Mechanism of hydrogen atom transfer in the photolytic rearrangement of *N*-bromophenylalaninamide derivatives

Christopher J. Easton,* Martin C. Merrett and Pasquale Razzino

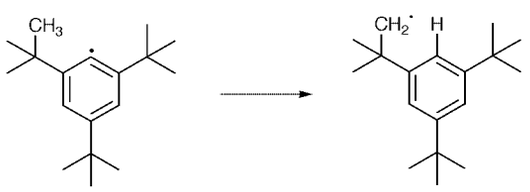
Research School of Chemistry, Australian National University, Canberra ACT 0200, Australia. E-mail: easton@rsc.anu.edu.au

Received (in Cambridge, UK) 11th November 1999, Accepted 31st January 2000
Published on the Web 13th March 2000

Photolysis of *N*-bromo-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide gave a 1 : 1 mixture of the diastereomers of 3-bromo-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide. Reactions carried out with various concentrations of the *N*-bromoamide, and in the presence of 4-*tert*-butyltoluene, showed that the ratio of the product bromophenylalanine derivatives to 4-*tert*-butylbenzyl bromide varied as a function of the concentration of the *N*-bromoamide, indicating that the bromophenylalanine derivatives are formed through an intermolecular process and not by intramolecular 1,4-hydrogen atom transfer of the corresponding amidyl radical. Results of reactions of *N*-bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-methylphenylalaninamide are also consistent with this interpretation. Reactions of stereoselectively β-deuteriated derivatives of *N*-bromo-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide established that the pro-*S* benzylic hydrogen of the phenylalaninamide is selectively abstracted, by a factor of *ca.* 3.8, in this intermolecular process.

Introduction

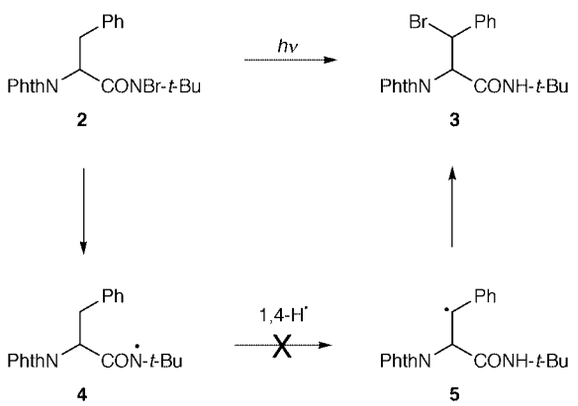
Hydrogen transfer reactions constitute an important aspect of free radical chemistry. Their intramolecular variants are well known[1] with the most common of these involving 1,5-hydrogen shifts. By comparison, intramolecular 1,4-hydrogen transfers occur less frequently[2,3] and only when the reactions are highly exothermic. Even then, such reactions are sometimes more complex than is immediately apparent, as illustrated by the rearrangement of the 2,4,6-tri-*tert*-butylphenyl radical **1** (Scheme 1), where it has been established that the intra-



1

Scheme 1

molecular 1,4-hydrogen migration involves quantum mechanical tunnelling.[3] Recently we reported anchimeric assistance in hydrogen atom transfer reactions when amino acid derivatives reacted with *N*-bromosuccinimide.[4] Associated with that study we observed that photolysis of the *N*-bromoamide **2** affords a 1 : 1 mixture of the diastereomers of the β-bromophenylalanine **3** (Scheme 2), and our initial results indicated that this rearrangement occurred *via* an intramolecular 1,4-hydrogen atom transfer reaction of the amidyl radical **4** to give the benzylic radical **5**. We have now carried out further experiments which do not alter the major conclusions of the original paper, that there is neighbouring group participation in the reactions involving *N*-bromosuccinimide, but they show that the hydrogen transfer in the reaction of the amidyl radical **4** is in fact an intermolecular process, where the benzylic hydrogen abstraction is stereoselective. The purpose of this paper is to correct the earlier report, based on the new evidence.



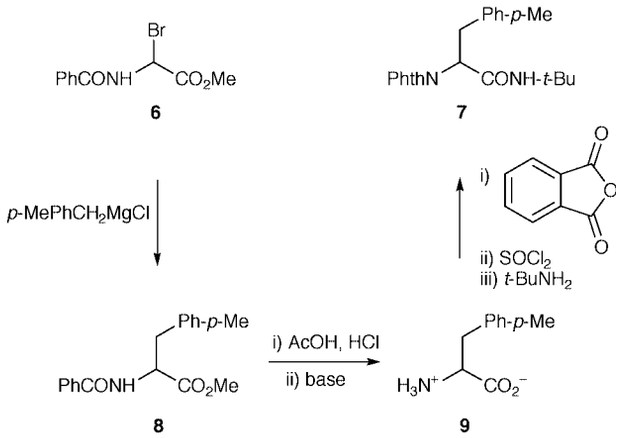
Scheme 2 Phth = phthaloyl.

