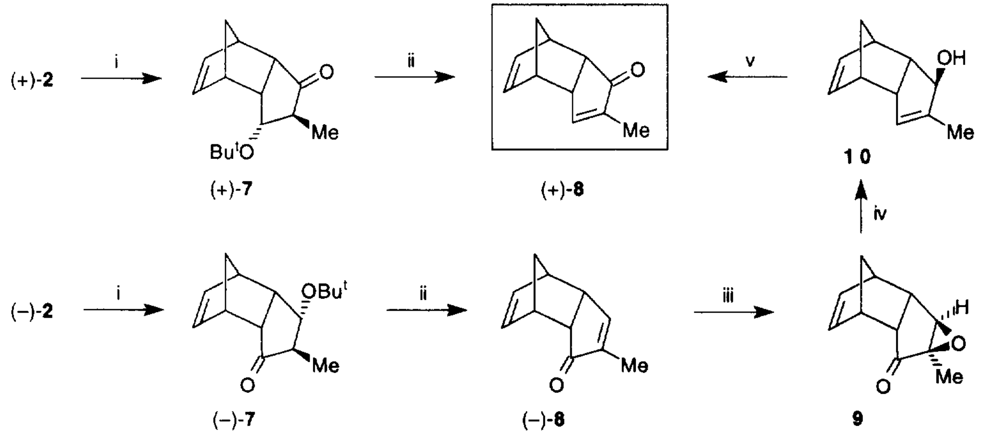


Scheme 2

Reagents and conditions: i, $NaBH_4$, MeOH, 0 °C (99%); ii, vinyl acetate (6 equiv.), lipase LIP, Bu^{t}OMe, room temp., 2 h [(+)-**5** (48%) and (+)-**4** (51%)]; iii, K_2CO_3, MeOH, room temp. (99%); iv, SO_3-pyridine complex (7 equiv.), DMSO, Et_3N [(+)-**2** (94%) and (−)-**2** (98%)]; v, $TiCl_4$ (1.2 equiv.), 0 °C, 5 min then 5% NaOH, room temp. [(+)-**6** (85%) and (−)-**6** (83%)].

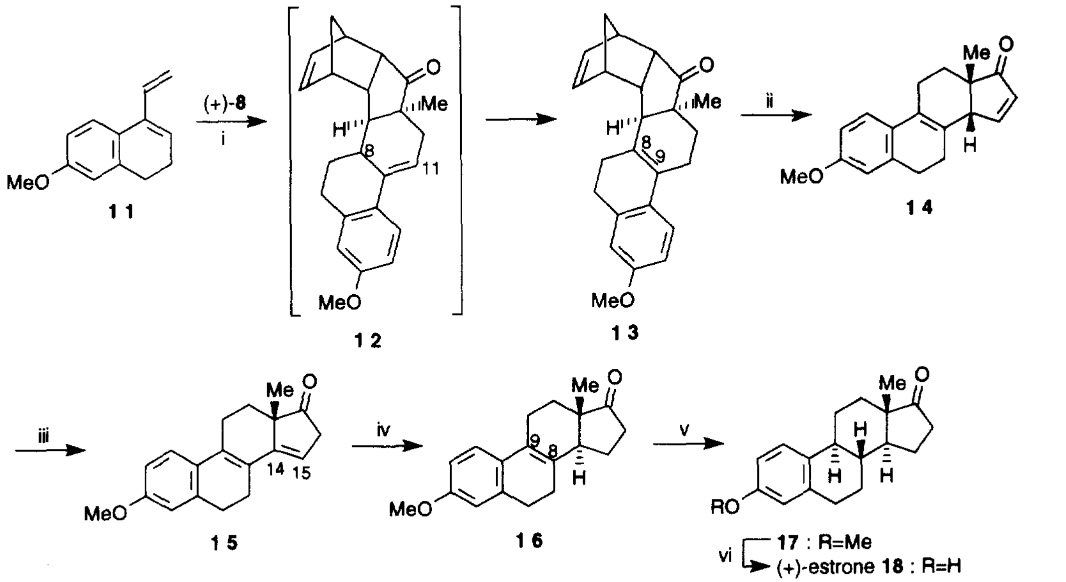
ing β-hydroxyketone of each which, on immediate treatment with aqueous sodium hydroxide in the same flask, afforded (+)-**6** in 85% yield with >99% ee from (+)-**2** and (−)-**6** in 83% yield with >99% ee from (−)-**2**, respectively (**Scheme 2**).

Having established the stereochemistry of the resolved products, the (+)-enantiomer (+)-**2** was treated with iodomethane at −78 °C in the presence of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) containing hexamethylphosphoric triamide (HMPA) to give stereoselectively the monomethyl product (+)-**7**, $[\alpha]_D^{25}$ +132.5 (*c* 1.55, $CHCl_3$), in 83% yield as the single isomer. Stereochemistry of **7** was determined by n.O.e. experiment which exhibited a significant interaction between the methyl protons and the butoxymethine



Scheme 3

Reagents and conditions: i, LDA, MeI, HMPA, THF, −78 °C ~ 0 °C [(+)-**7** (83%) and (−)-**7** (80%)]; ii, $TiCl_4$, CH_2Cl_2, 0 °C, 5 min then 5% NaOH, room temp. [(+)-**8** (84.5%) and (−)-**8** (86%)]; iii, 30% H_2O_2, 0.5 N NaOH, MeOH, 0 °C (86%); iv, $NH_2NH_2 \cdot H_2O$, AcOH (cat.), MeOH, 0 °C (60%); v, PCC, CH_2Cl_2 (80%).



