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# Allylic halogenation of unsaturated amino acids†

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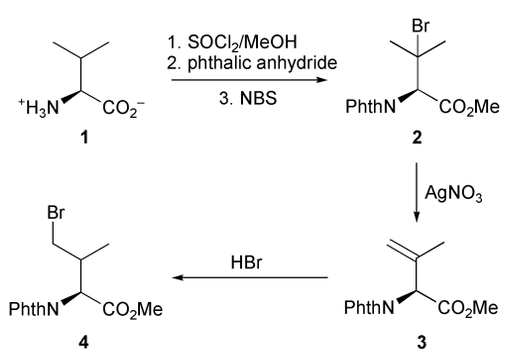
A range of dehydro amino acid derivatives has been prepared and subjected to halogenation using either molecular bromine or chlorine, or NBS. Allylic halogenation of the unsaturated amino acid side chains occurs through radical bromination with NBS. The procedure is complementary to treatment with chlorine, which also affords allyl halides. This latter and unusual reaction is shown through a deuterium labelling study to proceed *via* an ionic mechanism. The choice of NBS or chlorine for allyl halide synthesis is shown to depend on the potential to avoid competing reactions, such as halolactonization of leucine derivatives with chlorine, and hydrogen abstraction and bromine incorporation at multiple sites on treatment of isoleucine derivatives with NBS. The synthetic utility of the allyl halides prepared in this study is indicated through the synthesis of a cyclopropyl amino acid derivative and the extension of the carbon skeleton of an amino acid side chain.

## Introduction

Modification of the side chains of proteinogenic amino acids is a useful strategy in the synthesis of important derivatives of this class of compounds.[1] The principal advantages of this approach are the ready availability and low cost of the starting materials, and their homochirality. Methods involving modification of the functional groups in amino acids such as aspartate, serine and cysteine, have been well developed.[2] Alternatively, radical methodology provides a way to introduce functionality into the side chains of aliphatic amino acids.[3] While the α-position of amino acid derivatives is normally the most reactive towards hydrogen atom abstraction, the *N*-phthaloyl protecting group prevents reaction at this position. Instead, halogenations, such as bromination, usually then occur *via* the most stable side chain radicals.[4–6] The synthesis of the β-bromovaline derivative **2** illustrates this method (Scheme 1).[4] The halogenated amino acids can be elaborated to functionalise adjacent positions through hydrogen bromide elimination, followed by anti-Markovnikov hydrogen bromide addition, as shown through the synthesis of the γ-bromovaline derivative **4**.[7]



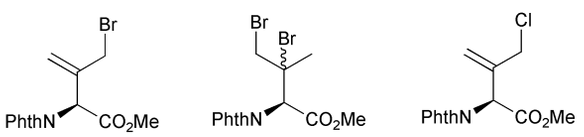

**1** **2** **3** **4**

**Scheme 1**

In order to extend the utility of this chemistry, we sought to explore alternative methods to elaborate compounds such as the amino acid derivatives **2** and **3**. To this end we have used the alkene **3** and related compounds to prepare the corresponding allyl halides, which are renowned for their synthetic versatility. Allylic halogenation has been accomplished through conventional free radical bromination,[8–10] as well as the little known ionic allylic chlorination.[11–17]

## Results and discussion

Standard radical bromination of the β,γ-dehydrovaline derivative **3** with NBS gave the allyl bromide **5** in 77% yield. Treatment with molecular bromine gave a 3 : 1 mixture of the diastereomers of the dibromide **6**. In contrast, reaction with molecular chlorine, in place of bromine, gave the allylic halogenation product **7** and not the corresponding addition product.




**5** **6** **7**

Presumably the alkene **3** reacts to give the bromide **5** by hydrogen atom abstraction from the γ′-position. This occurs in preference to loss of the α-hydrogen, due to the deactivating effect of the phthaloyl group.[4–6] The reaction with molecular bromine to give the dibromide **6** is a standard electrophilic addition. The chlorination is unusual, in that the product **7** is typical of a radical process, yet it is formed under conditions normally associated with ionic addition. Specifically, conducting the reaction in the dark and in the presence of hydroquinone, a radical scavenger, did not alter the outcome.

The mechanism of the allylic chlorination was investigated through a deuterium labelling study (Schemes 2 and 3). Tributyltin deuteride reduction of the allyl bromide **5** gave the β,γ-dehydrovaline derivative **8** with *ca.* 85% deuterium incorporation, as determined using mass spectrometry. Treatment of the alkene **8** with chlorine, under the conditions used for the reaction of the unlabelled analogue **3**, gave a *ca.* 4 : 3 : 3 mixture of the chlorides **7**, **10** and **11**, but none of the regioisomer **13** was detected. The $^1$H NMR spectrum of the product mixture showed signals for olefinic protons, at $\delta$ 5.59 and 5.42

† Electronic supplementary information (ESI) available: synthesis and characterisation of compounds **14**–**20** and **24**–**26**. See http://www.rsc.org/suppdata/ob/b3/b303719c/

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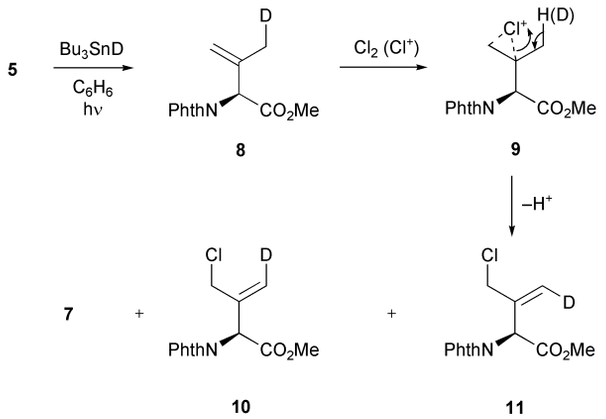
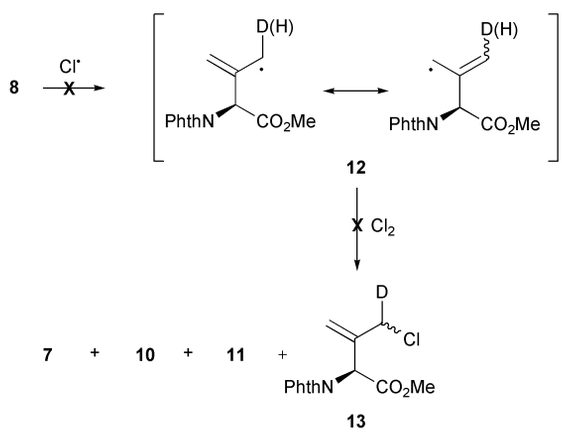


