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Synthesis of β-Hydroxy-β-(fluoronitrophenyl)alanines: Vital Components in the Assembly of Biologically Active Cyclic Peptides

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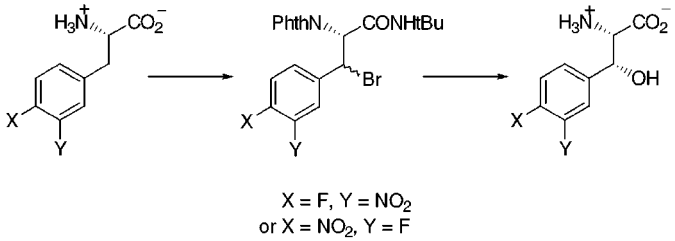
ABSTRACT



Numerous biologically active cyclic peptides, such as the antibiotic vancomycin, contain amino acid residues connected through side-chain biaryl or aryl–alkyl ether linkages. Nucleophilic aromatic substitution reactions have recently been shown to provide a general method for the formation of such ether linkages, and consequently the synthesis of functionalized fluoronitro-substituted aromatic amino acids is of great interest. Herein, a method for the stereospecific synthesis of 3-fluoro-4-nitro- and 4-fluoro-3-nitro-*threo*-β-hydroxyphenylalanine is described.

Recent advances in nucleophilic aromatic substitution (S_NAr) reactions of fluoronitro-substituted aromatic amino acids have shown the S_NAr methodology to be exceptionally useful for the synthesis of biologically active cyclic peptides containing biaryl or alkyl−aryl ether linkages.[1−5] In particular, 4-fluoro-3-nitro-β-hydroxyphenylalanine derivatives have been used extensively in the synthesis of vancomycin and its analogues.[2] Additionally, S_NAr reactions of 3-fluoro-4-nitrophenylalanine derivatives have been employed in the synthesis of cyclic peptides such as the cycloisodityrosine-containing peptides,[3] K-13,[4] and the cyclopeptide alkaloids.[5]

Several syntheses of 4-fluoro-3-nitro-β-hydroxyphenylalanine derivatives have been reported, all of which proceed via aldol-type reactions of glycine anion equivalents with 4-fluoro-3-nitrobenzaldehyde, utilizing either Evans[2a,6] or Schollkopf[3b] chiral auxiliaries or enzyme-mediated reactions.[7] Although synthesis of the (2*S*,3*S*)-isomer (*erythro*-isomer) of 4-fluoro-3-nitro-β-hydroxyphenylalanine using Evans' imide enolate methodology occurs with high diastereoselectivity and in high yield,[6a] synthesis of the (2*S*,3*R*)-isomer

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(*threo*-isomer) is often associated with low diastereoselectivity and poor yields.[3b,6b,8]

To date, no synthesis of 3-fluoro-4-nitro-β-hydroxyphenylalanine has been reported. Derivatives of 3-fluoro-4-nitro-β-hydroxyphenylalanine may provide an entry to the synthesis of 3′-bridged ethers of arylalanine derivatives, such as those present in the phomopsins,[9] thereby complementing the present methods for the preparation of 4′-bridged ethers such as those present in vancomycin.

A high-yielding, stereospecific route to both the 3-fluoro-4-nitro- and 4-fluoro-3-nitro-(2*S*,3*R*)-β-hydroxyphenylalanines, **10a** and **10b**, achieved by elaboration of the bromination−hydrolysis methodology developed by Easton and Hutton[10,11] is presented here.

Recent studies by the author[10] have shown that the hydrolysis of *N*-phthaloyl-β-bromoarylalanine methyl esters provides the corresponding β-hydroxyarylalanine derivatives, with the selectivity being controlled by facially selective stabilization of the intermediate benzylic cation by the neighboring ester moiety (Figure 1a). The introduction of

