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A simple synthesis of 6-deoxoteasterone and its 20-epimer ☆

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Abstract—6-Deoxoteasterone, a brassinolide biosynthetic intermediate, and its 20-epimer were synthesized from steroidal 17-olefin and chiral α-alkoxyaldehyde using a Lewis acid mediated carbonyl-ene reaction as the key step. In this reaction, unusual stereoselectivity was observed.

Brassinolide (BL) **1** (Scheme 1) is a steroidal plant hormone and exhibits a wide variety of biological activity at very low concentrations.[1,2] Because of its complicated structure and low natural abundance, many researchers have attempted the chemical synthesis of BL. Special emphasis has been placed on the stereoselective construction of its side chain, where four contiguous asymmetric carbons are present, requiring multiple step reactions. This synthesis still remains a challenging problem to the synthetic community. Here we report a novel, and simple method for constructing the BL side chain using a Lewis acid mediated carbonyl-ene reaction[3] as the key step.

One of the simplest ways to form a carbon–carbon bond under mild condition is the use of a Lewis acid mediated ene reaction. This scheme has frequently been utilized for the introduction of a steroidal side chain to tetracyclic nucleus.[4–12] It is well known that ene reaction between various enophiles and (*Z*)-17-ethylidenesteroid give only compounds with the configuration of the naturally occurring steroids at C-20.[†] Besides the introduction of the alkyl side chain, carbonyl-ene reactions have the advantage of generating a hydroxyl group at C22 with the desired conformation through the choice of an appropriate combination of Lewis acid and aldehyde.[5,7,8,11] However, previous applications seemed to require multiple step reactions to complete construction of the BL side chain. Here, we designed carbonyl-ene reaction between a chiral α-alkoxyaldehyde **2** and steroidal 17-olefin followed by simple hydrogenation to introduce the C22–C28 fragment in BL (Scheme 1).

Synthesis of **2** is shown in Scheme 2. Optically active epoxide **3**[13] was used as a chiral template. The oxirane ring of **3** was cleaved by copper mediated Grignard reaction[14] to give a mixture of 1,2-diol derivative **4** and 1,3-diol derivative **5** in the ratio of 87/13. After chromatographic separation, pure **4** was obtained in 74% yield. The secondary hydroxyl group of **4** was protected as the benzyl ether to yield **6** quantitatively. Subsequent removal of trityl group gave half protected diol **7** in 73% yield. Oxidation of **7** with the Dess–Martin periodinane[15] afforded the desired aldehyde **2** in 91% yield without epimerization.

Carbonyl-ene reaction between **2** and (*Z*)-3β-acetoxypregna-5,17-diene **8**[16] using Me_2AlCl, which is routinely used as the Lewis acid in many cases, was unsuccessful. $MeAlCl_2$ among of various Lewis acids, was found to be the most effective. Thus equimolar amount of **2** and **8** reacted smoothly at −78 °C in the presence of $MeAlCl_2$ (3 equiv), and the ene adduct **9** was obtained in 65% yield. To determine the configurations of C20 and C22, **9** was subjected to basic hydrolysis followed by catalytic hydrogenation to yield triol **10** (Scheme 3). Unexpectedly, ^1H NMR chemical shifts of protons in the side chain moiety of **10** were not agreed with those reported for BL,[17] but well agreed with those reported for 20-epibrassinolide.[18] Thus **10** proved to be epimer of

Keywords: Brassinolide; 6-Deoxoteasterone; 20-Epi-6-deoxoteasterone; Carbonyl-ene reaction; Methylaluminum dichloride; α-Alkoxyaldehyde.

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† Ene reaction between (*E*)-17-ethylidenesteroid and methyl propiolate gave 20-'unnatural' steroid.[12]

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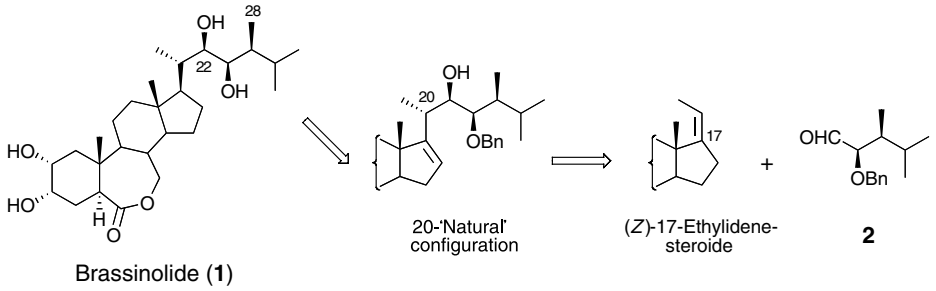
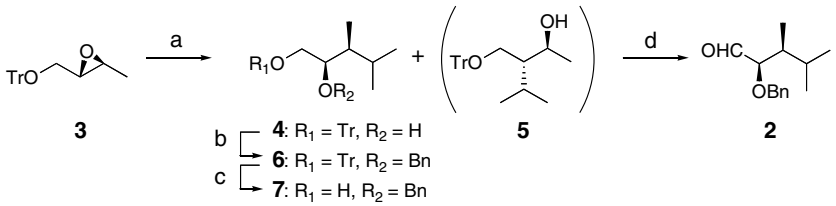
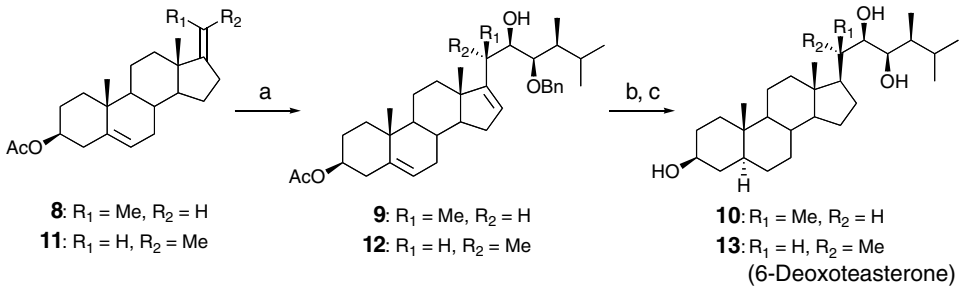


Scheme 1.