**Scheme 2**



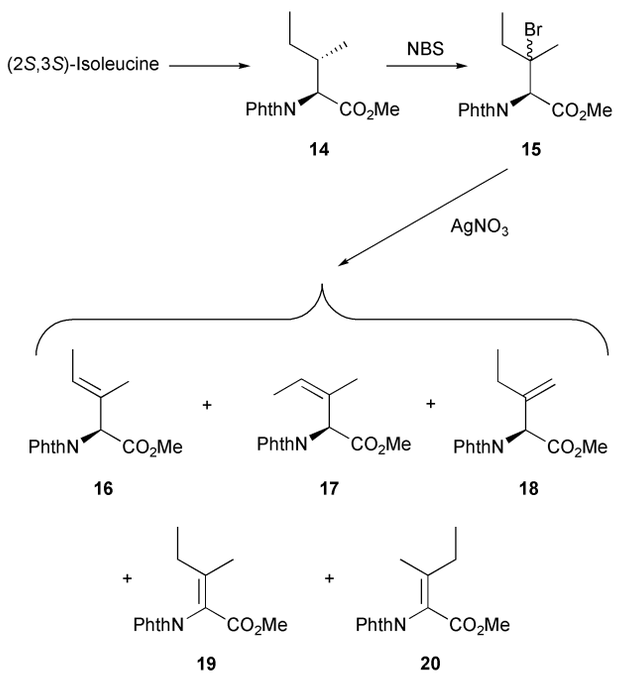
**Scheme 3**

for the unlabelled chloride **7**, and at $\delta$ 5.58 and 5.41 for the deuterides **10** and **11**, in the ratio *ca.* 4 : 4 : 3 : 3, respectively. One pair of doublets at $\delta$ 4.37 and 4.23 for the geminal chloromethylene protons of the chlorides **7**, **10** and **11** was also observed. Corresponding signals for the diastereomers of the isomeric chloride **13** were not evident, even though these would be expected to be distinct due to a lack of geminal proton–proton coupling. The outcome of the reaction of the deuteride **8** is inconsistent with a radical pathway, proceeding *via* the intermediate **12**, as this would lead to a mixture of the chlorides **7**, **10**, **11** and **13** (Scheme 3). Instead, the results show that reaction proceeds *via* an ionic pathway, presumably involving the chloronium ion **9** (Scheme 2). Taking the 85% deuterium content of the starting material **8** and the 60% labelling of the product mixture **7**, **10** and **11** into account, the intermediate ion **9** shows a non-statistical preference for loss of hydrogen over deuterium, corresponding to a small isotope effect.[18]

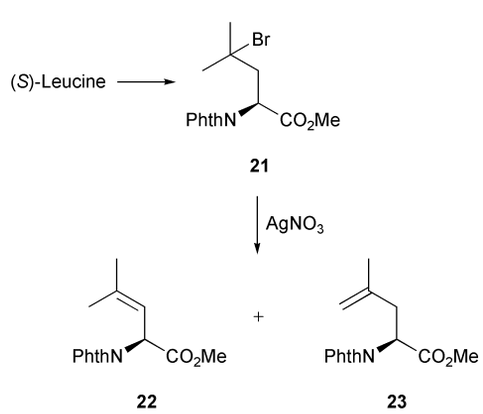
The ionic allylic chlorination has literature precedent in the reaction of hydrocarbon substrates such as isobutene.[11–17] With 1,1-disubstituted olefins of this type, the corresponding chloronium ions are asymmetric, and react by proton loss from adjacent to the more substituted and therefore more positively charged carbon. In the reactions of less substituted olefins, the chloronium ions show greater bridging and less carbocation character and react by chloride addition. Reactions with molecular bromine are thought to involve classical bridged bromonium ion intermediates, which also react by halide addition.[19,20] This accounts for the different reaction pathways of the alkene **3** with molecular chlorine by allylic substitution and bromine by addition.

The radical allylic bromination and ionic allylic chlorination of the dehydrovaline derivative **3** result in analogous products, and there is little advantage to either method in this case. This is not always true, as shown in the following reactions of leucine and isoleucine derivatives.

The procedure used to prepare the valine derivative **3** was applied to access the dehydroisoleucine derivatives **16**–**18** (Scheme 4) and the dehydroleucine derivatives **22** and **23** (Scheme 5). (2*S*,3*S*)-Isoleucine was protected as the *N*-phthaloyl methyl ester **14**, which was treated with NBS to give the β-bromoisoleucine derivatives **15**. Elimination of hydrogen bromide by treatment with dry silver nitrate in acetonitrile gave a mixture of the β,γ-dehydroisoleucine derivatives **16**–**18**, and a small amount of the α,β-dehydroisoleucine derivatives **19** and **20**. The β,γ-dehydroisoleucine derivatives **16**–**18** were separated by chromatography. (*S*)-Leucine was protected and brominated to give the γ-bromoleucine derivative **21** as described previously.[21] Treatment of the bromide **21** with dry silver nitrate in acetonitrile resulted in a mixture of the β,γ- and γ,δ-dehydroleucine derivatives **22** and **23**, which were separated by chromatography.



**Scheme 4**

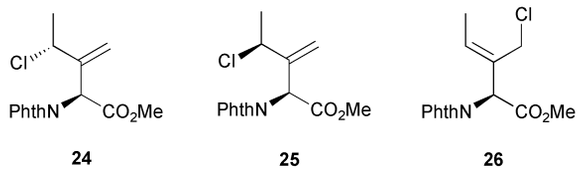


**Scheme 5**

Bromination of the dehydroisoleucine derivative **16** with NBS gave a complex mixture of products, from which it was impractical to isolate individual species. Products are likely to have arisen from hydrogen abstraction from each of the allylic methyl groups, followed by bromine incorporation at either end of both of the intermediate allyl radicals. By analogy, the bromination of **17** and **18** would also be expected to give complex mixtures.

