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A Novel Strategy for the Enantioselective Synthesis of the Steroidal Framework Using Cascade Ring Expansion Reactions of Small Ring Systems –Asymmetric Total Synthesis of (+)-Equilenin

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Abstract

Enantioselective synthesis of (+)-equilenin (**1**) utilizing a novel strategy is described. The key steps are two cascade ring expansion reactions of small ring systems; 1) chiral (salen)Mn^{III} complex-catalyzed cascade reaction of cyclopropylidene; 2) Pd^{II}-mediated cascade reaction of the cyclobutanol.

keywords: Asymmetric synthesis; Rearrangement; Steroids and sterols; Stereocontrol

Steroids are one of the most widely distributed groups of natural products displaying a variety of physiologically important features, so that numerous synthetic approaches have been developed.[1] Here, we disclose a novel strategy for the enantioselective synthesis of (+)-equilenin (**1**) based on two cascade ring expansion reactions of small ring systems as outlined in Scheme 1. Our plan for constructing steroidal C,D rings exploits a Pd^{II}-mediated cascade ring expansion and insertion process involving a cyclobutanol derivative, methodology of which has previously been reported by us (**3**→**2**, Scheme 1).[2] The chiral cyclobutanone **4**, a precursor of **3**, could be prepared *via* chiral (salen)Mn^{III} complex-catalyzed asymmetric epoxidation[3] of the cyclopropylidene **5**, followed by its enantiospecific rearrangement.[4]

First of all, the triflate **7**, prepared from the hydroxynaphthaldehyde **6**[5] (61%), was subjected to Stille reaction[6] with *tri-n*-butylvinylstannane to give the vinylnaphthaldehyde **8** (98%), which upon Wittig reaction with cyclopropylidene-triphenylphosphorane under modified McMurry conditions[7] afforded the cyclopropylidene derivative **5** (70%) (Scheme 2). With the cyclopropylidene **5** in hand, the critical cascade asymmetric epoxidation–ring expansion reaction was examined. When a mixture of **5** and a 5 mol% of (*R,R*)-(salen)Mn^{III} complex **9** was treated with sodium hypochlorite as a oxidant[3], the reaction successfully proceeded to provide the desired chiral cyclobutanone **4** (78% e.e., 55% yield) in one step *via* oxaspiropentane intermediate **10**[8].

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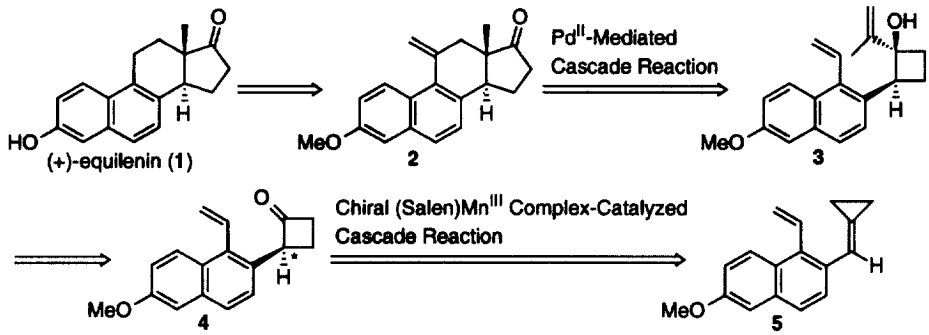
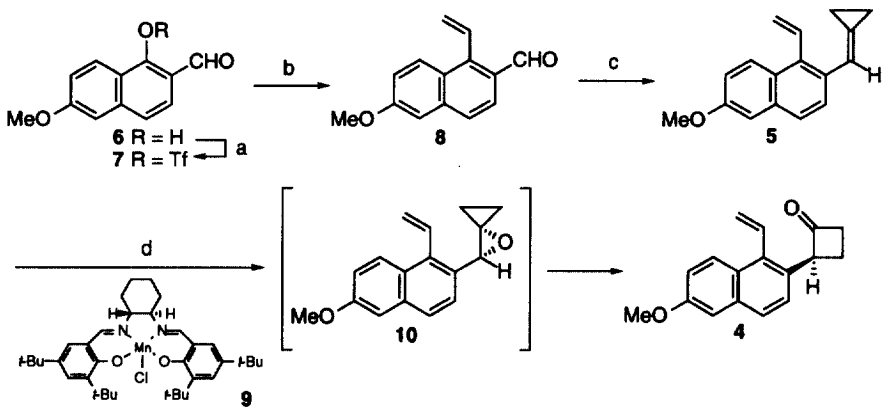


