Pergamon

Tetrahedron, Vol. 52, No. 20, pp. 7025-7036, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00307-9

Neighbouring Group Effects Promote Substitution Reactions over Elimination and Provide a Stereocontrolled Route to Chloramphenicol

Christopher J. Easton,*[a] Craig A. Hutton,[b] Martin C. Merrett[a] and Edward R. T. Tiekink[b]

[a] Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia

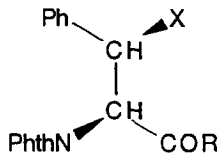
[b] Department of Chemistry, University of Adelaide, South Australia 5005, Australia

Abstract: In reactions of β-brominated valine and *p*-nitrophenylalanine derivatives to give β-hydroxy amino acid derivatives the carboxyl group, when protected as an amide, exerts a neighbouring group effect to facilitate the substitution process, and reduce competing elimination reactions. As a consequence of the effect, the (2*R*,3*R*)- and (2*R*,3*S*)-stereoisomers of 3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide both react to give (2*S*,3*R*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, providing a stereoconvergent route to chloramphenicol.

INTRODUCTION

Neighbouring group participation by amido and aminocarbonyl substituents is well known[1] and the chemical and biochemical implications of this phenomenon in reactions of amino acid derivatives have attracted considerable attention.[2-6] For example, it appears that the biochemistry of asparagine incorporated in peptides is influenced by the interaction of the side chain aminocarbonyl moiety with the peptide bonds,[2] while amides derived from either the amino[3,4] or carboxyl group[5] of an amino acid are known to be able to act as nucleophiles or provide anchimeric assistance in solvolysis reactions, *via* 1,5-participation. Recently we reported[7] much greater diastereoselectivity in the synthesis of the hydroxyamides **1d** and **2d** from the bromoamides **1c** and **2c** than in the conversion of the corresponding bromoesters **1a** and **2a** to the hydroxyesters **1b** and **2b**. The enhanced stereoselectivity was attributed to neighbouring group participation by the aminocarbonyl substituent in the reactions of the bromides **1c** and **2c**. Consistent with this proposal, the extent of anchimeric assistance displayed by amides is known to be larger than that shown by esters,[6] although 1,4-participation by amides appears to be unusual. We now report reactions of the bromides **3a,c-5a,c**, in which it is apparent that the neighbouring group effect changes the course of reaction, favouring substitution over elimination, as well as controlling the stereochemistry in the conversion of the bromides **3a,c** and **4a,c** to the alcohols **3b,d** and **4b,d**.

During the course of the present work a stereospecific route to chloramphenicol **6** was also developed. The industrial synthesis of this broad spectrum antibiotic involves the condensation of benzaldehyde with β-nitroethanol[8] but a disadvantage of that and other approaches[9] is that they involve the formation of racemic products which need to be resolved. An asymmetric synthesis based on azide ring-opening of the epoxide **7** has been reported.[10] Alternatively, (*S*)-phenylalanine has been used to obtain the chloramphenicol precursor **9**



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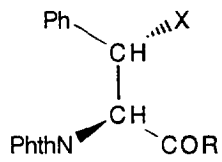

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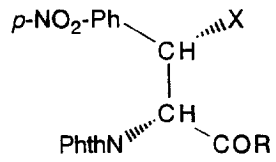

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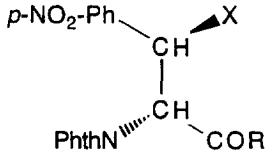

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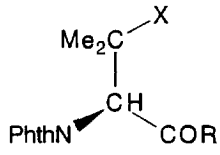
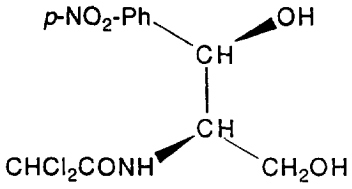


5

a) X = Br, R = OMe
b) X = OH, R = OMe
c) X = Br, R = $NHCMe_3$
d) X = OH, R = $NHCMe_3$

in a multi-step synthesis (Scheme 1), in which diastereocontrol was achieved by utilising 1,5-neighbouring group participation in the hydrolytic rearrangement of the benzamide **8**.[4]



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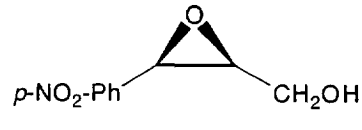

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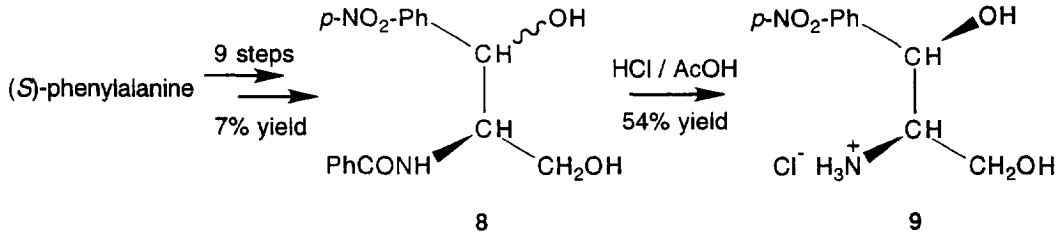
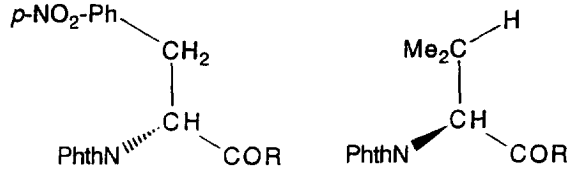


