Chinese Chemical Letters Vol. 14, No. 9, pp 889 – 902, 2003
http://www.imm.ac.cn/journal/ccl.html

Studies on the Model Synthesis of the Brassinolide and Dolicholide Side Chains

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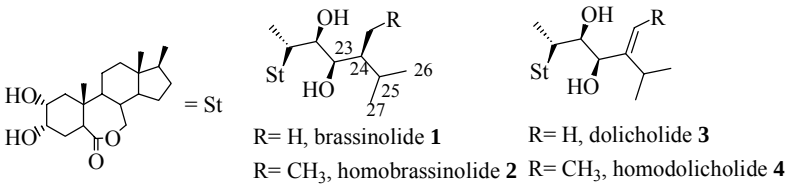
Abstract: A stereoselective synthesis of brassinolide and dolicholide, which involves construction of the side chain enantiomers by a highly stereoselective aldol reaction of aldehyde **5** with the anion of α-silyloxy ketone **6** is described.

Keywords: Brassinolide, dolicholide, side chain, aldol reaction.

Brassinolide **1** as well as its analogues **2, 3, 4** (**Figure 1**) are a new type of promoting material for plant growth[1, 2]. Owing to their novel structural features and their remarkable physiological activity, much effort has been expanded on the development of methods for their syntheses and biosynthesis[3]. So far the work on the steroidal nuclei of **1** is rather successful. The main differences of various synthetic routes of **1** are the syntheses of the side chains[3]. With our previous findings[4], we report here a new method for constructing the side chain of **1** and related compounds, which is stereoselective and produces high yields.

Figure 1



R= H, brassinolide **1**
R= CH_3, homobrassinolide **2**
R= H, dolicholide **3**
R= CH_3, homodolicholide **4**

On the basis of the structure characteristic of brassinolide **1** and dolicholide **3**, we synthesized **12** and **11**, which were the side chain enantiomers of **1** and **3** using aldehyde **5** as starting material. Aldehyde **5** was prepared in two steps from ethyl (*S*)-(-)-lactate by *p*-methoxybenzylation[5] and the DIBAL-H reduction. This aldehyde was then used in an aldol reaction with the lithium enolate of α-silyloxy ketone **6**[4]. The anion was generated in THF from the α-silyloxy ketone **6** and LDA and was cooled to –78 °C before addition of the aldehyde. The temperature was maintained for 1.5 h and was allowed to warm up to 0°C, then the reaction was quenched with dilute hydrochloric acid,

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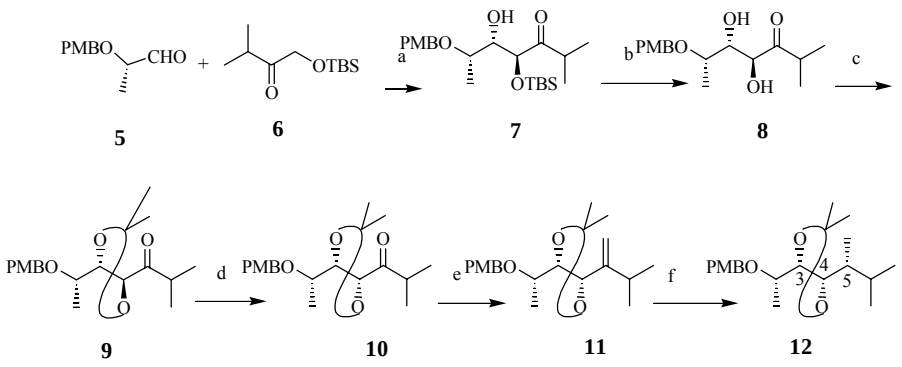
the 3*S*, 4*R* intermediate **7**[6] was obtained in 83% yield (**Scheme 1**). When the aldol reaction mixture was maintained below –78 °C for 3 h and the reaction was quenched with dilute hydrochloric acid at this temperature under these conditions (kinetic), the 22*S*, 23*S* intermediate **13**[6] was obtained in 75% yield (**Scheme 2**). Mukaiyama-type aldol reaction[7] of silyl enol ethers **15**[8] and aldehyde **5** turned out to be more efficient than the direct reaction of the lithium enolate of **6**. Reaction of **15a** and aldehyde **5** mediated by $TiCl_4$ afforded aldol products with silylated aldol products. Without isolation of the products, treatment of the product mixture with *n*-Bu_4NF afforded desilylated aldol products, under these conditions, the 3*S*, 4*S* intermediate **14**[6] was obtained in 63% yield (**Scheme 3**).

