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Synthesis of Cyclopropyl Amino Acid Derivatives

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Abstract

Derivatives of α,β-methanovaline, α,β-methanophenylalanine and β-methyl-α,β-methanoalanine have been prepared by regioselective side-chain functionalization of suitably protected amino acid derivatives, followed by cyclization with either sodium hydride or 1,8-diazabicyclo[5.4.0]undec-7-ene. The approach used in this work illustrates a method for the synthesis of cyclopropyl amino acid derivatives which is complementary to existing procedures.

Introduction

Natural and synthetic cyclopropyl amino acids (α,β-methano amino acids) and their derivatives are of interest as mechanistic probes in studies of ethylene biosynthesis,[1–5] as enzyme inhibitors,[6,7] and for incorporation into peptides to investigate structure–activity relationships.[8–13] The most common method for the synthesis of cyclopropyl amino acids is the cyclopropanation of α,β-dehydro amino acid derivatives.[13–17] Other syntheses have involved the alkylation and subsequent

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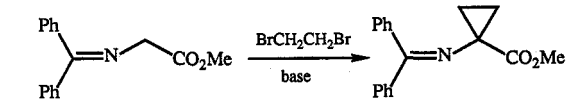
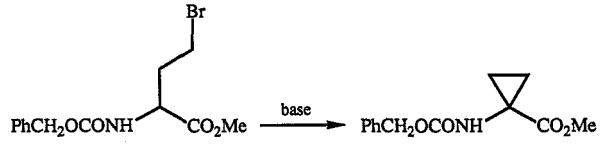
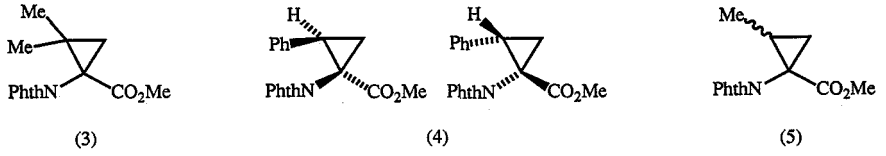
cyclization of certain *N*-substituted glycine derivatives,[18] a simple example of which is shown in Scheme 1. In a related procedure, the α,β-methanoalanine derivative (2) was formed through cyclization of the corresponding γ-substituted α-aminobutyric acid derivative (1) (Scheme 2).[19] In the work described in this report, we have used procedures, complementary to the last approach, for the synthesis of the cyclopropyl amino acid derivatives (3)–(5).



Scheme 1

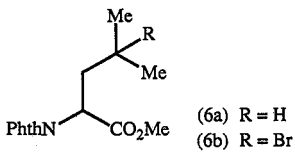


Scheme 2

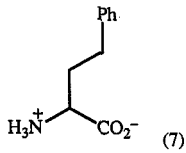


Results and Discussion

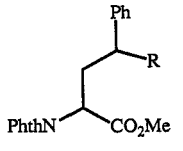
Recent studies[20,21] have shown that treatment of *N*-phthaloyl-protected amino acid derivatives with *N*-bromosuccinimide results in side-chain bromination. Accordingly, reaction of *N*-phthaloylleucine methyl ester (6a) with *N*-bromosuccinimide gave a good yield of the γ-bromoleucine derivative (6b).[21] Treatment of the bromide (6b) with sodium hydride in tetrahydrofuran afforded, after chromatography and crystallization from diethyl ether/light petroleum, the α,β-methanovaline derivative (3) in 67% yield.



