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A Convenient Synthesis of (*S*)-*O*-Benzyl-*N*-*tert*-butoxycarbonyl-β-tyrosine[*]

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(*S*)-β-Tyrosine, *i.e.* (*S*)-3-amino-3-(4-hydroxyphenyl)propanoic acid is an amino acid component of biologically active peptides – edeine A and B, isolated from the fermentation broth of *Bacillus brevis Vm4* strain [1]. The (R)-isomer of β-tyrosine has also been isolated from the hydrolysates of cyclodepsipeptide jaspamide produced by the sponge of *Jaspis johnstoni* [2,3]. This peptide exhibits a broad spectrum of biological properties including antifungal, insecticidal, antinematodal, and cytotoxic activities. Chondramides A-D a group of another cyclodepsipeptides produced by *Chondromyces crocatus* (Myxobacteria) contain also (*R*)-β-tyrosine and posess potent cytostatic and antifungal properties [4]. Geodiamolides H and I isolated from marine sponge *Geodia sp.* constitute a novel group of cytotoxic peptide containing (*R*)-β-tyrosine [5].

There are several approaches described for the preparation of enantiomerically pure β-tyrosine. One of the used methods is based on the optical resolution of a racemic β-tyrosine *via* its *L*-menthyl ester [6]. Several repetitive recrystallizations afforded pure (*R*)-β-tyrosine derivative in 26% overall yield. A more direct approach involves application of Penicillin G acylase for enantioselective acylation of a racemic β-tyrosine methyl ester with phenylacetic acid [7]. In this manner, (*R*)-β-tyrosine derivative was obtained in 38% yield. Asymmetric syntheses leading to the preparation of enantiomerically pure β-tyrosine derivatives gained more attention in recent years. Enantioselective reduction of a β-keto ester in the presence of *N,N′*-dibenzoyl-*D*-cystine, as a chiral auxiliary, followed by nucleophilic displacement of a β-hydroxy group with HN_3 under Mitsunobu conditions and final azido group reduction yielded the protected (*R*)-β-tyrosine derivative [8]. Aldol type reaction of *N*-benzhydrylimines derived from *p*-acetoxybenzaldehyde with the ketene silyl acetal obtained from *t*-butyl acetate, mediated by a chiral Lewis acid-Brønsted acid combined system leads to preparation of β-tyrosine derivative with high enantioselectivity [9]. Another example of a (*R*)-β-tyrosine derivative preparation is the

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[*] Dedicated to Prof. E. Borowski on the occasion of his 75th birthday.

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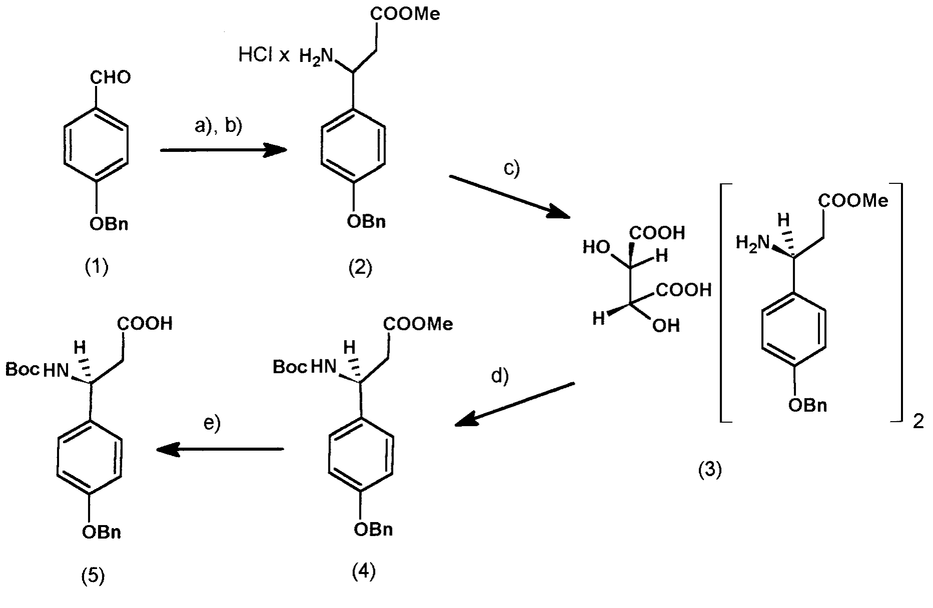
application of the Wolff rearrangement of diazoketone generated from (*S*)-4-hydroxyphenylglycine [10]. (*R*)-*β*-Tyrosine-O-methyl ether methyl ester synthesis was accomplished *via* the stereospecific palladium catalyzed acylation of an enantiomerically pure dihydropyrimidinone obtained from (*S*)-asparagine, followed by reduction of the heterocyclic intermediate with $NaBH_4$ and its acid hydrolysis [11]. Addition of allylmagnesium bromide to O-(1-phenylbutyl)aldehyde oxime results in the formation of corresponding N-hydroxylamine which can be eventually converted into *N*-protected (*S*)-*β*-tyrosine derivative [12]. The asymmetric nucleophilic addition of Reformatsky type reagent obtained *in situ* from diethylzinc and iodoacetic acid ester to an imine prepared from 4-methoxybenzaldehyde and 2-amino-4-methoxyphenol in the presence of diisopropyl (*S,S*)-tartrate as a chiral auxiliary, yielded (*R*)-*β*-tyrosine derivative [13]. Stereoselective addition of lithium amide derived from (*R*)-N-(*α*-methylbenzyl)amine to methyl *p*-benzyloxycinnamate followed by debenzylation in the presence of palladium hydroxide gave the enantiomerically pure methyl ester of (*S*)-*β*-tyrosine in good yield [14].