8 9

Scheme 1

RESULTS AND DISCUSSION

The *p*-nitrophenylalanine derivatives **10a** and **10b** were prepared using standard procedures, and treated with *N*-bromosuccinimide to give 1:1 mixtures of the diastereomers of the corresponding bromides **3a** and **4a**, and **3c** and **4c**. The bromoesters **3a** and **4a** were separated through fractional crystallisation and their relative stereochemistry was determined through X-ray crystallographic analysis of the (2*S*,3*R*)-diastereomer **4a**.[11] [Note that the Cahn-Ingold-Prelog designation at the α-carbon of the bromides **3a,c-5a,c** is reversed by comparison with that of the corresponding non-halogenated amino acid derivatives **10a,b** and **11a,b**, due to the change in priority of the substituents.] The stereochemistry of the bromoamides **3c** and **4c** was assigned by comparison of the spectral properties of the (2*S*,3*R*)-diastereomer **4c** with those of a racemic sample. That sample was prepared by bromination of the racemic analogue of the nitrophenylalanine derivative **10b**, then separated from its diastereomer by fractional crystallisation and its structure was determined through X-ray crystallographic analysis.[11] The ^{1}H NMR spectra of the bromides **3a,c** and **4a,c** show the same trends as previously observed with the corresponding phenylalanine derivatives **1a,c** and **2a,c**.[7] The signals corresponding to the carboxyl protecting groups occur at lower chemical shift for the (2*S*,3*S*)-diastereomers **3a** and **3c** than for the corresponding (2*S*,3*R*)-diastereomers **4a** and **4c**, while the (2*S*,3*S*)-diastereomers **3a** and **3c** exhibit the β-proton signal at higher chemical shift, the α-proton at lower chemical shift, and a larger coupling constant between the α- and β-protons, than for the corresponding (2*S*,3*R*)-diastereomers **4a** and **4c**. The bromides **5a**[12] and **5c** were prepared by halogenation of the amino acid derivatives **11a** and **11b**, which had each been prepared from (*S*)-valine.



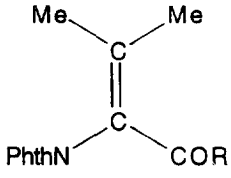
10 **11**

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

The valine derivative **5a** reacted with silver nitrate in aqueous acetone, at room temperature for 24 h, to give a crude product containing the alcohol **5b** and the dehydrovaline derivatives **12a** and **13a** in the ratio *ca.* 3.5:1:3.5. Chromatography of the mixture afforded the alcohol **5b** in 43% yield, and the alkenes **12a** and **13a**, in yields of 8 and 34%, respectively. The corresponding reaction of the valinamide **5c** afforded a *ca.* 2:1 mixture of the alcohol **5d** and the alkene **13b**, from which the components were isolated in 63 and 26% yield, respectively. The ^{1}H NMR spectrum of the crude product of the reaction of the valinamide **5c** showed no indication of formation of the alkene **12b**.

The *p*-nitrophenylalanine derivatives **3a,c** and **4a,c** required more vigorous conditions to react. On one occasion, treatment of the bromoester **4a** at 65 °C for 48 h gave the alcohol **3b** in 63% yield, with the dehydrophenylalanine derivatives **14a** and **15a** also being isolated as a 2:3 mixture in 25% yield. Repeated experiments afforded the alcohol **3b** in only 10-30% yield, with higher proportions of the alkenes **14a** and

15a. Under similar conditions, the bromide **3a** gave only the alkene **15a**, in 84% yield, and neither the alcohol **3b** nor the alkene **14a** were detected in the crude product. The analogous reaction of a 1:1 mixture of the bromides **3a** and **4a** carried out using silver sulfate, in place of the nitrate salt, gave mainly the alkene **15a** and only small quantities of either the (*E*)-isomer **14a** or the alcohol **3b**. In contrast, treatment of a 1:1 mixture of



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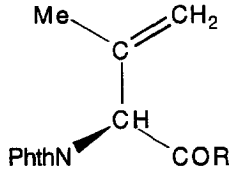
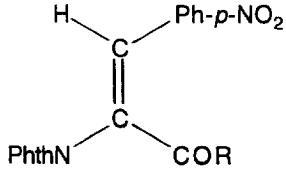


13

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

the bromoamides **3c** and **4c** with silver sulfate over 3 days under similar conditions gave only the substitution product **3d** in 64% yield. Reaction of the bromoamides **3c** and **4c** using silver nitrate was complicated by competing formation of a second product, which was tentatively identified as the nitrate **16**. There was no indication of the presence of either of the alkenes **14b** or **15b** in the ^1H NMR spectra of the crude products obtained from these reactions of the bromoamides **3c** and **4c**.

The stereochemistry of the dehydrophenylalanine derivatives **14a** and **15a** was assigned on the basis of their ^1H NMR spectra, in which the resonance due to the vinylic proton of the (*E*)-isomer **14a** was observed at δ 7.28, 0.85 ppm upfield from that of the corresponding signal for the (*Z*)-alkene **15a**. This is consistent with the general trend displayed by dehydrophenylalanine derivatives.[13] The stereochemistry of the alcohols **3b** and **3d** is apparent from their ^1H NMR spectra, which show a much closer correlation with the spectra of the corresponding hydroxyphenylalanine derivatives **1b** and **1d** than with those of the respective diastereomers **2b** and **2d**. The assignment of stereochemistry of the alcohols **3b** and **3d** is further supported by hydrolysis to the free amino acid **18** and comparison of the physical and spectral properties of that material with literature data.[14-16]



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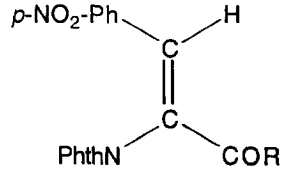

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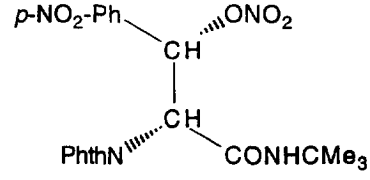
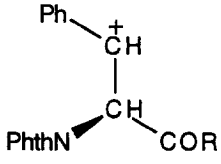


