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A Highly Efficient Asymmetric Synthesis of Methoxyhomophenylalanine Using Michael Addition of Phenethylamine.

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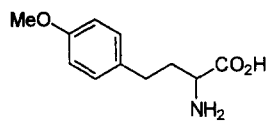
Abstract: A practical method for (*S*)-*p*-methoxyhomophenylalanine (*S*)-**1** by using diastereoselective Michael addition as a key step was reported. Thus, the Michael addition of (*S*)-1-phenethylamine (*S*)-**3** to *p*-methoxy-*trans*-benzoylacrylic acid **2** was performed in a highly stereoselective (up to 98% d.e. and up to 90% yield) fashion and, subsequently, the resultant adduct **4a** was catalytically hydrogenated to afford (*S*)-**1** almost quantitatively. The most likely mechanism of the addition reaction was dynamic resolution.

Optically active homophenylalanines (2-amino-4-phenylbutanoic acids) have been serving as potential constituents of many pharmaceuticals which function as protease inhibitors[1] and neuronal receptor ligands[2]. In particular, *p*-methoxyhomophenylalanine (**1**) has received intense attraction, since it could be used as precursors for a potent β– adrenergic agonist[2b] or dopamine D2 agonist[2d].



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Although several papers have appeared to produce the amino acid **1**[2b,2d,3], there is only limited literature on practical synthetic methods that permit construction of *either* the (*S*)-form *or* (*R*)-form of **1**[2b,3a]. We now describe herein a highly efficient method for the preparation of the two enantiomers by diastereoselective Michael-type addition of optically active amines as a key step. The adduct can easily be converted to the desired product **1** by hydrogenolysis.

The outline of this idea is shown in Scheme 1. Although a benzoylacrylic ester is known to be utilized for construction of the homophenylalanine moieties in ACE inhibitors[1c], the ester needs subsequent hydrolysis in order to give free amino acids. To pursue a more straightforward methodology, we selected *p*-methoxy-benzoylacrylic acid **2**[4], which could be easily made by Friedel-Crafts reaction of anisole with maleic anhydride[5], as a Michael acceptor. With **2**, we also anticipated that the Michael adduct of **2** with **3** might precipitate from the reaction mixture due to its zwitter-ionic character thus it allowing easy isolation. Furthermore, we employed (*S*)-1-phenethylamine **3** as a chiral amine nucleophile in the reaction because of its easy availability (See Scheme 1).

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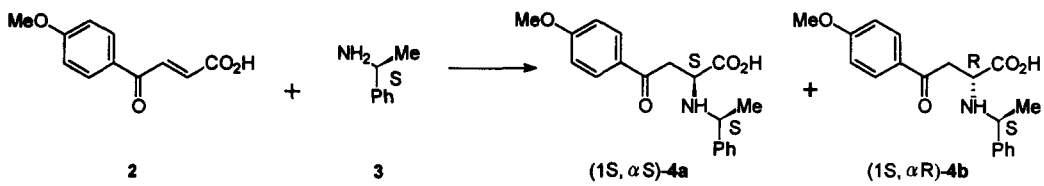


Scheme 1 The Michael addition of **3** to **2**

For the Michael reaction, we only treated **2** with (*S*)-**3** (1equiv.) in ethanol under stirring. First, we conducted the reaction at 30°C; after a 16hr reaction period, we found that the resultant adduct **4a** with (1*S*, α*S*)[6]-configuration was slightly soluble in ethanol, and precipitated out of the reaction mixture in 38% yield (a d.e. value of the precipitate was 96%[7] as shown in Table 1, entry 1. See also entry 2.). The other diastereomer **4b** with (1*S*, α*R*)[6]-configuration, in contrast, exclusively remained in the filtrate in 30% yield (entry 1). These observations showed that the addition proceeded to give a reasonable total yield but with poor diastereoselectivity (ca. 10% d.e.), which is similar, in terms of % de, to the previous report using the same amine, as a chiral auxiliary[8].

Table 1 Results of the Reaction of **2** with Phenethylamine (*S*)-**3**.