Scheme 1. Retrosynthesis of (+)-equilenin

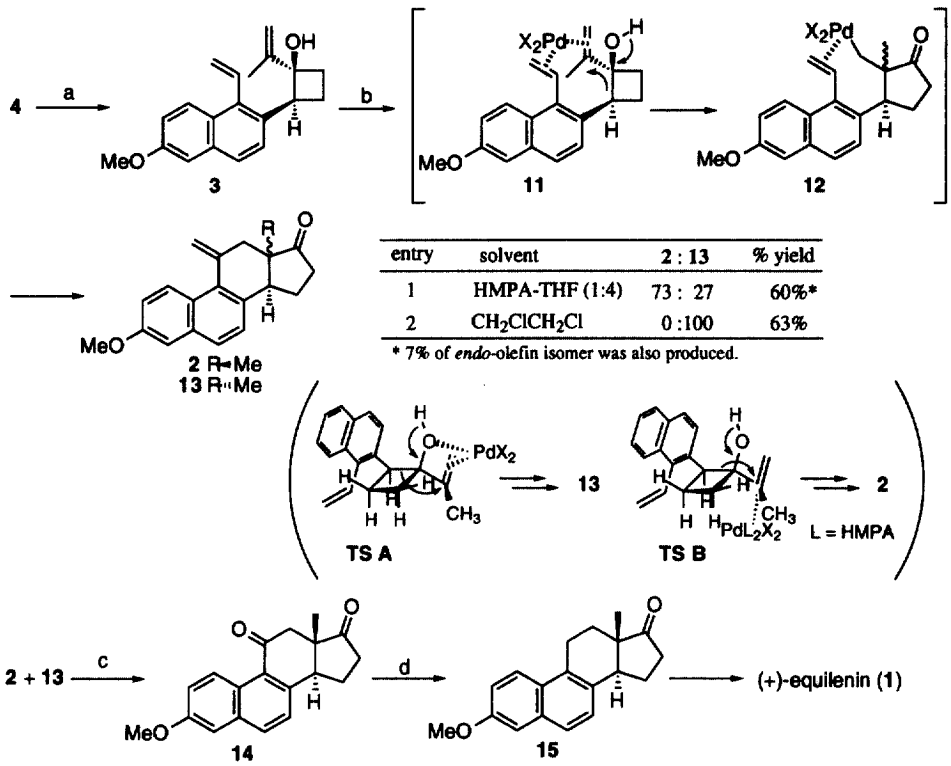


Scheme 2. Reagents and conditions. a) Tf_2O, DMAP, pyridine, 0°C, 61%; b) *tri-n*-butylvinylstannane, $Pd(PPh_3)_4$, LiCl, THF, reflux, 98%; c) cyclopropylidenetriphenylphosphorane, NaH, THF, 62°C, 70%; d) 5 mol % catalyst **9**, NaClO, 4-PPNO, CH_2Cl_2, 0°C, 55%, 78% e.e.

The chiral cyclobutanone **4** was then converted stereoselectively to the isopropenylcyclobutanol **3** by Grignard reaction with isopropenylmagnesium bromide in the presence of cerium trichloride[9] (82%) (Scheme 3). Next, the second crucial stage in the synthesis, Pd^{II}-mediated cascade ring expansion–insertion reaction, had to be investigated.[2] On the basis of our previous results, we further examined various reaction conditions to construct diastereoselectively the *trans*-naphthohydrindan from **3**. Consequentry, the *trans*-fused product **2** was selectively produced *via* ring expansion–insertion reaction (**11**→**12**) utilizing $Pd(OAc)_2$[10] (1 eq.) in HMPA-THF (1:4) (entry 1) (**2**:**13** = 73:27, 60%, and 7% of *endo*-olefin isomer). Interestingly, when the solvent was changed to 1,2-dichloroethane, the *cis*-fused product **13** was obtained as a sole product (63%) (entry 2). These remarkable effects indicate that solvent polarity is an important factor to control the diastereoselectivity of products. Thus, in non-polar solvent such as 1,2-dichloroethane, the ring expansion reaction has been suggested to proceed *via* intermediate **TS A** to give **13**, in which palladium was associated with olefin and internal alcohol.

In contrast, in the case of polar solvent such as HMPA, the reaction seems to proceed *via* **TS B** to give **2** in which palladium was associated with only olefin because solvent itself associated to palladium as a ligand.

To complete the synthesis of equilenin, the mixture (73:27) of **2** and **13** was treated with osmium tetroxide and sodium periodate to furnish diketone **14**[11] after the separation of its diastereomer (59% from **2** prepared by entry 1). Finally, the selective reduction of the benzylic ketone of **14** was carried out by hydrogenolysis on Pt-C in the presence of $PdCl_2$[12] to afford equilenin methyl ether **15**[13] (82%), which could be optically pure form after recrystallization. Since **15** has been converted to **1** with boron tribromide,[13] our asymmetric synthesis of (+)-equilenin (**1**) was achieved.