16

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

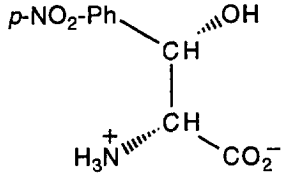
Elimination reactions of the bromovalinate **5a**, to give the alkenes **12a** and **13a**, compete with the substitution reaction, to give the alcohol **5b**. By comparison, the reaction of the bromovalinamide **5c** gives a better yield of the substitution product **5d**. This is not merely a steric effect of the bulky aminocarbonyl substituent to retard elimination. Under these circumstances, the amide **5c** would be expected to react more slowly than the ester **5a**, whereas in competitive experiments the opposite was observed, with the amide **5c**

reacting *ca.* six times faster than the ester **5a**. Instead, the effect of the aminocarbonyl substituent to promote substitution over elimination, and increase the rate of reaction of the bromide **5c**, indicates a neighbouring group effect of the protected carboxyl group to stabilise the carbocation intermediate in the substitution reaction. The neighbouring group effect is also seen in the reactions of the nitrophenylalanine derivatives **3a,c** and **4a,c**, to promote substitution over elimination, and to give the alcohol **3d** with a high degree of stereocontrol from the reaction of the bromoamides **3c** and **4c**. The predominant reaction of the esters **3a** and **4a** is elimination, whereas the amides **3c** and **4c** react by substitution. As shown previously,[7] the bromophenylalanine derivatives **1a,c** and **2a,c** react to give the corresponding alcohols **1b,d** and **2b**. Presumably, in the absense of an electron withdrawing group on the aromatic ring, the carbocations **17a,b** form in the substitution reactions without competing elimination. In that case the only effect of the neighbouring group is to enhance the stereoselectivity in the production of the alcohols **1b,d** and **2b**. The nitrophenylalanine derivatives **3a** and **4a** react predominantly by elimination. When the carboxyl group is protected as an amide, however, the destabilising effect of the nitro substituent on the intermediate carbocation is diminished to the extent that substitution now becomes the favoured reaction pathway.



17

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



18

On treament with hydrochloric acid in aqueous acetic acid, the hydroxynitrophenylalanine derivative **3d** hydrolysed to the corresponding free amino acid **18**. The synthetic procedure used to prepare the alcohol **18**, in 29% yield from (*R*)-*p*-nitrophenylalanine, was repeated using racemic *p*-nitrophenylalanine and the (*S*)-enantiomer as starting materials, to obtain the corresponding racemate and the (2*S*,3*R*)-enantiomer of the alcohol **18**. The spectral properties of these compounds were found to be identical to those reported.[14-16] Previously, the racemate of the alcohol **18** has been converted to the corresponding methyl ester, the enantiomers of that compound have been resolved by complexation with tartaric acid, and the (2*S*,3*R*)-stereoisomer has been elaborated to chloramphenicol **6**.[16] Now stereocontrolled access to the (2*S*,3*R*)-enantiomer of the alcohol **18**, as a consequence of neighbouring group participation by an aminocarbonyl substituent to facilitate substitution over elimination and control the stereochemistry of the former, offers a more direct route for synthesis of the antibiotic **6**.

EXPERIMENTAL

General. M.p.s were determined on a Reichert hot-stage apparatus and are uncorrected. IR spectra were recorded as nujol mulls, liquid films or as solutions in chloroform, on a Hitachi 270-30 spectrometer. ^1H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on a Bruker ACP-300 or a GEMINI 300

spectrometer, in $CDCl_3$ with Me_4Si as the internal standard, unless otherwise stated. Electron impact (ei) mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Fast atom bombardment (fab) mass spectra were recorded on a VG ZAB 2HF spectrometer. Optical rotations were measured using a Perkin Elmer 241 polarimeter. Microanalyses were performed by Chemical and Microanalytical Services Pty. Ltd., Melbourne, Australia. Chromatography was performed on Merck-Keiselgel 60 (230-400 mesh ASTM), using ethyl acetate and light petroleum (b.p. 66-68 °C) as eluants. Organic solutions were dried over $MgSO_4$.

All solvents were purified and dried using standard methods. (*S*)-Valine, (*RS*)-*p*-nitrophenylalanine, and (*S*)- and (*R*)-*p*-nitrophenylalanine were purchased from Sigma Chemical Co.

(R)-N-Phthaloyl-p-nitrophenylalanine. A mixture of (*R*)-*p*-nitrophenylalanine monohydrate (1.78 g, 7.81 mmol), phthalic anhydride (1.27 g, 8.58 mmol) and triethylamine (1.1 cm^3, 7.95 mmol) was heated at reflux in toluene (60 cm^3) for 3 h, during which time water was continuously removed using a Dean-Stark condenser. The resultant mixture was cooled in an ice bath and then it was concentrated under reduced pressure. The residue dissolved in dichloromethane and the solution was washed with dilute aqueous hydrochloric acid and water, then it was dried and concentrated under reduced pressure. Crystallisation of the solid residue from a mixture of ethyl acetate and light petroleum yielded the title compound as a pale yellow crystalline solid (2.57 g, 97%), m.p. 203-207 °C; $[\alpha]_{578}^{25}$ +234.5° (c, 0.31 in MeOH); δ_H 8.09 (d, *J* 8.7 Hz, 2 H, ArH), 7.72-7.83 (m, 4 H, phth), 7.36 (d, *J* 8.7 Hz, 2 H, ArH), 5.26 (dd, *J* 7.3 and 9.2 Hz, 1 H, α-H) and 3.72 (m, 2 H, β-H).

(RS)-N-Phthaloyl-p-nitrophenylalanine. This compound was prepared from (*RS*)-*p*-nitrophenylalanine, as described above for the synthesis of the corresponding (*R*)-isomer, and obtained in 93% yield, m.p. 185-187 °C.

(S)-N-Phthaloyl-p-nitrophenylalanine. This compound was prepared from (*S*)-*p*-nitrophenylalanine monohydrate, as described above for the synthesis of the corresponding (*R*)-enantiomer, and obtained in 57% yield, m.p. 200-202 °C (lit.[17] 204.7 °C); $[\alpha]_{578}^{19}$ -230.2° (c, 0.086 in MeOH) (lit.[17] -232.5° (c, 1.55 in MeOH)).