(6a) R = H
(6b) R = Br



(7)



(8a) R = H
(8b) R = Br
(8c) R = Cl

In order to obtain the α,β-methanophenylalanine derivative (4) by a route analogous to that used to obtain the α,β-methanovaline derivative (3),

[18] O'Donnell, M. J., Bruder, W. A., Eckrich, T. M., Shullenberger, D. F., and Staten, G. S., *Synthesis*, 1984, 127.
[19] Prochazka, Z., Budesinsky, M., Smolikova, J., Trska, P., and Jost, K., *Collect. Czech. Chem. Commun.*, 1982, **47**, 2291.
[20] Easton, C. J., Tan, E. W., and Hay, M. P., *J. Chem. Soc., Chem. Commun.*, 1989, 385.
[21] Easton, C. J., Hutton, C. A., Rositano, G., and Tan, E. W., *J. Org. Chem.*, 1991, **56**, 5618.

homophenylalanine (7) was used as the starting material. Reaction of the amino acid (7) with phthalic anhydride, followed by treatment with methanol that had been pretreated with thionyl chloride, gave *N*-phthaloylhomophenylalanine methyl ester (8a). This material reacted with *N*-bromosuccinimide to give the crude γ-bromohomophenylalanine derivative (8b), as a 1 : 1 mixture of diastereomers. After chromatography of the mixture and crystallization from dichloromethane/light petroleum, the bromide (8b) was isolated in 69% yield. Bromination at the benzylic position of the amino acid derivative (8a) is consistent with reaction via the most stable radical intermediate.[20,21]

The reaction of the homophenylalanine derivative (8a) with sulfuryl chloride in carbon tetrachloride, under irradiation with ultraviolet light, was investigated as an alternative to bromination. The procedure gave a 1 : 1 mixture of the diastereomers of the chloride (8c), but the yield of purified material was only 16%. The chlorination was much less efficient than the bromination, and it was difficult to separate the chloride (8c) from the unreacted amino acid derivative (8a) by chromatography. Thus, bromination was found to be the better method for side-chain functionalization of the homophenylalanine derivative (8a).

The bromide (8b) was treated with sodium hydride in tetrahydrofuran to give the *cis*-α,β-methanophenylalanine derivative (4) in 38% yield after chromatography and crystallization from dichloromethane/light petroleum. The stereochemistry of the α,β-methanophenylalanine derivative (4) was determined by X-ray crystallographic analysis.[22] Analysis of the ^{1}H n.m.r. spectrum of the crude mixture from reaction of the bromide (8b) indicated that the *cis*-α,β-methanophenylalanine derivative (4) and the corresponding *trans*-isomer (not isolated) were present in the ratio *c.* 30 : 1. Presumably the diastereoselective formation of the *cis*-cyclopropyl amino acid derivative (4) reflects a preferred orientation for cyclization of the anion derived from the bromide (8b), but the basis of this preference is not obvious.

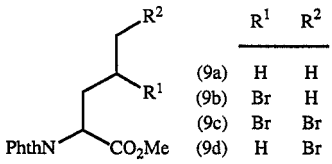
In attempts to improve the yield of the α,β-methanophenylalanine derivative (4), alternatives to the use of sodium hydride were investigated. When the bromide (8b) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene in tetrahydrofuran, the cyclopropyl amino acid derivative (4) was obtained in 71% yield after isolation and purification.

The approach used in the synthesis of the α,β-methano amino acid derivatives (3) and (4) was found to be unsuitable for the preparation of the β-methyl-α,β-methanoalanine derivative (5). The amino acid derivative (9a), prepared from norvaline as described above for the synthesis of the homophenylalanine derivative (8a), was inert to bromination under the conditions used to prepare the bromides (6b) and (8b). This can be attributed to the inability of the norvaline derivative (9a) to form a radical sufficiently stable to induce hydrogen abstraction by bromine atom.

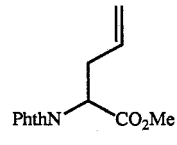
Instead, the cyclopropyl amino acid derivative (5) was synthesized from *N*-phthaloylallylglycine methyl ester (10), which had been prepared from allylglycine as described above for the synthesis of the homophenylalanine derivative (8a). When the allylglycine derivative (10) was dissolved in a freshly prepared solution

[22] Easton, C. J., Mahadevan, I. B., Tiekink, E. R. T., and Ward, C. M., *Z. Kristallogr.*, 1991, in press.