Reactions of the alkenes **16**–**18** with chlorine gave the allyl chlorides **24**–**26** respectively, as a single product in each case,

although the yields were only modest (28–37%). Presumably, the alkenes **16**–**18** form chloronium ions, which each react by proton loss from adjacent to the more substituted and electropositive carbon. The chlorides **24** and **25** are discrete diastereo-




mers. Their stereochemistry at the α-position is assumed to be the same as that of the starting materials **16** and **17**. While it was not practical to unambiguously determine their configurations adjacent to chlorine, the assignments given are based on the models for reaction illustrated in Fig. 1.

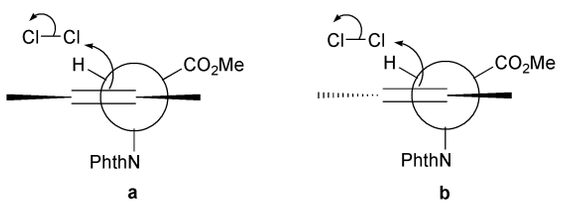
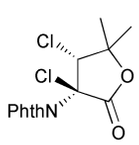



**Fig. 1** Preferred orientations for the reactions of the *E*-alkene **16** (**a**) and the *Z*-isomer **17** (**b**) with chlorine.

Treatment of the β,γ-dehydroleucine derivative **22** with chlorine gave the lactone **27**. The relative stereochemistry of this material was assigned using X-ray crystallographic analysis (Fig. 2). Unfortunately numerous crystallization strategies only ever yielded low quality thin plate crystals, so the analysis is of low precision. Chlorination of the γ,δ-dehydroleucine derivative **23** under standard conditions gave the allyl chloride **28** and the dichlorolactones **29** and **30**, which were separated by chromatography. Reaction of the γ,δ-dehydroleucine derivative **23** with molecular bromine gave the bromolactone diastereomers **31**. Bromination of the alkene **23** using NBS resulted in conversion to the allyl bromide **32**.



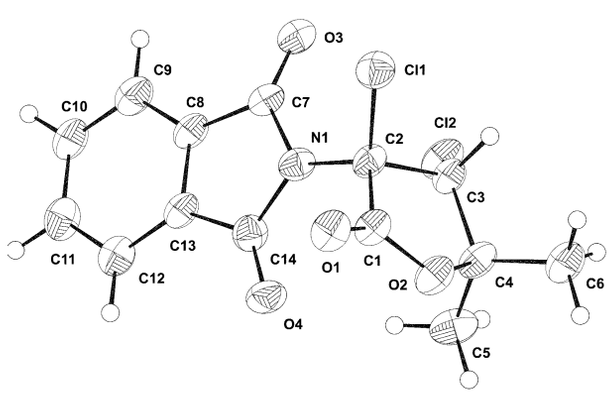
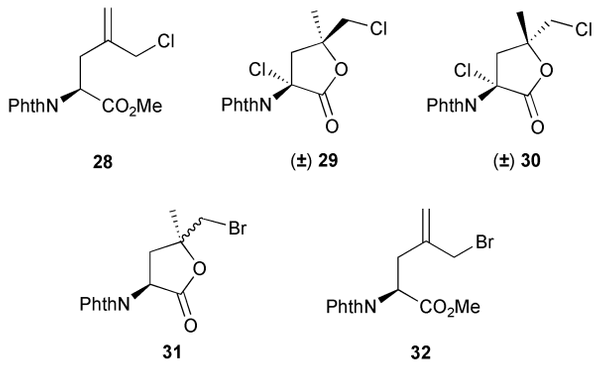




**Fig. 2** Structure of (2*RS*,3*RS*)-*N*-phthaloyl-2,3-dichloro-4-hydroxyleucine γ-lactone **27** as determined by X-ray crystallography. Displacement ellipsoids indicate 30% probability level.

The NBS reaction of the alkene **23** affords the single product **32**, consistent with hydrogen atom abstraction from the side chain methyl group. Hydrogen transfer from the allylic methylene is probably disfavoured by steric hindrance associated with the adjacent bulky protecting groups. The diastereomers **31**




are formed through halolactonization of the alkene **23** with bromine.[22] This differs from the bromine addition observed with the dehydrovaline derivative **3** to give the dibromide **6**, where the corresponding cyclization would form a more strained β-lactone. Halolactonization effectively competes with allylic halogenation in the chlorination of the alkenes **22** and **23** (Fig. 3). Again, this is not a limitation in the analogous chlorinations of the alkenes **3** and **16**–**18**, where the corresponding β-lactones are likely to be too strained to form. Halolactonization involves the carboxy group as a nucleophile. In the allylic chlorinations, it may well be also acting as a base to deprotonate the intermediate chloronium ions. The preference for intramolecular proton transfer *via* a five- or six-membered transition state then accounts for the outcomes of the chlorination of the alkenes **3**, **16**–**18** and **23**, to give the allyl halides **7**, **24**–**26** and **28**, respectively, rather than the corresponding α,β-dehydro-γ-chloro amino acid derivatives in the first four cases, and the β,γ-dehydro-δ-chloro amino acid derivative in the fifth example.

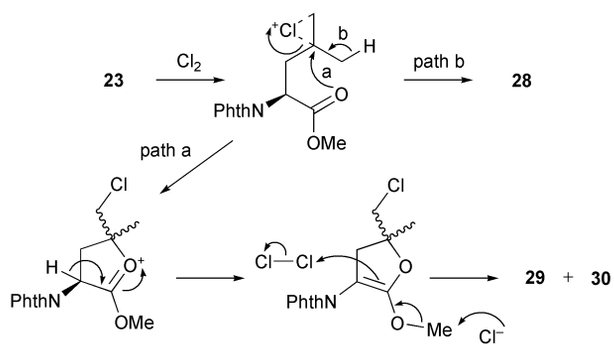
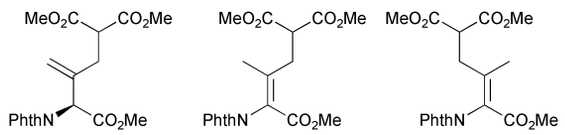



**Fig. 3** Proposed mechanism of formation of the chlorides **28**–**30**.

The above reactions of the alkenes **3**, **16**–**18**, **22** and **23** show that allylic halogenation of amino acid side chains can be achieved through either radical bromination or the complementary ionic chlorination. The choice of method depends on the potential for competing reactions, such as halolactonization in the latter case, and the possibility of hydrogen abstraction and bromine incorporation at multiple sites in the former. Thus, either ionic chlorination or radical bromination is suitable for allylic halogenation of the valine derivative **3**, whereas chlorination of the isoleucine derivative **16** and bromination of the leucine derivative **23** are preferable to the alternative combinations. In the former case the synthetic utility is also compromised by the difficulties experienced in preparing the starting alkene **16**. The reactions were carried out in carbon tetrachloride which may further limit the synthetic utility of this process, although there is every reason to expect that similar results would be obtained in commercial alternative solvents such as α,α,α-trifluorotoluene.