(R)-N-Phthaloyl-p-nitrophenylalanine Methyl Ester **10a**. (*R*)-*N*-Phthaloyl-*p*-nitrophenylalanine (2.50 g, 7.35 mmol) was dissolved in dry methanol (50 cm^3) which had been pretreated with thionyl chloride (400 mg, 3.36 mmol). The solution was stirred under anhydrous conditions for 16 h, then it was concentrated under reduced pressure. The residue dissolved in dichloromethane, and the solution was washed with aqueous sodium carbonate and water, then it was dried and concentrated under reduced pressure. Recrystallisation of the residue from a mixture of dichloromethane and light petroleum gave the title compound **10a** as a colourless solid (2.24 g, 86%), m.p. 121-122 °C; ν_{max}/cm^{-1} 1775, 1750, 1715, 1600, 1520, 1390, 1345, 1240, 860 and 720; δ_H 8.06 (d, *J* 8.6 Hz, 2 H, ArH), 7.72-7.82 (m, 4 H, phth), 7.45 (d, *J* 8.6 Hz, 2 H, ArH), 5.31 (dd, *J* 5.5 and 10.9 Hz, 1 H, α-H), 3.81 (s, 3 H, OMe), 3.77 (dd, *J* 5.5 and 14.3 Hz, 1 H, β-H) and 3.71 (dd, *J* 10.9 and 14.3 Hz, 1 H, β'-H); *m/z* (ei) (%) 354 (M^+, 12), 295 (37), 278 (14), 218 (36), 207 (100), 190 (37), 176 (25), 130 (33), 104 (17) and 76 (21).

(2S,3S)-3-Bromo-N-phthaloyl-p-nitrophenylalanine Methyl Ester **3a** *and (2S,3R)-3-Bromo-N-phthaloyl-p-nitrophenylalanine Methyl Ester* **4a**. To a solution of (*R*)-*N*-phthaloyl-*p*-nitrophenylalanine methyl ester **10a** (2.20 g, 6.21 mmol) in carbon tetrachloride (40 cm^3), *N*-bromosuccinimide (1.20 g, 6.74 mmol) was added

and the mixture was heated at reflux for 4 h, while it was irradiated with a 250 W mercury lamp. The mixture was then allowed to cool, before it was filtered. The filtrate was washed with water and dried, then it was concentrated under reduced pressure, to give a 1:1 mixture of the title compounds **3a** and **4a** as a colourless solid (2.69 g, 100%). Fractional recrystallisation of the mixture from a combination of dichloromethane and light petroleum gave the (2*S*,3*S*)-bromide **3a** (1.17 g, 43%), m.p. 198-201 °C; ν_{max}/cm^{-1} 1775, 1750, 1720, 1600, 1525, 1340, 1215, 1100, 820 and 715; δ_H 8.27 (d, *J* 8.8 Hz, 2 H, ArH), 7.82-7.99 (m, 4 H, phth), 7.78 (d, *J* 8.8 Hz, 2 H, ArH), 6.02 (d, *J* 11.2 Hz, 1 H, β-H), 5.51 (d, *J* 11.2 Hz, 1 H, α-H) and 3.59 (s, 3 H, OMe); *m/z* (ei) (%) 434/432 (M^+, 2), 375 (6), 373 (6), 353 (4), 352 (9), 321 (6), 294 (29), 293 (17), 287 (10), 285 (10), 247 (7), 219 (16), 218 (100), 190 (30), 130 (18), 104 (40) and 76 (37) (Found: C, 49.8; H, 3.0; N, 6.5. Calc. for $C_{18}H_{13}BrN_2O_6$: C, 49.9; H, 3.0; N, 6.5%). Further recrystallisation gave the (2*S*,3*R*)-bromide **4a** (1.07 g, 40%), m.p. 195-197 °C; ν_{max}/cm^{-1} 1775, 1755, 1720, 1605, 1525, 1390, 1350, 855 and 720; δ_H 8.07 (d, *J* 8.7 Hz, 2 H, ArH), 7.68-7.76 (m, 4 H, phth), 7.56 (d, *J* 8.7 Hz, 2 H, ArH), 5.97 (d, *J* 10.3 Hz, 1 H, β-H), 5.59 (d, *J* 10.3 Hz, 1 H, α-H) and 3.83 (s, 3 H, OMe); *m/z* (ei) (%) 434/432 (M^+, 1), 375 (3), 373 (3), 353 (6), 352 (3), 321 (7), 294 (20), 293 (12), 287 (3), 285 (3), 247 (5), 219 (15), 218 (100), 190 (29), 130 (16), 104 (28) and 76 (26) (Found: C, 49.8; H, 3.0; N, 6.6. Calc. for $C_{18}H_{13}BrN_2O_6$: C, 49.9; H, 3.0; N, 6.5%). The structure of the bromide **4a** was confirmed through X-ray crystallographic analysis.[11]

*(*RS*)*-N-tert-*Butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide*. To a suspension of (*RS*)-*N*-phthaloyl-*p*-nitrophenylalanine (2.00 g, 5.88 mmol) in dichloromethane (40 cm^3), triethylamine (0.81 cm^3, 5.85 mmol) was added. The resultant solution was cooled to 0 °C, then ethyl chloroformate (0.56 cm^3, 5.86 mmol) was added. That mixture was stirred for 10 min, then *tert*-butylamine (0.61 cm^3, 5.85 mmol) was added and the solution was warmed to room temperature. After stirring for a further 30 min, the mixture was filtered and the filtrate was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate and water, then it was dried and concentrated under reduced pressure. The residue was chromatographed to give the title compound, as a colourless crystalline solid after recrystallisation from a mixture of ethyl acetate and light petroleum (1.26 g, 54%), m.p. 215-216 °C, ν_{max}/cm^{-1} 3316, 2920, 2848, 1774, 1714, 1658, 1554, 1516, 1456, 1382, 1344, 1220, 1088, 1016, 888, 874, 766 and 726; δ_H 8.03 (d, *J* 8.6 Hz, 2 H, ArH), 7.77-7.69 (m, 4 H, phth), 7.33 (d, *J* 8.6 Hz, 2 H, ArH), 5.93 (br s, 1 H, NH), 5.02 (t, *J* 8.4 Hz, 1 H, α-H), 3.65 (d, *J* 8.4 Hz, 2 H, β-H) and 1.33 (s, 9 H, CMe_3); δ_C 29.1, 35.2, 52.4, 56.4, 124.2, 124.3, 130.3, 131.6, 135.1, 145.4, 147.4, 167.1 and 168.3; *m/z* (ei) (%) 395 (M^+, 5), 352 (5), 341 (10), 256 (20), 236 (5) and 213 (10) (Found: C, 63.6; H, 5.3; N, 10.5. Calc. for $C_{21}H_{21}N_3O_5$: C, 63.8; H, 5.3; N, 10.6%).

