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Stereocontrolled Synthesis of β-Hydroxyphenylalanine and β-Hydroxytyrosine Derivatives

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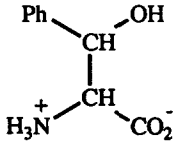
Abstract: Side-chain bromination of *N*-phthaloyl-(*S*)-phenylalanine and tyrosine derivatives, followed by treatment of the product bromides with silver nitrate in aqueous acetone, affords the corresponding (2*S*,3*R*)-β-hydroxy-α-amino acids, enantiospecifically and diastereoselectively. The diastereoselectivity depends on the carboxyl protecting group. *tert*-Butyl esters display greater stereoselectivity than the corresponding methyl esters, presumably as a result of a steric effect, while *N*-*tert*-butylamides react diastereospecifically due to a combination of steric and electronic effects.

INTRODUCTION

β-Hydroxyphenylalanine **1** and β-hydroxytyrosine **2** are important naturally occurring amino acids. They have been implicated as precursors in the biosynthesis of the hypertensive agents adrenalin and noradrenalin,[1] and of the antibiotic chloramphenicol,[2] and as components of peptidases[3] and esterases.[4] They have also been identified as components of biologically active cyclic peptides. As examples, vancomycin contains two residues of β-hydroxytyrosine **2**, one with the (2*S*,3*R*)-stereochemistry and the other with the (2*R*,3*R*)-stereochemistry,[5] lysobactin[6] contains β-hydroxyphenylalanine **1** of the (2*S*,3*R*)-stereochemistry, while phomopsin A[7] contains β-hydroxyphenylalanine **1** and bouvardin[8] contains a residue of β-hydroxytyrosine **2**, each with the (2*S*,3*S*)-stereochemistry. Hydroxy amino acids are also of interest as enzyme inhibitors.[9-11] For example, β-hydroxyphenylalanine **1** has been shown to inhibit *Neisseria gonorrhoeae* bacterial strains[10] and the lactose operon in *Escherichia coli*.[11]



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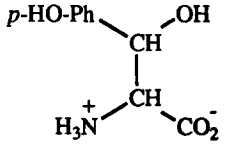

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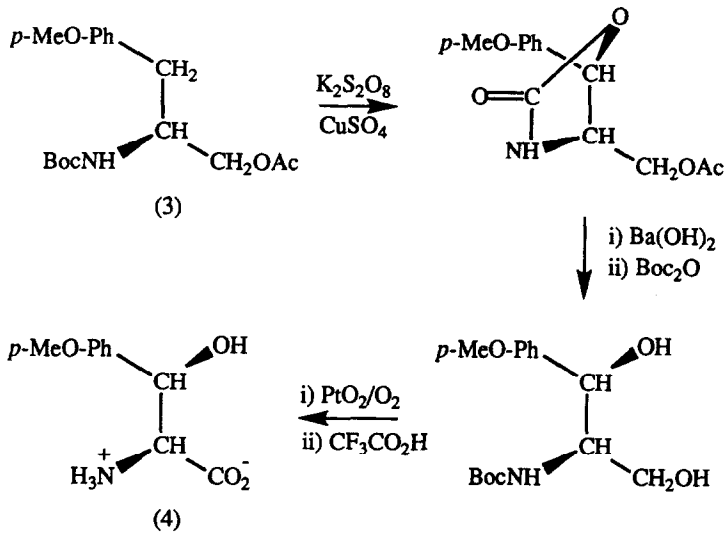
As a consequence of their biochemical activity, there is considerable interest in efficient routes for the stereocontrolled synthesis of the hydroxy amino acids **1** and **2**, and related compounds. Many asymmetric syntheses of β-hydroxy amino acids *via* condensation of glycine equivalents with aldehydes have been reported.[12-15] General and versatile methods have been developed by Schöllkopf *et al.*,[13] by Seebach and co-workers[14] and by Evans and Weber.[15] Although these procedures give products of high enantiomeric excess,



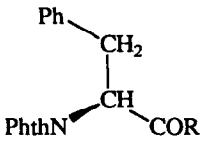
Scheme 1

there remains a strong demand for compounds which are enantiomerically pure. A method for the enantiospecific synthesis of β-hydroxy-α-amino acids from D-glucose has been reported by Rao *et al.*,[16] but the procedure involves many steps. Shimamoto and Ohfune[17] have developed a novel synthesis of (2*S*,3*R*)-β-hydroxy-*O*-methyltyrosine **4**, by direct benzylic oxidation of the *N*-*tert*-butoxycarbonyltyrosinol derivative **3** (Scheme 1). This procedure is limited by its lack of generality, however, with attempts to synthesize the (2*S*,3*R*)-isomer of β-hydroxyphenylalanine **1** *via* an analogous pathway being unsuccessful.[17]

Recently we reported[18] preliminary details of a complementary method for the enantiospecific and diastereoselective synthesis of β-hydroxy-α-amino acids, which involved direct side-chain bromination of amino acid derivatives[19,20] followed by treatment of the product bromides with aqueous silver nitrate. For example, the phenylalanine derivative **5a** gave a 1:1 mixture of the diastereomeric bromides **6a** and **7a**, and that mixture gave a 5:1 mixture of the (2*S*,3*R*)-hydroxyphenylalanine derivative **8a** and the (2*S*,3*S*)-diastereomer **9a**. We now report our investigation of the origin of the stereoselectivity of the hydrolysis, together with full details of our earlier work. We also describe an unusual substituent effect which results in the enantiospecific and diastereospecific synthesis of derivatives of β-hydroxyphenylalanine and β-hydroxytyrosine.

