Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5107–5108

TETRAHEDRON LETTERS

Novel construction of the brassinolide side chain

Lizeng Peng, Huawei Liu, Tao Zhang, Fengzhi Zhang, Tiansheng Mei, Yi Li and Yulin Li*

National Laboratory of Applied Organic Chemistry, Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China

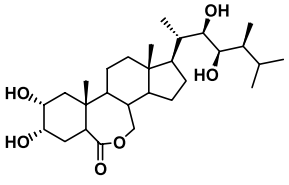
Received 21 February 2003; revised 21 April 2003; accepted 2 May 2003

Abstract—A stereoselective synthesis of brassinolide, which involves construction of the side chain by a highly stereoselective aldol reaction between 20*S*-6β-methoxy-3α,5-*cyclo*-5α-pregnane-20-carboxaldehyde **2** and ketone **3** or **4** catalyzed by L-proline, is described.

Although considerable efforts have been devoted to the total synthesis of brassinolide **1** (Fig. 1) and related compounds over the past three decades and notable progress has been made in this field, the stereocontrolled construction of the side chain of **1** still represents an ongoing challenge for total synthesis.[1]

In continuation of our ongoing project on the total synthesis of brassinolide **1** and related compounds,[2] we describe herein a new method for constructing the side chain of **1** by a highly stereoselective and high-yielding aldol reaction between the hydroxyacetone **3** (or TBS-protected hydroxyacetone **4**) and 20*S*-6β-methoxy-3α,5-*cyclo*-5α-pregnane-20-carboxaldehyde **2** using L-proline as the catalyst.

The synthesis commenced from the known[3] aldehyde **2**, and at once we noticed that good yield and regioselectivity (up to 19:1) of the direct aldol reaction between **3** (or **4**) and aldehyde **2** using L-proline[4] as the catalyst (Scheme 1). This aldol reaction does not require the pre-generation of enolates or enolate equivalents. Due to its simplicity and its mild reaction conditions, this process can be considered as an efficient method to synthesize the optically active 1,2-diol units that are the very important intermediates in organic synthesis. When unprotected hydroxyacetone **3** was used in the aldol reaction, the *anti* aldol **5a** was obtained along with its *syn* isomer **6a** in 84% yield in a ratio of 5:1 as determined by TLC and ^{1}H NMR. When TBS-protected hydroxyacetone **4** was used in the aldol reaction, the *anti* aldol **5b** with its *syn* isomer **6b** and regioisomeric product **7**[5] were obtained in 80% yield in a ratio of 75:20:5.



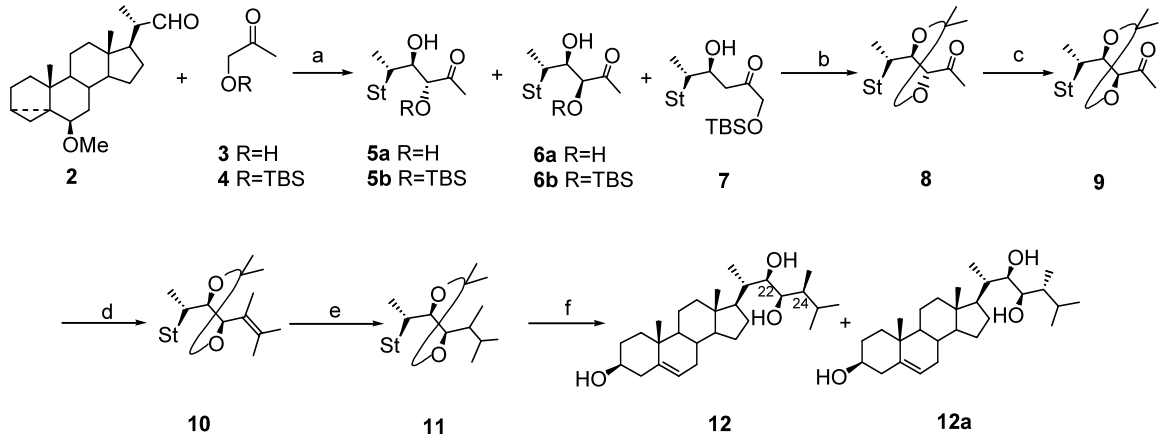
brassinolide 1

Figure 1.