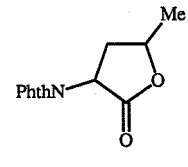
of hydrogen bromide in acetic acid, and the resultant solution was stirred at room temperature for 30 h, a product was obtained which, on chromatography, gave a 2:1 mixture of the diastereomers of the bromide (9b) in 50% yield, and a 4·5:1 mixture of the diastereomers of the lactone (11) in 27% yield.



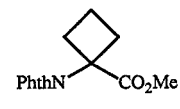
	R^1	R^2
(9a)	H	H
(9b)	Br	H
(9c)	Br	Br
(9d)	H	Br



(10)



(11)



(12)

With aged solutions of hydrogen bromide in acetic acid, the time taken to produce the bromide (9b) and the lactone (11) increased significantly; indeed, the starting material (10) was consumed faster than the products (9b) and (11) were formed. When a reaction was carried out under these circumstances and monitored by thin-layer chromatography, workup after consumption of the majority of the starting material (10), but prior to the formation of substantial quantities of the bromide (9b) and the lactone (11), gave a 1:1 mixture of the diastereomers of the dibromide (9c), in 26% yield. The formation of the dibromide (9c) can be attributed to the presence of bromine in aged acetic acid solutions of hydrogen bromide. Evidently, the addition of bromine to the allylglycine derivative (10) to give the dibromide (9c) is reversible, which accounts for the eventual formation of the γ-bromide (9b) and the lactone (11).

When the γ-bromonorvaline derivative (9b) was treated with sodium hydride in tetrahydrofuran, the cyclopropyl amino acid derivative (5) was obtained in 74% yield as a 3:1 mixture of diastereomers after chromatography and crystallization from dichloromethane/light petroleum.

The allylglycine derivative (10) was also used in an attempt to produce the cyclobutyl amino acid derivative (12). Thus, treatment of the allylglycine derivative (10) with hydrogen bromide in carbon tetrachloride, under irradiation with ultraviolet light, and in the presence of 2,2′-azobisisobutyronitrile in order to facilitate the free radical addition process, afforded the δ-bromonorvaline derivative (9d), as a colourless oil in 83% yield. The bromide (9d) was treated with sodium hydride in tetrahydrofuran or alternatively with 1,8-diazabicyclo[5.4.0]undec-7-ene in tetrahydrofuran, but failed to afford the cyclobutyl amino acid derivative (12). Only decomposition products and the unreacted bromide (9d) were recovered from these reactions.

On this basis, the approach of side-chain functionalization of amino acid derivatives, followed by cyclization, appears to be unsuitable for the preparation of cyclobutyl amino acid derivatives. However, the method does provide a procedure for the synthesis of cyclopropyl amino acid derivatives, which is complementary to existing methods.

Experimental

General experimental details have been reported previously.[23] Chromatography was performed on silica.

