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A concise and stereoselective synthesis of the brassinolide and related compounds' side chains

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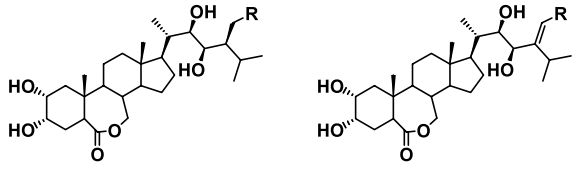
Abstract—A stereoselective synthesis of brassinolide, which involves construction of the side chain by highly stereoselective aldol reaction of 20*S*-6β-methoxy-3α,5-*cyclo*-5α-pregnane-20-carboxadehyde **5** with the anion of α-silyloxy ketone **6** is described.

Brassinolide **1** and related compounds **2**–**4** (Fig. 1) are powerful plant growth promoting steroids.[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.

Stigmasterol was converted to 20*S*-6β-methoxy-3α,5-*cyclo*-5α-pregnane-20-carboxadehyde **5** according to well-known procedures.[5] 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 0.5 h and was allowed to warm up to 0°C, then the reaction was quenched with dilute hydrochloric acid, the 22*R*,23*S* intermediate **7**[6] was obtained in 79% 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*R*,23*R* intermediate **14**[6] was obtained in 70% yield (Scheme 2). When the aldol reaction was allowed to warm up to 0°C before quenching, the major product was 22*R*,23*S* isomer **7**, which was the more stable product at higher temperature. Mukaiyama-type aldol reaction of silyl enol ether **16**[7] and aldehyde **5** turned out to be more efficient than the direct reaction of the lithium enolate of **6**. Reaction of **16** 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 22*R*,23*R* intermediate **15**[6] was obtained in 78% yield (Scheme 3).



R= H, brassinolide 1
R= CH_3, homobrassinolide 2

R= H, dolicholide 3
R= CH_3, homodolicholide 4

Figure 1.

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[8] in methanol at reflux for 0.5 h affected the epimerization of C-23 center of the acetonide to the desired *threo* acetonide **10**,[9] which showed identical spectral data with that obtained from the diol **15**. After Witting olefination, the product **11** was hydrogenated by treated with PtO_2 in the EtOAc to give a 70: 30 (^{1}H NMR) mixture of isomers of the desired product **12**, which is not separable, in virtually quantitative yield. The coupling constant for H-23 to H-24 (J=4.0 Hz) in the

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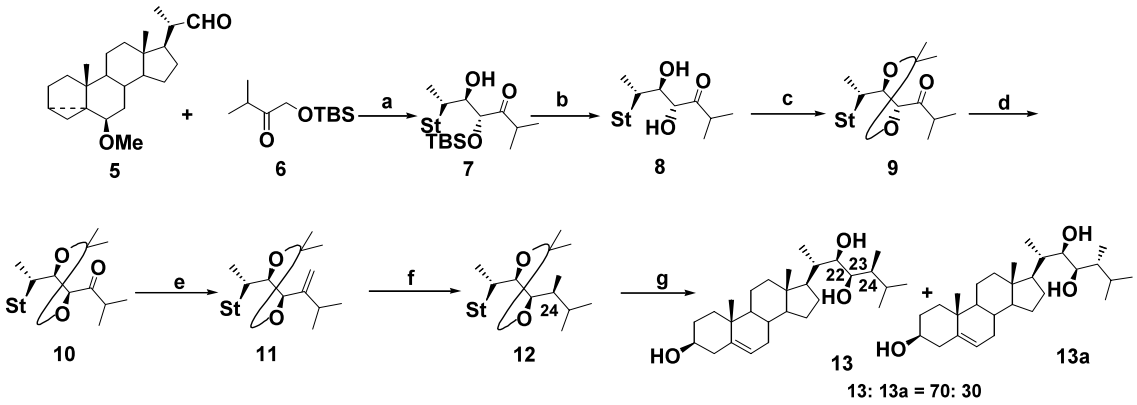
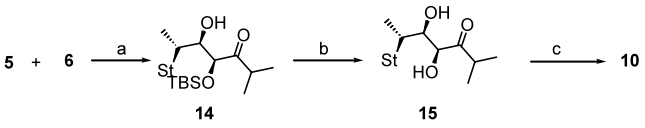


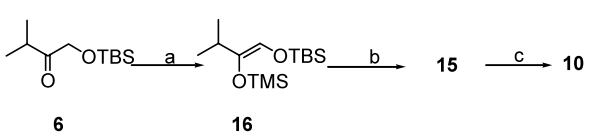
Scheme 1. *Reagents and conditions*: (a) LDA, THF, −78 to 0°C, 1.5 h, 79%; (b) TBAF, THF, rt, 5 min, 95%; (c) $(CH_3)_2C(OCH_3)_2$, DMF, *p*-TsOH, 2 h, 87%; (d) K_2CO_3, MeOH, reflux, 0.5 h, 89%; (e) Ph_3PCH_3I, *n*-BuLi, THF, rt, 16 h, 75%; (f) PtO_2, EtOAc, H_2, rt, 40 h, 98%(24*S*/24*R*=70:30); (g) *p*-TsOH, MeOH, reflux, 0.5 h, 85%.

major product was smaller than that for H-23 to H-24 (J=6.8 Hz) in the minor product and the stereochemistry at C-24 was therefore tentatively assigned as 24*S*.[10] The stereochemistry of the side chain was confirmed by converting the acetonide **12** to the known triol derivative **13** [mp 216–218°C, lit.[11a] mp 219–220°C] along with **13a**[12] (which can be separated easily by flash column chromatography on SiO_2) by treatment with *p*-TsOH[10b] in refluxing MeOH. The triol **13** has been synthesized earlier[11] by different routes and its conversion to brassinolide is known.[11b] The observed stereochemistry in favor of the 24*S* isomer may be a result of the directing influence that the chiral acetonide group at C-22 and C-23 has on the addition of hydrogen.