Scheme 1

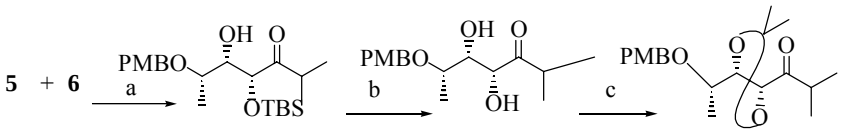


5 **6** **7** **8**

9 **10** **11** **12**

Reagents and conditions: a) LDA, THF, –78 °C -0 °C, 1.5 h, 83%; b) TBAF, THF, r. t., 5 min, 92%; c) $(CH_3)_2C(OCH_3)_2$, DMF, *p*-TsOH, 2 h, 84%; d) K_2CO_3, MeOH, reflux, 0.5 h, 93%; e) Ph_3PCH_3I, *n*-BuLi, THF, r. t., 8 h, 85%; f) PtO_2, MeOH, H_2, r. t., 6 h, 98% or 10% Pd/C, MeOH, r. t., 0.5 h, 98%.

Scheme 2



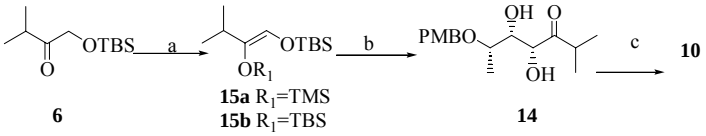
13 **14** **10**

Reagents and conditions: a) LDA, THF, –78 °C, 3 h, 75%; b) TBAF, THF, r. t., 5 min, 90%; c) $(CH_3)_2C(OCH_3)_2$, DMF, *p*-TsOH, 2 h, 88%.

Aldol **7** was desilylated by treatment with TBAF in THF and the diol **8** was transformed into *erythro* acetonide **9**. Treatment of **9** with potassium carbonate[9] in methanol under reflux for 0.5 h affected the epimerization of C-4 center of the acetonide to the desired *threo* acetonide **10**[9, 10], which showed identical spectral data with that obtained from the diol **14**. After Witting olefination, the product **11** was hydrogenated by treating with PtO_2 in the MeOH to give an 85: 15 (^{1}H NMR) mixture of isomers of the

desired product **12**[11] in virtually quantitative yield. The coupling constant for H-4 to H-5 (J = 3.2 Hz) in the major product was smaller than that for H-4 to H-5 (J = 6.8 Hz) in the minor product therefore the stereochemistry at C-5 was tentatively assigned as 5*S*. The observed stereochemistry in favor of the 5*S* isomer may be as a result of the directing influence of the chiral acetonide group at C-3 and C-4 on the addition of hydrogen.

Scheme 3



Reagents and conditions: a) $NaN(SiMe_3)_2$ (1.1 equiv), -78 °C, 30 min, then TMSCl or TBSCl (1.2 equiv), -78 °C-0 °C, 2.5 h, 88%; b) 1.$TiCl_4$, CH_2Cl_2, -78 °C, 4 h; 2. TBAF, THF, r. t., 5 min, 63%; c) $(CH_3)_2C(OCH_3)_2$, DMF, *p*-TsOH, 2 h, 86%.

The synthetic route of this model reaction reported here makes available side chains of brassinolide **1** and dolicholide **3** that may be of interest for structure-activity studies of this group of steroids. The work on the addition of α-silyloxy ketone **6** with the steroidal-aldehyde is in progress.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (Grant No. 20072012) and the Special Research Grant for Doctoral Sites in Chinese Universities (Grant No. 20010730001).