Results and discussion

In order to examine the mechanism of reaction of the bromoamide **2**, reactions of the related compounds **13**–**15** were also investigated. A variety of procedures was examined for the preparation of the bromides **2** and **13**–**15** from the corresponding amides **7** and **10**–**12**. When *tert*-butyl hypobromite was used as the reagent low product yields were obtained.[4] With hindered amides, acetyl hypobromite has been reported to give good yields of the corresponding bromoamides,[5] and it proved to be the reagent of choice in the present work. The amide **10** was prepared from phenylalanine as reported previously.[6] Using the same procedure, the deuterides **11** and **12** were obtained from the corresponding labelled phenylalanines,[7] each in approximately 98% diastereomeric excess and with approximately 99% deuterium incorporation. The *p*-methylphenylalanine derivative **7** was prepared from *N*-benzoyl-α-bromoglycine methyl ester **6**,[8,9] as outlined in Scheme 3.[10]

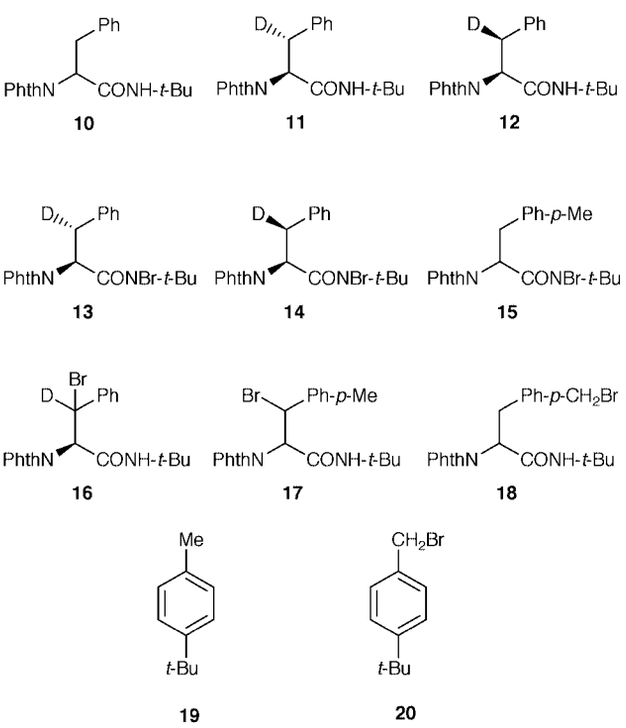
Photolysis of a 1.5 mmol dm^{-3} solution of the bromoamide **2** in carbon tetrachloride afforded a 1 : 1 mixture of the diastereomers of the bromide **3**, which was identical to the material formed by treatment of the phenylalaninamide **10** with *N*-bromosuccinimide.[6,9,11] The reaction was complete in

DOI: 10.1039/a908968c



Scheme 3

5 minutes, indicating that it is an efficient chain process. The analogous reaction of each of the deuterides **13** and **14** afforded the benzylic bromide **16**, as a 1:1 mixture of the diastereomers in each case. The sample of the bromide **16** obtained from the deuteride **13** contained *ca.* 85% deuterium, as determined by mass spectrometry and by integration of the peaks corresponding to the α- and residual β-protons of each stereoisomer in the ^{1}H NMR spectrum. A similar analysis showed that the sample prepared from the deuteride **14** contained *ca.* 28% deuterium. These results correspond to diastereoselective loss of the pro-*S* hydrogen and, based on the assumption that the deuterium isotope effects for loss of the pro-*R* and pro-*S* hydrogens are identical, they correlate with a deuterium isotope effect of 1.5 and a stereoselectivity of *ca.* 3.8.



The reaction of a 1.5 mmol dm^{-3} solution of the bromoamide **15** afforded a 1:1 mixture of the diastereomers of the β-bromophenylalanine derivative **17**, together with the bromomethylphenylalanine derivative **18**, in the ratio *ca.* 10:1. When the reactions of the bromoamides **2** and **15** were repeated in the presence of 4-*tert*-butyltoluene **19**, production of the brominated phenylalanine derivatives **3**, **17** and **18** was accompanied by formation of the benzyl bromide **20**. Studies of the effect on the product ratios of changing the relative concentrations of the reactants **2**, **15** and **19** were also undertaken, and the results of these experiments are shown in Tables 1 and 2. Repeat experiments afforded product ratios which varied by less than 10% from those shown.

Table 1 Ratio of the bromides **20** and **3** obtained by photolysis[a] of the bromoamide **2**[b] in the presence of 4-*tert*-butyltoluene **19**

4-*tert*-Butyltoluene **19** concentration (mmol dm^{-3})	Bromoamide **2** concentration (mmol dm^{-3})	
	0.65	2.60
0.92	1:16	1:32
3.46	1:4	1:13

[a] In carbon tetrachloride with a 300 W ultraviolet lamp for 5 min. [b] Used as a *ca.* 1:1 mixture with the amide **10**.

Table 2 Ratio of the bromides **20**, **17** and **18** obtained by photolysis[a] of the bromoamide **15**[b] in the presence of 4-*tert*-butyltoluene **19**

4-*tert*-Butyltoluene **19** concentration (mmol dm^{-3})	Bromoamide **15** concentration (mmol dm^{-3})	
	1.0	5.0
1.0	1:8:1	1:32:5
5.0	1:3:0.2	1:7:1

[a] In carbon tetrachloride with a 300 W ultraviolet lamp for 5 min. [b] Used as a *ca.* 1:1 mixture with the amide **7**.