Scheme 3. Reagents and conditions. a) isopropenylmagnesium bromide, $CeCl_3$, THF, –78°C, 82%; b) $Pd(OAc)_2$, solvent, RT (see above); c) OsO_4, $NaIO_4$, acetone-H_2O, 59% from **2** (entry 1); d) H_2, Pt-C, $PdCl_2$, EtOH, RT, 82%.

In summary, a new type of cascade ring expansion reactions of small ring systems has been successfully applied to an asymmetric synthesis of (+)-equilenin (**1**).

Acknowledgments

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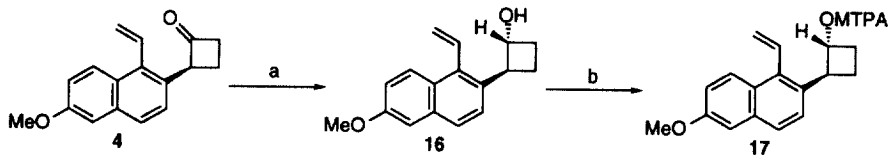
8. The spectral data for **4**: $[\alpha]_D^{25}$ +37.5 (c 0.2 in $CHCl_3$); IR (neat) 1780 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.21-2.22 (1H, m), 2.24-2.55 (1H, m), 3.07-3.13 (1H, m), 3.18-3.27 (1H, m), 3.91 (3H, s), 4.95-5.05 (1H, m), 5.44 (1H, dd, *J*= 2.2 and 18.0 Hz), 5.76 (1H, dd, *J*= 2.2 and 12.0 Hz), 7.08 (1H, dd, *J*= 12.0 and 18.0 Hz), 7.11-7.15 (2H, m), 7.35 (1H, d, *J*= 8.8 Hz), 7.65 (1H, d, *J*= 8.8 Hz), 7.96 (1H, d, *J*= 8.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.6, 44.9, 55.3, 63.3, 106.1, 118.8, 122.2, 125.3, 126.8, 127.3, 127.4, 129.4, 133.9, 134.1, 135.6, 157.6, 209.5; MS *m/z* 252 (M^+); HRMS calcd for $C_{17}H_{16}O_2$ 252.1149 (M^+), found 252.1150. Enantiomeric excess was determined by HPLC analysis (Chiralcel OA column, 10% isopropanol-hexane, 0.5 mL/min, λ=254 nm, 23°C, retension times 21.1min (*R*), 26.2min(*S*)). Absolute configuration was determined by Kusumi's procedure using MTPA esters **17**, which were prepared by reduction of the cyclobutanone **4**, followed by esterification of the major isomer **16** with (*R*) or (*S*)-MTPA (see below): Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.



Reagents and conditions. a) $NaBH_4$, MeOH, RT, 57% (and 35% of its diastereomer); b) (*R*)-, and (*S*)-MTPA acid, DCC, DMAP, CH_2Cl_2, RT, quant.

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10. When $PdCl_2(CH_3CN)_2$ was used, *endo*-olefin isomers were obtained exclusively. In this case, it is presumed that H-Pd$^+$ complex which was produced *in situ* caused olefin isomeriasion. In case of using $Pd(OAc)_2$, it seems that H-Pd$^+$ complex wasn't effectively produced for less acidity of AcOH than that of HCl generated *in situ* resulted to preserve the isomerizasion.
11. The spectral data for **14**: m.p. 182°C (decomp.), $[\alpha]_D^{25}$ -31.7 (c 0.1 dioxane); IR ($CHCl_3$) 1660, 1740 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, s), 2.08-2.22 (1H, m), 2.35-2.52 (1H, m), 2.58-2.77 (2H, m), 2.70 (1H, d, *J*= 18.9 Hz), 2.94 (1H, d, *J*= 18.9 Hz), 3.34 (1H, dd, *J*= 6.3 and 12.5 Hz), 3.94 (3H, s), 7.15 (1H, d, *J*= 2.8 Hz), 7.29-7.38 (2H, m), 7.98 (1H, d, *J*= 8.7 Hz), 9.22 (1H, d, *J*= 8.7 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 15.0, 21.9, 35.8, 46.0, 48.8, 48.9, 55.3, 106.6, 121.8, 123.7, 126.7, 127.0, 128.0, 134.1, 140.9, 157.6, 199.0, 217.8; MS *m/z* 292 (M^+); HRMS calcd for $C_{19}H_{18}O_3$ 294.1256 (M^+), found 294.1246.
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13. Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc. Chem. Commun.* **1990**, 1544. The spectral data for **15**: m.p. 198°C (decomp.), lit., m.p. 199°C (decomp.). $[\alpha]_D^{23}$ +78.7° (c 0.1 dioxane), lit., $[\alpha]_D^{29}$ +81.9° (c 0.4 dioxane). The ^{1}H-NMR spectrum was in complete agreement with that of an authentic sample.