*(*R*)*-N-tert-*Butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide* **10b.** This compound was prepared from (*R*)-*N*-phthaloyl-*p*-nitrophenylalanine, as described above for the synthesis of the corresponding racemate, and obtained in 72% yield, m.p. 230 °C (dec.); $[\alpha]_D^{25}$ +117.0° (c, 0.227 in $CHCl_3$).

*(*S*)*-N-tert-*Butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide*. This compound was prepared from (*S*)-*N*-phthaloyl-*p*-nitrophenylalanine, as described above for the synthesis of the corresponding racemate, and obtained in 79% yield, m.p. 230 °C (dec.); $[\alpha]_D^{21}$ -120.8° (c, 0.418 in $CHCl_3$).

*(*2RS,3RS*)-3-Bromo-*N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide and (*2RS,3SR*)-3-Bromo-*N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide*. To a solution of (*RS*)-*N-tert*-butyl-*N*$^{\alpha}$-phthaloyl-*p*-nitrophenylalaninamide (771 mg, 1.95 mmol) in a mixture of carbon tetrachloride and dichloromethane (4:1, 50

cm^3), *N*-bromosuccinimide (695 mg, 3.90 mmol) was added and the mixture was heated at reflux for 3 h, while it was irradiated with a 250 W mercury lamp. The mixture was then allowed to cool, before it was filtered. The filtrate was washed with water, then it was dried and concentrated under reduced pressure, to give a 1:1 mixture of the title compounds as a colourless solid (905 mg, 98%), m.p. 194-210 °C; ν_{max}/cm^{-1} 3380, 3350, 2950, 2920, 2850, 1775, 1715, 1670, 1520, 1460, 1380, 1350, 1280, 1220, 1110, 1090, 1060, 880, 720 and 700; *m/z* (fab) (%) 476/474 ($M+H^+$, 40%), 420/418 (20), 295 (30), 154 (100) and 136 (90) (Found: C, 53.1; H, 4.2; N, 8.9. Calc. for $C_{21}H_{20}BrN_3O_5$: C, 53.2; H, 4.3; N, 8.9%). Fractional recrystallisation of the mixture of isomers from a combination of dichloromethane and light petroleum afforded a sample of (2*RS*,3*SR*)-3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, δ_H 8.08 (d, *J* 8.9 Hz, 2 H, ArH), 7.79-7.64 (m, 4 H, phth), 7.56 (d, *J* 8.9 Hz, 2 H, ArH), 6.23 (br s, 1 H, NH), 6.18 (d, *J* 11.4 Hz, 1 H, β-H), 5.29 (d, *J* 11.4 Hz, 1 H, α-H) and 1.41 (s, 9 H, CMe_3); δ_C 29.1, 46.4, 52.9, 60.7, 124.3, 124.5, 129.3, 129.4, 131.2, 135.1, 145.3, 164.8 and 167.5. The structure of this material was confirmed through X-ray crystallographic analysis.[11] The ^1H and ^{13}C NMR spectra of the mixture of diastereomers showed resonances for the (2*RS*,3*RS*)-isomer, δ_H 8.26 (d, *J* 8.9 Hz, 2 H, ArH), 7.98-7.81 (m, 4 H, phth), 7.77 (d, *J* 8.9 Hz, 2 H, ArH), 6.27 (br s, 1 H, NH), 6.20 (d, *J* 11.7 Hz, 1 H, β-H), 5.19 (d, *J* 11.7 Hz, 1 H, α-H) and 1.11 (s, 9 H, CMe_3); δ_C 28.8, 49.1, 52.4, 62.7, 124.5, 124.6, 130.0, 130.1, 131.6, 135.3, 148.3, 163.9 and 168.3.

(2S,3S)-3-Bromo-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide* **3c** *and (2S,3R)-3-Bromo*-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide* **4c**. A 1:1 mixture of these compounds was prepared from (*R*)-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate, and obtained in 95% yield.

(2R,3R)-3-Bromo-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide and (2R,3S)-3-Bromo*-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide*. A 1:1 mixture of these compounds was prepared in quantitative yield from (*S*)-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate.

Treatment of (2S,3S)-3-Bromo-N-*phthaloyl*-p-*nitrophenylalanine Methyl Ester* **3a** *with Silver Nitrate in Aqueous Acetone*. To a solution of the bromide **3a** (50 mg, 0.12 mmol) in acetone (3 cm^3), a solution of silver nitrate (25 mg, 0.15 mmol) in water (2 cm^3) was added. The resultant mixture was stirred at 65 °C in the dark for 48 h, then it was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with dichloromethane and the organic extracts were dried and concentrated under reduced pressure. Recrystallisation of the residue from a mixture of dichloromethane and light petroleum gave the (*Z*)-*p*-nitrophenylalanine derivative **15a** as large colourless prisms (34 mg, 84%), m.p. 133-134 °C; ν_{max}/cm^{-1} 1780, 1720, 1600, 1530 and 1345; δ_H 8.16 (d, *J* 8.8 Hz, 2 H, ArH), 8.13 (s, 1 H, β-H), 7.92-7.83 (m, 4 H, phth), 7.55 (d, *J* 8.8 Hz, 2 H, ArH), 3.87 (s, 3 H, OMe); *m/z* (ei) (%) 352 (M^+, 90), 342 (63), 293 (41), 292 (46), 247 (24), 218 (15), 190 (18), 166 (21), 104 (100) and 76 (73); *m/z* (ei) 352.068 (M^+) [Calc. for $C_{18}H_{12}N_2O_6$ (M^+) *m/z* 352.070]. Neither the alcohol **3b** nor the alkene **14a** were detected in the crude product.