The reaction to produce the bromide **20** must involve an intermolecular hydrogen atom transfer from the *tert*-butyltoluene **19** and, as expected on that basis, increasing the concentration of the latter while maintaining that of either of the *N*-bromoamides **2** or **15** resulted in a corresponding increase in the ratio of the product bromides **20**:**3**, or **20**:**17** and **18**. Increasing the concentration of either of the *N*-bromoamides **2** or **15** while maintaining that of the *tert*-butyltoluene **19** resulted in a corresponding decrease in the ratio of the product bromides **20**:**3**, or **20**:**17** and **18**. This is strong evidence that the bromides **3**, **17** and **18** are also formed through intermolecular hydrogen atom transfer.

The correlation of the relative concentrations of the *tert*-butyltoluene **19** and the *N*-bromoamides **2** and **15** used, with the ratios of the products **20**:**3**, and **20**:**17** and **18** formed, is not exact, but the deviations can be attributed to a variety of factors. For example, the ratio in which the various products continue to form during the course of a competitive reaction varies as the corresponding starting materials become depleted to different extents. Therefore the product ratio will depend on the extent to which reaction proceeds. This will be affected by the initial ratio of the *tert*-butyltoluene **19** to the *N*-bromoamides **2** and **15**. Another factor which complicates the present work is that the *N*-bromoamides **2** and **15** are converted into their reduced forms **10** and **7**, respectively, during the course of reaction. While the bromides **3**, **17** and **18** are likely to be produced *via* hydrogen transfer from both the corresponding amides **10** and **7** and *N*-bromoamides **2** and **15**, the kinetics of these processes are likely to be different.

Nevertheless, the results are unambiguous. For example, since the bromides **20**, **17** and **18** formed in the ratio 1:8:1 when the initial concentration of both the *N*-bromoamide **15** and the *tert*-butyltoluene **19** was 1 mmol dm^{-3}, in the reaction involving a 5 mmol dm^{-3} initial concentration of each reagent the expected product ratio would be 1:8:1 if all the products formed through intermolecular hydrogen atom transfer, 1:1.6:1 if only the bromophenylalanine derivative **17** was produced by intramolecular hydrogen abstraction, or 1:1.6:0.2 if formation of both of the bromides **17** and **18** involved intramolecular hydrogen transfer. The observed product ratio of

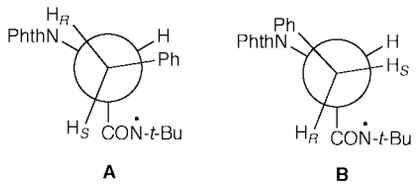


Fig. 1 Eclipsed conformers of the amidyl radical **4** required for intramolecular hydrogen transfer.

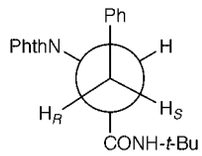


Fig. 2 Preferred conformation of the phenylalaninamide **10**.

1 : 7 : 1 (Table 2) is clearly consistent with the first of these cases. Based on this analysis, at most one eighth of the reaction to produce the bromide **17** is intramolecular, even when the most dilute concentration of the substrate **15** is used.

Thus it is apparent that the bromophenylalanine derivative **3** does not form from the bromoamide **2** *via* an intramolecular 1,4-hydrogen atom transfer reaction of the amidyl radical **4** to give the benzylic radical **5**. Analogous 1,5- and 1,6-hydrogen transfer reactions have been observed with amino acid derivatives[12–14] and it is likely that similar reactions occur in biological systems.[14] However, it appears that the smaller transition state required for 1,4-migration is not accessible, at least in this case.

Owing to the stereoselectivity observed in the reactions of the deuterides **13** and **14**, and the relatively low reactivity of competitive substrates such as the *tert*-butyltoluene **19**, initially we concluded that the bromophenylalanine derivative **3** formed through an intramolecular process.[4] As seen from the results in Table 1, transfer of the bromine to the β position of the phenylalanine derivative **2** is favoured over halogenation of the methyl group of the *tert*-butyltoluene **19** by a factor of *ca*. 10. By comparison, in reactions of the phenylalaninamide **10** and the *tert*-butyltoluene **19** with *N*-bromosuccinimide, hydrogen atom transfer from the latter is preferred. The present work shows that this change in relative reactivity reflects the different nature of the hydrogen abstracting species, which are presumably the amidyl radical **4** in the reaction of the bromoamide **2** and bromine atom in the reaction with *N*-bromosuccinimide, rather than indicating that the reaction of the bromoamide **2** is intramolecular.