RESULTS AND DISCUSSION

As previously reported,[20,21] treatment of the phenylalaninamide **5c** with *N*-bromosuccinimide gave a 1:1 mixture of the diastereomeric bromides **6c** and **7c**, which were separated by fractional crystallization. The absolute stereochemistry of the bromides **6c** and **7c** is predetermined by that of the phenylalanine derivative **5c**, while their relative stereochemistry has been determined previously, for each of the corresponding racemates, through their *anti*-elimination to dehydro amino acid derivatives on treatment with potassium fluoride.[21]



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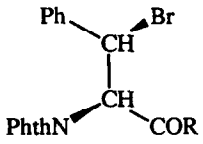

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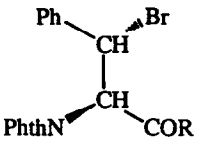

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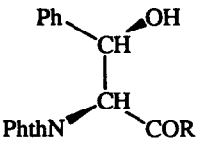

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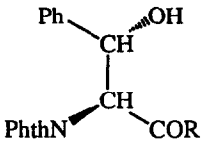

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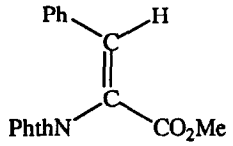

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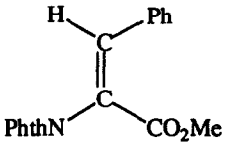
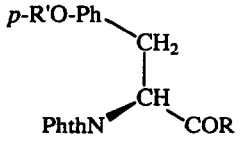


(11)

a) R = OMe
b) R = $OCMe_3$
c) R = $NHCMe_3$

Bromination of the ester **5a** gave a 1:1 mixture of the bromides **6a** and **7a**, which were separated by fractional crystallization. The relative stereochemistry of each of the bromo esters **6a** and **7a** was determined using the procedure reported[21] for determining the stereochemistry of the corresponding bromo amides **6c** and **7c**. Treatment of the bromo ester **6a** with potassium fluoride produced the (*Z*)-dehydrophenylalanine derivative **10** in 88% yield, but none of the (*E*)-isomer **11**. The structure and stereochemistry of the (*Z*)-alkene **10** was confirmed through X-ray crystallographic analysis.[22] Treatment of the bromide **7a** with potassium fluoride gave a 2:1 mixture of the (*E*)-dehydrophenylalanine derivative **11** and the (*Z*)-alkene **10**. The stereochemistry of the (*E*)-alkene **11** was confirmed by comparison of its ^{1}H NMR spectrum with that of the (*Z*)-isomer **10**, where the signal due to the vinylic proton of the (*E*)-alkene **11** occurred 0.9 ppm upfield from that of the (*Z*)-isomer **10**.[21,23] Presumably the bromides **6a** and **7a** undergo selective *anti*-elimination, on which basis the bromide **6a** that gave only the (*Z*)-alkene **10** can be assigned the (2*R*,3*R*)-stereochemistry, while the bromide **7a** which gave mainly the (*E*)-alkene **11** can be assigned the (2*R*,3*S*)-stereochemistry. Note that the Cahn-Ingold-Prelog designation at the α-carbon of the bromides **6a** and **7a** is reversed by comparison with that of the precursor **5a**, due to the change in the priority of substituents.

The *tert*-butyl ester **5b** and the tyrosine derivatives **12a** and **12b** reacted with *N*-bromosuccinimide to give the corresponding benzylic bromides **6b** and **7b**, **13a** and **14a**, and **13b** and **14b**. The diastereomeric bromophenylalanine derivatives **6b** and **7b** were separated by fractional crystallization. Although the diastereomeric tyrosine derivatives **13a** and **14a**, and **13b** and **14b**, were not completely separated, due to their instability, samples enriched in each stereoisomer were obtained by chromatography. The relative stereochemistry of the bromides **6b**, **7b**, **13a,b** and **14a,b** was determined by comparison of their ^{1}H NMR spectra with those of the bromides **6a,c** and **7a,c** (Table 1), which follow a general trend. The signals corresponding to the carboxyl protecting groups occur at lower chemical shift for the (2*R*,3*R*)-diastereomers **6a-c** and **13a,b** than for the corresponding (2*R*,3*S*)-diastereomers **7a-c** and **14a,b**. Also, the (2*R*,3*R*)-stereoisomers **6a-c** and **13a,b** exhibit the β-proton signal at higher chemical shift, the α-proton signal at lower chemical shift, and a larger coupling constant between the α- and β-protons, than for the corresponding (2*R*,3*S*)-diastereomers **7a-c** and **14a,b**. The cause of these effects may be explained by considering, as an example, the preferred conformation of each of the bromides **6a** and **7a** (Figure 1). It can be seen that with the



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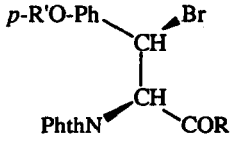

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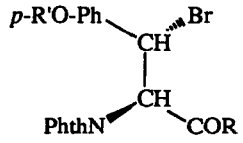

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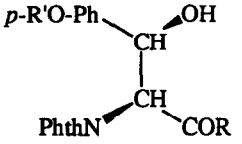

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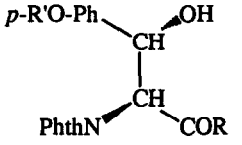


(16)

a) R = OMe, R' = Ac
b) R = $NHCMe_3$, R' = Ac
c) R = OMe, R' = H
d) R = $NHCMe_3$, R' = H

(2*R*,3*R*)-isomer **6a**, the phenyl group is situated close to the ester moiety, and the shielding effect of the phenyl group may explain the lower chemical shift of the signal due to the ester group protons. In the case of the (2*R*,3*S*)-bromide **7a**, π,π-stacking between the phthalimido and phenyl groups would cause rotation about the Cα-Cβ bond, such that the dihedral angle between the α- and β-protons would be less than 180°, thereby explaining the lower coupling constant observed between the α- and β-protons for the (2*R*,3*S*)-diastereomer **7a** than for the (2*R*,3*R*)-diastereomer **6a**.[24]

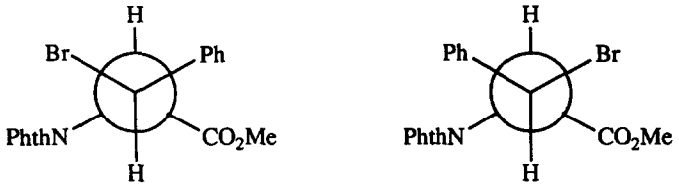
The reactions of the amino acid derivatives **5a-c** and **12a,b** to give the corresponding bromides **6a-c** and **7a-c**, and **13a,b** and **14a,b** occur without discernible asymmetric induction, presumably as a result of the low activation energy for halogen transfer to the intermediate benzylic radicals.[25]

Treatment of the (2*R*,3*R*)-bromophenylalanine derivative **6a** with silver nitrate in acetone/water[26] gave a

Table 1. ^{1}H NMR Spectral Data of the Bromides **6a-c**, **7a-c**, **13a,b** and **14a,b**.