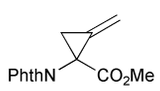
The following examples indicate the synthetic utility of such amino acid allyl halides. Cyclopropyl amino acids are of interest as a result of their high strain energy and biological properties.[23–28] Treatment of **5** with sodium hydride, as

described previously for the synthesis of cyclopropyl amino acids from saturated γ-bromo amino acids,[23,24] gave the cyclopropyl amino acid **33**, albeit in a low yield of 20%. The structure of this material was determined using X-ray crystallographic analysis (Fig. 4). Allyl halides are also useful in intermolecular carbon–carbon bond forming reactions. To demonstrate the application of this to the extension of amino acid side chains, the allyl bromide **5** was treated with dimethyl malonate anion to give a mixture of the isomers **34**–**36**, in the




**34** **35** **36**

ratio *ca.* 2 : 1 : 2, and a combined yield of 66%. Even though these studies are only preliminary, they serve to highlight the potential of amino acid allyl halides in synthesis, regardless of the method by which they are generated.




**33**

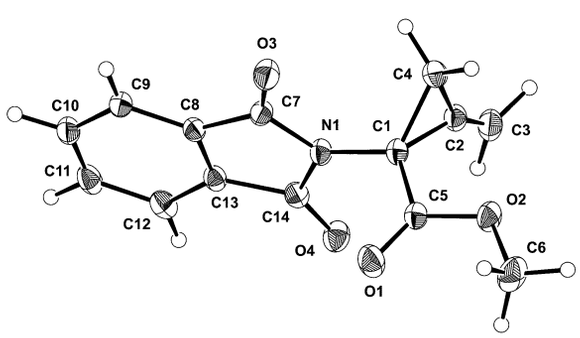



**Fig. 4** Structure of 1-phthalimido-2-methylenecyclopropanecarboxylic acid methyl ester **33** as determined by X-ray crystallography. Displacement ellipsoids indicate 30% probability level.

## Experimental

### General

NMR spectra were recorded in $CDCl_3$ on either a Varian Gemini 300 or a VXR 500S spectrometer. Electron impact (EI) mass spectra were obtained using a VG Autospec double focussing trisector mass spectrometer operating at 70 eV. Fast atom bombardment (FAB) mass spectra were obtained using a ZAB-Seq4F mass spectrometer with a glycerol/thioglycerol +1% TFA matrix. Infrared (IR) spectra were recorded as thin films on a Perkin Elmer 1800 infrared spectrophotometer. Ultraviolet–visible (UV) spectra were recorded using a Shimadzu UV-2101PC UV-Vis scanning spectrophotometer. Microanalyses were performed by the Research School of Chemistry Microanalytical Service at the Australian National University, on a Carlo-Erba 1106 autoanalyser.

An Osram Ultra-Vitalux (240 V, 300 W, E27) sunlamp was used as the light source, to initiate radical reactions, at a distance of 5–10 cm from the reaction vessel. Chromatography was performed with Merck Kieselgel 60 (230–400 mesh ATSM) eluting with ethyl acetate (EtOAc)–petroleum spirit unless otherwise indicated. High performance liquid chromatography (HPLC) was carried out utilising two Waters 510 solvent pumps, a Waters 717 plus Autosampler, a Waters 486 Tuneable Absorbance Detector and a Waters Fraction Collector, in conjunction with a Compaq Deskpro Data Station running Waters Millennium 32 chromatography management software, and either a Waters Symmetry Prep™ C18 7 μm column (19 × 300 mm) (column A), or a Waters Nova-Pak® Silica 6 μm column (19 × 300 mm) (column B).

Solvents were generally used as purchased. Anhydrous tetrahydrofuran (THF) was obtained by distillation from potassium benzophenone ketyl. $CCl_4$ was purified according to the procedure described by Armarego and Perrin.[29] Solutions were dried over $MgSO_4$. (*S*)-Valine (**1**), (2*S*,3*S*)-isoleucine, and (*S*)-leucine were obtained from Aldrich Chem. Co. (*S*)-*N*-Phthaloyl-3,4-dehydrovaline methyl ester (**3**)[7] and (*S*)-4-bromo-*N*-phthaloylleucine methyl ester (**21**)[21] were prepared as previously described. Stock solutions of chlorine were prepared by passing chlorine through $CCl_4$ at room temperature. Chlorine concentrations were determined by measuring the absorbances at 380 nm with a pathlength of 1 mm. Calibration graphs for the UV response to chlorine concentration were prepared by measuring the absorbances at 380 nm of a set of standard solutions of chlorine in $CCl_4$. The concentrations of chlorine in the standard solutions were determined by iodometric titration.[30]

Single crystal X-ray diffraction data were obtained for **27** and **33** using a Nonius Kappa CCD diffractometer with graphite-monochromated Mo-Kα radiation ($\lambda$ = 0.71069 Å). Intensity data were collected at 200 K to $2\theta_{max}$ = 50.7° for **27** and 55° for **33**. The structures were solved by direct methods: **27**,[31a] **33**[31b] and refined on *F* by full-matrix least-squares.[32] Non-hydrogen atoms were refined with anisotropic displacement parameters.