N-*Phthaloyl-α,β-methanovaline Methyl Ester (3)*

A stirred solution of the bromoleucine derivative (6b)[21] (0·50 g, 1·41 mmol) in freshly distilled tetrahydrofuran (20 ml) was treated under nitrogen with sodium hydride (80% in oil; 0·07 g, 2·33 mmol). After 24 h at room temperature, the mixture was concentrated under reduced pressure and the residue dissolved in ethyl acetate and water. The organic layer was separated, washed with water, dried, filtered, and then concentrated under reduced pressure to give an oil which was chromatographed, and crystallized from diethyl ether/light petroleum to afford N-*phthaloyl-α,β-methanovaline methyl ester* (3), as colourless crystals (0·26 g, 67%), m.p. 95–97° (Found: C, 65·9; H, 5·5; N, 5·1. $C_{15}H_{15}NO_4$ requires C, 65·9; H, 5·5; N, 5·1%). ^{1}H n.m.r. ($CDCl_3$) δ 1·20, s, 3H, CCH_3; 1·51, s, 3H, CCH_3; 1·52, d, J 5·9 Hz, 1H, Cβ'–H; 1·89, d, J 5·9 Hz, 1H, Cβ'–H′; 3·65, s, 3H, OCH_3; 7·76, m, 2H, ArH; 7·88, m, 2H, ArH. ^{13}C n.m.r. ($CDCl_3$) δ 19·2, q; 23·3, q; 28·4, t; 29·8, s; 41·0, s; 52·6, q; 123·4, d; 129·3, s; 134·1, d; 168·4, s; 170·4, s. ν_{max} 1770, 1734, 1440, 1302, 1251, 1212, 1143, 1104, 720 cm^{-1}. Mass spectrum m/z 273 (M).

N-*Phthaloylhomophenylalanine Methyl Ester (8a)*

An intimate mixture of homophenylalanine (7) (2·0 g, 11 mmol) and phthalic anhydride (1·7 g, 11 mmol) was heated with stirring for 0·65 h in an oil bath maintained at 140–145°. On cooling, the mixture was dissolved in methanol (30 ml), and the solution was concentrated to 15 ml before being added to methanol (15 ml) that had been pretreated with thionyl chloride (1 ml, 14 mmol). The resultant mixture was stirred overnight at room temperature, then concentrated under reduced pressure, and the residual oil was diluted with methanol. Removal of the solvent gave a product which was chromatographed to yield N-*phthaloylhomophenylalanine methyl ester* (8a) as a pale yellow oil (3·46 g, 96%), b.p. 175°/0·03 mm (block) (Found: C, 70·5; H, 5·3; N, 4·4. $C_{19}H_{17}NO_4$ requires C, 70·6; H, 5·3; N, 4·3%). ^{1}H n.m.r. ($CDCl_3$) δ 2·60, m, 4H, Cβ–H_2, Cγ–H_2; 3·72, s, 3H, OCH_3; 4·88, m, 1H, Cα–H; 7·15, m, 5H, ArH; 7·80, m, 4H, ArH. ν_{max} 1794, 1744, 1720, 1388, 1098, 708 cm^{-1}. Mass spectrum m/z 323 (M).

*γ-Bromo-*N*-phthaloylhomophenylalanine Methyl Ester (8b)*

A mixture of the homophenylalanine derivative (8a) (1·0 g, 3·1 mmol), *N*-bromosuccinimide (0·56 g, 3·1 mmol) and 2,2′-azobisisobutyronitrile (*c.* 2 mg) in refluxing carbon tetrachloride (50 ml) was irradiated with a 250-W mercury lamp for 2 h. The cooled reaction mixture was diluted with carbon tetrachloride (40 ml), washed with water, dried, and concentrated under reduced pressure, to give crude *γ-bromo-*N*-phthaloylhomophenylalanine methyl ester* (8b), as a 1:1 mixture of diastereomers. ^{1}H n.m.r. ($CDCl_3$) δ 3·15, m, 2H, Cβ–H_2; 3·73, s, 0·5×3H, OCH_3; 3·75, s, 0·5×3H, OCH_3; 4·91, t, J 7·6 Hz, 1H, Cα–H; 5·10, t, J 7·5 Hz, 0·5×1H, Cγ–H; 5·21, dd, J 5·9, 9·2 Hz, 0·5×1H, Cγ–H; 7·20, m, 5H, ArH; 7·80, m, 4H, ArH. ν_{max} 1774, 1744, 1716, 1264, 1216, 722, 704 cm^{-1}. Mass spectrum m/z 322 (M − Br). Chromatography of the mixture and crystallization from dichloromethane/light petroleum gave various mixtures of the diastereomers of the bromide (8b) as colourless crystals (0·86 g, 69%). A 5:1 mixture of the diastereomers of the bromide (8b) had m.p. 112–118° (Found: C, 56·8; H, 4·0; N, 3·5. $C_{19}H_{16}BrNO_4$ requires C, 56·7; H, 4·0; N, 3·5%).