Compound	Stereochemistry	Chemical shift (δ) / *J* (Hz)				
		α-H	β-H	$J_{\alpha,\beta}$	Carboxyl protecting group	OAc
6a	2*R*,3*R*	5.42	5.95	11.2	3.50	-
7a	2*R*,3*S*	5.55[a]	5.92[a]	10.5	3.80	-
6b	2*R*,3*R*	5.47	6.06	11.4	1.16	-
7b	2*R*,3*S*	5.49	5.85	10.4	1.48	-
6c	2*R*,3*R*	5.28	6.25	11.8	1.03	-
7c	2*R*,3*S*	5.32	6.04	11.4	1.43	-
13a	2*R*,3*R*	5.46	6.03	11.2	3.56	2.30
14a	2*R*,3*S*	5.56	5.93	10.4	3.81	2.19
13b	2*R*,3*R*	5.17	6.22	11.8	1.05	2.31
14b	2*R*,3*S*	5.30	6.08	11.5	1.38	2.20

[a]Assigned with the aid of proton-carbon heterocorrelation NMR spectroscopy.

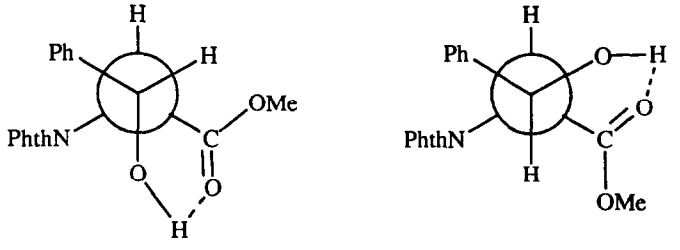


(6a) (7a)

Figure 1. Preferred Conformation of each of the Bromides **6a** and **7a**.

2:1 mixture of the (2*S*,3*R*)-β-hydroxyphenylalanine derivative **8a** and the (2*S*,3*S*)-diastereomer **9a**. The ratio of the diastereomers **8a** and **9a** was determined through analysis of the ^{1}H NMR spectrum of the crude reaction mixture. Recrystallization of the crude product gave the (2*S*,3*R*)-β-hydroxyphenylalanine derivative **8a**, in 75% yield, the stereochemistry of which was determined using X-ray crystallographic analysis.[27] Purification of the (2*S*,3*S*)-alcohol **9a** in the recrystallization mother liquor was achieved using HPLC. Treatment of the (2*R*,3*S*)-bromide **7a** under the same conditions as described for the hydrolysis of the (2*R*,3*R*)-bromide **6a** gave only the (2*S*,3*R*)-hydroxyphenylalanine derivative **8a**, in 93% yield.

The ^{1}H NMR spectra of the hydroxyphenylalanine derivatives **8a** and **9a** follow a general trend displayed in the spectra of the alcohols **8a-c**, **9a-c**, **15a,c** and **16a,c**, described herein (Table 2). The chemical shifts of the signals due to the α– and β–protons and the carboxyl protecting groups of the (2*S*,3*R*)-isomers **8a-c** and **15a,c** are significantly higher than those of the corresponding (2*S*,3*S*)-isomers **9a-c** and **16a,c**. Also, the (2*S*,3*R*)-isomers **8a-c** and **15a,c** each exhibit a smaller coupling constant between their α- and β-protons than is observed for the corresponding (2*S*,3*S*)-isomers **9a-c** and **16a,c**. The correlation of the coupling constants with the stereochemistry may be attributed to the alcohols **8a-c**, **9a-c**, **15a,c** and **16a,c** adopting hydrogen-bonded conformations, as shown in Figure 2 for the phenylalanine derivatives **8a** and **9a**. The dihedral angle between the α- and β-protons of the (2*S*,3*R*)-isomers **8a-c** and **15a,c** in these conformations would be approximately 60°, whereas that angle would be approximately 180° for the (2*S*,3*S*)-isomers **9a-c** and **16a,c**, hence the coupling constant between the α- and β-protons of each of the (2*S*,3*R*)-isomers **8a-c** and **15a,c** would be smaller than that observed for each of the corresponding (2*S*,3*S*)-isomers **9a-c** and **16a,c**.



(8a) (9a)

Figure 2. Hydrogen-bonded Conformation of each of the Alcohols **8a** and **9a**.

Table 2. ^{1}H NMR Spectral Data of the Alcohols **8a-c**, **9a-c**, **15a-d** and **16a,c**.

Compound	Stereochemistry	Chemical shift (δ) / *J* (Hz)				
		α-H	β-H	$J_{\alpha,\beta}$	Carboxyl protecting group	OAc
8a	2*S*,3*R*	5.51	5.71	4.6	3.86	-
9a	2*S*,3*S*	5.02	5.52	8.4	3.79	-
8b	2*S*,3*R*	5.44	5.67	4.6	1.52	-
9b	2*S*,3*S*	4.95	5.49	8.0	1.28	-
8c	2*S*,3*R*	5.11	5.63	6.2	1.30	-
9c	2*S*,3*S*	4.61	5.39	8.3	1.15	-
15a	2*S*,3*R*	5.48	5.67	5.0	3.78	2.19
16a	2*S*,3*S*	5.02	5.54	8.2	3.74	2.17
15b	2*S*,3*R*	5.08	5.63	6.3	1.31	2.26
15c	2*S*,3*R*	5.44	5.64	4.8	3.85	-
16c	2*S*,3*S*	4.97	5.49	8.6	3.78	-
15d	2*S*,3*R*	5.11	5.62	6.9	1.27	-