In the course of our studies centered on edeine antibiotic analogues [15–17], we required orthogonally protected (*S*)-*β*-tyrosine, *i.e.* (*S*)-*O*-benzyl-*N*-*tert*-butoxycarbonyl-*β*-tyrosine to be used in peptide synthesis. Therefore, we report here a practical synthetic approach to protected (*S*)-*β*-tyrosine, which starts from inexpensive starting materials, proceeds in good yields and may be applicable to multi-gram operation. Starting from 4-benzyloxybenzaldehyde **1** only four steps are necessary to prepare protected (S)-*β*-tyrosine (Scheme 1).



Scheme 1. Reagents and conditions: a) $CH_2(COOH)_2$, CH_3COONH_4, EtOH, 5 h, 70%; b) MeOH, $SOCl_2$, 48 h, 85%; c) L-(+)-tartaric acid, MeOH, –25°C, 1–2 weeks, 48%; d) Boc_2O, Et_3N, MeOH r.t. 24 h, 93%; e) 0.2 M NaOH/THF, 24 h, r.t. 93%.

Condensation of 4-benzyloxybenzaldehyde with malonic acid and ammonium acetate in EtOH while heating under reflux, afforded racemic *β*-tyrosine, which was then esterified in usual way to yield the amino acid methyl ester hydrochloride **2**. The ester **2** after neutralization with aqueous $NaHCO_3$ was treated with 0.5 equivalent of L-(+)-tartaric acid dissolved in hot MeOH and kept at –25°C for 1–2 weeks. Recrystallization of diastereomeric salt **3** from MeOH yielded the single enantiomer **3** which then was converted into its Boc derivative in good yield. Comparison of optical rotation measured for **4** with the reported value given in the literature for (*R*)-*β*-tyrosine derivative, allowed to establish unequivocally the absolute configuration of **4** as *S*. Alkaline treatment of **4** with equimolar amount of 0.2 M NaOH in THF yielded the title compound **5** in high yield.

In conclusion, we have developed a new, mild and efficient synthetic procedure to protected (*S*)-*β*-tyrosine from inexpensive reagents. Moreover, the procedure described here can be easily adapted especially for larger scale work.

All reagents and solvents were of reagent grade and purchased from commercial sources. All melting points are uncorrected. The optical rotations were measured on a Autopol II Rudolph Research polarimeter. ^1H NMR spectra were recorded on a Gemini Varian 200 MHz or Unity Varian 500 MHz spectrometers using TMS as an internal standard. Microanalyses were performed on a Carlo Erba CHNS-O-EA1108 instrument.