The deuterium isotope effect of 1.5 for the reactions of the deuterides **13** and **14** indicates that there is little carbon–hydrogen bond homolysis in the transition state of the hydrogen transfer step for reaction of the *N*-bromoamide **2**. On this basis the stereoselective abstraction of the pro-*S* benzylic hydrogen illustrated in the reactions of the deuterides **13** and **14** most likely reflects a conformational preference of the substrate, and this is consistent with either an intra- or intermolecular hydrogen transfer. The conformers required for the putative intramolecular hydrogen transfer are illustrated in Fig. 1 and, of these, conformer A would be preferred on steric grounds. Reaction of this conformer would result in abstraction of the pro-*S* hydrogen. However, the stereoselectivity is also consistent with an intermolecular process. The ^{1}H NMR spectra of the deuterides **11** and **12** and the respective coupling constants $J_{\alpha,\beta}$ of 6 and 10 Hz indicate that the preferred conformation of the *S*-enantiomer of the phenylalaninamide **10** is as shown in Fig. 2. This is the only staggered conformation which will give rise to the large coupling constant between the α-proton and the pro-*R* β-hydrogen. In this conformation, steric interactions affecting the hydrogen atom transfer would be expected to result in stereoselective loss of the pro-*S* hydrogen, as this site is less hindered to approach of the hydrogen abstracting species and loss of this hydrogen would relieve nonbonding interactions between the phenyl and phthalimido groups. Such steric interactions must be substantive, given the observed stereoselectivity which is noteworthy for a free radical process.[15]

Experimental

General

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Infrared spectra were recorded on an Hitachi 270-30 or a Perkin-Elmer 683 infrared spectrophotometer, calibrated against polystyrene film, as Nujol mulls between sodium chloride plates. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on a GEMINI 300 spectrometer, in deuteriochloroform with tetramethylsilane as the internal standard, unless stated otherwise. Electron impact mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Microanalyses were performed by the Microanalytical Services Unit of the Research School of Chemistry, Australian National University. Silica chromatography was performed under positive pressure using Merck-Keiselgel 60 (230–400 mesh ASTM), with between 20 and 50% ethyl acetate in light petroleum (bp 66–68 °C) as the eluent, unless stated otherwise.

4-*tert*-Butyltoluene **19** and an authentic sample of 4-*tert*-butylbenzyl bromide **20** were purchased from Aldrich Chemical Co.

Preparations

***N*-Benzoyl-*p*-methylphenylalanine methyl ester 8.** Using the procedure of Castelhano *et al*.,[10] a solution of *p*-methylbenzylmagnesium chloride, prepared from *p*-methylbenzyl chloride (24.0 g, 0.17 mol) and magnesium turnings (4.15 g, 0.17 mol) in diethyl ether (150 cm^3), was added *via* cannula to a solution of *N*-benzoyl-α-bromoglycine methyl ester[8,9] **6** (21.1 g, 78 mmol) in ether (250 cm^3) maintained at −78 °C. The mixture was allowed to warm to room temperature and stirred for 18 h, then saturated aqueous ammonium chloride was added. The organic layer was separated and washed with saturated aqueous sodium chloride, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residual oil was chromatographed on silica, eluting with a gradient of light petroleum–ethyl acetate to afford compound **8** as an oil (10.3 g, 44%). A small sample of the oil was triturated with light petroleum–ether to give a colourless amorphous powder, which recrystallized from light petroleum–ether to give crystals, mp 89–90 °C (Found: C, 72.70; H, 6.55; N, 4.80. $C_{18}H_{19}NO_3$ requires C, 72.71; H, 6.44; N, 4.71%); $\tilde{\nu}_{max}$/cm^{-1} 3320, 3060, 3020, 2950, 2925, 2860, 1740, 1650, 1605, 1580, 1525, 1490, 1440, 1215, 810, 715, 695; δ_H 2.30 (s, 3H), 3.17 (dd, *J* 5.5 and 14, 1H), 3.25 (dd, *J* 6 and 14, 1H), 3.75 (s, 3H), 5.06 (m, 1H), 6.76 (br d, *J* 8 Hz, 1H), 7.0–7.1 (m, 4H), 7.3–7.5 (m, 3H), 7.70–7.75 (m, 2H); δ_C 20.7, 37.0, 52.0, 53.4, 126.7, 128.8, 129.0, 131.4, 132.5, 133.6, 136.3, 166.6, 171.8; *m*/*z* 297.1365 (M^+, $C_{18}H_{19}NO_3$ requires 297.1364), 280 (8%), 238 (13), 176 (85), 161 (7), 145 (23), 122 (15), 105 (100), 91 (13), 77 (48).

***p*-Methylphenylalanine 9.** A mixture of *N*-benzoyl-*p*-methylphenylalanine methyl ester **8** (3.4 g, 11.4 mmol), aqueous hydrochloric acid (36%, 24 cm^3) and glacial acetic acid (16 cm^3) was heated at reflux for 3 h, then cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate, then the aqueous fraction was concentrated under reduced pressure. The residue was dissolved in ethanol (20 cm^3), aniline (0.78 g, 8.4 mmol) added, and the solution stored at *ca*. 4 °C for 16 h. The precipitate which formed was isolated by filtration to give compound **9** as

an off-white powder (1.04 g, 51%), mp 235–238 °C; $\tilde{\nu}_{max}$/cm^{-1} 3392, 2920, 2851, 2710, 2542, 1618, 1586, 1502, 1445, 1411, 1346, 1322, 1309, 1290, 856, 805; δ_H (D_2O) 2.31 (s, 3H), 3.05 (dd, *J* 8 and 14.5, 1H), 3.23 (dd, *J* 5 and 14.5, 1H), 3.94 (dd, *J* 5 and 8 Hz, 1H), 7.21 (m, 4H); *m*/*z* 179.095 (M^+, $C_{10}H_{13}NO_2$ requires *m*/*z* 179.095), 135 (20%), 105 (100), 91 (13), 77 (15).