The stereochemical courses of the substitution reactions of the bromides **6a** and **7a** indicate that they occur *via* different mechanisms. It appears that the (2*R*,3*R*)-bromide **6a** reacts *via* the carbocation **17a**, while the (2*R*,3*S*)-bromide **7a** undergoes an S_N2 reaction. This variation in the mechanisms and the stereochemical courses of the reactions can be rationalized by considering the preferred conformation of each of the bromides **6a** and **7a** (Figure 1). In the preferred conformation of the (2*R*,3*R*)-bromide **6a**, the phenyl and β-hydrogen substituents are already in the orientation required to form the most stable conformation of the carbocation **17a** (Figure 3). This orientation also allows for delocalization of the developing positive charge by the ester carbonyl group, as the ester moiety is situated in the plane of the developing unoccupied orbital. S_N2 substitution is disfavored for this conformation of the bromide **6a**, as the ester moiety blocks attack of water from behind the carbon-bromine bond. For these reasons, the carbocation **17a** forms, with subsequent nucleophilic attack of water preferentially from the less hindered face, opposite the ester group, giving rise to the alcohols **8a** and **9a** in a 2:1 ratio. In its preferred conformation, the (2*R*,3*S*)-bromide **7a** is not aligned to lead directly to the most stable conformation of the carbocation **17a**. In fact, the bromide **7a** can only react to give the carbocation **17a** either initially in a less stable conformation or without delocalization of the developing positive charge by the ester carbonyl group. These processes are energetically less favourable than the reaction of the bromide **6a** to give the carbocation **17a** and, instead, the bromide **7a** reacts *via* the S_N2 pathway with inversion of configuration.

Subsequent hydrolyses were performed using 1:1 mixtures of the diastereomeric bromides **6b,c** and **7b,c**, and **13a,b** and **14a,b**, thereby avoiding their separation. For comparison, reaction of a 1:1 mixture of the bromides **6a** and **7a** gave the alcohols **8a** and **9a** in the expected 5:1 ratio. Initially, the reaction of the *tert*-butyl esters **6b** and **7b** was examined, because it was envisaged that the more bulky ester group would increase the stereoselectivity of the reaction. In the event, the alcohols **8b** and **9b** were formed in an 8:1 ratio, as

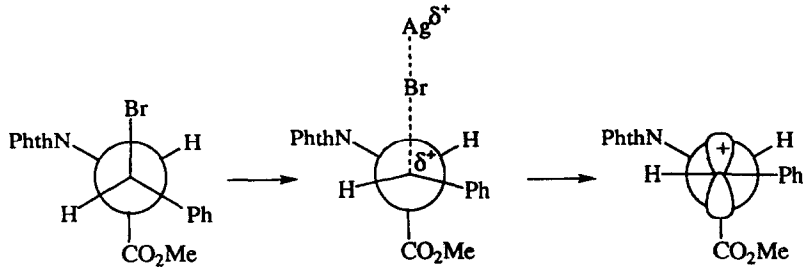
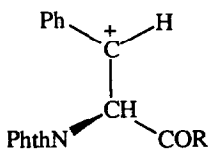


Figure 3. Direct Formation of the Most Stable Conformation of the Carbocation **17a** from the Preferred Conformation of the Bromide **6a**.

determined through analysis of the ^1H NMR spectrum of the crude reaction mixture. The (2*S*,3*R*)-isomer **8b** was isolated in 81% yield, after recrystallization of the crude product. Presumably, by analogy with the reaction of the methyl ester **7a**, the reaction of the (2*R*,3*S*)-bromide **7b** occurs with complete inversion of stereochemistry. The reaction of the (2*R*,3*R*)-bromide **6b** must therefore occur to give an approximately 3.5:1 ratio of the alcohols **8a** and **9a**. The increased selectivity of the reaction of the *tert*-butyl ester **6b**, compared to that of the methyl ester **6a**, can be attributed to the relative extent of the steric effects of the respective ester moieties, blocking one face of each of the corresponding intermediate carbocations **17b** and **17a**.

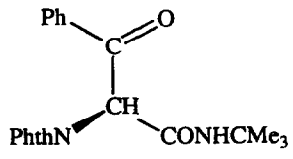
Treatment of a mixture of the phenylalaninamides **6c** and **7c** with silver nitrate in acetone/water gave only the (2*S*,3*R*)-alcohol **8c**, in 93% yield. In order to determine that none of the stereoisomer **9c** was produced in this reaction, an authentic sample was prepared. Oxidation of the alcohol **8c** with Jones reagent[28] gave the ketone **18**, which was reduced with sodium borohydride in ethanol to give a 1.2:1 mixture of the alcohols **8c** and **9c**. It is possible that some racemization occurred during this oxidation-reduction sequence, but the absolute stereochemistry of the alcohol **9c** is of no consequence in determining the diastereoselectivity of the reaction of the bromides **6c** and **7c**. When the ^1H NMR spectrum of the crude reaction mixture obtained from the hydrolysis of the bromides **6c** and **7c** was compared with that of the alcohol **9c**, the former showed no signal corresponding to the *tert*-butyl group of the alcohol **9c**, even though the ^{13}C satellite peaks of that signal for the alcohol **8c** (J_{CH} = 126.7 Hz) were clearly visible, with a signal to noise ratio of greater than 10:1. On that basis the hydrolysis of the mixture of the bromides **6c** and **7c** gave the (2*S*,3*R*)-alcohol **8c** in >99.9% diastereomeric excess.