*γ-Chloro-*N*-phthaloylhomophenylalanine Methyl Ester (8c)*

A mixture of the homophenylalanine derivative (8a) (0·25 g, 0·77 mmol), sulfuryl chloride (0·065 ml, 0·81 mmol) and 2,2′-azobisisobutyronitrile (*c.* 2 mg) in refluxing carbon tetrachloride (15 ml) was irradiated with a 250-W mercury lamp for 2·25 h. The cooled reaction

[23] Easton, C. J., and Peters, S. C., *Aust. J. Chem.*, 1990, **43**, 87.

mixture was washed with saturated aqueous sodium bicarbonate and water, dried, and concentrated under reduced pressure to give a 1:1 mixture of the diastereomers of γ-chloro-*N*-phthaloylhomophenylalanine methyl ester (8c) contaminated with the starting material (8a). Chromatography of the mixture, followed by crystallization from dichloromethane/light petroleum, gave a 3:1 mixture of the diastereomers of the chloride (8c) as colourless crystals (45 mg, 16%), m.p. 100–111° (Found: C, 63·4; H, 4·3; N, 3·9. $C_{19}H_{16}ClNO_4$ requires C, 63·8; H, 4·5; N, 3·9%). ^{1}H n.m.r. ($CDCl_3$) δ 3·00, m, 2H, Cβ–H_2; 3·73, s, 0·25×3H, OCH_3; 3·75, s, 0·75×3H, OCH_3; 4·80, dd, *J* 5·5, 9·2 Hz, 0·75×1H, Cα–H; 5·00, dd, *J* 5·8, 7·8 Hz, 0·25×1H, Cα–H; 5·10, dd, *J* 6·2, 7·7 Hz, 0·25×1H, Cγ–H; 5·25, dd, *J* 4·5, 10·7 Hz, 0·75×1H, Cγ–H; 7·25, m, 5H, ArH; 7·74, m, 2H, ArH; 7·84, m, 2H, ArH. ν_{max} 1774, 1744, 1714, 1268, 1226, 720, 616 cm^{-1}. Mass spectrum *m/z* 322 (M − Cl).

cis-N-*Phthaloyl-α,β-methanophenylalanine Methyl Ester (4)*

(i) Treatment of the γ-bromohomophenylalanine derivatives (8b) (0·50 g, 1·25 mmol) with sodium hydride in tetrahydrofuran, as described above for the preparation of the α,β-methanovaline derivative (3), gave cis-N-*phthaloyl-α,β-methanophenylalanine methyl ester* (4) as colourless crystals (152 mg, 38%), m.p. 131·5–132·5°, after chromatography, and crystallization from dichloromethane/light petroleum (Found: C, 70·9; H, 4·9; N, 4·4. $C_{19}H_{15}NO_4$ requires C, 71·0; H, 4·7; N, 4·4%). ^{1}H n.m.r. ($CDCl_3$) δ 2·27, dd, *J* 6·6, 9·9 Hz, 1H, Cβ′–H; 2·43, dd, *J* 6·6, 8·5 Hz, 1H, Cβ′–H; 3·38, dd, *J* 8·5, 9·9 Hz, 1H, Cβ–H; 3·72, s, 3H, OCH_3; 7·12, m, 5H, ArH; 7·72, m, 4H, ArH. ν_{max} 1782, 1724, 1440, 1404, 1272, 732 cm^{-1}. Mass spectrum *m/z* 321 (M).