Methyl (*R,S*)-3-amino-3-(4-benzyloxyphenyl)propanoate (2). A mixture containing 4-benzyloxybenzaldehyde 25 g, (0.12 mol), malonic acid 12.3 g, (0.12 mol), ammonium acetate 18.2 g (0.24 mol) in ethanol (60 ml) was refluxed for 5 h. The solid product was filtered off, washed with diethyl ether (50 ml) and methanol (50 ml) and purified by a Soxhlet extraction, to give 22.2 g of (*R,S*)-3-amino-3-(4-benzyloxyphenyl)propanoic acid as white crystals, which was suspended in methanol (300 ml), chilled to 0°C and thionyl chloride 13 ml (0.1 mol) was added. After 48 h the solvent was removed and the solid residue was crystallized from a mixture of methanol/ethyl ether to obtain 25 g (85%) of **2** as fine white crystals. M.p. 168–169°C. ^1H NMR (CD_3OD): 2.9 (m, 2), 3.7 (s, 3), 4.4 (m, 1), 4.7 (s, 2), 6.9–7.4 (br. m, 9). Anal. Calcd. for $C_{17}H_{20}NO_3Cl$: C, 63.45; H, 6.26; N, 4.35. Found: C, 63.35; H, 6.21; N, 4.22.

Methyl (*S*)-3-amino-3-(4-benzyloxyphenyl)propanoate L-tartaric acid salt (3). A solution of **2** 12.8 g (39.8 mmol) was dissolved in chloroform (300 ml) and washed with saturated $NaHCO_3$ solution (2×200 ml). The organic layer was dried over $MgSO_4$ and evaporated. The solid residue was dissolved in refluxing methanol (500 ml) and then hot solution of L-tartaric acid 3 g (19.9 mmol) in methanol (60 ml) was added. The clear solution was then kept at –25°C for 10 days. The crystals were filtered off, washed with cold methanol to give **3** (6.1 g, 84%). M.p. 174–176°C. $[\alpha]_D = +10.9$ (c 1.5, DMSO). The salt was recrystallized twice from methanol to furnish 4.7 g (57%) of **3** with m.p. 181–182°C. $[\alpha]_D = +16$ (c 1.5, DMSO). Anal. Calcd. for $C_{38}H_{44}N_2O_{12}$: C, 63.32; H, 6.15; N, 3.89. Found: C, 62.79; H, 6.32; N, 3.81.

Methyl (*S*)-3-tert-butoxycarbonylamino-3-(4-benzyloxyphenyl)propanoate (4). A solution of **3** 2.7 g, (6.3 mmol) in methanol (200 ml), was treated with triethylamine 1.8 ml (13 mmol) and a solution of di-tert-butyldicarbonate 1.4 g

(6.4 mmol) in methanol (20 ml) was added. The reaction mixture was stirred overnight, the solvent was evaporated and the solid residue was dissolved in ethyl acetate (150 ml). The organic layer was washed with water (3×20 ml), 0.1 M $KHSO_4$ solution (10 ml) dried over $MgSO_4$ and concentrated. Crystallization from ethyl acetate – hexane mixture yielded 2.25 g (93%) of **4**. M.p. 105–107°C. $[\alpha]_D = -50.7$ (c 1, MeOH). For (R) enantiomer, lit. [6] m.p. 111–113°C, $[\alpha]_D = +49.4$ (c 1, MeOH). ^{1}H NMR ($CDCl_3$): 1.4 (s, 9), 2.85 (m, 2), 3.6 (s, 3), 5.1 (s and m, 3), 5.35 (br. s, 1), 6.94 (d, 2), 7.22 (d, 2), 7.39 (m, 5). Anal. Calcd. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 67.97; H, 7.34; N, 3.63.

(*S*)-3-tert-Butoxycarbonylamino-3-(4-benzyloxyphenyl)propanoic acid (5). To a solution of **4** 1.6 g (4.2 mmol) in THF (20 ml) 0.2 M NaOH (22 ml) was added and left stirring for 24 at room temperature. The reaction mixture was concentrated to 20 ml, acidified with 0.1 M $KHSO_4$ to pH 2.5 and extracted with ethyl acetate (2×20 ml). The organic phase was washed with water and brine then dried over $MgSO_4$ and evaporated. The residue was crystallized from a mixture of ethyl acetate - hexane to yield 1.52 g (93%) of **5**. M.p. 141–142°C. $[\alpha]_D = -48$ (c 1, MeOH). ^{1}H NMR ($CDCl_3$): 1.2 (s, 9), 2.9 (m, 2), 5.1 (br. s, 3), 5.3 (br. s, 1), 6.95 (d, 2), 7.23 (d, 2), 7.38 (m, 5). Anal. Calcd. for $C_{21}H_{25}NO_5\ H_2O$: C, 64.78; H, 6.42; N, 3.59. Found: C, 64.64; H, 6.86; N, 3.50.

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