The diastereoselectivity of the hydrolysis of the mixture of the bromo amides **6c** and **7c** is at least 100-fold greater than that for the reaction of the bromo esters **6b** and **7b**. This may be attributed to the relative



(17)

a) R = OMe
b) R = $OCMe_3$
c) R = $NHCMe_3$



(18)

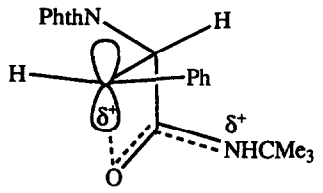


Figure 4. Stabilization of the Carbocation **17c** by the Amido Substituent.

extent of conformational preference of the carbocations **17b** and **17c**. A carbonyl oxygen of an amido group is approximately six orders of magnitude more basic than that of an ester,[29] therefore the extent of interaction of the amido substituent with the unoccupied orbital of the carbocation **17c** (Figure 4) is likely to be much greater than the analogous interaction of the ester group in the carbocation **17b**. This will result in a greater conformational preference of the carbocation **17c** and a greater tendency for approach of the nucleophile to the face of the carbocation **17c** opposite to that through which the amido group stabilization occurs.

A substituent effect analogous to that observed in the reactions of the phenylalanine derivatives **6a,c** and **7a,c** was also observed with the corresponding tyrosine derivatives **13a,b** and **14a,b**. Treatment of a 1:1 mixture of the diastereomeric esters **13a** and **14a** under the standard hydrolysis conditions gave a 6:1 mixture of the alcohols **15a** and **16a**, in 86% yield. The hydroxytyrosine derivatives **15a** and **16a** were unstable and deacetylated slowly on exposure to moisture. Hence, the crude product was completely deacetylated by treatment with a catalytic amount of *p*-toluenesulfonic acid in methanol, to give a 6:1 ratio of the alcohols **15c** and **16c**, from which the (2*S*,3*R*)-isomer **15c** was isolated, in 72% yield, by recrystallization. HPLC of the mother liquor afforded a pure sample of the (2*S*,3*S*)-alcohol **16c**. Reaction of a 1:1 mixture of the tyrosinamides **13b** and **14b** gave only the (2*S*,3*R*)-stereoisomer **15b**, in 88% yield, which on deacetylation afforded only the alcohol **15d**, in 93% yield. Within the limits of detection using ^{1}H NMR spectroscopy, the reaction of the mixture of the bromides **13b** and **14b** was diastereospecific, as there was no evidence of formation of either of the alcohols **16b** or **16d**.

The reactions of the amino acid derivatives **5a-c** and **12a,b** with *N*-bromosuccinimide, and the subsequent treatment of the product bromides **6a-c**, **7a-c**, **13a,b** and **14a,b** with silver nitrate in aqueous acetone, described above, exemplify an efficient route for the stereocontrolled synthesis of hydroxy amino acid derivatives. The alcohols **8a** and **8c** were also used to prepare the (2*S*,3*R*)-stereoisomer of the corresponding free amino acid **1**. Treatment of the ester **8a** with hydrazine to remove the phthaloyl group,[30] followed by acid-catalysed hydrolysis of the ester moiety, gave the hydrochloride salt of the (2*S*,3*R*)-stereoisomer of β-hydroxyphenylalanine **1**. Alternatively, the salt was obtained by treatment of the ester **8a** with a 2:1 mixture of 6N hydrochloric acid and glacial acetic acid, at reflux. In each case the free amino acid was prepared from the hydrochloride salt by crystallization from aniline in ethanol. Treatment of the amide **8c** with a 2:1 mixture of 6N hydrochloric acid and glacial acetic acid, at reflux, followed by crystallization of the crude product from aniline in ethanol, also gave the corresponding free amino acid, in 78% yield. The relative and absolute stereochemistry of samples of the free amino acid, prepared from the amino acid derivatives **8a** and **8c**, was established by comparison of their ^{1}H NMR spectra[31] and optical rotation properties[32] with literature data. This confirmed that the syntheses of the (2*S*,3*R*)-diastereomer of the alcohol **1** from (*S*)-phenylalanine occurred with

retention of chirality at the α-position. It follows that identical procedures could be used in the elaboration of (*R*)-amino acids. Thus, the procedures described above are suitable for the enantiospecific and diastereospecific synthesis of β-hydroxy-α-amino acids and their derivatives, particularly the (2*S*,3*R*)- and (2*R*,3*S*)-stereoisomers.

EXPERIMENTAL

General. General experimental details have been reported previously.[20] ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, in deuteriochloroform unless otherwise stated. Infrared spectra were recorded as solutions in dichloromethane. Organic solutions were dried by stirring over anhydrous magnesium sulfate.

(*S*)-Phenylalanine and (*S*)-tyrosine were purchased from Sigma Chemical Co., and used to prepare the amino acid derivatives **5a-c** and **12a,b**, respectively, using standard procedures.[20,21,33]

Bromination of the Amino Acid Derivatives 5a-c and 12a,b. Reactions of the amino acid derivatives **5a-c** and **12a,b** with *N*-bromosuccinimide were carried out as described previously[20,21] for the bromination of the racemate of the amide **5c**, except that the reactions of the esters **5a,b** and **12a** were performed in carbon tetrachloride, instead of the 3:1 mixture of carbon tetrachloride/dichloromethane that was used with the amides **5c** and **12b**. The reactions gave 1:1 mixtures of the diastereomeric bromides **6a-c** and **7a-c**, and **13a,b** and **14a,b**, which were separated by fractional crystallization in the cases of the phenylalanine derivatives **6a-c** and **7a-c**, from hexane/dichloromethane in the cases of **6a,b** and **7a,b**, and from hexane/2-propanol in the case of **6c** and **7c**.

(2*R*,3*R*)-3-Bromo-*N*-phthaloylphenylalanine Methyl Ester (6a): 42%; mp 142-143 °C; ν_{max} 1778, 1755, 1709, 708 cm^{-1}; MS (EI) *m/e* 389 and 387 (M^+, 6%), 330 (8), 328 (8), 308 (65), 307 (18), 276 (89), 249 (92), 248 (100), 242 (32), 240 (32), 218 (59), 190 (46), 162 (39), 130 (22), 105 (46), 103 (28), 77 (17). Anal. Calcd for $C_{18}H_{14}BrNO_4$: C, 55.8; H, 3.7; N, 3.6. Found: C, 55.7; H, 3.7; N, 3.6.

