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New method in synthesizing an optical active intermediate for (*R*,*R*)-formoterol

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Abstract

(*R*)-1-(4-Methoxyphenyl)propan-2-amine **2a**, an optical active intermediate for (*R*,*R*)-formoterol, was synthesized from D-alanine in 65% overall yield by using a simple route, which contained protecting amino group, cyclization, coupling with Grignard reagent, reduction and deprotection.

Keywords: (*R*)-1-(4-Methoxyphenyl)propan-2-amine; Formoterol; Intermediate; Synthesis

Fomoterol **1** (Fig. 1) is a new long-lasting β_2-adrenoceptor agonist which offers high selectivity for β_2-adrenoceptor, fast onset action and excellent safety [1]. Fomoterol is commercialized in the racemic form (*R*,*R* and *S*,*S*). But the *R*,*R* isomer **1a** is 5 times of intrinsic activity and 18 times of β_2-selectivity compared to *S*,*S* isomer **1b** [2]. Growing interest has been put into synthesizing (*R*,*R*)-formoterol [3] and one of the key procedures in this task is to prepare (*R*)-1-(4-methoxyphenyl)propan-2-amine **2a**.

Nichols et al. [4] reported the preparation of **2a** starting from 1-(4-methoxyphenyl)ethanone. However, this approach was not economical because of the expensive optically active amine reagent and low yield in fractional recrystallization. Kohno et al. [5] synthesized **2a** from expensive L-tyrosine, which was also too complicated. Recently, González-Sabín [6] reported a new method for preparing **2a** *via* enantioselective acetylation of racemic **2** catalyzed by *Candida antarctica* lipase B. This method also had a number of disadvantages that include applying costly enzyme catalyst and low overall yield. We herein reported a new synthetic approach of **2a** as outlined in Scheme 1.

D-Alanine was protected by CbzCl as the known method [7] to afford **4**, cyclizing with polyformaldehyde in the presence of TsOH in refluxed toluene to get **5**. **7** was obtained from **5** *via* coupling with Grignard reagent **6** in THF and treating by HCl [8]. Reduction of **7** by Et_3SiH in TFA [9] and Pd/C with H_2 in alcohol respectively gave the final product **2a** [10,11].

In summary, we have provided a concise route starting from inexpensive D-alanine to prepare an optically active intermediate **2a** in synthesizing (*R*,*R*)-formoterol in five steps with 65% overall yield.

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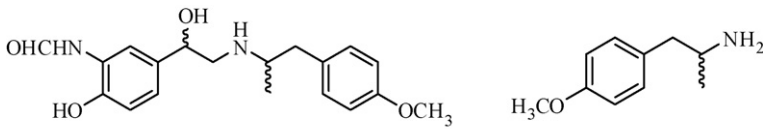
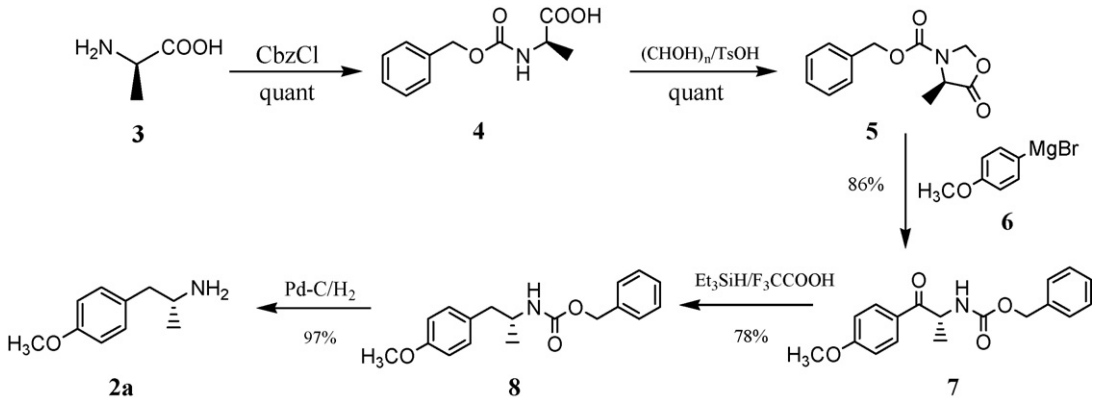


1 1a: R,R
1b: S,S

2 2a:R
2b:S

Fig. 1. The structure of compounds **1** and **2**.



Scheme 1. The synthetic route of (*R*)-1-(4-methoxyphenyl)propan-2-amine.

Acknowledgments

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[8] Procedure for compound **7**: To solution of compound **5** (1.96 g, 8.33 mmol) in dry THF (20 mL) was added Grignard reagent **6** (10 mmol) in dry THF (10 mL) dropwised at 0 °C in about 1 h, kept the temperature and stirred for another 2 h. 6 mol/L HCl (20 mL) was slowly added and stirred at room temperature for 12 h, then extracted with EtOAc 30 mL, washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to get compound **7** (2.24 g, 7.16 mmol) as a yellow oil, yield 86%.
[9] Procedure for compound **8**: Et_3SiH (1.16 g, 10 mmol) was added dropwise to a stirred solution of compound **7** (1.57 g, 5 mmol) in TFA (10 mL) at 0 °C in 0.25 h, followed by warming to room temperature for 10 h. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (30 mL), the organic extracts was washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting yellow oil was purified by column chromatography to get compound **8** (1.17 g, 3.9 mmol) as a colorless solid, mp 88–90 °C, yield 78%.
[10] Procedure for compound **2a**: A solution of compound **8** (1.0 g, 3.3 mmol) in alcohol (15 mL) was hydrogenated on 5% Pd/C (0.2 g) at atmospheric pressure and room temperature for 12 h. After removal of the catalyst, the filtrate was concentrated to get compound **2a** (0.53 g, 3.2 mmol) as a colorless oil, yield 97%.
[11] Selected data for compound **2a**: IR (KBr): 3360, 3283, 2958, 1612, 1582, 1514, 1245, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.09 (d, 2H, J = 8.4 Hz), 6.83 (d, 2H, J = 8.4 Hz), 3.78 (s, 3H), 3.12 (m, 1H), 2.65 (dd, 1H, J = 5.2, 13.4 Hz), 2.48 (dd, 1H, J = 8.0, 13.2 Hz), 2.03 (b, 2H), 1.11 (d, 3H, J = 6.4 Hz); MS (m/z): 166 ($[M + H]^+$); $[\alpha]_D^{20}$ 35.6 (c 1.02, $CHCl_3$); hydrochloride of **2a**: $[\alpha]_D^{20}$ 22.7 (c 2.05, H_2O), lit. [3]: $[\alpha]_D^{20}$ 22.5 (c 2.00, H_2O).