Scheme 4

Reagents and conditions: i, **11** (2.5 equiv.), $TiCl_4$ (2 equiv.), CH_2Cl_2, –78 °C, 1.5 h (75%); ii, diphenyl ether, reflux, 1.15 h (71%); iii, LiHMDS, HMPA, THF, –78 °C then AcOH (75%); iv, H_2, 5% Pd-$CaCO_3$ (71%); v, Et_3SiH, CF_3CO_2H, benzene, CH_2Cl_2 (65%); vi, BBr_3, CH_2Cl_2, 0 °C (80%).

proton indicating the *exo*-methyl structure. The remarkable stability of the β-alkoxy ketone functionality observed under these strong basic conditions may be due to the bulky *tert*-butoxy group which made the proper *anti-trans*-disposition between the alkoxy and the enolate system required for β-elimination very difficult. To carry out β-elimination, (+)-**7** was first exposed to titanium(IV) chloride[8] in dichloromethane at 0 °C, then the mixture containing the β-hydroxyketone was treated directly with aqueous sodium hydroxide in the same flask to afford the (+)-enone (+)-**8**, $[\alpha]_D^{27}$ +83.8 (*c* 1.65, $CHCl_3$), serving as the key intermediate in 85% yield.

On the other hand, (–)-**2** was transformed into the enantiomeric (–)-enone (–)-**8**, $[\alpha]_D^{24}$ –85.4 (*c* 1.4, $CHCl_3$), in a comparable overall yield *via* the enantiomeric methyl ketone (–)-**7**, $[\alpha]_D^{24}$ –134.6 (*c* 1.4, $CHCl_3$), on the same treatment. To invert the stereochemistry, the enantiomer (–)-**8** obtained was treated with alkaline hydrogen peroxide to give the single epoxide **9**, $[\alpha]_D^{23}$ –192.1 (*c* 1.3, $CHCl_3$), stereoselectively. Exposure of **9** to hydrazine hydrate in methanol containing acetic acid[9] induced reductive cleavage to give the allyl alcohol **10**, $[\alpha]_D^{24}$ +97.2 (*c* 0.8, $CHCl_3$), which gave the key (+)-enone (+)-**8** on oxidation. Overall yield of the enantiomerization of (–)-**8** to (+)-**8** under these Wharton conditions[9] was 41% (**Scheme 3**).

In order to construct (+)-estrone **18**, the enone (+)-**8** thus obtained was reacted with Dane's diene[10] **11** to give the hexacyclic adduct **12** by Lewis acid-mediated Diels-Alder reaction.[4,11,12] Thus, when (+)-**8** was treated with 2.5 equivalents of **11** in dichloromethane containing two equivalents of titanium(IV) chloride at –78 °C, regio- and stereo-selective cycloaddition and concurrent allylic hydrogen migration of the adduct **12** occurred to afford the single styryl product **13**, mp 89-91 °C, $[\alpha]_D^{26}$ +90.9 (*c* 1.1, $CHCl_3$), in 75% yield within 2 h. Although regio- and stereo-chemistry of the product could not be determined at this stage, subsequent conversion clarified the structure of **13** to be as shown. The observed hydrogen migration from the C8 to C11 during the cycloaddition conditions was rather advantageous for the later conversion as stereoselective hydrogenation of the C8-C9 double bond has already been carried out.[3,4]

Upon thermolysis in boiling diphenyl ether, the expected retro-Diels-Alder reaction of **13** took place without difficulty to give the known tetracyclic compound **14**, mp 151-153 °C, $[\alpha]_D^{25}$ +651.7 (*c* 0.7, $CHCl_3$) [lit.[4]: mp 160 °C, $[\alpha]_D^{20}$ +671.6 (*c* 0.95, $CHCl_3$)], in 71% yield. At this point, the stereochemistry of **13** was determined unambiguously though the stereochemistry of the C8 stereogenic center of the transient **12** remained uncertain. By following the established procedure, **14** was transformed into estrapentaene[13] methyl ether **15**, mp 141-144 °C, $[\alpha]_D^{24}$ −98.46 (*c* 0.9, $CHCl_3$) [lit.[4]: mp 145-146 °C, $[\alpha]_D^{20}$ −102.6 (*c* 0.904, $CHCl_3$)], in 75% yield on treatment with lithium hexamethyldisilazide in THF containing HMPA at −78 °C followed by acetic acid in the same flask.[4] Catalytic hydrogenation of **15** afforded 8,9-didehydroestrone methyl ether **16**, mp 119-121 °C, $[\alpha]_D^{22}$ +42.6 (*c* 1.0, $CHCl_3$) [lit.[4]: mp 123-125 °C, $[\alpha]_D^{20}$ +30.3 (*c* 0.991, $CHCl_3$)], in 71% yield, which was further reduced with triethylsilane in the presence of trifluoroacetic acid[4,12,14] to give (+)-estrone methyl ether **17**, mp 171-172 °C, $[\alpha]_D^{27}$ +163.4 (*c* 0.4, $CHCl_3$) [lit.[12]: mp 174-175.5 °C, $[\alpha]_D^{33}$ +159.2 (*c* 0.72, $CHCl_3$)], in 65% yield. Finally, **17** was treated with boron tribromide[12] to give (+)-estrone **18**, mp 259 °C, $[\alpha]_D^{27}$ +149.6 (*c* 0.44, $CHCl_3$) [lit.[12]: mp 265.0-266.5 °C, $[\alpha]_D^{32}$ +153.2 (*c* 0.31, $CHCl_3$)], in 80% yield. Overall yield of (+)-estrone **18** from the racemic starting material (±)-**2** was 8% involving a convergent sequence.

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