(2*R*,3*S*)-3-Bromo-*N*-phthaloylphenylalanine Methyl Ester (7a): 40%; mp 121-122 °C; ^{13}C NMR δ 47.6, 53.1, 57.0, 123.6, 128.1, 128.6, 128.9, 130.9, 134.3, 137.1, 166.3, 167.2; ν_{max} 1774, 1758, 1718, 727 cm^{-1}; MS (EI) *m/e* 389 and 387 (M^+, 2%), 330 (5), 328 (5), 308 (32), 276 (59), 249 (79), 248 (85), 242 (24), 240 (24), 218 (56), 190 (62), 169 (11), 167 (11), 161 (26), 130 (33), 104 (82), 102 (64), 76 (100). Anal. Calcd for $C_{18}H_{14}BrNO_4$: C, 55.8; H, 3.7; N, 3.6. Found: C, 56.2; H, 3.7; N, 3.7.

(2*R*,3*R*)-3-Bromo-*N*-phthaloylphenylalanine *tert*-Butyl Ester (6b): 41%; mp 152-153 °C; ν_{max} 1780, 1738, 1720, 1420, 1390, 1050, 840, 710 cm^{-1}; MS (EI) *m/e* 431 and 429 (M^+, 0.02%), 375 (9), 373 (9), 330 (11), 328 (11), 294 (4), 276 (2), 249 (93), 248 (94), 232 (15), 220 (10), 204 (44), 165 (7), 130 (8), 104 (38), 102 (32), 76 (36), 57 (100).

(2*R*,3*S*)-3-Bromo-*N*-phthaloylphenylalanine *tert*-Butyl Ester (7b): 39%; mp 118-119 °C; ν_{max} 1780, 1748, 1726, 1390, 715 cm^{-1}; MS (EI) *m/e* 431 and 429 (M^+, 0.01%), 375 (7), 373 (7), 330 (10), 328 (10), 294 (6), 276 (3), 249 (75), 248 (100), 232 (11), 220 (8), 204 (28), 165 (5), 130 (6), 104 (27), 102 (25), 76 (26), 57 (66).

(2*R*,3*R*)-3-Bromo-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide (6c): 43%; mp 208-209 °C; ν_{max} 3350, 1700, 1530, 1450, 1365, 710 cm^{-1}; MS (EI) *m/e* 430 and 428 (M^+, 5%), 415 (0.2), 413 (0.2), 375 (0.6), 373 (0.6), 330 (2), 328 (2), 249 (100), 232 (6), 220 (3), 204 (5), 165 (2), 130 (3), 104 (8), 102 (7), 76 (6). Anal. Calcd for $C_{21}H_{21}BrN_2O_3$: C, 58.8; H, 4.9; N, 6.5. Found: C, 58.6; H, 5.0; N, 6.8.

(2*R*,3*S*)-3-Bromo-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide (7c): 41%; mp 188-191 °C; ν_{max} 3375, 1775, 1705, 1530, 1380, 720 cm^{-1}; MS (EI) *m/e* 430 and 428 (M^+, 1%), 415 (0.1), 413 (0.1), 375 (0.2), 373 (0.2), 330 (1), 328 (1), 249 (100), 232 (10), 220 (3), 204 (4), 165 (2), 130 (3), 104 (12), 102 (10), 76 (13). Anal. Calcd for $C_{21}H_{21}BrN_2O_3$: C, 58.8; H, 4.9; N, 6.5. Found: C, 58.8; H, 4.9; N, 6.6.

(2*R*,3*R*)-*O*-Acetyl-3-bromo-*N*-phthaloyltyrosine Methyl Ester (13a) and (2*R*,3*S*)-*O*-Acetyl-3-bromo-*N*-phthaloyltyrosine Methyl Ester (14a): 1:1 mixture; 97%; MS (EI) *m/e* 447 and 445 (M^+, 0.3%), 405 (0.3), 403 (0.3), 388 (0.6), 386 (0.6), 366 (8), 334 (17), 324 (5), 306 (5), 292 (16), 264 (100), 218 (12), 187 (7), 163 (9), 147 (10), 138 (14), 121 (35), 104 (22), 86 (38), 76 (19); MS (EI) *m/e* 445.018 (M^+). Calc. for $C_{20}H_{16}BrNO_6$: *m/e* 445.016.

(2*R*,3*R*)-*O*-Acetyl-3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyltyrosinamide (13b) and (2*R*,3*S*)-*O*-Acetyl-3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyltyrosinamide (14b): 1:1 mixture; 97%; ν_{max} 1780, 1726, 1675, 1608, 1394, 1160, 720 cm^{-1}; MS (EI) *m/e* 488 and 486 (M^+, 2%), 446 (1), 444 (1), 403 (14), 388 (1), 386 (1), 361 (10), 308 (31), 265 (100), 248 (5), 121 (11), 118 (10), 104 (14), 76 (9); MS (EI) *m/e* 486.080 (M^+). Calc. for $C_{23}H_{23}BrN_2O_5$: *m/e* 486.079.

(2*S*,3*R*)-3-Hydroxy-*N*-phthaloylphenylalanine Methyl Ester (8a) and (2*S*,3*S*)-3-Hydroxy-*N*-phthaloylphenylalanine Methyl Ester (9a). To a solution of a 1:1 mixture of the bromides **6a** and **7a** (1.0 g, 2.6 mmol) in acetone (40 ml) was added a solution of silver nitrate (0.66 g, 3.9 mmol) in water (40 ml), and the resultant mixture was stirred in the dark at rt for 24 h, then it was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with dichloromethane, and the organic solution was dried and then concentrated under reduced pressure, to give a 5:1 mixture of the alcohols **8a** and **9a** (0.77 g, 92%), as determined from the ^1H NMR spectrum. Recrystallization of the mixture from hexane/dichloromethane gave the alcohol **8a** as colourless crystals (0.63 g, 75%): mp 185-186 °C; $[\alpha]_D^{16}$ -67.0° (c, 0.6 in EtOH); ν_{max} 3580, 3420, 1780, 1745, 1715, 1390, 1215, 1020, 720 cm^{-1}; MS (FAB) *m/e* 326 ($M+H^+$, 77%), 308 (100), 248 (54), 219 (19), 160 (27), 149 (23), 131 (21), 105 (48), 104 (33), 91 (42). Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.5; H, 4.7; N, 4.3. Found: C, 66.7; H, 4.7; N, 4.4.

