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Simple, Catalytic Enantioselective Syntheses of Estrone and Desogestrel

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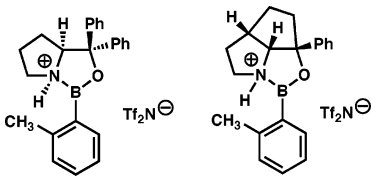
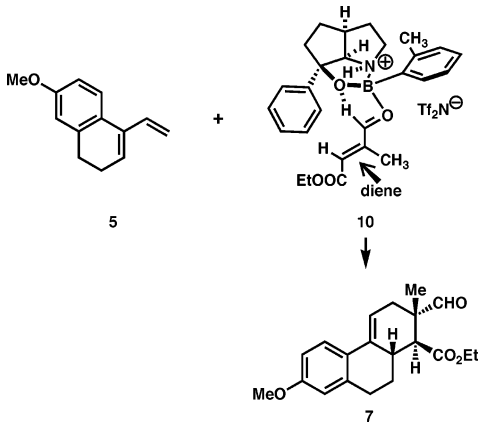
Recent studies have demonstrated that the oxazaborolidinium salt **1** and the corresponding triflate are exceptionally potent and versatile chiral Lewis acids for many enantioselective Diels−Alder reactions.[1−6] Using a wide variety of dienes and dienophiles, many reactions have been demonstrated to proceed with excellent yield, enantioselectivity, and structure selectivity. We report in this paper a number of important further developments in this area, including (1) efficient synthesis of the catalyst **2** and its enantiomer and (2) the application of **2** to the enantioselective synthesis of estrone (**3**) and the important third-generation oral contraceptive desogestrel (**4**).



The new synthesis of estrone (**3**) commenced with **5** (Dane's diene) and followed the pathway that is summarized in Scheme 1. The use of Dane's diene for the synthesis of steroids, first discussed almost 70 years ago,[7,8] has a long and convoluted history,[9,10] but for the most part had been disappointing until the more modern studies of Quinkert's group.[11] Although the Quinkert synthesis proceeds from **5** with modest yields and enantioselectivity, it is limited practically by the need for large quantities of Ti(IV)−TADDOL catalyst (2 equiv), long reaction times (several days) at −80 °C, and a not easily available dienophile component. As shown in Scheme 1, the reaction of Dane's diene[12] with the readily available ester aldehyde **6**[13] under catalysis by 0.2 equiv of **2** affords the Diels−Alder adduct **7** with 97:3 enantioselectivity and in 92% isolated yield. Enantiomerically pure **7**, mp 121−122 °C, was obtained from this product simply by one recrystallization from CH_2Cl_2−hexanes.[14] Reaction of **7** with methylmagnesium bromide (2 equiv in THF at −40 °C for 1 h) afforded a γ-hydroxy ester which was directly reduced ($LiAlH_4$ in THF at 0 °C for 1 h) to the corresponding 1,4-diol, which in turn was oxidized by the Swern reagent from Me_2SO and oxalyl chloride in CH_2Cl_2 (−78 °C for 30 min and −78 °C to 20 °C over 30 min) to give the keto aldehyde **8** in 78% overall yield from **7**. Base-catalyzed aldol cyclization followed by acid treatment provided the dienone **9** (Torgov diene)[15] in 80% yield. The synthesis of estrone from **9** proceeds by the known sequence: (1) stereospecific reduction of the 14,15-double bond of **9** (H_2, Pd−C) to form the C/D trans-fused dihydro derivative of **9**, (2) reduction of the 8,9-double bond (Et_3SiH−CF_3CO_2H) to form the B/C/D trans-anti-trans tetrahydro derivative of **9**, and (3) HBr-catalyzed methyl ether cleavage.[11b] The synthesis of estrone outlined in Scheme 1 is short, efficient, and enantio- and stereocontrolled.

Because the amino alcohol precursor of catalyst **2** can be recovered easily for reuse from the initial Diels−Alder step, we believe that the process shown in Scheme 1 is also practical and economical.