The ^{1}H n.m.r. spectrum of the crude mixture obtained from the reaction of the bromide (8b) showed the presence of the *cis*-α,β-methanophenylalanine derivative (4) and the corresponding *trans*-isomer (δ 1·89, dd, *J* 6·2, 9·9 Hz, 1H, Cβ′–H; 2·50, dd, *J* 6·2, 9·1 Hz, 1H, Cβ′–H; 3·18, apparent t, *J* 9·5 Hz, 1H, Cβ–H; 3·72, s, 3H, OCH_3; 7·12, m, 5H, ArH; 7·72, m, 4H, ArH) in the ratio *c.* 30:1.

(ii) A solution of the γ-bromohomophenylalanine derivative (8b) (0·40 g, 0·99 mmol) in tetrahydrofuran (25 ml) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0·26 g, 1·71 mmol), and the mixture was heated at reflux for 6 h. The solvent was then removed under reduced pressure, and the residue was dissolved in dichloromethane. The resultant solution was washed with dilute hydrochloric acid followed by water, and then dried, and concentrated under reduced pressure. The residue was chromatographed to give the α,β-methanophenylalanine derivative (4) (0·23 g, 71%), which was identical to the sample obtained as described above.

N-*Phthaloylallylglycine Methyl Ester (10)*

Treatment of allylglycine (2·0 g, 17 mmol) with phthalic anhydride and subsequently with methanol that had been pretreated with thionyl chloride, as described above for the synthesis of the homophenylalanine derivative (8a), gave N-*phthaloylallylglycine methyl ester* (10) as colourless crystals (3·9 g, 87%), m.p. 43·5–45·5°, after chromatography, and crystallization from ethyl acetate/light petroleum [Found: *m/z* 259·085. $C_{14}H_{13}NO_4$ (M) requires *m/z* 259·085]. ^{1}H n.m.r. ($CDCl_3$) δ 3·00, m, 2H, Cβ–H_2; 3·75, s, 3H, OCH_3; 5·00, m, 3H, Cα–H, Cδ–H_2; 5·72, m, 1H, Cγ–H; 7·74, m, 2H, ArH; 7·86, m, 2H, ArH. ν_{max} 1713, 1697, 1254, 1218, 717 cm^{-1}.

γ-Bromo-N-*phthaloylnorvaline Methyl Ester (9b) and*
N-*(5-Methyl-2-oxotetrahydrofuran-3-yl)phthalimide (11)*

The allylglycine derivative (10) (1·5 g, 5·8 mmol) was dissolved in a freshly prepared saturated solution of hydrogen bromide in acetic acid (40 ml), and the resultant solution stirred at room temperature for 30 h. The solvent was removed under reduced pressure, and the residue dissolved in ethyl acetate. The solution was then washed with saturated aqueous sodium bicarbonate followed by water, dried, and concentrated under reduced pressure. Chromatography of the residue gave a 2:1 mixture of the diastereomers of *γ-bromo*-N-*phthaloylnorvaline methyl ester* (9b) as a colourless oil (0·98 g, 50%) (Found: C, 49·0; H, 4·2; N, 4·0. $C_{14}H_{14}BrNO_4$ requires C, 49·4; H, 4·2; N, 4·1%). ^{1}H n.m.r. ($CDCl_3$) δ

1·76, d, *J* 6·6 Hz, 0·33×3H, CCH_3; 1·77, d, *J* 6·7 Hz, 0·66×3H, CCH_3; 2·48, ddd, *J* 7·4, 8·5, 15·0 Hz, 0·66×1H, Cβ–H; 2·65, ddd, *J* 3·9, 11·3, 15·3 Hz, 0·33×1H, Cβ–H; 2·87, m, 0·33×1H, Cβ–H′; 2·88, ddd, *J* 5·1, 6·8, 15·0 Hz, 0·66×1H, Cβ–H′; 3·74, s, 0·66×3H, OCH_3; 3·75, s, 0·33×3H, OCH_3; 3·91, m, 0·33×1H, Cγ–H; 4·32, m, 0·66×1H, Cγ–H; 5·12, apparent t, *J* 7·0 Hz, 0·66×1H, Cα–H; 5·29, dd, *J* 3·9, 11·4 Hz, 0·33×1H, Cα–H; 7·77, m, 2H, ArH; 7·89, m, 2H, ArH. ν_{max} 1776, 1754, 1720, 1442, 1260, 1222, 1088, 720 cm^{-1}. Mass spectrum *m/z* 341, 339 (M).