The structure of the alcohol **8a** was confirmed through X-ray crystallographic analysis.[27]

Reactions of the bromides 6b,c and 7b,c, and 13a,b and 14a,b, with silver nitrate in aqueous acetone. These reactions were performed using the procedure described above for the reaction of the mixture of the bromides **6a** and **7a**.

(2*S*,3*R*)-3-Hydroxy-*N*-phthaloylphenylalanine *tert*-Butyl Ester (8b) and (2*S*,3*S*)-3-Hydroxy-*N*-phthaloylphenylalanine *tert*-Butyl Ester (9b). Reaction of a 1:1 mixture of the bromides **6b** and **7b** gave an 8:1 mixture of the alcohols **8b** and **9b**. The ratio of the diastereomers **8b** and **9b** was determined from the ^1H NMR spectrum of the mixture. Recrystallization of the mixture from hexane/dichloromethane gave the alcohol **8b** as colourless crystals: 81%; mp 125-127 °C; ν_{max} 3440, 1785, 1738, 1712, 1604, 1552, 1392, 1194, 1108, 844, 720 cm^{-1}; MS (FAB) *m/e* 368 ($M+H^+$, 8%), 312 (44), 294

(55), 276 (23), 266 (10), 250 (100), 232 (11), 205 (13), 160 (19), 105 (21), 91 (20), 87 (25), 57 (93). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.7; H, 5.8; N, 3.8. Found: C, 68.7; H, 5.9; N, 3.8.

(2*S*,3*R*)-3-Hydroxy-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide (8c). Reaction of a 1:1 mixture of the bromides **6c** and **7c** gave the alcohol **8c**, as colourless crystals from hexane/dichloromethane: 93%; mp 195-197 °C; ν_{max} 3352, 3275, 1778, 1704, 1644, 717 cm^{-1}; MS (FAB) *m/e* 367 ($M+H^+$, 68%), 307 (3), 289 (2), 266 (4), 260 (18), 250 (100), 232 (7), 187 (10), 160 (17), 154 (24), 136 (18), 107 (8), 105 (6), 77 (6). Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.8; H, 6.1; N, 7.7. Found: C, 68.8; H, 6.0; N, 7.7.

(2*S*,3*R*)-3-Hydroxy-*N*-phthaloyltyrosine Methyl Ester (15c) and (2*S*,3*S*)-3-Hydroxy-*N*-phthaloyltyrosine Methyl Ester (16c). Reaction of a 1:1 mixture of the bromides **13a** and **14a** gave an 86% yield of a 6:1 mixture of the alcohols **15a** and **16a**: ν_{max} 3580, 3410, 1775, 1752, 1712, 1552, 1392, 1184, 1118, 852, 710 cm^{-1}; MS (FAB) *m/e* 384 ($M+H^+$, 13%), 366 (79), 334 (100), 324 (7), 306 (35), 292 (38), 264 (58), 219 (34), 187 (23), 160 (15), 154 (37), 136 (33), 107 (17), 105 (13), 104 (12), 89 (17), 77 (19); MS *m/e* 365.090 (M^+). Calc. for $C_{20}H_{15}NO_6$: *m/e* 365.090. The ratio of the diastereomers **15a** and **16a** was determined from the ^1H NMR spectrum of the mixture.

The acetate moieties of the alcohols **15a** and **16a** were found to hydrolyse slowly on exposure to moisture and the mixture was therefore deacetylated without further purification. A mixture of the acetates **15a** and **16a** (0.87 g, 2.27 mmol), *p*-toluenesulfonic acid monohydrate (100 mg, 0.5 mmol) and water (1 ml) in methanol (20 ml) was stirred at rt for 6 h, then it was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water, and the organic phase was separated and washed with 10% aqueous sodium carbonate, then it was dried and concentrated under reduced pressure, to give a 6:1 mixture of the alcohols **15c** and **16c** (0.74 g, 96%). The ratio of the diastereomers **15c** and **16c** was determined from the ^1H NMR spectrum of the mixture. Recrystallization of the mixture from hexane/ethyl acetate gave the alcohol **15c** as a white solid (556 mg, 72%); mp 200-201 °C; $[\alpha]_D^{16}$ -70.7° (c, 0.4 in EtOH); ν_{max} 3582, 3405, 1775, 1750, 1714, 1516, 1392, 1172, 850, 715 cm^{-1}. MS (FAB) *m/e* 342 ($M+H^+$, 2%), 324 (10), 307 (12), 292 (11), 289 (7), 264 (5), 232 (14), 231 (17), 219 (9), 154 (100), 137 (63), 136 (77), 107 (30), 105 (12), 89 (29), 77 (31). Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.3; H, 4.4; N, 4.1. Found: C, 63.3; H, 4.4; N, 4.0.

(2*S*,3*R*)-3-Hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyltyrosinamide (15d). Reaction of a 1:1 mixture of the bromides **13b** and **14b** gave the alcohol **15b** as colourless crystals; 88%; mp 202-204 °C; ν_{max} 3600, 3440, 3390, 1775, 1710, 1685, 1515, 1390, 1220, 860, 720 cm^{-1}; MS (FAB) *m/e* 425 ($M+H^+$, 43%), 308 (67), 266 (100), 248 (4), 187 (16), 160 (26), 154 (23), 136 (37), 107 (18), 105 (10), 89 (17), 77 (22); MS *m/e* 406.154 (M^+-H_2O). Calc. for $C_{23}H_{22}N_2O_5$: *m/e* 406.153.