Treatment of (2S,3R)-3-Bromo-N-*phthaloyl*-p-*nitrophenylalanine Methyl Ester* **4a** *with Silver Nitrate in Aqueous Acetone*. The reaction of the bromide **4a**, carried out as described above for the reaction of the stereoisomer **3a**, afforded an oil which was chromatographed. Elution afforded a 2:3 mixture of the dehydrophenylalanine derivatives **14a** and **15a** as a viscous oil (25%). The ^1H NMR spectrum of the mixture

showed resonances for the (*Z*)-isomer **15a**, identical to those described above, and signals for the (*E*)-isomer **14a**, δ_H 8.26 (d, *J* 8.7 Hz, 2 H, ArH), 7.80-7.98 (m, 4 H, phth), 7.60 (d, *J* 8.7 Hz, 2 H, ArH), 7.28 (s, 1 H, β-H) and 3.72 (s, 3 H, OMe). Continued elution gave the β-hydroxy-*p*-nitrophenylalanine derivative **3b** as colourless needles (63%), after recrystallisation from a mixture of dichloromethane and light petroleum, m.p. 183-185 °C; ν_{max}/cm^{-1} 3604, 3421, 1779, 1752, 1714, 1614, 1526, 1392, 1352 and 1182; δ_H 8.13 (d, *J* 8.9 Hz, 2 H, ArH), 7.82-7.73 (m, 4 H, phth), 7.54 (d, *J* 8.9 Hz, 2 H, ArH), 5.79 (dd, *J* 4.4 and 10.0 Hz, 1 H, β-H), 5.53 (d, *J* 4.4 Hz, 1 H, α-H), 5.34 (d, *J* 10.0 Hz, 1 H, OH) and 3.89 (s, 3 H, OMe); *m/z* (fab) (%) 371 ($M+H^+$, 9), 353 (3), 321 (3), 307 (11), 289 (9), 219 (3), 154 (100), 137 (66), 136 (79), 107 (28), 89 (33) and 77 (31).

(2RS,3SR)-3-Hydroxy-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide*. To a solution of a 1:1 mixture of (2*RS*,3*RS*)-3-bromo-*N-tert*-butyl-*N*$^{\alpha}$-phthaloyl-*p*-nitrophenylalaninamide and the (2*RS*,3*SR*)-isomer (265 mg, 0.56 mmol) in acetone (10 cm^3) and water (10 cm^3), silver sulfate (263 mg, 0.84 mmol) was added and the suspension was heated at 65 °C in the dark for 3 days. The mixture was then cooled to room temperature and concentrated under reduced pressure. The residue dissolved in dichloromethane and the solution was washed with saturated brine, then it was dried and concentrated under reduced pressure. The residue was chromatographed, to give the title compound as an off-white crystalline solid (154 mg, 67%), m.p. 209-210 °C; ν_{max}/cm^{-1} 3700, 3400, 3160, 3000, 2920, 2270, 1830, 1800, 1720, 1650, 1610, 1570, 1480, 1390 and 1110; δ_H 8.14 (d, *J* 8.8 Hz, 2 H, ArH), 7.81-7.71 (m, 4 H, phth), 7.54 (d, *J* 8.8 Hz, 2 H, ArH), 6.01 (br s, 1 H, NH), 5.68 (dd, *J* 4.9 and 8.3 Hz, 1 H, β-H), 5.17 (d, *J* 4.9 Hz, 1 H, α-H), 4.93 (d, *J* 8.3 Hz, 1 H, OH) and 1.37 (s, 9 H, CMe_3); δ_C 168.6, 164.9, 147.4, 134.7, 131.1, 126.6, 123.9, 123.6, 71.7, 59.9, 52.3 and 28.6; *m/z* (ei) (%) 412 ($M+H^+$, 1), 384 (2), 378 (2), 356 (1), 294 (82), 260 (100) and 204 (30) (Found: C, 61.0; H, 5.3; N, 10.0. Calc. for $C_{21}H_{21}N_3O_6$: C, 61.3; H, 5.2; N, 10.2%).

(2R,3S)-3-Hydroxy-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide* **3d**. This compound was prepared from a 1:1 mixture of the bromides **3c** and **4c**, as described above for the synthesis of the corresponding racemate, and obtained in 64% yield, m.p. 226-228 °C; $[\alpha]_D^{25}$ +84.1° (c, 0.453 in $CHCl_3$). There was no indication of the presence of either of the alkenes **14b** or **15b** in the ^1H NMR spectrum of the crude reaction mixture.

(2S,3R)-3-Hydroxy-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide*. This compound was prepared from a 1:1 mixture of (2*R*,3*R*)- and (2*R*,3*S*)-3-bromo-*N-tert*-butyl-*N*$^{\alpha}$-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate, and obtained in 62% yield, m.p. 220-222 °C; $[\alpha]_D^{20}$ -83.1 (c, 0.083 in $CHCl_3$).

Treatment of (2RS,3RS)- and (2RS,3SR)-3-Bromo-N-*phthaloyl*-p-*nitrophenylalanine Methyl Ester with Silver Sulfate in Aqueous Acetone*. A 1:1 mixture of the title bromides was treated with silver sulfate in aqueous acetone, as described for the reaction of the bromoamides **3c** and **4c**. Analysis of the crude reaction mixture by ^1H NMR spectroscopy showed that the racemate of the alcohol **3a** and the alkenes **14a** and **15a** were present in the ratio *ca.* 1:1:10.

Treatment of (2RS,3RS)- and (2RS,3SR)-3-Bromo-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide with Silver Nitrate in Aqueous Acetone*. The reaction of a 1:1 mixture of the title bromides, carried out as

described above for the reaction of the bromoester **3a**, afforded an oil which was chromatographed. Elution afforded the nitrate **16** (19%), m.p. 192 °C (dec.); ν_{max}/cm^{-1} 3720, 3460, 3390, 3190, 3020, 2950, 2290, 1830, 1800, 1740, 1670, 1630, 1550, 1490, 1400, 1370, 1320, 1300, 1240, 1190 and 1110; δ_H 8.30 (d, *J* 8.9 Hz, 2 H, ArH), 7.81-7.92 (m, 4 H, phth), 7.77 (d, *J* 8.9 Hz, 2 H, ArH), 7.19 (d, *J* 10.7 Hz, 1 H, β-H), 5.89 (br s, 1 H, NH), 4.90 (d, *J* 10.7 Hz, 1 H, α-H) and 1.14 (s, 9 H, CMe_3); δ_C 167.6, 163.1, 148.6, 141.8, 134.9, 131.2, 129.1, 124.1, 124.1, 78.1, 57.8, 52.2 and 28.3; *m/z* (ei) (%) 457 ($M+H^+$, 30), 393 (15), 307 (40), 286 (100) and 260 (30). Continued elution gave (2*RS*,3*SR*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide (54%), identical to the sample obtained as described above. There was no indication of the presence of either of the alkenes **14b** or **15b** in the ^1H NMR spectrum of the crude product.