### Treatment of (*S*)-*N*-phthaloyl-3,4-dehydrovaline methyl ester (3) with NBS

NBS (0.76 g, 4.3 mmol) was added to a solution of the alkene **3** (1.1 g, 4.2 mmol) in $CCl_4$ (40 $cm^3$) under a nitrogen atmosphere and the mixture was heated at reflux for 2 h while being irradiated with a sunlamp. The mixture was then cooled and filtered. The filtrate was washed with water, dried and concentrated under reduced pressure, and the residue was chromatographed on silica, affording (*S*)-4′-bromo-*N*-phthaloyl-3,4-dehydrovaline methyl ester (**5**) (1.1 g, 77%) as a yellow oil. $\nu_{max}/cm^{-1}$ 3492, 2952, 1776, 1722, 1614, 1470, 1438, 1382, 1340, 1304, 1256, 1212, 1108, 1088, 1028, 960, 912, 792, 720, 700, 668; $\delta_H$ (300 MHz) 7.92–7.88 (2 H, m), 7.80–7.76 (2 H, m), 5.72 (1 H, s), 5.62 (1 H, s), 5.41 (1 H, s), 4.28 (1 H, d, *J* 10.8), 4.13 (1 H, d, *J* 10.8), 3.79 (3 H, s); $\delta_C$ (75 MHz) 167.2, 166.5, 137.9, 134.2, 131.3, 123.3, 121.2, 53.3, 52.6, 33.4; *m*/*z* (EI) 339 ($M^{+\bullet}$, 24%), 337 ($M^{+\bullet}$, 22), 280 (20), 278 (20), 258 (100), 218 (22), 202 (31), 200 (44), 199 (32), 198 (31), 160 (26), 130 (40), 104 (65); Found *m*/*z* (EI): $M^{+\bullet}$, 336.9958. $C_{14}H_{12}{}^{79}BrNO_4$ requires 336.9950.

### Treatment of (*S*)-*N*-phthaloyl-3,4-dehydrovaline methyl ester (3) with bromine

A solution of bromine in $CCl_4$ (6 $cm^3$, 0.13 M) was added to the alkene **3** (0.12 g, 0.46 mmol) in $CCl_4$ (40 $cm^3$). The mixture was stirred at room temperature for 16 h, then concentrated under reduced pressure. When analysed using $^1H$ NMR spectroscopy, the residue showed a *ca.* 3 : 1 mixture of diastereomers of 3,4-dibromo-*N*-phthaloylvaline methyl ester (**6**). $\delta_H$ (300 MHz) 7.95–7.78 (4 H, m), 5.49 and 5.61 (0.75 and 0.25 H, s and s), 4.73 and 4.63 (0.75 and 0.25 H, d and d, *J* 10.7 and 10.7), 3.98 and 3.91 (0.25 and 0.75 H, d and d, *J* 10.7 and 10.7), 3.75 and 3.71 (2.25 and 0.75 H, s and s), 2.13 and 2.02 (0.75 and 2.25 H, s and s); *m*/*z* (EI) 422 ($MH^+$, 11%), 420 ($MH^+$, 20), 418 ($MH^+$, 12), 362 (8), 360 (19), 358 (19), 340 (80), 338 (78), 308 (18), 306 (18), 280 (81), 278 (78), 250 (70), 248 (75), 218 (100), 200 (100), 190 (64), 130 (77), 104 (78); Found *m*/*z* (EI): $M^{+\bullet}$, 416.9220. $C_{14}H_{13}{}^{79}Br_2NO_4$ requires 416.9212.

### Treatment of (*S*)-*N*-phthaloyl-3,4-dehydrovaline methyl ester (3) with chlorine

A solution of chlorine in $CCl_4$ (0.4 $cm^3$, 2.4 M) was added to a solution of the alkene **3** (79 mg, 0.31 mmol) in $CCl_4$ (10 $cm^3$).

The mixture was stirred for 1 h at room temperature, then concentrated under reduced pressure. The residue was chromatographed on silica, affording (*S*)-4′-chloro-*N*-phthaloyl-3,4-dehydrovaline methyl ester (**7**) (48 mg, 53%) as a colourless oil. (Found: C, 57.18; H, 4.22; N, 4.75%. $C_{14}H_{12}ClNO_4$ requires: C, 57.25; H, 4.12; N, 4.77%); $\nu_{max}/cm^{-1}$ 3040, 2960, 1780, 1750, 1720, 1620, 1475, 1440, 1390, 1340, 1300, 1230, 1120, 1095, 1030, 920; $\delta_H$ 7.98–7.75 (4 H, m), 5.68 (1 H, s), 5.59 (1 H, s), 5.42 (1 H, s), 4.37 (1 H, d, *J* 12.1), 4.22 (1 H, d, *J* 12.1), 3.80 (3 H, s); *m*/*z* (EI) 295 ($M^{+\bullet}$, 1%), 293 ($M^{+\bullet}$, 3), 258 (100), 236 (10), 234 (25), 200 (10), 199 (10), 198 (10), 160 (20), 130 (20), 104 (25).

### (*S*)-4′-Deutero-*N*-phthaloyl-3,4-dehydrovaline methyl ester (8)

A solution of dibenzoyl peroxide (15 mg) in benzene (1 $cm^3$) was added to a solution of tributyltin deuteride[33,34] (0.30 g, 1.0 mmol) and the bromide **5** (0.32 g, 0.95 mmol) in benzene (20 $cm^3$) under argon. The mixture was heated at reflux for 0.5 h while being irradiated with a sunlamp. The solvent was then removed under reduced pressure and the residue was chromatographed on silica to afford the title compound **8** (0.14 g, 57%) as a colourless solid, mp 74–76 °C; $\delta_H$ (500 MHz) 7.87 (2 H, dd, *J* 3.0, 5.5), 7.74 (2 H, dd, *J* 3.0, 5.5), 5.37 (1 H, s), 5.13 (1 H, s), 5.10 (1 H, s), 3.78 (3 H, s), 1.89 (2.15 H, m); $\delta_C$ (75 MHz) 168.1, 167.1, 138.3, 134.2, 131.7, 123.6, 117.4, 57.0, 52.7, 20.4 (t, *J* 20.0); *m*/*z* (EI) 260 ($M^{+\bullet}$, 21%), 228 (32), 201 (100), 183 (10), 160 (13), 149 (22), 130 (38), 104 (42), 76 (40). The $^1H$ and $^{13}C$ NMR spectra of the deuteride **8** are consistent with those of the unlabelled analogue **3**.[7]

