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Note

Novel Synthesis of Optically Active Bishomotyrosine Derivatives Using the Friedel-Crafts Reaction in Triflic Acid

Yuta MURAI, Yasuyuki HASHIDOKO, and Makoto HASHIMOTO†

Division of Applied Science, Graduate School of Agriculture, Hokkaido University, Kita 9, Nishi 9, Kita-ku, Sapporo 060-8589, Japan

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We report here a novel synthesis of optically active bishomotyrosine. The bishomotyrosine skeleton was constructed by using a Friedel-Crafts reaction between phenol and optically active *N*-Tfa-Glu(Cl)-OMe in triflic acid under the mild condition. Reduction and subsequent deprotection then afforded bishomotyrosine derivatives without any loss of optical purity.

Key words: bishomotyrosine; phenol; Friedel-Crafts reaction; Fries rearrangement; triflic acid

We developed on developing the synthesis of bishomotyrosine (bhTyr, 2-amino-5-(4-hydroxyphenyl)pentanoic acid), which has an elongated two-carbon chain, as we considered that this compound may have versatile use in enzyme structure-activity studies. bhTyr has been found in the active components of AM-toxin III,[1] which is a host-specific phytotoxic metabolite produced by *Alternaria mali*, that causes leaf spot disease in apples.[2–4] The bhTyr skeleton has also recently been found as a constituent in Largamides C, an unusual cyclic peptide from the marine cyanobacterium of *Oscillatoria* sp.[5] The synthesis of bhTyr was reported by Izumiya *et al.* over three decades ago[6] using a classical diethyl acetoamidomalonate amino acid method and enzymatic resolution to afford an optically pure (*S*)-form. However, the phenol hydroxyl group has to be protected by a methyl group to construct the amino acid skeleton, and then deprotected under acidic conditions in the last synthetic step. The enzyme resolution of acetyl-protected bhTyr afforded an optically pure (*S*)-form, but few reports of the synthesis and analysis of the (*R*)-form have been published. There are many reports of the synthesis of natural and unnatural amino acid derivatives; these methods include enzymatic resolution,[7] Suzuki coupling,[8] diastereoselective Michael addition[9] and catalytic asymmetric hydrogenation.[10] These methods require special reagents or precursors and the phenolic hydroxyl groups would not be expected to tolerate the synthetic conditions. Little success has been reported for the synthesis of elongated carbon in the side chain of Tyr without protecting the phenolic hydroxyl groups.[11] The establishments of synthetic methods for unprotected phenolics for amino acid derivatives could be very useful. We report in this paper the first synthetic methods for optically active bhTyr featuring the Friedel-Crafts reaction or Fries rearrangement with trifluoromethanesulfonic acid (triflic acid, TfOH), and a novel synthesis of the optically active regioisomer, 2-amino-5-(2-hydroxyphenyl)pentanoic acid (*ortho*-bishomotyrosine, *o*-bhTyr).

One of the retrosynthetic methods for of bhTyr is presented in Scheme 1. The reduction of the benzyl carbonyl group and deprotection of compound I would afford bhTyr. Compound I could be prepared by two methods: first, by the Friedel-Crafts acylation of phenol II and protected glutamic acid γ-acid chloride III: second, by Fries rearrangement of IV. The synthesis of IV follows from the same precursors as those for the direct synthesis of compound I. Although these retrosynthetic methods are very simple, the actual synthesis of bhTyr in this way has not been previously reported. One of the most important drawbacks is the solubility of α-amino acid derivatives in an organic solvent. The Friedel-Crafts reaction has generally proceeds by combined use of a Lewis acid and such organic solvents as CH_2Cl_2, CH_3NO_2 and nitrobenzene. Since the α-amino acid equivalents become insoluble in these organic solvents in the presence of a Lewis acid, the reaction mixture forms a suspension. The reaction has to be set up with excess aromatics as the reagents and solvent, and heated to improve the yield.[12] It is very difficult to apply a stoichiometric reaction with an acyl donor and acyl acceptor by using the previous method.