(2RS,3SR)-3-Hydroxy-p-*nitrophenylalanine*. A mixture of (2*RS*,3*SR*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide (85 mg, 0.21 mmol) in a 2:1 mixture of 6N hydrochloric acid and acetic acid (10 cm^3) was heated at reflux for 5 h and stirred overnight at room temperature, before it was concentrated under reduced pressure. Water (10 cm^3) was added to the residue, then the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (10 cm^3) and to that solution aniline (0.7 cm^3) in dichloromethane (10 cm^3) was added. The mixture was let stand at 4 °C for 24 h and the material which crystallised was separated by filtration and washed with dichloromethane, to give the title compound as an off-white powder (27 mg, 58%), m.p. 192-193 °C (lit.[14] 187-188 °C (dec.)); ν_{max}/cm^{-1} 3550, 3200, 2920, 2870, 1610, 1590, 1530, 1460, 1380, 1350, 1200, 1110, 1010, 865, 855, 740 and 710; δ_H (CF_3CO_2D) 8.33 (d, *J* 8.8 Hz, 2 H, ArH), 7.74 (d, *J* 8.8 Hz, 2 H, ArH), 5.77 (d, *J* 3.9 Hz, 1 H, β-H) and 4.70 (d, *J* 3.9 Hz, 1 H, α-H); δ_C (D_2O) 173.5, 149.6, 149.0, 129.1, 126.0, 72.7 and 62.5; *m/z* (fab) (%) 227 ($M+H^+$). The ^1H NMR spectral data for this compound is consistent with that reported.[14]

(2R,3S)-3-Hydroxy-p-*nitrophenylalanine* **18**. This compound was prepared from the alcohol **3d**, as described above for the synthesis of the corresponding racemate, and obtained in 69% yield, m.p. 200-203 °C (lit.[15] 174-176 °C); $[\alpha]_D^{25}$ +35.3° (c, 0.102 in 1N HCl) (lit.[15] $[\alpha]_D^{25}$ +27° (c, 0.5 in H_2O)).

(2S,3R)-3-Hydroxy-p-*nitrophenylalanine*. This compound was prepared from the (2*S*,3*R*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate, and obtained in 54% yield, m.p. 204-205 °C; $[\alpha]_D^{20}$ -36.4° (c, 0.176 in 1N HCl) (lit.[16] $[\alpha]_D^{21.5}$ -33.8° (c, 5 in 1N HCl)).

(S)-N-tert-*Butyl*-N^{α}-*phthaloylvalinamide* **11b**. To a suspension of *(S)-N*-phthaloylvaline[12] (15.57 g, 63 mmol) in dichloromethane (60 cm^3), triethylamine (6.37 g, 63 mmol) was added. The resulting solution was cooled to 0 °C, then ethyl chloroformate (6.87 g, 63 mmol) was added and the mixture was stirred for 15 min. *tert*-Butylamine (4.60 g, 63 mmol) was added and the mixture was allowed to warm to room temperature, then it was stirred for a further 40 min. The mixture was filtered and the filtrate was washed with water, then it was dried and concentrated under reduced pressure. A portion (*ca.* 4.6 g, 25%) of the residue was chromatographed, to give the title compound **11b** as a colourless crystalline solid (2.60 g), m.p. 144-147 °C; $[\alpha]_D^{21}$ +32.3° (c, 8.7 in $CHCl_3$); ν_{max}/cm^{-1} 3400, 3365, 2920, 2850, 1760, 1710, 1680, 1550, 1530, 1470, 1400, 1070 and 715; δ_H 7.81-7.91 (m, 4 H, phth), 7.13 (br s, 1 H, NH), 4.35 (d, *J* 11.3 Hz, 1 H, α-H), 2.88 (m, 1 H, β-H), 1.39 (s, 9 H, CMe_3), 1.15 (d, *J* 6.7 Hz, 3 H, CH_3) and 0.87 (d, *J* 6.5 Hz, 3 H, CH_3'); δ_C 21.6, 21.7, 29.8, 30.6, 53.3, 66.7, 125.6, 133.4, 136.3, 169.9 and 170.5; *m/z* (ei) (%) 303 ($M+H^+$, 1), 275

(1), 260 (5) and 202 (100) (Found: C, 67.3; H, 7.6; N, 9.2%. Calc. for $C_{17}H_{22}N_2O_3$: C, 67.5; H, 7.3; N, 9.3%).

(R)-3-Bromo-N-tert-*butyl*-N$^{\alpha}$-*phthaloylvalinamide* **5c**. A mixture of *N*-bromosuccinimide (1.18 g, 6.6 mmol) and the amide **11b** (1.33 g, 4.4 mmol) in carbon tetrachloride (60 cm^3) was heated at reflux for 2 h, while it was irradiated with a 250 W mercury lamp. The mixture was then cooled to 0 °C and filtered. The filtrate was washed with water, then it was dried and concentrated under reduced pressure, to give the title compound **5c** as fine colourless needles, after recrystallisation from a mixture of light petroleum and ether (1.54 g, 92%), m.p. 139-141 °C; $[\alpha]_D^{20}$ +11.6° (c, 3.03 in $CHCl_3$); ν_{max}/cm^{-1} 3380, 2920, 2850, 1710, 1530, 1460, 1380, 1080 and 720; δ_H 7.67 (m, 4 H, phth), 5.28 (s, 1 H, α-H), 2.07 (s, 3 H, CH_3), 1.86 (s, 3 H, CH_3') and 1.30 (s, 9 H, CMe_3); δ_C 30.5, 35.0, 35.4, 54.0, 67.7, 68.1, 125.8, 133.3, 136.6, 166.0 and 170.2; *m/z* (ei) (%) 381/383 ($M+H^+$, 5), 380/382 (5), 279/381 (5), 365/367 (10), 325/327 (15), 308/310 (15) and 301 (100) (Found: C, 53.7; H, 5.5; N, 7.1. Calc. for $C_{17}H_{21}BrN_2O_3$: C, 53.6; H, 5.6; N, 7.3%).