The key Diels−Alder reaction **5** + **6** → **7** for the above synthesis of estrone was predicted to proceed in the required way using catalyst **2** on the basis of previous studies and the mechanistic model that these investigations had produced.[1−5] The catalyst−dienophile complex **10** when attacked by diene **5** from the sterically less shielded front side directs the [4+2]-cycloaddition to the observed product **7**. There are several reasons for the strong preference for [4+2]-cycloaddition to complex **10**. Oxazaborolidinium-catalyzed Diels−Alder reactions of α,β-enals are generally much faster than those of the corresponding α,β-unsaturated esters, so that the formyl complexation route via **10** is preferred. The formyl complex is further stabilized by a formyl C−H···O hydrogen bond as indicated in **10** and as described in detail previously.[16] The strong electron-



donating effect of the methoxy substituent of diene **5** enhances the nucleophilicity of the endocyclic diene terminus of **5** over that of the terminal methylene carbon. It is this interesting property of diene **5** that is responsible for the high regioselectivity that characterizes the catalytic Diels−Alder reaction of **5** with **6** to give adduct **7**. Related work in these laboratories has shown that the *tert*-butyldimethylsilyl analogue of **5** shows the same type of regioselectivity, but to an even greater degree than the methyl ether **5**.[6]

The enantioselective total synthesis of desogestrel **4** was carried out by a series of early steps that paralleled those shown in Scheme 1 for the synthesis of estrone. The synthetic pathway for desogestrel is outlined in Scheme 2. The catalytic enantioselective [4+2]-cycloaddition of **5** and α,β-enal **11** proceeded efficiently to form the required adduct **12** with 66:1 enantioselectivity, and enantiomerically pure **12** was obtained by a single recrystallization. The transformation of **12** to the tetracyclic dienone **14** via **13** also occurred smoothly, as with **7** → **9** and using essentially the same procedures. The conversion of **14** to desogestrel (**4**) can be

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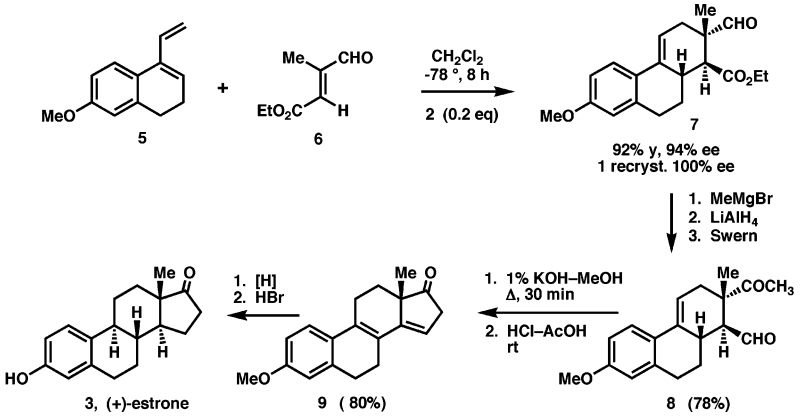
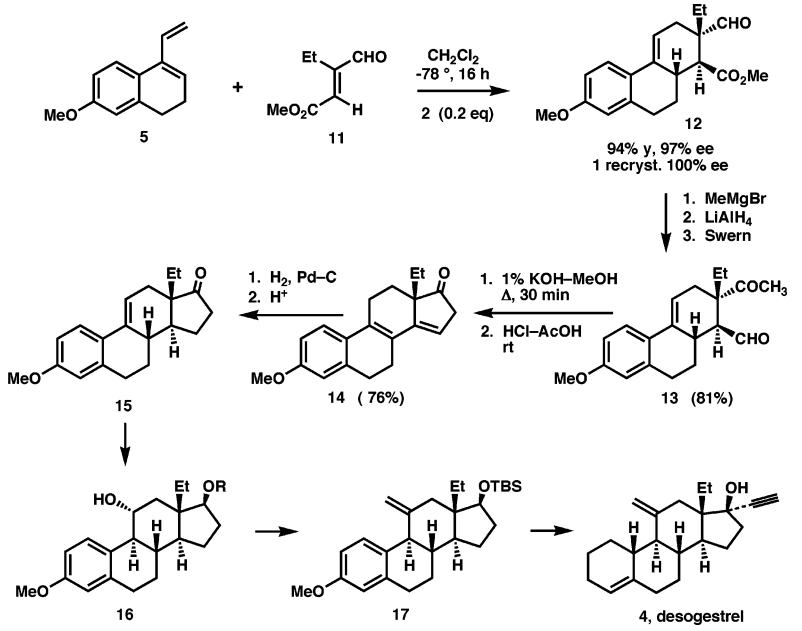
Scheme 1