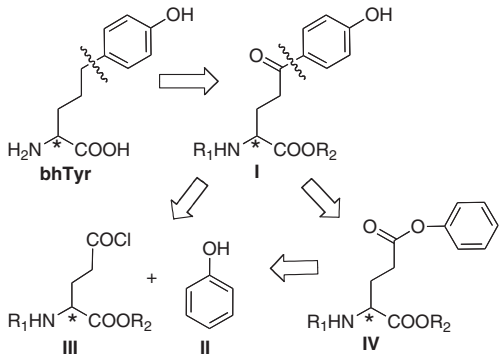
TfOH is known to be a super-acid and has been used as a catalyst in Friedel-Crafts acylation[13] and alkylation.[14] The reactions is most likely to proceed by the formation of trifluoromethanesulfonic–carboxylic anhydrides as an active species for the origin of acyl chloride,[15,16] and this anhydride then reacts to form aromatics. On the other hand, TfOH also has high solubility for α-amino acid derivatives at room temperature.[17–19] We therefore planned to apply a Friedel-Crafts reaction for the synthesis of bhTyr from phenol by using the this favorable reaction. It is noteworthy that the phenol has several reactions with acyl halides under acidic conditions. Several requirements were necessary for a successful reaction. *O*-Acylation and subsequently Fries rearrangement and Friedel-Crafts C-acylation has to be maintained for successful bhTyr synthesis. The protective groups of glutamic acid also have to be stable under acidic conditions. Trifluoroacetamide and a methyl ester were therefore respectively selected for N- and C-terminal protection.

O-Acylation of the phenol: *N*-Tfa-Glu(Cl)OMe **2** was prepared in an optically active form by using to the same

† To whom correspondence should be addressed. Tel/Fax: +81-11-706-3849; E-mail: hasimoto@abs.agr.hokudai.ac.jp

method as that in the literature.[20] Diluted TfOH in CH_3CN (5%) promoted *O*-acylation of phenol **1** with a stoichiometric amount of **2** at room temperature within an hour.[21] The phenyl ester of an amino acid has normally been prepared with carbodiimides as a promoter, although the conversion has not been quantitative. However, diluted triflic acid promoted the *O*-acylation reaction effectively under mild conditions.

Friedel-Crafts acylation of phenol and *N*-Tfa-Glu(Cl)-OMe: *N*-Tfa-Glu(Cl)-OMe **2**, which has higher reactivity than *N*-Tfa-glutamic anhydride, was subjected to direct C-acylation of phenol **1**. A reaction mixture of **2**, phenol **1** and $AlCl_3$ in CH_3NO_2 became heterogeneous, and no product could be detected even though the suspension was refluxed over night in preliminary experiments. However, the reaction mixture was homogeneous at room temperature in neat TfOH. The acylation was completed within an hour, and no hydrolyzed acyl chloride was detected by an NMR analysis of the crude reaction mixture. The product consisted of two regioisomers with *p*- and *o*-orientation of the hydroxyl group, the proportion being nearly 9:1 for the *p*- (**4**) and *o*- (**5**) isomer, respectively.[22]

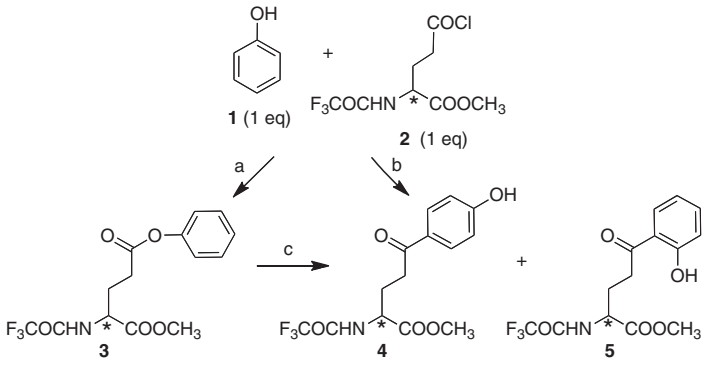


Scheme 1. Retrosynthesis of bhTyr.

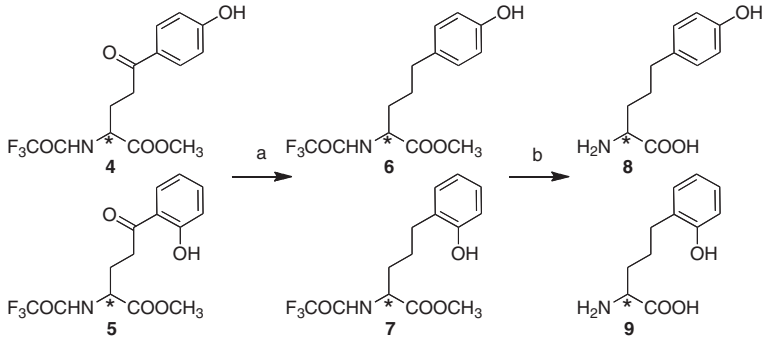
Fries rearrangement of *N*-Tfa-Glu(OBn)-OMe **3**: *N*-Tfa-Glu(OBn)-OMe **3** was subjected to Fries rearrangement by using neat TfOH at room temperature. The reaction rate was slightly lower than that by the Friedel-Crafts reaction, but the isolation yield and proportion of the regioisomer were almost the same when comparing the products of the Friedel-Crafts reaction and Fries rearrangements (Scheme 2).

