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Substituent Effects in the Stereoconvergent Synthesis of β-Hydroxyphenylalanine Derivatives

Craig A. Hutton

School of Chemistry, The University of Melbourne, Parkville, Victoria 3052, Australia

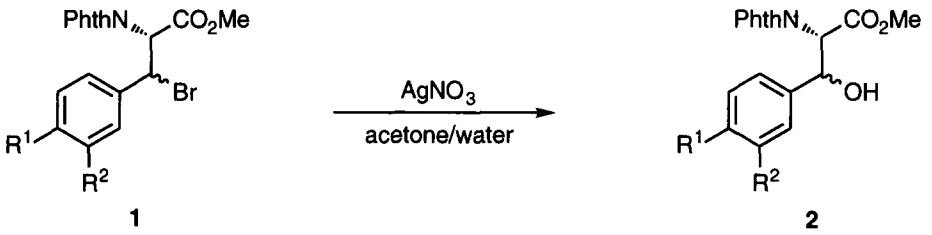
Abstract: The degree of stereoconvergence in the synthesis of β-hydroxyarylalanine derivatives from the corresponding β-bromoarylalanine derivatives is governed by the electronic nature of the aryl substituents, and controlled by facially selective stabilisation of the benzylic cation through the neighbouring ester moiety. Introduction of electron donating aryl substituents results in a decrease in selectivity, whereas electron withdrawing substituents induce an increase in selectivity for the *threo*-β-hydroxyarylalanine diastereomer. © 1997 Elsevier Science Ltd.

The synthesis of β-hydroxyarylalanine derivatives has attracted much recent interest due to their presence in a wide range of important biologically active peptides. Particular attention has been focussed on the synthesis of β-hydroxyarylalanine derivatives present in the vancomycin group,[1] and those present in cycloisodityrosine-containing peptides such as bouvardin.[2] While many elegant syntheses of β-hydroxyarylalanine compounds have been developed,[3] several problems have been encountered when applying these to the synthesis of natural products, such as low diastereoselectivity[1b,2a] and moderate chemical yields.[1b]

A short, stereoselective synthesis of β-hydroxyphenylalanine and β-hydroxytyrosine derivatives was developed by Easton and Hutton several years ago,[4] and recently this method has been exploited in the synthesis of the (2*S*,3*R*)-β-hydroxytyrosine residue present in vancomycin,[1c] and utilised in a synthesis of chloramphenicol.[5] This procedure provides selective formation of *threo*-β-hydroxyphenylalanine derivatives, and was rationalised by a facially selective attack of water on to the cationic intermediate.

The hydrolysis of a series of β-bromoarylalanine derivatives **1** is now presented, allowing the factors which determine the stereoselectivity of the conversion of β-bromoarylalanine derivatives **1** to the corresponding β-hydroxyarylalanine derivatives **2** to be resolved. It is hereby demonstrated that the level of stereoselectivity observed correlates with the degree of conformational restriction of the carbocation intermediate, which is ultimately determined by the electronic nature of the aryl substituents.

The protected arylalanine derivatives required for this study were prepared under standard conditions.[4-6] Subsequent treatment with *N*-bromosuccinimide in refluxing CCl_4 under irradiation by a 250W tungsten lamp for 1.5-6 h provided the corresponding β-bromoarylalanine derivatives **1a-i** (1:1 mixture of diastereomers) in 86-100% yield. Treatment of the bromides **1a-h** with silver nitrate in aqueous acetone for 16-96 h gave the β-hydroxyarylalanine derivatives **2a-h** in 69-93% yield (Scheme 1). Table 1 summarises the results of the hydrolysis reactions.



1 **2**

Scheme 1

Table 1: Hydrolysis reactions of bromoarylalanine derivatives **1** to give hydroxyarylalanine derivatives **2**.

entry	R^1	R^2	**2** *threo:erythro*
a	MeO	MeO	1:1
b	MeO	H	1.7:1
c	H	H	5:1
d	AcO	AcO	5:1
e	AcO	H	6:1
f	I	H	6:1
g	AcO	I	7:1
h	AcO	Cl	9:1[1c]
i	NO_2	H	-

Entry c shows that with no aryl substituents, hydrolysis of the β-bromophenylalanine derivative **1c** gives a 5:1 ratio of the *threo*- and *erythro*-diastereomers of the β-hydroxyphenylalanine derivative **2c**. Comparison of entries b and c indicates that incorporation of the strongly electron donating 4-methoxy substituent reduces the selectivity of the hydrolysis reaction substantially, from a *threo:erythro* ratio of 5:1 to 1.7:1. The stereoselectivity observed for the hydrolysis of the *O*-acetyltyrosine derivative **1e** is similar to that for the unsubstituted phenylalanine derivative **1c**. This is in accord with the inductive and resonance effects of the acetoxy group opposing each other, such that the 4-acetoxy substituent is close to electronically neutral.