***N*-Phthaloyl-*p*-methylphenylalanine.** A mixture of *p*-methylphenylalanine **9** (1.13 g, 6.3 mmol), phthalic anhydride (0.98 g, 6.6 mmol) and triethylamine (128 mg, 1.26 mmol) in toluene (40 cm^3) was heated at reflux for 2 h, with azeotropic removal of water, then concentrated under reduced pressure. The residue was partitioned between dichloromethane and aqueous hydrochloric acid (1 mol dm^{-3}), the aqueous phase extracted with dichloromethane, and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure, to give the required compound as a colourless crystalline solid (1.98 g, 100%). A small sample of this material was recrystallized from ether–light petroleum; mp 194–196 °C (Found: C, 69.65; H, 4.93; N, 4.47. $C_{18}H_{15}NO_4$ requires C, 69.89; H, 4.89; N, 4.53%); $\tilde{\nu}_{max}$/cm^{-1} 3500, 2920, 2950, 1775, 1715, 1610, 1515, 1470, 1390, 1115, 1100, 1090, 720; δ_H 2.23 (s, 3H), 3.56 (d, *J* 8, 2H), 5.20 (t, *J* 8, 1H), 6.99 (d, *J* 8, 2H), 7.05 (d, *J* 8 Hz, 2H), 7.65–7.80 (m, 4H); δ_C 21.0, 33.8, 53.1, 123.5, 128.6, 129.2, 131.4, 133.2, 134.1, 136.4, 167.4, 174.7; *m*/*z* 309 (M^+, 20%), 264 (7), 246 (9), 162 (100), 130 (19), 105 (55), 91 (13), 77 (23).

***N*-*tert*-Butyl-N^{α}-phthaloyl-*p*-methylphenylalaninamide 7.** To a suspension of *N*-phthaloyl-*p*-methylphenylalanine (0.93 g, 3.0 mmol) in carbon tetrachloride (30 cm^3), thionyl chloride (1.07 g, 9.0 mmol) and pyridine (95 mg, 1.2 mmol) were added and the mixture was heated at reflux for 2 h, then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in carbon tetrachloride (30 cm^3) and *tert*-butylamine (0.66 g, 9.0 mmol), and the mixture heated at reflux for 0.5 h, then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and the solution washed with aqueous hydrochloric acid (1 mol dm^{-3}) and saturated aqueous sodium bicarbonate solution, then dried ($MgSO_4$), filtered and concentrated under reduced pressure, to give compound **7** as a colourless solid (1.04 g, 95%). A small sample of this material was recrystallized from ethyl acetate to give colourless crystals, mp 210–211 °C (Found: C, 72.20; H, 6.57; N, 7.55. $C_{22}H_{24}N_2O_3$ requires C, 72.51; H, 6.64; N, 7.59%); $\tilde{\nu}_{max}$/cm^{-1} 3300, 2920, 2850, 1775, 1715, 1665, 1560, 1460, 1380, 1365, 1300, 1225, 875, 740, 715; δ_H 1.30 (s, 9H), 2.23 (s, 3H), 3.43 (dd, *J* 10 and 14, 1H), 3.52 (dd, *J* 7 and 14, 1H), 4.97 (dd, *J* 7 and 10 Hz, 1H), 5.82 (br s, 1H), 7.04 (m, 4H), 7.65–7.75 (m, 4H); δ_C 20.8, 26.5, 34.7, 51.5, 56.6, 123.3, 128.6, 129.2, 131.4, 133.7, 134.0, 136.3, 167.3, 168.0; *m*/*z* 364 (M^+, 80%), 305 (15), 264 (100), 246 (43), 217 (56), 202 (22), 173 (98), 105 (86).

(2*S*,3*R*)-[3-$^2H_1$]-*N*-*tert*-Butyl-N^{α}-phthaloylphenylalaninamide 11. Compound **11** was prepared from the corresponding labelled phenylalanine[7] using the procedure employed for the preparation of *N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide **10**,[6] mp 186–188 °C; δ_H 1.31 (s, 9H), 3.56 (d, *J* 6, 1H), 4.98 (d, *J* 6 Hz, 1H), 5.8 (br s, 1H), 7.2 (m, 5H), 7.6–7.8 (m, 4H); *m*/*z* 351 (M^+, 99% $^2H_1$). The ^{1}H NMR spectrum showed that the deuteride **11** was contaminated with *ca.* 1% of the diastereomer. Other physical and spectral data are consistent with those reported for the unlabelled analogue.[6]