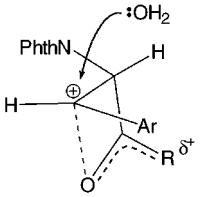
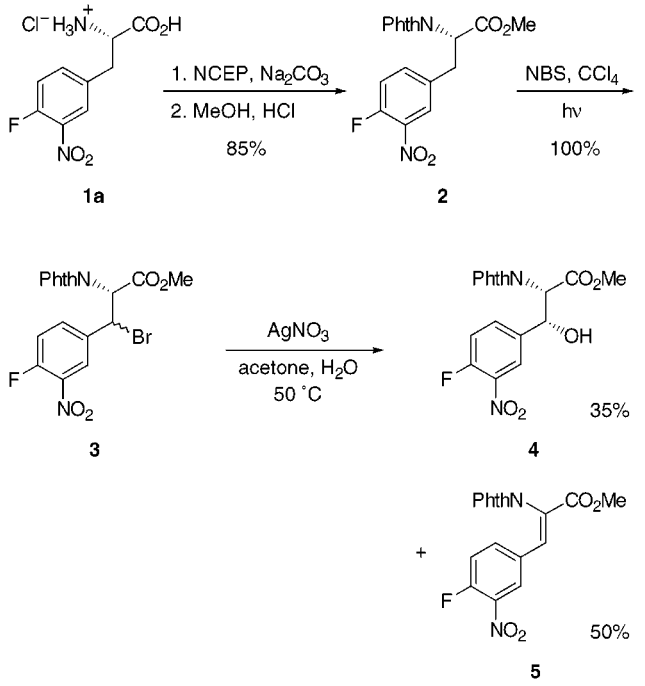


Figure 1. Facially selective stabilization of cationic intermediate through a neighboring group effect: (a) R = OMe; (b) R = NHtBu.

electron-withdrawing substituents onto the aromatic ring was shown to result in increased selectivity for the *threo*-isomer of the β-hydroxyarylalanine derivative. Consequently, it was anticipated that the presence of the electron-withdrawing fluoro and nitro groups in bromide **3** would furnish a highly diastereoselective conversion of **3** to the alcohol **4** under the reported conditions. Initial efforts toward the synthesis of β-hydroxy-β-(fluoronitrophenyl)alanine **10a** were therefore conducted following preparation of the protected fluoronitrophenylalanine derivative **2** from (*S*)-4-fluoro-3-nitrophenylalanine **1a**[12] under standard conditions.[10] Subsequent treatment of **2** with NBS gave a 1.1:1 mixture of the *threo*- and *erythro*-diastereomers, respectively, of the bromide **3**, in quantitative yield (Scheme 1).

Scheme 1

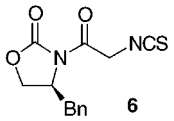


Treatment of the bromide **3** with silver nitrate in aqueous acetone under standard conditions (20 °C, 24 h) resulted in only 5% conversion of the bromide. Heating of the mixture at 50 °C for 3 days was required to drive the reaction to completion, with the reduced rate of reaction attributed to destabilization of the intermediate carbocation by the electron-withdrawing aryl substituents. Hydrolysis of the bromide **3** did indeed proceed with relatively high diastereoselectivity (95:5 *threo*:*erythro*); however, alcohol **4** was isolated in only moderate yield (35%). The (*Z*)-dehydroarylalanine derivative **5** was also isolated from the reaction mixture, in 50% yield, indicating that elimination of hydrogen bromide becomes competitive with production of the corresponding alcohol as sufficiently electron withdrawing aromatic substituents destabilize formation of the benzylic carbocation.

Reactions of the corresponding 3-fluoro-4-nitrophenylalanine derivatives were not attempted as the 3-fluoro and 4-nitro substituents are significantly more electron withdrawing than the corresponding 4-fluoro and 3-nitro substituents, suggesting that substitution at the benzylic center would be further disfavored.

Due to the prevalence of the elimination reaction of the bromoester **3**, a different carboxyl protecting group was employed. Amide groups have been shown to favor substitution reactions over elimination in similar systems, as well as furnishing the substitution products with very high stereoselectivity.[13] This is attributed to an increased magnitude of the neighboring group effect by the amide moiety (Figure 1b) compared to that for the corresponding ester

(8) Evans (ref 2a) reports that the stannous triflate mediated aldol reaction of **6** with 4-fluoro-3-nitrobenzaldehyde proceeds to give the corresponding *threo*-β-hydroxy amino acid derivative with 95:5 diastereoselectivity, whereas Zhu et al. (ref 6b) report that the identical reaction gives only moderate diastereoselectivity and chemical yield.