Chromatography of the reaction mixture also gave a 4·5:1 mixture of the diastereomers of *N-(5-methyl-2-oxotetrahydrofuran-3-yl)phthalimide* (11) as colourless crystals (0·39 g, 27%), m.p. 179–185°, after recrystallization from dichloromethane/light petroleum [Found: *m/z* 201·078. $C_{12}H_{11}NO_2$ ($M-CO_2$) requires *m/z* 201·079]. ^{1}H n.m.r. ($CDCl_3$) δ 1·50, d, *J* 6·5 Hz, 0·18×3H, CH_3; 1·58, d, *J* 6·1 Hz, 0·82×3H, CH_3; 2·88, ddd, *J* 3·1, 10·0, 13·0 Hz, 0·18×1H, C4–H; 2·43, ddd, *J* 10·4, 12·0, 12·2 Hz, 0·82×1H, C4–H; 2·66, ddd, *J* 5·7, 9·2, 12·2 Hz, 0·82×1H, C4–H′; 2·79, m, 0·18×1H, C4–H′; 4·70, m, 1H, C5–H; 4·95, m, 0·18×1H, C3–H; 5·18, dd, *J* 9·2, 12·0 Hz, 0·82×1H, C3–H; 7·77, m, 2H, ArH; 7·86, m, 2H, ArH. ν_{max} 1772, 1714, 1210, 720 cm^{-1}.

γ,δ-Dibromo-N-phthaloylnorvaline Methyl Ester (9c)

Treatment of the allylglycine derivative (10) (0·25 g, 0·97 mmol) with a stored solution of hydrogen bromide in acetic acid, as described above for the preparation of the bromide (9b) and the lactone (11), gave a 1:1 mixture of the diastereomers of *γ,δ-dibromo-N-phthaloylnorvaline methyl ester* (9c) as colourless crystals (103 mg, 26%), m.p. 88–103°, after chromatography and crystallization from dichloromethane/light petroleum (Found: C, 40·1; H, 3·2; N, 3·4. $C_{14}H_{13}Br_2NO_4$ requires C, 40·1; H, 3·1; N, 3·3%). ^{1}H n.m.r. ($CDCl_3$) δ 2·40, ddd, *J* 6·5, 9·1, 15·4 Hz, 0·5×1H, Cβ–H; 2·64, ddd, *J* 3·6, 11·3, 15·2 Hz, 0·5×1H, Cβ–H; 3·33, m, 1H, Cβ–H′; 3·64, dd, *J* 9·0, 10·7 Hz, 0·5×1H, Cδ–H; 3·71, dd, *J* 9·7, 10·4 Hz, 0·5×1H, Cδ–H; 3·76, s, 0·5×3H, OCH_3; 3·78, s, 0·5×3H, OCH_3; 3·85, dd, *J* 4·4, 10·4 Hz, 0·5×1H, Cδ–H′; 3·89, dd, *J* 4·4, 10·7 Hz, 0·5×1H, Cδ–H′; 3·98, m, 0·5×1H, Cγ–H; 4·52, m, 0·5×1H, Cγ–H; 5·16, apparent t, *J* 6·8 Hz, 0·5×1H, Cα–H; 5·28, dd, *J* 3·6, 11·8 Hz, 0·5×1H, Cα–H; 7·78, m, 2H, ArH; 7·90, m, 2H, ArH. ν_{max} 1780, 1744, 1714, 1258, 720 cm^{-1}. Mass spectrum *m/z* 421, 419, 417 (M).