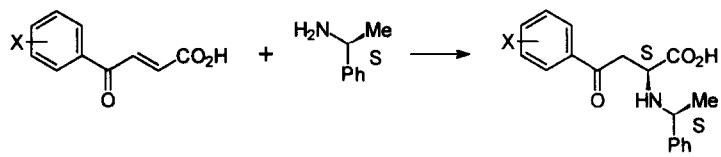
Entry	Reaction conditions		Precipitate		Filtrate
	3 (equiv.)	temp (oC)	yield of 4a * (%)	d.e. of 4a (%)	yield of 4b ** (%)
1	(1.0)	30	38	96	30
2	(1.0)	40	61	90	n.d. ***
3	(1.1)	40	71	97	15
4	(0.9)	40	42	85	n.d. ***
5	(1.1)	50	78	98	n.d. ***
6	(1.1)	60	90	97	n.d. ***

*Yields of **4a** were determined on the basis of the precipitated by HPLC analysis by calculation using the ratio of **4a** and **4b** obtained by HPLC; see text. **Yields of **4b** remaining in the mother liquors were determined by HPLC analysis after quenching with phosphate buffer (pH=2.5); see text. n.d.***: not determined

Since **4a** and **4b** were considered to be a Mannich base, the diastereomer **4b** remaining in the solution should rapidly revert into **2** (retro-Michael reaction) catalytically by the base[9] or on heating in the reaction mixture, and the Michael reaction should then recur: in that event, the (1*S*, α*S*)-form **4a** would be obtained as a precipitate quantitatively. Application of 1.1 equiv. 1-phenethylamine **3** improved the yield of the isolated precipitate to 71% with excellent d.e. (entry 3. As shown in entry 4, utilization of 0.9 equiv. of **3**, on the contrary, retarded the reaction to give a yield of 42%. The d.e. value in **4a** of the precipitate was also relatively low.) Finally, higher reaction temperatures enhanced the yield of **4a** to no less than 90%, achieving an efficient and almost quantitative reaction[10] (entry 5, 6). The above data suggest that both the precipitation of **4a** and the isomerization of **4b** through retro-Michael addition impart a mechanistic rationale to this diastereoselective Michael addition as shown in Scheme 2.

Scheme 2 The most likely mechanism of the diastereoselective Michael addition; dynamic resolution

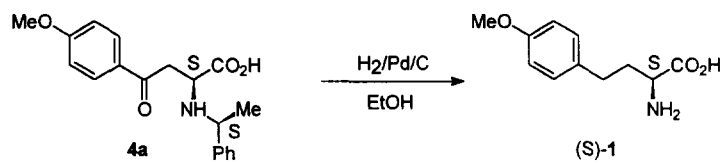
Table 2 Results of the Reaction of Phenethylamine (*S*)-**3** to Benzoylacrylic Acids[10].



Entry	X =	Solvent	d.e.[7] (%)	Yield (%)	Entry	X =	Solvent	d.e.[7] (%)	Yield (%)
1	*p*-H	MeOH	94	80	5	*p*-NO_2	EtOH	95	85
2	*p*-F	MeOH	90	70	6	*p*-Ph	MeOH	99	87
3	*p*-Cl	EtOH	99	85	7	*p, m*-$(OMe)_2$	MeOH	95	80
4	*p*-Me	EtOH	97	95					

The dynamic resolution[11] in Michael addition is, to our knowledge, the first application to an amino acid synthesis. Importantly, this reaction can be applied to a series of benzoylacrylic acids as shown in Table 2. >90% d.e. values of the precipitate were shown through analysis of both ^{1}H NMR and reverse phase HPLC analysis and the yields were also satisfactory. In the light of these results, we propose that this type Michael addition provide a broadly applicable approach to the substituted homophenylalanines.

In the final process for the preparation of (*S*)-*p*-methoxy-homophenylalanine (*S*)-**1**, both deoxygenation and removal of the 1-methylbenzyl group in **4a** through catalytic hydrogenolysis proceeded with negligible racemization, as shown in Scheme 3; the hydrogenolysis of **4a** was carried out at 50 °C over 10% Pd-C under atmospheric pressure of hydrogen in ethanol-1N H_2SO_4 (1:3, v/v) for 24hr. After removal of the metal catalyst by filtration, (*S*)-**1** was obtained as a colorless crystal in a yield of 90% on cooling[12]. The $[\alpha]^{20}_D$ value of **1** was +42.0 (c = 0.1, 5M HCl), [Lit.[3d] for (*S*)-**1**, $[\alpha]^{20}_D$ = +42.2], therefore we obtained (*S*)-**1** in >98% e.e.