Aldols **5b** and **6b** were desilylated by treatment with TBAF in THF and the diols **5a** and **6a** were transformed into *erythro* acetonide **8** and *threo* acetonide **9**, respectively. Treatment of **8** with potassium carbonate[6] in methanol at reflux for 0.5 h affected the epimerization of C-23 center of the acetonide to the desired *threo* acetonide **9**,[7] which showed identical spectral data with those of the acetonide obtained from diol **6a**. After Wittig olefination, product **10** was hydrogenated in the presence of PtO_2 in EtOAc to give a 75:25 (by 400 MHz ^{1}H NMR) mixture of isomers of the desired product **11**, which was not separable, in virtually quantitative yield. The coupling constant for H-23 to H-24 ($J=4.0$ Hz) in the major product was smaller than that ($J=6.8$ Hz) in the minor product and the stereochemistry at C-24 was therefore tentatively assigned as 24*S* for the former.[8] The stereochemistry of the side chain was confirmed by converting compound **11** to the known triol derivative **12** [mp 216–218°C, lit.[9a] mp 219–220°C; $[\alpha]_D^{20}=-31.5$ (*c* 0.6, EtOH), lit.[9a] $[\alpha]_D=-33$ (*c* 0.21, EtOH)] along with **12a** (which could be separated easily by flash column chromatography on SiO_2) by treatment with *p*-TsOH[8b] in refluxing MeOH. The triol **12** has been synthesized

* Corresponding author. Fax: +86-931-8912283; e-mail: liyl@lzu.edu.cn

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)01178-X



Scheme 1. *Reagents and conditions*: (a) L-proline, DMSO, rt, 12 h; (b) $(CH_3)_2C(OCH_3)_2$, DMF, *p*-TsOH, 2 h, 90%; (c) K_2CO_3, MeOH, reflux, 0.5 h, 85%; (d) $Ph_3PCH(CH_3)_2I$, *n*-BuLi, THF, rt, 16 h, 55%; (e) PtO_2, EtOAc, H_2, rt, 40 h, 98% (24*S*/24*R* = 75:25); (f) *p*-TsOH, MeOH, reflux, 0.5 h, 85%.

earlier[9] by different routes and its conversion to brassinolide is known.[9b]

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

Acknowledgements

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

1. For a recent review of the syntheses of brassinolide, see: Huang, L. F. In *Advances in Steroid Chemistry*; Zhou, W. S.; Zhuang, Z. P., Eds.; Science Press: Beijing, 2002; pp. 251–300.
2. Peng, L. Z.; Li, Y. L.; Li, W. D. Z. *Tetrahedron Lett*. **2003**, *44*, 3991–3993.
3. Wiersig, J. R.; Waespe-Sarcevic, N.; Dijerassi, C. *J. Org. Chem*. **1979**, *44*, 3374–3382.
4. (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc*. **2002**, *124*, 827–833; (b) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2000**, *122*, 2395–2396; (c) List, B.; Pojarliev, P.; Castello, C. *Org. Lett*. **2001**, *3*, 573–575; (d) List, B. *Tetrahedron* **2002**, *58*, 5573–5590; (e) List, B. *Synlett* **2001**, *11*, 1675–1686; For reviews and highlights of the L-proline-catalyzed direct asymmetric aldol reaction in various contexts, see: (f) Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed*. **2001**, *40*, 529–532; (g) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Eur. J*. **2001**, *8*, 37–44; (h) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem*. **2002**, *67*, 1595–1601; (i) Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904–1905.
5. The phenomenon that the regioisomeric product was obtained in L-proline-catalyzed aldol reaction was not observed in previous papers.[4]
6. For examples, see: (a) Lee, A. W. M.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Walker, F. J. *J. Am. Chem. Soc*. **1982**, *104*, 3515–3516; (b) Lee, A. W. M. *Magn. Reson. Chem*. **1985**, *23*, 468–469.
7. For application of the epimerization of α-carbonyl as key step in natural products syntheses, see: (a) Li, W. D. Z.; Li, Y.; Li, Y. L. *Tetrahedron Lett*. **1999**, *40*, 965–968; (b) Nagaoka, H.; Miyaoka, H.; Miyakoshi, T.; Yamada, Y. *J. Am. Chem. Soc*. **1986**, *108*, 5019–5021.
8. (a) Donanbauer, J. R.; Greaves, A. M.; McMorris, T. C. *J. Org. Chem*. **1984**, *49*, 2833–2834; (b) McMorris, T. C.; Chavez, R. G.; Patil, P. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 295–302.
9. (a) Takahashi, T.; Ootake, A.; Yamada, H.; Tsuji, J. *Tetrahedron Lett*. **1985**, *26*, 69–72; (b) Fung, S.; Siddall, J. B. *J. Am. Chem. Soc*. **1980**, *102*, 6580–6581.