The benzyl carbonyl groups of **4** and **5** were reduced with Pd/C under an H_2 atmosphere to respectively afford **6** and **7** in high yields.[23] Finally, both protective groups were removed under the acidic conditions to afford bhTyr **8**[24] and *o*-bhTyr **9**[25] in quantitative yields. Chiral HPLC (Chirobiotic T (Astec), 4.6 × 250 mm, eluted with 10% EtOH–H_2O, 1.0 mL/min flow rate, UV detection at 210 nm) and an optical rotation analysis indicated that synthetics **8** and **9** had maintained the optical purity of starting material *N*-Tfa-Glu(Cl)-OMe (Scheme 3).

TfOH had catalytic activity for the Friedel-Crafts reaction and Fries rearrangement, and high solubility for the α-amino acid derivatives. The character of TfOH promoted the synthesis of bhTyr derivatives from phenol



Scheme 2. Conditions for *O*-Acylation, Friedel-Crafts Acylation and Fries Rearrangement for Phenol **1** and *N*-Tfa-Glu(Cl)-OMe **2**.
Reagents and conditions: a) 5% TfOH–CH_3CN, room temperature, 30 min (*S*)- 96%, (*R*)- 91%; b) TfOH, room temperature, 1 h, (*S*)-**4** 91%, (*S*)-**5** 6%, and (*R*)-**4** 87%, and (*R*)-**5** 11%; c) TfOH, room temperature, 2 h, (*S*)-**4** 90%, (*S*)-**5** 5%, (*R*)-**4** 91%, and (*R*)-**5** 4%.



Scheme 3. Synthesis of bhTyr **8** and *o*-bhTyr **9**.
Reagents and conditions: a) H_2–Pd/C, room temperature, 1.5 and 7 h for **4** and **5**, respectively; (*S*)-**6** 98%, (*R*)-**6** 96%, (*S*)-**7** 85%, and (*R*)-**7** 88%; b) 6 N HCl, 80 °C, 6 h; (*S*)-**8** 99%, (*R*)-**8** 94%, (*S*)-**9** 99%, and (*R*)-**9** 99%.

and glutamic acid derivatives. The enzymatic resolutions of the racemate was not required, because the optical purity of Glu was maintained during the synthesis. These simple synthetic routes enabled us to report the first synthesis of (*R*)-bhTyr and both stereoisomers of *o*-bhTyr.

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21) (*S*)-**3**, $[\alpha]_D$ +26.0 (*c* 1.0, $CHCl_3$); (*R*)-**3**, $[\alpha]_D$ −25.5 (*c* 1.0, $CHCl_3$).
22) (*S*)-**4**, $[\alpha]_D$ −4.0 (*c* 1.0, MeOH); (*S*)-**5**, $[\alpha]_D$ +35.0 (*c* 1.0, $CHCl_3$); (*R*)-**4**, $[\alpha]_D$ +4.0 (*c* 1.0, MeOH); (*R*)-**5**, $[\alpha]_D$ −35.0 (*c* 1.0, $CHCl_3$).
23) (*S*)-**6**, $[\alpha]_D$ −11.0 (*c* 1.0, MeOH); (*R*)-**6**, $[\alpha]_D$ +11.0 (*c* 1.0, MeOH); (*S*)-**7**, $[\alpha]_D$ +37.0 (*c* 1.0, $CHCl_3$); (*R*)-**7**, $[\alpha]_D$ −37.0 (*c* 1.0, $CHCl_3$).
24) (*S*)-**8**, $[\alpha]_D$ +11.0 (*c* 1.0, H_2O), chiral HPLC $t_R = 6.76$ min, mp 218–220 °C; (*R*)-**8**, $[\alpha]_D$ −11.0 (*c* 1.0, H_2O), chiral HPLC $t_R = 8.77$ min, mp 217–219 °C.
25) (*S*)-**9**, $[\alpha]_D$ +5.5 (*c* 1.0, H_2O), chiral HPLC $t_R = 9.69$ min, mp 191–193 °C; (*R*)-**9**, $[\alpha]_D$ −5.0 (*c* 1.0, H_2O), chiral HPLC $t_R = 11.9$ min, mp 192–194 °C.