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A Concise and Stereoselective Synthesis of the Cathasterone's Side Chain

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Abstract: A concise and stereoselective synthesis of cathasterone's side chain using methyl isopropyl ketone **3** as the fragment is described.

Keywords: Cathasterone, side chain, aldol reaction.

Brassinolide **1** and cathasterone **2,** which was the logical biosynthetic precursor of **1,** (**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 synthesis and biosynthesis[3], but few on the synthesis of **2**. In our previous work, we found methyl isopropyl ketone **3** and α-siloxy ketone **4** have high regioselectivity at –78°C[4]. And we have used **4** as the C_5-segment to construct C-23 to C-27 fragment of the side chain of **1** recently[5], now we report here a concise and stereoselective synthesis of cathasterone's side chain using methyl isopropyl ketone **3** as the fragment.

The synthesis commenced from the known6 aldehyde 5. This aldehyde was then used in an aldol reaction with the lithium enolate of ketone 4. The anion was generated in THF from the ketone 4 and LDA was cooled to –78°C before addition of the aldehyde. The temperature of –78°C was maintained for 0.5 h, then allowed to warm up to 0°C. The reaction was quenched with dilute hydrochloric acid. The aldol, **7** and **6** were obtained in yield of 79%. The ratio of **7 : 6** was **3 : 1**, determined by TLC and 1H NMR (**Scheme 1**). The stereochemistry at C-22 is predicted by the Cram or Felin-Anh model for the transition state[7].

Then **8** was obtained by using TBSCl to protect C-23 hydroxy group of aldol **7**. After Wittig olefination, the product **9** was hydrogenated by treatment with PtO_2 in the EtOAc to give a 65: 35 (by 400 MHz ^{1}H NMR) mixture of the isomers of the desired product **10,** which was not separable, for the influence of the chiral group at C-22. 22*S*, 24*S* **11**[8] and 22*S*, 24*R* **12**[9] (which can be separated easily by flash column chromatography on SiO_2) were obtained by treatment with TBAF in THF in virtually quantitative yield in the ratio of 35: 65.

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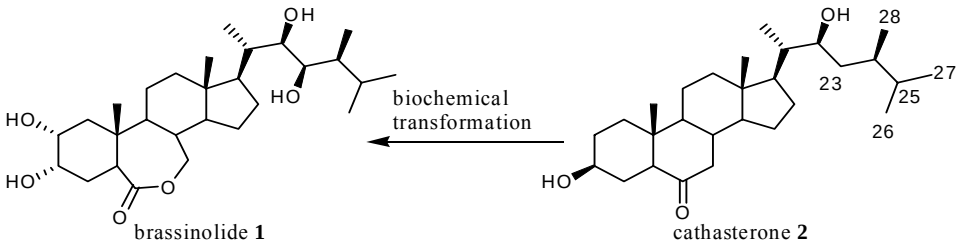
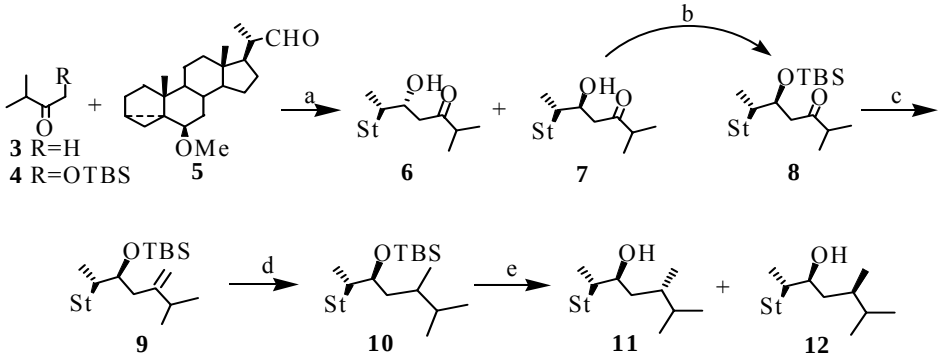
Figure 1



Scheme 1



Reagents and conditions: a) LDA, THF, –78 °C -0 °C, 1.5 h, 79%; b) TBSCl, Imid, DMF, 96%; c) $Ph_3P^+CH_3I^-$, *n*-BuLi, THF, r.t., 16 h, 70%; d) PtO_2, EtOAc, H_2, r.t., 40 h, 98%; e) TBAF, THF, r.t., 25 min, 95%.

The synthetic route reported here makes available to synthesize the side chain of cathasterone that may be of interest for structure-activity studies of this group of steroids.

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8. $[\alpha]_D^{20}$ +13.0 (*c* 0.2, $CHCl_3$); IR (film): 1648 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.77 (t, 1H, *J* = 6.4 Hz, H-23); 3.33 (s, 3H, OCH_3); 2.78 (t, 1 H, *J* = 2.7 Hz, H-6); LR-MS (EI) *m/z* (%): 430 (M^+, 24). HRMS calcd. for $C_{28}H_{47}O_1$ ($C_{29}H_{50}O_2$-OCH_3) 399.3621, found 399.3633.

9. $[\alpha]_D^{20}$ +23.0 (*c* 0.2, $CHCl_3$); IR (film): 1648 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δppm 3.78 (t, 1H, *J* = 6.4 Hz, H-23); 3.34 (s, 3H, OCH_3); 2.79 (t, 1 H, *J* = 2.7 Hz, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.3 13.1 15.7 16.2 19.3 21.0 21.5 22.8 24.3 25.0 27.7 29.7 29.8 30.6 33.4 34.7 35.1 35.3 35.5 40.3 42.9 43.1 43.4 48.1 53.3 56.2 56.6 71.8 82.4 LR-MS (EI) *m/z* (%): 430 (M^+, 24). HRMS calcd. for $C_{28}H_{47}O_1$ ($C_{29}H_{50}O_2$-OCH_3) 399.3621, found 399.3633.

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