(2*S*,3*S*)-[3-$^2H_1$]-*N*-*tert*-Butyl-N^{α}-phthaloylphenylalaninamide 12. Compound **12** was prepared from the corresponding labelled phenylalanine[7] using the procedure employed for the preparation of *N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide **10**,[6] mp 187–188 °C; δ_H 1.31 (s, 9H), 3.47 (d, *J* 10, 1H), 4.98 (d, *J* 10 Hz, 1H), 6.1 (br s, 1H), 7.2 (m, 5H), 7.6–7.8 (m, 4H); *m*/*z* 351 (M^+, 99% $^2H_1$). The ^{1}H NMR spectrum showed that the deuteride **12** was contaminated with *ca.* 1% of the diastereomer. Other physical and spectral data are consistent with those reported for the unlabelled analogue.[6]

General procedure for *N*-bromoamides 2 and 13–15. A suspension of the amide **7**, **10**, **11** or **12** (0.25 mmol) in a solution of acetyl hypobromite in carbon tetrachloride (*ca.* 0.15 mol dm^{-3}, 10 cm^3, 1.5 mmol), that had been prepared using the method of Beebe and Wolfe,[5] was stirred at room temperature for 1 h. The mixture was then concentrated under reduced pressure, to give a crude mixture of the *N*-bromoamide **2**, **13**, **14** or **15** and the corresponding starting material **7**, **10**, **11** or **12**. Chromatography of the mixture on silica afforded the bromoamide **2**, **13**, **14** or **15**, which was used without further purification or characterization, other than to record the ^{1}H NMR spectrum. *N*-Bromo-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide **2**: δ_H 1.48 (s, 9H), 3.52 (dd, *J* 5.5 and 14.5, 1H), 3.59 (dd, *J* 10.5 and 14.5, 1H), 5.69 (dd, *J* 5.5 and 10.5 Hz, 1H), 7.18 (m, 5H), 7.65–7.80 (m, 4H). (2*S*,3*R*)-[3-$^2H_1$]-*N*-Bromo-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide **13**: δ_H 1.47 (s, 9H), 3.51 (d, *J* 5, 1H), 5.66 (d, *J* 5 Hz, 1H), 7.19 (m, 5H), 7.65–7.80 (m, 4H). (2*S*,3*S*)-[3-$^2H_1$]-*N*-Bromo-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide **14**: δ_H 1.47 (s, 9H), 3.56 (d, *J* 11, 1H), 5.66 (d, *J* 11 Hz, 1H), 7.17 (m, 5H), 7.65–7.80 (m, 4H). *N*-Bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-methylphenylalaninamide **15**: δ_H 1.47 (s, 9H), 2.23 (s, 3H), 3.47 (dd, *J* 5 and 14, 1H), 3.57 (dd, *J* 11 and 14, 1H), 5.66 (dd, *J* 5 and 11, 1H), 6.99 (d, *J* 8, 2H), 7.10 (d, *J* 8 Hz, 2H), 7.65–7.80 (m, 4H).

General procedure for photolysis of the *N*-bromoamides 2 and 13–15. A solution of the crude *N*-bromoamide **2**, **13**, **14** or **15** at a concentration of approximately 1.5 mmol dm^{-3} in carbon tetrachloride, contained in a Pyrex flask under a nitrogen atmosphere, was irradiated with a Phillips MLU 300-W ultraviolet lamp for 5 min, then cooled and concentrated under reduced pressure. Chromatography of the residue on silica, eluting with a gradient of light petroleum–dichloromethane, afforded the product bromides **3** and **16**–**18**.

3-Bromo-N-tert-butyl-N^{α}-phthaloylphenylalaninamide 3. *N*-Bromo-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide **2** (50 mg, 0.12 mmol) afforded, after chromatography, a 1:1 mixture of the diastereomers of the bromide **3** (34 mg, 68%). One diastereomer had δ_H 1.40 (s, 9H), 5.32 (d, *J* 11, 1H), 6.05 (d, *J* 11 Hz, 1H), 6.41 (br s, 1H), 7.1–7.4 (m, 5H), 7.60–7.75 (m, 4H). The other diastereomer had δ_H 1.02 (s, 9H), 5.22 (d, *J* 12, 1H), 5.76 (br s, 1H), 6.17 (d, *J* 12 Hz, 1H), 7.3–7.6 (m, 5H), 7.75–8.00 (m, 4H). The physical and spectroscopic properties of the bromide **3** are consistent with those reported previously.[6,9,11]

[3-$^2H_1$]-3-Bromo-N-tert-butyl-N^{α}-phthaloylphenylalaninamide 16. (a) (2*S*,3*R*)-[3-$^2H_1$]-*N*-Bromo-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide **13** (12 mg, 0.028 mmol) afforded, after chromatography, a 1:1 mixture of the diastereomers of the bromide **16** (7 mg, 58%); *m*/*z* 429 (M^+, 85% $^2H_1$) and 431 (M^+, 86% $^2H_1$). One diastereomer had δ_H 1.40 (s, 9H), 5.31 (s, 0.85H), 5.31 (d, *J* 11, 0.15H), 6.06 (d, *J* 11 Hz, 0.15H), 6.35 (br s, 1H), 7.1–7.4 (m, 5H), 7.60–7.75 (m, 4H). The other diastereomer had δ_H 1.02 (s, 9H), 5.23 (s, 0.86H), 5.23 (d, *J* 12, 0.14H), 5.80 (br s, 1H), 6.19 (d, *J* 12 Hz, 0.14H), 7.3–7.6 (m, 5H), 7.75–8.00 (m, 4H). The physical and spectroscopic properties of the bromide **16** are consistent with those reported previously for the unlabelled analogue.[6,9,11]