Introduction of 3-oxy substituents results in a further decrease in selectivity (entries a & d compared to entries b & e, respectively). Whilst hydrolysis of the 3,4-diacetoxy derivative **1d** is only slightly less

selective than that of the 4-acetoxy derivative **1e**, hydrolysis of the 3,4-dimethoxy substituted compound **1a** occurs non-selectively, with the diastereomers of the β-hydroxydopa derivative **2a** produced in a 1:1 ratio. These results are in accord with literature precedent,[7] which reveals that although isolated 3-oxy substituents are electron withdrawing due to an inductive effect, 3,4-dimethoxy substituted aryl groups are more electron donating than the corresponding 4-methoxy analogues due to an electrostatic interaction between the 3-oxygen lone pairs and the 4-oxygen atom bearing a partial positive charge.

When electron withdrawing substituents are present, such as entries f-h, stereoselectivity of the hydrolysis reaction increases. The 4-iodo substituent is weakly electron withdrawing and results in a slight increase in selectivity (from 5:1 to 6:1 ratio of diastereomers) of the hydrolysis of compound **1f**, compared to that of **1c**. Strongly electron withdrawing substituents, such as the 3-iodo and 3-chloro substituents in entries g and h, result in a further increase in selectivity. Attempted hydrolysis of the 4-nitrophenylalanine derivative **1i** under standard reaction conditions gives no reaction. More forcing conditions result only in elimination of HBr to give the corresponding dehydroamino acid derivative.[5]

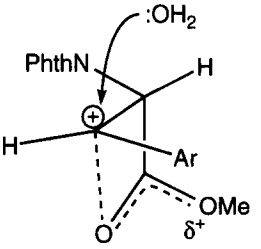


Figure 1. Conformationally restricted cation intermediate in the stereoselective hydrolysis of **1** to give **2**.

These results demonstrate that the stereoselectivity of the hydrolysis of β-bromoarylalanine derivatives **1** is determined by the electronic nature of the aryl substituents, and suggest that stabilisation of the benzylic cation, when not fulfilled by the aryl moiety, is forced to occur through participation of the neighbouring ester group. When the aryl substituents are strongly electron donating, the benzylic cation is adequately stabilised by delocalisation of the positive charge through the aryl substituents. The cationic intermediate is not conformationally restricted, and attack of water occurs with equal efficacy from both faces to give a mixture of *threo*- and *erythro*-diastereomers of the corresponding β-hydroxyarylalanine derivative **2**. Conversely, without delocalisation of the positive charge through the aryl substituents, significant neighbouring group participation from the ester moiety is necessary to stabilise the carbocation. This 1,4-stabilisation (Figure 1) locks the cationic intermediate into a conformation with the bulky phthalimido and aryl groups in a near antiperiplanar relationship. Water attacks the intermediate preferentially from one face to give the *threo*-β-hydroxyarylalanine derivative selectively. As the aryl substituents become progressively more electron withdrawing in nature, the amount of neighbouring group participation (and consequently conformational restriction) increases in order to sustain the electron demand of the carbocation, and as a result the stereoselectivity increases.

The electronic nature of aryl substituents has previously been shown to effect the stereoselectivity of benzylic substitution reactions,[8] and has been attributed to a variation of the cationic nature, or S_N1 *vs.* S_N2 character, of the reaction pathway. However, the increased selectivity observed for the hydrolysis of bromides **1** with electron withdrawing substituents cannot be due to increased S_N2 character of the substitution reaction. Conversely, the diastereoconvergent production of *threo*-β-hydroxyarylalanine derivatives **2** from a mixture of diastereomers of the corresponding β-bromoarylalanine derivatives **1** infers that an S_N1 process is occurring. In this case, the electron demand of the carbocation influences the degree of conformational restriction of the cationic intermediate, and ultimately governs the stereoselectivity of the substitution reaction.

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