The synthetic route reported here makes available side chains of brassinolide and related compounds that may be of interest for structure–activity studies of this group of steroids.



Scheme 2. *Reagents and conditions*: (a) LDA, THF, −78°C, 3 h, 70%; (b) TBAF, THF, rt, 5 min, 93%; (c) $(CH_3)_2C(OCH_3)_2$, DMF, *p*-TsOH, 2 h, 90%.



Scheme 3. *Reagents and conditions*: (a) $NaN(SiMe_3)_2$ (1.1 equiv.), −78°C, 30 min, then TMSCl (1.2 equiv.), −78 to 0°C, 2.5 h, 88%; (b) 1. 5, $TiCl_4$, CH_2Cl_2, −78°C, 4 h; 2. TBAF, THF, rt, 5 min, 78%; (c) $(CH_3)_2C(OCH_3)_2$, DMF, *p*-TsOH, 2 h, 86%.

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References

1. Grove, M. D.; Spencer, G. F.; Rohwedder, W. K.; Mandava, N.; Worley, J. F.; Warthen, J. D., Jr.; Steffens, G. L.; Flippen-Anderson, J. L.; Cook, J. C., Jr. *Nature* **1979**, *281*, 216.
2. Adam, G.; Marquardt, V. *Phytochemistry* **1986**, *25*, 1787 and references cited therein.
3. (a) Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116; (b) For a recent review of the syntheses of brassinolide, see: Zhou, W. S.; Zhuang, Z. P.; Huang, L. F. *Advances in Steroid Chemistry*; Science Press: Beijing, 2002; p. 251 and references cited therein.
4. Li, W. D. Z.; Li, Y.; Li, Y. L. *Tetrahedron Lett.* **1999**, *40*, 965 and references cited therein.
5. Anderson, G. D.; Powers, T. J.; Djerassi, C.; Fayos, J.; Clardy, J. *J. Am. Chem. Soc.* **1975**, *97*, 388.
6. (a) For a recent review of nucleophilic additions to chiral carbonyl compounds, see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191; (b) The stereochemistry at C-22 is predicted by the Cram or Felin–Anh model for the transition state. ^{1}H NMR evidence is in accord with this since coupling constant between H-22 and H-23 in 22*R*,23*R* isomer **14** (J=3.6 Hz) indicates the preferred conformation for the side chain shown. For the 22*R*,23*S* isomer **7** the corresponding couping constant (J=8.8 Hz) indicates a preferred conformation for the side chain in which the dihedral angle between H-22 and H-23 is about 180°.
7. (a) Kim, K. S.; Hong, S. D. *Tetrahedron Lett.* **2000**, *41*, 5909; (b) The corresponding TMS enol ether is stable enough to be purified by flash column chromatography on SiO_2; (c) The geometry of silyl enol ether **16** was deduced as *Z* by ^{1}H NMR and GC (>98%) analysis and compared with literature.[7a].

8. For example, see: (a) Lee, A. W. M.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Walker, F. J. *J. Am. Chem. Soc.* **1982**, *104*, 3515; (b) Lee, A. W. M. *Magn. Reson. Chem.* **1985**, *23*, 468.
9. For application of the epimerization of α-carbonyl as key step in natural products syntheses, see Ref. 4 and Nagaoka, H.; Miyaoka, H.; Miyakoshi, T.; Yamada, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5019.
10. (a) Donanbauer, J. R.; Greaves, A. M.; McMorris, T. C. *J. Org. Chem.* **1984**, *49*, 2833; (b) McMorris, T. C.; Chavez, R. G.; Patil, P. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 295.
11. (a) Takahashi, T.; Ootake, A.; Yamada, H.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 69; (b) Fung, S.; Siddall, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 6580.
12. *Selected spectral data*
Compound **13**: mp 216–218°C; $[\alpha]_D^{20}=-30.6$ (*c* 0.7, MeOH); IR (film): 3532 cm^{-1}; ^1H NMR (400 MHz, C_5D_5N): δ 0.81 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.12 (d, $J=6.8$ Hz, 6H), 1.17 (d, $J=6.8$ Hz, 6H), 3.85 (m, 1H, 3-H), 3.99 (d, $J=8.8$ Hz, 1H, 22-H), 4.13 (d, $J=8.8$ Hz, 1H, H-23), 5.43 (m, 1H, CH=); EIMS *m/z* 432 (M^+), 399, 361, 332, 313, 273; HRMS (ESI): calcd for $C_{28}H_{48}O_3$+H (M^++H) 433.3683, found 433.3688.
Compound **13a**: mp 196–198°C; $[\alpha]_D^{20}=-22.0$ (*c* 0.3, MeOH); IR (film): 3538 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.71 (s, 3H, CH_3), 0.87 (t, $J=7.2$ Hz, 6H, 2×CH_3), 0.93 (d, $J=6.8$ Hz, 3H), 0.99 (d, $J=6.8$ Hz, 3H), 1.01 (s, 3H, CH_3), 3.42 (t, 1H, $J=4.4$ Hz, 22-H), 3.72 (d, $J=4.4$ Hz, 1H, 23-H), 5.37 (m, 1H, CH=); EIMS *m/z* 432 (M^+), 381, 361, 343, 313, 255; HRMS (ESI): calcd for $C_{28}H_{48}O_3$+H (M^++H) 433.3683, found 433.3676.