Treatment of (R)-3-Bromo-N-*phthaloylvaline Methyl Ester* **5a** *with Silver Nitrate in Aqueous Acetone*. The reaction of the bromide **5a**,[12] carried out at room temperature for 14 h, but otherwise as described above for the reaction of the nitrophenylalanine derivative **3a**, afforded an oil which was chromatographed. Elution gave the α,β-dehydrovaline derivative **12a** (40 mg, 8%), m.p. 81-82 °C; δ_H 7.40-8.10 (m, 4 H, phth), 3.68 (s, 3 H, OMe), 2.43 (s, 3 H, CH_3) and 1.88 (s, 3 H, CH_3') (Found: C, 64.7; H, 5.1; N, 5.4. Calc. for $C_{14}H_{13}NO_4$: C, 64.8; H, 5.1; N, 5.4%). Continued elution afforded the β,γ-dehydrovaline derivative **13a** (0.15 g, 34%); ν_{max}/cm^{-1} 2950, 1780, 1748, 1728, 1470, 1440, 1386, 1293, 1245, 1203, 1113, 915 and 717; δ_H 7.75-7.92 (m, 4 H, phth), 5.38 (br s, 1 H, γ-H), 5.14 (br s, 1 H, γ-H'), 5.11 (s, 1 H, α-H), 3.79 (s, 3 H, OMe) and 1.92 (s, 3 H, β-CH_3); *m/z* (ei) (%) 259 (M^+, 8), 227 (20) and 200 (100). Further elution gave the β-hydroxyvaline derivative **5b** (0.21 g, 43%), m.p. 86-87 °C; ν_{max}/cm^{-1} 3544, 1767, 1725, 1275 and 717; δ_H 7.91-7.80 (m, 4 H, phth), 4.41 (br s, 1 H, OH), 3.77 (s, 3 H, OMe), 1.53 (s, 3 H, CH_3) and 1.31 (s, 3 H, CH_3'); *m/z* (ei) (%) 262 ($M-CH_3^+$, 10), 246 (5), 230 (28), 219 (100), 188 (74), 187 (98) and 160 (74) (Found: C, 60.6; H, 5.5; N, 5.1. Calc. for $C_{14}H_{15}NO_5$: C, 60.6; H, 5.5; N, 5.1%). Analysis of the crude reaction mixture by ^1H NMR spectroscopy showed the alcohol **5b** and the alkenes **12a** and **13a** to be present in the ratio *ca.* 3.5 : 1 : 3.5.

Treatment of (R)-3-Bromo-N-tert-*butyl*-N$^{\alpha}$-*phthaloylvalinamide* **5c** *with Silver Nitrate in Aqueous Acetone*. The reaction of the bromide **5c**, carried out as described above for the reaction of the ester **5a**, afforded an oil which was chromatographed. Elution gave the β,γ-dehydrovaline derivative **13b** as a colourless oil (26%); ν_{max}/cm^{-1} 3450, 2975, 2950, 1780, 1710, 1695, 1525, 1460, 1475 and 1385; δ_H 7.89-7.73 (m, 4 H, phth), 6.28 (br s, 1 H, NH), 5.27 (s, 1 H), 5.23 (s, 1H), 5.21 (s, 1H), 1.89 (s, 3 H, CH_3) and 1.43 (s, 9 H, CMe_3); δ_C 169.8, 167.3, 141.6, 136.1, 133.8, 125.4, 119.5, 62.5, 53.7, 30.5 and 22.8; *m/z* (ei) (%) 300 (M^+, 5) and 200 (100) (Found: C, 68.0; H, 7.0; N, 9.0. Calc. for $C_{17}H_{20}N_2O_3$: C, 68.0; H, 6.7; N, 9.3%). Further elution afforded the alcohol **5d**, as colourless crystals after recrystallisation from a mixture of ether and light petroleum (63%), m.p. 135-136 °C; ν_{max}/cm^{-1} 3328, 3084, 2972, 2928, 2248, 1774, 1720, 1660, 1614, 1550, 1470, 1384, 1224, 1176, 1144, 1088, 1048, 992, 956, 912, 878, 788, 774, 724 and 646; δ_H 7.84-7.79 (m, 2 H, phth), 7.73-7.69 (m, 2 H, phth), 7.30 (br s, 1 H, NH), 4.61 (s, 1 H, α-H), 4.25 (br s, 1 H, OH),

1.41 (s, 3 H, CH_3), 1.30 (s, 9 H, CMe_3) and 1.22 (s, 3 H, CH_3); *m/z* (ei) (%) 318 (M^+, 50), 300 (10), 259 (50), 201 (100), 187 (100) and 160 (95) (Found: C, 64.3; H, 7.2; N, 8.7. Calc. for $C_{17}H_{22}N_2O_4$: C, 64.1; H, 7.0; N, 8.8%). The structure of the alcohol **5d** was confirmed through X-ray crystallographic analysis.[11] Analysis of the crude reaction mixture by ^1H NMR spectroscopy showed the alcohol **5d** and the alkene **13b** were present in the ratio *ca.* 2 : 1.

Competitive Hydrolysis Reactions of the Bromides **5a** *and* **5c**. The relative rates of reaction of the bromides **5a** and **5c** with silver nitrate were determined by treating an equimolar ratio of the substrates at a concentration of approximately 0.1 mM in aqueous acetone (1:1, v/v) with the silver salt (1.4 equiv.) at room temperature, in the presence of *N-tert*-butylbenzamide (0.5 equiv.) as an internal standard. Aliquots of the reaction mixture were sampled at intervals and worked up as described for the preparative studies, then analysed by ^1H NMR spectroscopy. Integration of peaks characteristic of the residual bromides **5a** and **5c** and the internal standard, and comparison with the spectra of the corresponding starting mixtures, were used to determine the percentage of each substrate remaining, from which the ratios of the logarithms of those percentages were used to calculate the relative rates of reaction. Relative rates of duplicate experiments varied by less than 10%.

ACKNOWLEDGEMENT. This work was supported by a grant from the Australian Research Council.

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(*Received in UK* 6 *March* 1996; *accepted* 21 *March* 1996)