References and Notes

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6. (a) For the recent review of nucleophilic additions to chiral carbonyl compounds, see: A. Mengel, O. Reiser, *Chem. Rev.* **1999,** *99*, 1191. (b) The stereochemistry at C-3 is predicted by the Cram or Felin-Anh model for the transition state. According to the ^{1}HNMR data, the preferred conformation of ismer **14** is *3S, 4S*. Since the coupling constant of H-3 and H-4 is 3.6 Hz. While the preferred comformation of isomer **8** is *3S,4R*. The J value of H-3 and H-4 is 8.8 Hz., the dihehral angle between H-3 and H-4 is about 180°.
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8. (a) S. K. Kwan, D. H. Sung, *Tetrahedron Lett*., **2000**, *41*, 5909. (b) The corresponding TMS and TBS enol ethers are stable enough to be purified by flash column chromatography on SiO_2. (c) The geometry of silyl enol ethers **15** was deduced as *Z* by ^{1}H NMR and GC (> 98%) analysis and compared with literature[8a].
9. For examples, see: (a) P. A. Lee, V. S. Martin, S. Masamune, *et al.*, *J. Am. Chem. Soc.*, **1982**, *104,* 3515. (b) A. W. M. Lee, *Magnetic Resonance in Chemistry*, **1985**, *23*, 468.
10. Compound **11**: IR (film) 2957, 2927, 1601, 1472, 1072, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (d, 2 H, J = 8.4 Hz), 6.88 (d, 2 H, J = 8.4 Hz), 5.01 (s, 1 H), 5.00 (s, 1 H), 4.64

(d, 1 H, *J* = 11.6 Hz), 4.48 (d, 1 H, *J* = 11.6 Hz), 4.40 (d, 1 H, *J* = 8.4 Hz,), 3.81 (s, 3 H), 3.78 (dd, 1 H, *J* = 8.4, 4.4 Hz), 3.53 (m, 1 H), 2.29 (m, 1 H), 1.46 (s, 3 H), 1.44 (s, 3 H), 1.22 (d, 3 H, *J* = 6.6 Hz), 1.07 (d, 3 H, *J* = 6.8 Hz), 1.04 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1, 153.3, 130.7, 129.4, 113.7, 111.3, 108.7, 83.3, 80.5, 72.8, 70.6, 55.3, 29.2, 27.2, 26.9, 23.5, 23.2, 16.4, 16.2; EIMS, *m/z*: 334 (M^+, 9); HRMS (ESI): found $(M+H)^+$, 335.2215; $C_{20}H_{34}O_2$+H calcd. $(M+H)^+$ 335.2217. Compound **12**: IR (film) 2954, 2933, 1611, 1466, 1085, 1006 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.28 (d, 2 H, *J* = 8.4 Hz), 6.88 (d, 2 H, *J* = 8.4 Hz), 4.63 (d, 1 H, *J* = 11.6 Hz), 4.49 (d, 1 H, *J* = 11.6 Hz), 4.04 (dd, 1 H, *J* = 7.6, 3.2 Hz), 3.81 (s, 3 H), 3.75 (dd, 1 H, *J* = 7.6, 4.4 Hz), 3.53 (m, 1 H), 1.60 (m, 2 H), 1.40 (s, 3 H), 1.38 (s, 3 H), 1.21 (d, 3 H, *J* = 6.8 Hz), 0.92 (d, 3 H, *J* = 6.8 Hz), 0.89 (d, 3 H, *J* = 6.8 Hz), 0.86 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 131.0, 129.3, 113.7, 108.5, 82.1, 78.3, 73.9, 70.7, 55.3, 40.5, 31.1, 29.7, 27.4, 27.1, 21.0, 19.2, 16.0, 9.8, 16.2; EIMS, *m/z*: 336 (M^+, 12); HRMS (ESI): found $(M+H)^+$, 337.2379. $C_{20}H_{34}O_2$+H calcd. $(M+H)^+$ 337.2373.

Received 9 September, 2002