Scheme 2. Reagents and conditions: (a) *i*-PrMgCl, Li_2CuCl_4, THF–Et_2O (2/1), −78 °C to rt, overnight; (b) NaH, BnBr, DMF, rt, overnight; (c) 90% aq AcOH, 90 °C, 15 min; (d) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min.



Scheme 3. Reagents and conditions: (a) **2**, $MeAlCl_2$, CH_2Cl_2–hexane (2/1), −78 °C, 30 min; (b) NaOH, MeOH, reflux, 15 min; (c) H_2, Pd–C, 40 °C, overnight.

6-deoxoteasterone **13**, one of the intermediates in the BL biosynthetic pathway, with respect to C20. This stereochemical outcome were unusual comparing with hitherto known ene reactions between (*Z*)-17-ethylidenesteroid and various enophile, which gave only 20-'natural' steroid as mentioned above.

We would like to comment on this unique reaction mechanism. There are four possible transition states (TSs) that can be assumed in this carbonyl-ene reaction between (*Z*)-17-ethylidenesteroid and the aldehyde with the aluminum reagent used as the Lewis acid[‡] (Fig. 1). In TSs **A** and **B**, the aldehyde–Lewis acid complex locates on the α face of the steroidal D-ring to lead to the 20-'natural' steroid as product. In TSs **C** and **D**, on the other hand, the aldehyde–Lewis acid complex locates on the β face of the D-ring to give the 20-'unnatural' steroid. It has been considered that repulsion between the C18 methyl group and the aldehyde–Lewis acid complex is the most important steric factor, which favors α face attack as in TSs **A** and **B**. When the aliphatic moiety of the aldehyde is relatively small,[§] TS **A** is more favorable between these two TSs since the steric repulsion between the Lewis acid and the D-ring adversely works for the formation of TS **B**. However, in the case of reaction between **2** and **8**, it is likely that the considerably bulky alkyl group of **2** also makes TS **A** unstable to prevent the α face attack. Consequently, the reaction proceeds mainly on the β face as in TSs **C** or **D**. TS **C** is relatively unfavorable due to the steric interaction between the C18 methyl group and **R**. Therefore TS **D** is considered to be the most stable among the four possible TSs for the present case, giving (20*R*,22*R*)-stereochemistry.

Even in TS **D**, steric hindrance hampered the smooth reaction. The acidity of Me_2AlCl, a typical Lewis acid for the carbonyl-ene reaction, was too moderate to overcome the steric hindrance. The stronger Lewis acid, $MeAlCl_2$,

[‡] Alkyl moiety of aldehyde (**R**) and aluminum reagent are considered to locate *anti*.[7,11]

[§] Houston and co-workers reported that ene reaction proceeded via TS **B** when **R** is aromatic, and no reaction occurred when **R** is *t*-Bu using Me_2AlCl.[11]

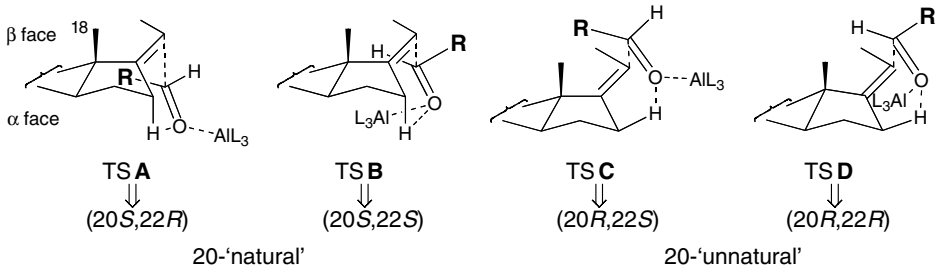


Figure 1. Possible transition states for the carbonyl-ene reaction.

was required for the reaction to proceed. In this regard, Jackson and co-workers have reported that $EtAlCl_2$ could mediate the intermolecular carbonyl-ene reactions of olefins and ketones, an enophile with considerably low reactivity, to give ene adducts in low to moderate yield.[19]

To verify the assumed reaction mechanism, we performed a carbonyl-ene reaction between **2** and (*E*)-3β-acetoxypregna-5,17-diene **11**.[20] The reaction proceeded smoothly under the same conditions as those for (*Z*)-isomer **8**, and ene adduct **12** was obtained in 52% yield, which was converted to triol **13**. As expected, analytical data of **13** was identical with those reported for 6-deoxoteasterone.[21]

In summary, we have developed the shortest method reported to date to construct the BL side chain using a carbonyl-ene reaction as a key step. We have also synthesized 6-deoxoteasterone and its 20-epimer. Further investigation of the scope and limitations of this type carbonyl-ene reaction are now in progress.

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