### Treatment of (*S*)-4′-deutero-*N*-phthaloyl-3,4-dehydrovaline methyl ester (8) with chlorine

The deuteride **8** was treated with chlorine as described above for reaction of the unlabelled analogue **3**, to give a mixture of the alkenes **7**, **10** and **11** (66%), as a colourless oil. $\delta_H$ (500 MHz) 7.89 (2 H, dd, *J* 3.0, 5.5), 7.76 (2 H, dd, *J* 3.0, 5.5), 5.69 (1 H, s), 5.59 (0.4 H, s), 5.58 (0.3 H, s), 5.42 (0.4 H, br s), 5.41 (0.3 H, br s), 4.36 (1 H, d, *J* 12.5), 4.21 (1 H, d, *J* 12.5), 3.79 (3 H, s); $\delta_C$ (75 MHz) 167.7, 167.0, 138.0, 134.4, 131.6, 123.7, 121.2, 53.5, 53.0, 45.9; *m*/*z* (EI) 296 ($M^{+\bullet}$, 8%), 295 ($M^{+\bullet}$, 3%), 294 ($M^{+\bullet}$, 25%), 293 ($M^{+\bullet}$, 11%), 259 (100). The $^1H$ and $^{13}C$ NMR spectra of this mixture are consistent with those of the alkene **7**.

### (*S*)-*N*-Phthaloyl-3,4-dehydroleucine methyl ester (22) and (*S*)-*N*-phthaloyl-4,5-dehydroleucine methyl ester (23)

Silver nitrate (2.6 g, 15 mmol) was added to a solution of the bromide **21** (3.6 g, 10 mmol) in dry acetonitrile (100 $cm^3$). The mixture was stirred in the dark at room temperature for 24 h. Saturated brine was then added and the mixture was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was partitioned between EtOAc and saturated aqueous ammonium chloride. The organic layer was separated, dried and concentrated. The residue was chromatographed on silica eluting with $CH_2Cl_2$–petroleum spirit (1 : 2, v/v) to give the alkene **22** (0.65 g, 24%) and the alkene **23** (1.0 g, 37%).

*(S)-N-Phthaloyl-3,4-dehydroleucine methyl ester* (**22**), colourless oil. $\delta_H$ (300 MHz) 7.90–7.65 (4 H, m), 5.80 (1 H, d, *J* 9.2), 5.64 (1 H, d, *J* 9.2), 3.75 (3 H, s), 1.77 (3 H, s), 1.76 (3 H, s). These spectral data are consistent with those reported.[35]

*(S)-N-Phthaloyl-4,5-dehydroleucine methyl ester* (**23**), colourless crystals, mp 77–78 °C. $\delta_H$ (300 MHz) 7.85–7.60 (4 H, m), 5.06 (1 H, dd, *J* 4.2 and 12.1), 4.67 (1 H, s), 4.63 (1 H, s), 3.73 (3 H, s), 3.07 (1 H, dd, *J* 12.1 and 14.2), 2.83 (1 H, dd, *J* 4.2 and 14.2), 1.73 (3 H, s). These spectral data are consistent with those reported.[35]

### Treatment of (*S*)-*N*-phthaloyl-3,4-dehydroleucine methyl ester (22) with chlorine

A solution of chlorine in $CCl_4$ (2.6 $cm^3$, 0.33 M) was added to a solution of the alkene **22** (260 mg, 0.95 mmol) in $CCl_4$ (5 $cm^3$). The mixture was stirred for 0.25 h, then concentrated under reduced pressure. The residue was chromatographed on silica to give (2*RS*,3*RS*)-*N*-phthaloyl-2,3-dichloro-4-hydroxyleucine γ-lactone (**27**) (62 mg, 20%) as colourless crystals, mp 139–141 °C. (Found: C, 51.51; H, 3.51; N, 4.31%. $C_{14}H_{11}Cl_2NO_4$ requires: C, 51.24; H, 3.38; N, 4.27%); $\nu_{max}/cm^{-1}$ 2993, 1794, 1736, 1468, 1346, 1257, 1107, 1000, 768, 720; $\delta_H$ (300 MHz) 7.93–7.79 (4 H, m), 5.00 (1 H, s), 1.78 (3 H, s), 1.59 (3 H, s); $\delta_C$ (75 MHz) 166.3, 162.2, 149.5, 134.8, 131.8, 124.3, 121.8, 53.2, 28.5, 26.5; *m*/*z* (FAB) 332 ($MH^+$, 11%), 330 ($MH^+$, 72%), 328 ($MH^+$, 100%), 280 (7), 258 (27), 246 (7); Found *m*/*z* (FAB): $MH^+$, 328.0143. $C_{14}H_{11}{}^{35}Cl_2NO_4$ requires 328.0143.

### Crystal structure determination of compound 27‡

$C_{14}H_{11}Cl_2NO_4$, $M_r$ = 328.15, monoclinic, space group $P2_1/a$ (no. 14), $a$ = 7.4491(5) Å, $b$ = 13.6937(10) Å, $c$ = 13.8646(10) Å, $\beta$ = 91.317(3)°, $V$ = 1413.9(2) $Å^3$, $T$ = 200 K, $Z$ = 4, $D_{calc}$ = 1.542 g $cm^{-3}$, $\mu$ = 0.47 $mm^{-1}$. A total of 14725 reflections were measured, corrected for absorption and merged to yield 2483 unique reflections ($R_{int}$ = 0.210). Final agreement factors for 1444 reflections with $I > 3\sigma(I)$ and 190 parameters were $R$ = 0.086, $wR$ = 0.0944 and $S$ = 1.01.

### Treatment of (*S*)-*N*-phthaloyl-4,5-dehydroleucine methyl ester (23) with chlorine

A solution of chlorine in $CCl_4$ (1.3 $cm^3$, 0.33 M) was added to a solution of the alkene **23** (120 mg, 0.44 mmol) in $CCl_4$ (5 $cm^3$). The mixture was stirred for 0.25 h, then concentrated under reduced pressure. The residue was chromatographed on silica to give the chloride **28** (41 mg, 31%), and the lactones **29** (28 mg, 19%) and **30** (28 mg, 19%).