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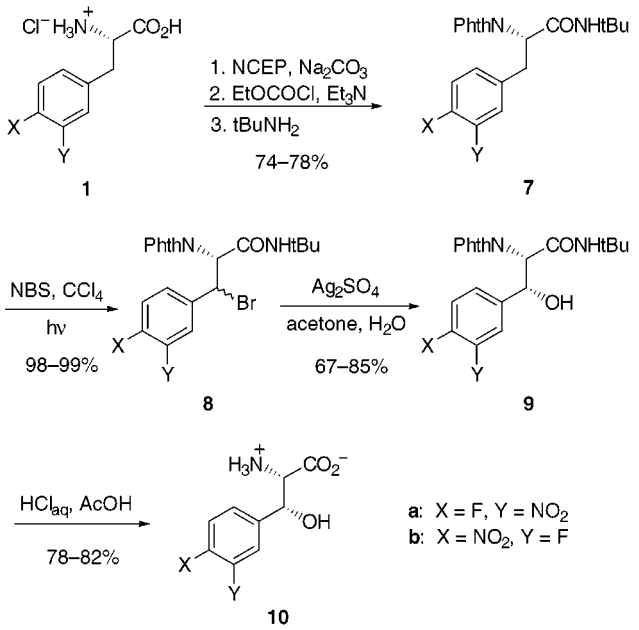
moiety (Figure 1a). The bromination−hydrolysis methodology was therefore attempted following protection of the carboxylic acid as its *N*-*tert*-butylamide derivative.

Introduction of the *N*-phthaloyl group was achieved by treatment of (*S*)-4-fluoro-3-nitrophenylalanine **1a** with *N*-carbethoxyphthalimide (NCEP). Subsequent treatment with ethyl chloroformate and triethylamine followed by *tert*-butylamine afforded the N^{α}-phthaloyl-*N*-*tert*-butylamide derivative **7a** in 78% yield (Scheme 2). Bromination of **7a**

Scheme 2



with NBS gave the bromide **8a** as a 1:1 mixture of diastereomers, in 99% yield. Treatment of the bromide **8a** with silver sulfate in aqueous acetone at 65 °C for 3 days gave the alcohol **9a** in 85% yield. Only the (2*S*,3*R*)-isomer of the alcohol **9a** was produced, and no product from elimination of HBr was detected, in accord with literature precedent.[13]

Subsequent deprotection of the β-hydroxyarylalanine derivative **9a** upon treatment with 5N HCl/acetic acid (2:1) gave the free amino acid, 4-fluoro-3-nitro-β-hydroxyphenylalanine **10a**, in 82% yield. This procedure therefore represents a rapid, stereospecific, and high-yielding conversion of the amino acid **1a** to the *threo*-β-hydroxyamino acid **10a**.

Similar conditions were employed in the preparation of 3-fluoro-4-nitro-β-hydroxyphenylalanine **10b**. Protection of (*S*)-3-fluoro-4-nitrophenylalanine **1b**[12] gave **7b** in 74% yield, and subsequent treatment with NBS gave the bromide **8b** (98%) as a 1:1 mixture of diastereomers (Scheme 2). More vigorous conditions were required to convert the bromide **8b** to the alcohol **9b** than for the corresponding reaction of the isomeric bromide **8a**, due to the increased electron-withdrawing nature of the 4-nitro and 3-fluoro substituents, relative to the 3-nitro and 4-fluoro substituents. Treatment of the bromide **8b** with silver sulfate in aqueous acetone at 85 °C for 4 days in a sealed vessel gave the alcohol **9b** in 59% yield, with recovery of the bromide **8b** in 12% yield. Longer reaction times and higher reaction temperatures did not result in increased yields of the alcohol **9b**, though lower amounts of starting bromide **8b** were recovered. Deprotection of the β-hydroxyarylalanine derivative **9b** gave 3-fluoro-4-nitro-β-hydroxyphenylalanine **10b** in 78% yield.

These procedures therefore provide for the rapid, stereospecific synthesis of β-hydroxy-β-(fluoronitrophenyl)-alanines **10a** and **10b** which are suitable for incorporation into syntheses of a variety of biologically active ether-bridged cyclic peptides such as vancomycin.

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Supporting Information Available: Full experimental details and characterization for compounds **2**−**5** and **7**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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