Scheme 3 The hydrogenation of **4a**

In sum, it was demonstrated that a practical route to **1** was accomplished by the shortest process: Friedel-Crafts reaction, stereoselective Michael addition followed by only hydrogenolysis. Application of the same procedure should lead to general synthetic methodology for enantiomeric homophenylalanines.

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4. It should be pointed out here that the Michael addition of amines to benzoylacrylic acids has so far received little attention. See also: a) Lehmann, J.; Gossen, A. *Arch. Pharm. (Weinheim, Ger.)* **1988**, *321*, 443. b) Argalylan, S. G.; Khachikyan, R. D. *Arm. Khim. Zh.* **1978**, *31*, 273.
5. Berliner, E. *Organic Reactions*, **5**, John Wiley & Sons, Inc.: New York 1949; pp. 229-289 and references cited therein.
6. The (1*S*, α*S*) configuration of **4a** was determined by conversion into known (*S*)-*p*-methoxyhomophenylalanine **1** through hydrogenolysis; see text.
7. The d.e. values of the Michael adducts were readily determined by a reverse phase HPLC analysis using JASCO Finepak SIL C18-5 column by using pH 2.5 phosphate buffer-CH3CN=8:2 (v/v).
8. a) Shustov, G. V.; Rauk, A. *Tetrahedron Asymmetry* **1996**, *7*, 699. b) Davies, S. G.; Ichihara, O. *Tetrahedron Asymmetry* **1991**, *2*, 183. See also: c) Keese, R.; Hinderling, C. *Synthesis* **1996**, 695.
9. House, H. O. *Modern Synthetic Reactions*, W. A. Benjamin, Inc.: 1972; pp. 602-611. In addition, we observed based on ^{1}H NMR measurements that the cleavage of **4b** to *p*-methoxy-benzoylacrylic acid indeed took place to a small extent (ca. 20%) even in dimethylsulfoxide solution on standing at room temperature for 16hr.
10. The typical procedure for preparation of **4a** is as follows: To a vigorously stirred solution of *p*-methoxy-*trans*-benzoylacrylic acid (185mg, 0.9mmol) in 20mL ethanol at 40°C was added (*S*)-1-phenethylamine (121mg, 1.1 equiv.). The reaction mixture was stirred at the same temperature for 16hr, and the resultant white precipitate was filtered to afford 210mg of **4a** (d.e.97%) as a white solid (71%). The yield was obtained by the ratio of **4a** and **4b** of the HPLC Chart. An analytical sample was prepared by recrystallization from acetonitrile/pH 2.5 phosphate buffer = 1/1, v/v (white needles): Mp. 160-161°C; ^{1}H NMR [$(CD_3)_2SO$ - TFA,400MHz] δ 7.91 (d, J = 7.5 Hz, 2H), 7.5-7.3 (m, 5H), 7.05 (d, J = 7.5Hz, 2H), 4.53 (q, J = 6.3Hz, 1H), 3.82 (s, 3H), 3.76 (dd, J = 4.4, 5.0Hz, 1H), 3.60 (dd, J = 5.0, 18.0Hz, 1H), 3.55 (dd, J = 4.4,18.0Hz, 1H), 1.60 (d, J = 6.8Hz, 3H); FTIR (KBr Disk, cm^{-1}) 1680, 1600, 1570, 1380, 1250, 1180; $[\alpha]^{20}_D$ = +90.2 (c = 0.047, solvent: methanol/0.1N H_2SO_4 = 3/1, v/v).
11. a) Caddick, S.; Jenkins, K. *Chemical Society Reviews* **1996**, 447. b) Wards, R. S. *Tetrahedron Asymmetry* **1995**, *6*, 1475. c) Jacques, J.; Collet, A.; Wilens, S. H. *Enantiomers, Racemates, and Resolution*, John Wiley & Sons, Inc.: New York 1981 and references cited therein. d) Bruggink, A.; Ariaans, G. J. A.; Ebbers, E. J. *Chiral Europe '96*, p113-116 (abstract).
12. The ^{1}H NMR measurements of the reaction mixtures at appropriate time intervals have indicated that the order of the hydrogenation reaction rates may be roughly estimated to be PhCH(Me)−NH > C=O.