The acetate **15b** was hydrolysed, as described above for the hydrolysis of the mixture of the acetates **15a** and **16a**, to give a 93% yield of the alcohol **15d**, as a colourless solid after recrystallization from hexane/chloroform: mp 214-215 °C; ν_{max} 3590, 3546, 3410, 1772, 1712, 1685, 1366, 855, 717 cm^{-1}; MS (FAB) *m/e* 383 ($M+H^+$, 18%), 307 (3), 289 (4), 267 (48), 266 (100), 260 (16), 187 (15), 160 (15), 154 (26), 136 (17), 107 (8), 105 (8), 91 (10), 77 (9). Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 66.0; H, 5.8; N, 7.3. Found: C, 65.7; H, 5.8; N, 7.2.

Isomerization of (2*S*,3*R*)-3-Hydroxy-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide (8c). Jones reagent[28] (*ca.* 0.5 ml) was added dropwise to a vigorously stirred solution of the alcohol **8c** (0.5 g, 1.37 mmol) in acetone (20 ml), until the red/brown colour persisted. The reaction mixture was stirred

for a further 15 min at rt, then it was concentrated under reduced pressure. The residual oil was partitioned between dichloromethane and water. The organic layer was separated and washed with 10% aqueous sodium carbonate and with water, then it was dried and concentrated under reduced pressure. The residual oil was chromatographed on silica, eluting with ethyl acetate, to give the crude ketone **18**, which recrystallized from hexane/ethyl acetate as a colourless solid (0.33 g, 67%); ^{1}H NMR δ 1.34 (9H, s), 6.04 (1H, s), 7.21-7.56 (5H, m), 7.73-7.90 (4H, m); MS (EI) *m/e* 364 (M^+, 2%), 308 (1), 291 (2), 265 (40), 221 (6), 147 (72), 105 (43), 104 (87), 103 (58), 76 (100).

To a solution of the crude ketone **18** (100 mg, 0.27 mmol) in ethanol (5 ml) was added sodium borohydride (10 mg, 0.26 mmol). The mixture was stirred at rt for 10 min, then the reaction was quenched by the addition of dilute hydrochloric acid (*ca.* 1 ml). The mixture was concentrated under reduced pressure, and the residue was partitioned between dichloromethane and water. The organic layer was washed with 10% aqueous sodium carbonate and with water, then it was dried and concentrated under reduced pressure. Chromatography of the residual oil on silica gave a 1:1.2 mixture of **(2*S*,3*R*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide** (**9c**) and the diastereomer **8c** (84 mg, 84%), as determined from the ^{1}H NMR spectrum.

Reaction of the Bromide 6a with Potassium Fluoride. Treatment of the bromide **6a** with the 18-crown-6 complex of potassium fluoride in acetonitrile, as described previously[21] for the synthesis of *(Z)*-*N*-*tert*-butyl-N^{α}-phthaloyl-2,3-dehydrophenylalaninamide from the bromo amide **6c**, afforded *(Z)*-*N*-phthaloyl-2,3-dehydrophenylalanine methyl ester (**10**) as colourless crystals: 88%; mp 136-137 °C; ^{1}H NMR δ 3.82 (3H, s), 7.26-7.42 (5H, m), 7.78-7.90 (4H, m), 8.12 (1H, s); ν_{max} 1780, 1720, 1640, 1600 cm^{-1}; MS (EI) *m/e* 307 (M^+, 100%), 279 (52), 248 (27), 247 (34). Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.4; H, 4.3; N, 4.6. Found: C, 70.6; H, 4.2; N, 4.4.

The structure of the alkene **10** was confirmed through X-ray crystallographic analysis.[22]

Reaction of the Bromide 7a with Potassium Fluoride. Treatment of the bromide **7a** with the 18-crown-6 complex of potassium fluoride in acetonitrile, as described for the reaction of the bromide **6a**, afforded a 2:1 mixture of *(E)*-*N*-phthaloyl-2,3-dehydrophenylalanine methyl ester **11** and the (*Z*)-isomer **10**, in 82% yield. Recrystallization of the mixture from hexane/ethyl acetate gave the *(Z)*-alkene **10** in 18% yield, while concentration of the recrystallization mother liquor afforded a 47% yield of a 5:1 mixture of the alkenes **11** and **10**, as a clear oil; ν_{max} 1780, 1724, 1645, 1600, 1560 cm^{-1}; MS (EI) *m/e* 307 (M^+, 100%), 279 (49), 248 (12), 247 (27); ^{1}H NMR (**11**) δ 3.74 (3H, s), 7.23 (1H, s), 7.29-7.49 (5H, m), 7.80-7.93 (4H, m).

(2*S*,3*R*)-3-Hydroxyphenylalanine. A solution of the hydroxy ester **8a** (0.25 g, 0.77 mmol) in a 2:1 mixture of 6N hydrochloric acid and acetic acid (10 ml) was heated at reflux for 5 h, then it was cooled and concentrated under reduced pressure. The residue was taken up in water (10 ml) and the suspension was filtered. The filtrate was concentrated under reduced pressure, and the residue was dissolved in a mixture of ethanol (7 ml), aniline (0.7 ml) and dichloromethane (10 ml). The mixture was stored at 0 °C for 16 h, and the precipitate that formed was collected by filtration, to give the (2*S*,3*R*)-isomer of the free amino acid **1**, as a white powder (129 mg, 93%); mp 192-195 °C (lit.[32] 183-186 °C); $[\alpha]_D^{16}$ -49.7±0.5° (c, 0.4 in 6N HCl) (lit.[32]

$[\alpha]_D^{20}$ -50.2±2° (c, 2 in 6N HCl)); ^{1}H NMR (D_2O) δ 3.95 (1H, d, J = 4.4 Hz), 5.29 (1H, d, J = 4.4 Hz), 7.47 (5H, m). Anal. Calcd for $C_9H_{11}NO_3$: C, 59.7; H, 6.1; N, 7.7. Found: C, 59.9; H, 6.1; N, 7.8.

Treatment of the hydroxy amide **8c** with hydrochloric acid and acetic acid, as described above for the hydrolysis of the hydroxy ester **8a**, also gave the (2*S*,3*R*)-isomer of the free amino acid **1**, in 78% yield.

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