*(S)-5′-Chloro-N-phthaloyl-4,5-dehydroleucine methyl ester* (**28**), colourless oil. $\nu_{max}/cm^{-1}$ 3477, 2954, 2852, 1775, 1747, 1716, 1612, 1437, 1389, 1259, 1107, 1024, 1045, 720; $\delta_H$ (300 MHz) 7.90–7.70 (4 H, m), 5.10 (1 H, br s), 5.08 (1 H, dd, *J* 4.4, 11.7), 4.95 (1 H, br s), 4.14 (1 H, d, *J* 12.1), 4.00 (1 H, d, *J* 12.1), 3.77 (3 H, s), 3.23 (1 H, dd, *J* 4.4, 14.8), 3.12 (1 H, dd, *J* 11.7, 14.8); $\delta_C$ (75 MHz) 169.1, 167.5, 140.5, 134.3, 131.6, 123.6, 118.3, 53.0, 49.9, 46.9, 32.3; *m*/*z* (EI) 307 ($M^{+\bullet}$, 5%), 272 (100), 248 (62), 212 (56), 190 (39), 160 (37), 132 (50), 104 (51), 76 (55); Found *m*/*z* (EI): $M^{+\bullet}$, 307.0610. $C_{15}H_{14}{}^{35}ClNO_4$ requires 307.0611.

*(2RS,4SR)-2,5-Dichloro-4-hydroxy-N-phthaloylleucine γ-lactone* (**29**) and *(2RS,4RS)-2,5-dichloro-4-hydroxy-N-phthaloylleucine γ-lactone* (**30**) were obtained as separate species but were not distinguished on the basis of their relative stereochemistry. One was obtained as colourless crystals, mp 88–90 °C (Found: C, 51.54; H, 3.58; N, 4.19%. $C_{14}H_{11}Cl_2NO_4$ requires: C, 51.24; H, 3.38; N, 4.27%); $\delta_H$ (300 MHz) 7.92–7.70 (4H, m), 3.82 (1 H, d, *J* 11.5), 3.69 (1 H, d, *J* 11.5), 3.30 (1 H, d, *J* 15.1), 3.03 (1 H, d, *J* 15.1), 1.57 (3 H, s); $\delta_C$ (75 MHz) 166.6, 165.2, 135.1, 131.0, 124.1, 82.8, 73.3, 49.5, 47.5, 29.7; *m*/*z* (EI) 328 ($MH^+$, 1%), 248 (48), 212 (100), 167 (61), 132 (34), 104 (76), 76 (69). The diastereomer was obtained as colourless crystals, mp 118–120 °C (Found: C, 51.44; H, 3.45; N, 4.28%. $C_{14}H_{11}Cl_2NO_4$ requires: C, 51.24; H, 3.38; N, 4.27%); $\delta_H$ (300 MHz) 7.92–7.70 (4 H, m), 3.69 (2 H, s), 3.22 (1 H, d, *J* 15.3), 3.04 (1 H, d, *J* 15.3), 1.76 (3 H, s); $\delta_C$ (75 MHz) 166.8, 165.3, 135.0, 131.1, 124.1, 82.7, 73.1, 49.9, 47.8, 24.7; *m*/*z* (EI) 328 ($MH^+$, 2%), 248 (43), 212 (100), 167 (58), 132 (30), 104 (75), 76 (66).

‡ CCDC reference numbers 207407 (**33**) and 207408 (**27**). See http://www.rsc.org/suppdata/ob/b3/b303719c/ for crystallographic data in .cif or other electronic format.

### Treatment of (*S*)-*N*-phthaloyl-4,5-dehydroleucine methyl ester (23) with bromine

A solution of bromine in $CCl_4$ (3.8 $cm^3$, 0.11 M) was added to a solution of the alkene **23** (130 mg, 0.48 mmol) in $CCl_4$ (5 $cm^3$). The mixture was stirred for 0.25 h, then concentrated under reduced pressure. The residue was chromatographed on silica to give a *ca.* 3 : 1 mixture of diastereomers of 5-bromo-4-hydroxy-*N*-phthaloylleucine γ-lactone (**31**) (81 mg, 50%) as colourless crystals, mp 138–140 °C (Found: C, 49.62; H, 3.60; N, 4.05%. $C_{14}H_{12}BrNO_4$ requires: C, 49.73; H, 3.58; N, 4.14%); $\nu_{max}/cm^{-1}$ 3477, 2931, 1775, 1717, 1394, 1280, 1202, 1184, 1088, 956, 880, 718, 643; $\delta_H$ (500 MHz) 7.90–7.70 (4 H, m), 5.37 and 5.25 (0.25 and 0.75 H, dd and dd, *J* 9.9, 11.0 and 9.9, 11.0), 3.70 and 3.68 (0.75 and 0.25 H, d and d, *J* 10.5 and 11.0), 3.65 and 3.52 (0.75 and 0.25 H, d and d, *J* 10.5 and 11.0), 2.82 and 2.74 (0.25 and 0.75 H, dd and dd, *J* 11.0, 13.2 and 11.2, 12.7), 2.51 and 2.45 (0.75 and 0.25 H, dd and dd, *J* 9.9, 12.7 and 9.9, 13.2), 1.79 and 1.67 (0.75 and 2.25 H, s and s); $\delta_C$ 170.4, 169.6, 165.7 (2), 133.6, 133.5, 130.5 (2), 122.8, 122.7, 81.7, 81.2, 47.4, 46.9, 38.9, 37.9, 35.3, 35.2, 25.7. 23.5; *m*/*z* (EI) 340 ($MH^+$, 4%), 338 ($MH^+$, 4%), 214 (100), 196 (32), 174 (46), 160 (25), 130 (28), 104 (33), 76 (42); Found *m*/*z* (EI): $MH^+$, 340.0010. $C_{14}H_{13}{}^{81}BrNO_4$ requires 340.0007.