(b) (2*S*,3*S*)-[3-$^2H_1$]-*N*-Bromo-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide **14** (10 mg, 0.023 mmol) afforded, after chromatography, a 1:1 mixture of the diastereomers of the bromide **16** (8 mg, 80%); *m*/*z* 429 (M^+, 28% $^2H_1$) and 431 (M^+, 27% $^2H_1$). One diastereomer had δ_H 1.41 (s, 9H), 5.32 (s, 0.28H), 5.32 (d, *J* 11, 0.72H), 6.05 (d, *J* 11 Hz, 0.72H), 6.55 (br s, 1H), 7.1–7.4 (m, 5H), 7.60–7.75 (m, 4H). The other diastereomer

had δ_H 1.04 (s, 9H), 5.22 (s, 0.27H), 5.22 (d, *J* 12, 0.73H), 5.75 (br s, 1H), 6.17 (d, *J* 12 Hz, 0.73H), 7.3–7.6 (m, 5H), 7.75–8.00 (m, 4H).

3-Bromo-N-tert-butyl-N$^{\alpha}$-phthaloyl-p-methylphenylalaninamide ***17*** *and N-tert-butyl-N$^{\alpha}$-phthaloyl-p-bromomethylphenylalaninamide* ***18***. *N*-Bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyl-*p*-methylphenylalaninamide **15** (200 mg, 0.45 mmol) afforded, after chromatography, the bromide **18** (12 mg, 6%) as a colourless solid. Recrystallization from ether–light petroleum gave colourless crystals, mp 229–231 °C (Found: C, 59.47; H, 5.11; N, 6.14. $C_{22}H_{23}BrN_2O_3$ requires C, 59.60; H, 5.23; N, 6.32%); $\tilde{\nu}_{max}$/cm^{-1} 3303, 2967, 1776, 1726, 1658, 1379; δ_H 1.31 (s, 9H), 3.43 (dd, *J* 10 and 14.5, 1H), 3.57 (dd, *J* 6.5 and 14.5, 1H), 4.38 (s, 2H), 4.96 (dd, *J* 6.5 and 10, 1H), 5.82 (br s, 1H), 7.15 (d, *J* 8, 2H), 7.22 (d, *J* 8 Hz, 2H), 7.65–7.80 (m, 4H); δ_C 28.3, 33.0, 34.4, 51.3, 56.0, 123.0, 128.9, 131.2, 133.8, 135.9, 137.3, 167.0, 167.7; *m*/*z* 444 (M^+, 60%), 442 (M^+, 60), 364 (50), 363 (90), 345 (45), 344 (40), 343 (50), 342 (35), 307 (25), 264 (55), 263 (70), 262 (100), 217 (35), 216 (70). Continued chromatography afforded a 1:1 mixture of the diastereomers of the bromide **17** as a colourless oil (134 mg, 67%); *m*/*z* 444.0873 (M^+, $C_{22}H_{23}{}^{81}BrN_2O_3$ requires 444.0872), 442.0894 (M^+, $C_{22}H_{23}{}^{79}BrN_2O_3$ requires 442.0892), 344 (5%), 342 (5), 297 (5), 295 (5), 265 (40), 264 (100), 263 (85), 262 (20), 246 (25). One diastereomer had δ_H 1.03 (s, 9H), 2.19 (s, 3H), 5.22 (d, *J* 11.5, 1H), 5.78 (br s, 1H), 6.17 (d, *J* 11.5 Hz, 1H), 6.95–7.10 (m, 4H), 7.7–8.0 (m, 4H). The other diastereomer had δ_H 1.40 (s, 9H), 2.37 (s, 3H), 5.31 (d, *J* 11.5, 1H), 6.05 (d, *J* 11.5 Hz, 1H), 6.41 (br s, 1H), 7.15–7.25 (m, 4H), 7.60–7.75 (m, 4H). The ^{1}H NMR spectrum of the crude product mixture indicated that the bromides **17** and **18** were produced in the ratio *ca.* 10:1.

Photolysis of *N*-bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloylphenylalaninamide 2 in the presence of 4-*tert*-butyltoluene 19. Solutions of the bromoamide **2** (0.65 or 2.60 mmol dm^{-3}) and 4-*tert*-butyltoluene **19** (0.92 or 3.46 mmol dm^{-3}) were photolysed as described above. The ratios of the product bromides **3** and **20** were determined by analysis of the ^{1}H NMR spectra of the crude reaction mixtures and comparison with those of authentic samples and the results are shown in Table 1.

Photolysis of *N*-bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyl-*p*-methylphenylalaninamide 15 in the presence of 4-*tert*-butyltoluene 19. Solutions of the bromoamide **15** (1.0 or 5.0 mmol dm^{-3}) and *4-tert*-butyltoluene **19** (1.0 or 5.0 mmol dm^{-3}) were photolysed as described above. The ratios of the product bromides **17**, **18** and **20** were determined by analysis of the ^{1}H NMR spectra of the crude reaction mixtures and comparison with those of authentic samples and the results are shown in Table 2.