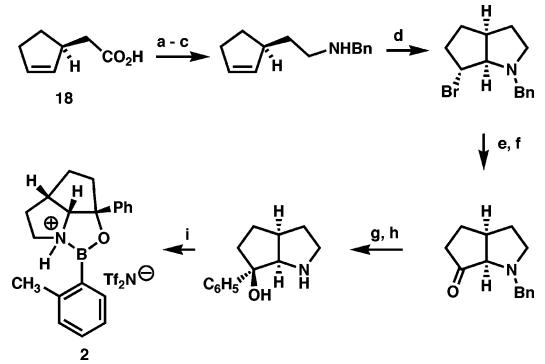
Scheme 2



conducted by a number of previously described routes, one of which is summarized in Scheme 2. Catalytic hydrogenation of **14** to the 14,15-dihydro derivative followed by acid-catalyzed transposition of the 8,9-double bond to the 9,11-position generates **15**[17] which has been converted by reaction with BH_3−THF and protection of hydroxyl at C(17) to the 17α-alcohol **16**.[18] Oxidation of **16** to the 11-keto derivative and Peterson methyleneation leads to **17**,[18] a late-stage intermediate in our recently published route to desogestrel (**4**).[19]

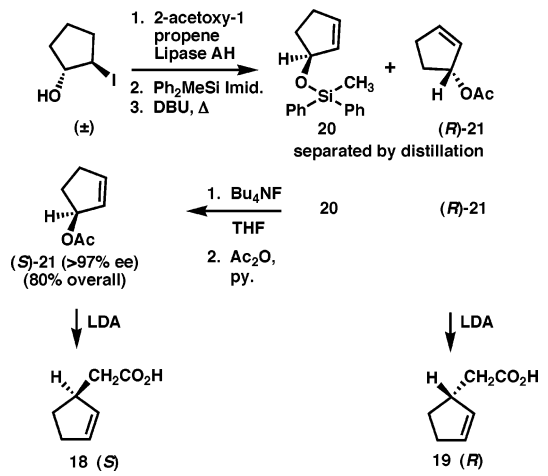
The syntheses of estrone and desogestrel described herein demonstrate the advances in multistep synthesis that can be realized with the widespread use of oxazaborolidinium cationic catalysts of the class represented by **1** and **2**. Catalysts **1** and **2** provide enantiomeric Diels−Alder adducts with similar enantioselectivities, although one may be somewhat more effective than the other depending on the substrates. Catalyst **2** and its enantiomer are readily prepared from (*S*)- and (*R*)-2-cyclopentenylacetic acid, **18** and **19**, respectively, by the route summarized in Scheme 3.[20] We have also developed an expedient and practical process for the synthesis of both (*S*)- and (*R*)-2-cyclopentenylacetic acid from (±)-*trans*-2-iodocyclopentanol[21] which is described in detail in the Supporting Information and flowcharted in Scheme 4. Enantioselective acetylation (Amano lipase AH), reaction with diphenylmethylsilylimidazole, followed by DBU, all in hexanes (one pot), gave after separation by distillation in vacuo the volatile acetate (*R*)-**21** (80% over three steps, >95% ee) and undistilled **20**. These were then efficiently transformed into **19** and **18**, respectively, as shown in Scheme 4.

Scheme 3 [a]



[a] (a) $SOCl_2$, 60 °C, 1 h. (b) $BnNH_2$, Et_3N, THF, 0 °C, 3 h (98% overall). (c) LAH, THF, reflux, 4 h (100%). (d) NBS, pentane, 0 °C, 2 h; then CuBr, CH_2Cl_2, 0 °C, 3 h (78%). (e) LiOH, DME−H_2O, reflux, 1 h (85%). (f) Me_2SO, ClCOCOCl, CH_2Cl_2, −78 °C, then substrate and Et_3N at −78 °C, 1 h (83%). (h) H_2 (1 atm), $Pd(OH)_2$−C, AcOH, CH_3OH, 2 h (94%). (i) (*o*-tolBO)$_3$, C_7H_8, reflux, 4 h; then concentration and addition of CH_2Cl_2 and $(CF_3SO_2)_2NH$.

Scheme 4



It is hoped that the synthetic methodology described above will be broadly useful for the synthesis of many complex chiral targets. Further illustrations are now being developed in our laboratory.

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Supporting Information Available: Experimental procedures for the synthetic sequences described herein, together with characterization data for reaction products. X-ray diffraction data (CIF) are provided for the product **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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