β-Methyl-N-phthaloyl-α,β-methanoalanine Methyl Ester (5)

Treatment of the γ-bromonorvaline derivative (9b) (0·50 g, 1·47 mmol) with sodium hydride in tetrahydrofuran, as described above for the preparation of the α,β-methanovaline derivative (3), gave a 3:1 mixture of the diastereomers of *β-methyl-N-phthaloyl-α,β-methanoalanine methyl ester* (5) as colourless crystals (0·28 g, 74%), m.p. 96–107°, after chromatography and crystallization from dichloromethane/light petroleum (Found: C, 65·0; H, 5·0; N, 5·4. $C_{14}H_{13}NO_4$ requires C, 64·9; H, 5·1; N, 5·4%). ^{1}H n.m.r. ($CDCl_3$) δ 1·13, d, *J* 6·2 Hz, 0·8×3H, CCH_3; 1·38, dd, *J* 5·6, 8·0 Hz, 0·8×1H, Cβ'–H; 1·46, d, *J* 6·0 Hz, 0·2×3H; CCH_3; 1·58, dd, *J* 5·4, 9·4 Hz, 0·2×1H, Cβ'–H; 1·76, dd, *J* 5·4, 8·8 Hz, 0·2×1H, Cβ'–H′; 1·86, m, 0·2×1H, Cβ–H; 1·95, dd, *J* 5·6, 9·5 Hz, 0·8×1H, Cβ'–H′; 2·14, m, 0·8×1H, Cβ–H; 3·66, s, 0·8×3H, OCH_3; 3·67, s, 0·2×3H, OCH_3; 7·77, m, 2H, ArH; 7·88, m, 2H, ArH. ν_{max} 1778, 1722, 1408, 1290, 730, 722 cm^{-1}. Mass spectrum *m/z* 259 (M).

δ-Bromo-N-phthaloylnorvaline Methyl Ester (9d)

Hydrogen bromide was bubbled through a stirred irradiated (250-W mercury lamp) mixture of the allylglycine derivative (10) (1·0 g, 3·86 mmol) and 2,2′-azobisisobutyronitrile (*c.* 2 mg) in carbon tetrachloride (50 ml) for 0·5 h. Irradition was continued for a further 0·5 h, then the mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate and water. The organic layer was washed with dilute aqueous potassium bicarbonate followed by water, and then dried, and concentrated under reduced pressure. Chromatography of the residue gave *δ-bromo-N-phthaloylnorvaline methyl ester* (9d) as a viscous oil (1·09 g, 83%) (Found: C, 48·8; H, 4·3; N, 4·1%; $M^{+\bullet}$, 339·009. $C_{14}H_{14}BrNO_4$ requires C, 49·4; H, 4·2; N, 4·1%; $M^{+\bullet}$, 339·011). ^{1}H n.m.r. ($CDCl_3$) δ 1·92, m, 2H, Cβ–H_2; 2·39, m, 2H,

Cγ–H_2; 3·42, t, J 6·7 Hz, 2H, Cδ–H_2; 3·75, s, 3H, CH_3; 4·87, dd, J 5·4, 10·2 Hz, 1H, Cα–H; 7·78, m, 2H, ArH; 7·89, m, 2H, ArH. ν_{max} 1776, 1746, 1720, 1262, 1228, 1106, 720 cm^{-1}. Mass spectrum m/z 341, 339 (M).

Treatment of δ-Bromo-N-phthaloylnorvaline Methyl Ester (9d) with Sodium Hydride and 1,8-Diazabicyclo[5.4.0]undec-7-ene

The bromide (9d) was treated with sodium hydride and 1,8-diazabicyclo[5.4.0]undec-7-ene, as described above for the preparation of the α,β-methanophenylalanine derivative (4). In each case, the only material identified through ^1H n.m.r. spectroscopic and thin-layer chromatographic analysis of the reaction mixture was the starting material (9d).

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