References

1 J. W. Wilt, in *Free Radicals*, ed. J. K. Kochi, Wiley, New York, 1973, vol. 1, p. 333; A. L. J. Beckwith and K. U. Ingold, in *Rearrangements in Ground and Excited States*, ed. P. de Mayo, Academic Press, New York, 1980, p. 161.

2 R. A. Johnson and F. D. Greene, *J. Org. Chem.*, 1975, **40**, 2186; L. Lunazzi, G. Placucci and L. Grossi, *J. Chem. Soc.*, *Perkin Trans. 2*, 1981, 703; L. Lunazzi, G. Placucci and L. Grossi, *Tetrahedron*, 1983, **39**, 159; D. Cassarini, L. Grossi, L. Lunazzi and G. Placucci, *J. Org. Chem.*, 1985, **50**, 703; B. C. Gilbert, D. J. Parry and L. Grossi, *J. Chem. Soc.*, *Faraday Trans. 1*, 1987, 77; E. J. Verner and T. Cohen, *J. Org. Chem.*, 1992, **57**, 1072; R. Janes and M. C. R. Symons, *J. Chem. Soc.*, *Faraday Trans.*, 1990, 2173; E. A. Hardwidge, C. W. Larson and B. S. Rabinovitch, *J. Am. Chem. Soc.*, 1970, **92**, 3278; R. A. Cormier, W. L. Schreiber and W. C. Agosta, *J. Chem. Soc.*, *Chem. Commun.*, 1972, 729; A. Padwa and R. Gruber, *J. Am. Chem. Soc.*, 1970, **92**, 107; A. Padwa and W. Eisenhardt, *J. Am. Chem. Soc.*, 1971, **93**, 1400; J. R. Scheffer, J. Trotter, R. A. Wostradowski, C. S. Gibbons and K. S. Bhandari, *J. Am. Chem. Soc.*, 1971, **93**, 3813; J. R. Scheffer, K. S. Bhandari, R. E. Gayler and R. H. Weikenkamp, *J. Am. Chem. Soc.*, 1972, **94**, 285.

3 G. Brunton, D. Griller, L. R. C. Barclay and K. U. Ingold, *J. Am. Chem. Soc.*, 1976, **98**, 6803; G. Brunton, J. A. Gray, D. Griller, L. R. C. Barclay and K. U. Ingold, *J. Am. Chem. Soc.*, 1978, **100**, 4197.

4 C. J. Easton and M. C. Merrett, *J. Am. Chem. Soc.*, 1996, **118**, 3035.

5 T. R. Beebe and J. W. Wolfe, *J. Org. Chem.*, 1970, **35**, 2056.

6 C. J. Easton, C. A. Hutton, P. D. Roselt and E. R. T. Tiekink, *Aust. J. Chem.*, 1991, **44**, 687.

7 C. J. Easton and C. A. Hutton, *J. Chem. Soc.*, *Perkin Trans. 1*, 1994, 3545.

8 R. Kober, K. Papadopoulos, W. Miltz, D. Enders, W. Steglich, H. Reuter and H. Puff, *Tetrahedron*, 1985, **41**, 1693.

9 C. J. Easton, C. A. Hutton, G. Rositano and E. W. Tan, *J. Org. Chem.*, 1991, **56**, 5614.

10 A. L. Castelhano, S. Horne, R. Billedeau and A. Krantz, *Tetrahedron Lett.*, 1986, **27**, 2435.

11 C. J. Easton, C. A. Hutton, P. D. Roselt and E. R. T. Tiekink, *Tetrahedron*, 1994, **50**, 7327.

12 C. J. Easton, *Chem. Rev.*, 1997, **97**, 53.

13 J. E. Baldwin, D. Brown, P. H. Scudder and M. E. Wood, *Tetrahedron Lett.*, 1995, **36**, 2105; H. Haber, H. Buchholz, R. Sukale and H.-G. Henning, *J. Prakt. Chem.*, 1985, **327**, 51; F. Kernchen and H.-G. Henning, *Monatsh. Chem.*, 1989, **120**, 253; P. Wessig, P. Wettstein, B. Giese, M. Neuburger and M. Zehnder, *Helv. Chim. Acta*, 1994, **77**, 829; A. G. Griesbeck and H. Mauder, *Angew. Chem.*, *Int. Ed. Engl.*, 1992, **31**, 73; A. G. Griesbeck, H. Mauder and I. Müller, *Chem. Ber.*, 1992, **125**, 2467; J. Rancourt, V. Gorys and E. Jolicoeur, *Tetrahedron Lett.*, 1998, **39**, 5339.

14 C. L. Hawkins and M. J. Davies, *J. Chem. Soc.*, *Perkin Trans. 2*, 1998, 1937.

15 M. P. Sibi and N. A. Porter, *Acc. Chem. Res.*, 1999, **32**, 163; D. P. Curran, N. A. Porter and B. Giese, *Stereochemistry of Radical Reactions*, VCH, Weinheim, 1995; N. A. Porter, B. Giese and D. P. Curran, *Acc. Chem. Res.*, 1991, **24**, 296.

Paper a908968c