### Treatment of (*S*)-*N*-phthaloyl-4,5-dehydroleucine methyl ester (23) with NBS

NBS (71 mg, 0.40 mmol) was added to a solution of the alkene **23** (110 mg, 0.40 mmol) in $CCl_4$ (5 $cm^3$) under nitrogen. The mixture was heated at reflux and irradiated with a sunlamp for 1 h, then it was cooled and filtered. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica, eluting with $CH_2Cl_2$–petroleum spirit (1 : 2, v/v), to give (*S*)-5′-bromo-*N*-phthaloyl-4,5-dehydroleucine methyl ester (**32**) (73 mg, 52%) as a colourless oil. (Found: C, 50.81; H, 4.04; N, 3.76%. $C_{15}H_{14}BrNO_4$ requires: C, 51.16; H, 4.01; N, 3.98%); $\nu_{max}/cm^{-1}$ 3477, 2954, 1775, 1747, 1715, 1436, 1388, 1243, 1105, 1024, 918, 719; $\delta_H$ (300 MHz) 7.90–7.70 (4 H, m), 5.14 (1 H, s), 5.06 (1 H, dd, *J* 4.4 and 11.8), 4.95 (1 H, s), 4.05 (1 H, d, *J* 10.5), 3.90 (1 H, d, *J* 10.5), 3.76 (3 H, s), 3.27 (1 H, dd, *J* 4.4, 14.8), 3.12 (1 H, dd, *J* 11.8, 14.8); $\delta_C$ (75 MHz) 168.1, 166.5, 139.8, 133.3, 130.6, 122.6, 117.8, 52.0, 48.9, 34.1, 31.7; *m*/*z* (EI) 353 ($M^{+\bullet}$, 6%), 351 ($M^{+\bullet}$, 6%), 272 (100), 240 (12), 212 (53), 160 (10), 130 (35), 104 (37), 76 (37); Found *m*/*z* (EI): $M^{+\bullet}$, 353.0083. $C_{15}H_{14}{}^{81}BrNO_4$ requires 353.0086.

### 2-Methylene-1-phthalimidocyclopropanecarboxylic acid methyl ester (33)

Sodium hydride (60% in mineral oil, 66 mg, 1.7 mmol) was added to a solution of the bromide **5** (0.55 g, 1.6 mmol) in THF (20 $cm^3$). The mixture was stirred at room temperature for 48 h, then diluted with $CH_2Cl_2$ (50 $cm^3$), washed with saturated aqueous ammonium chloride (2 × 50 $cm^3$), dried and concentrated under reduced pressure. The residue was chromatographed on silica to give the title compound (**33**) (84 mg, 20%) as colourless crystals, mp 139–140 °C (Found: C, 65.13; H, 4.40; N, 5.44%. $C_{14}H_{11}NO_4$ requires: C, 65.37; H, 4.31; N, 5.44%); $\nu_{max}/cm^{-1}$ 3486, 2925, 2854, 1780, 1725, 1437, 1391, 1284, 1112, 907, 720; $\delta_H$ (300 MHz) 7.90–7.70 (4 H, m), 6.17 (1 H, apparent t, *J* 2.5), 5.77 (1 H, apparent t, *J* 2.5), 3.70 (3 H, s), 2.69 (1 H, apparent dt, *J* 11.1, 2.5), 2.20 (1 H, apparent dt, *J* 11.1, 2.5); $\delta_C$ (75 MHz) 177.4, 168.2, 134.6, 132.2, 130.2, 123.9, 109.8, 53.3, 33.4, 20.3; *m*/*z* (EI) 257 ($M^{+\bullet}$, 100%), 242 (31), 198 (70), 132 (50), 104 (90), 76 (72); Found *m*/*z* (EI): $M^{+\bullet}$, 257.0685. $C_{14}H_{11}NO_4$ requires 257.0688.

### Crystal structure determination of compound 33‡

$C_{14}H_{11}NO_4$, $M_r$ = 257.24, triclinic, space group $P\bar{1}$, (no. 2), $a$ = 7.0050(2) Å, $b$ = 12.8848(4) Å, $c$ = 13.7023(5) Å, $\alpha$ = 91.151(1)°, $\beta$ = 94.660(1)°, $\gamma$ = 90.007(2)°, $V$ = 1232.40(7) Å$^3$, $Z$ = 4, $D_{calc}$ = 1.386 g $cm^{-3}$, $\mu$ = 0.103 $mm^{-1}$. A total of 17604 reflections were measured, corrected for absorption and merged to yield 2685 unique reflections ($R_{int}$ = 0.06). Hydrogen atom coordinates were refined. Final agreement factors for 2685 reflections with $I > 2\sigma(I)$ and 343 parameters were $R$ = 0.0456, $wR$ = 0.0507 and $S$ = 1.07.

### Alkylation of dimethyl malonate with (*S*)-4′-bromo-*N*-phthaloyl-3,4-dehydrovaline methyl ester (5)

A solution of *n*-butyllithium in hexanes (0.73 $cm^3$, 1.32 M) was added to a solution of dimethyl malonate (0.19 g, 1.4 mmol) in THF and the mixture was stirred for 10 min, then transferred by syringe to a solution of the bromide **5** (330 mg, 0.98 mmol) in THF (20 $cm^3$) under nitrogen. After stirring for 15 h, the mixture was concentrated under reduced pressure and the residue was taken up in EtOAc (20 $cm^3$). The solution was washed with saturated aqueous ammonium chloride (2 × 50 $cm^3$), dried and concentrated under reduced pressure. The residue was chromatographed on silica to give a mixture of the three alkenes **34**–**36** (250 mg, 66%), in a ratio *ca.* 2 : 1 : 2. Reverse phase HPLC (column A) eluting with 10% methanol in water was used to isolate compound **36**. The remaining compounds **34** and **35** were separated using normal phase HPLC (column B) eluting with 10% EtOAc–petroleum spirit.

*Dimethyl 2-phthalimido-5-methoxycarbonyl-3-methylene-hexane-1,6-dicarboxylate (***34**), colourless oil. (Found: C, 58.62; H, 4.99; N, 3.52%. $C_{19}H_{19}NO_8$ requires: C, 58.61; H, 4.92; N, 3.60%); $\nu_{max}/cm^{-1}$ 3480, 3004, 2955, 2847, 1721, 1467, 1436, 1385, 1205, 1030, 915, 720; $\delta_H$ (300 MHz) 7.95–7.70 (4 H, m), 5.40 (1 H, s), 5.26 (1 H, s), 5.21 (1 H, s), 3.77 (3 H, s), 3.72 (3 H, s), 3.71 (1 H, t, *J* 8.0), 3.66 (3 H, s), 2.79 (2 H, d, *J* 8.0); $\delta_C$ (75 MHz) 169.3 (2), 167.4, 138.7, 134.6, 132.0, 123.9, 118.5, 56.4, 53.2, 53.0, 52.9, 50.8, 32.9; *m*/*z* (EI) 389 ($M^{+\bullet}$, 4%), 357 (77), 326 (53), 298 (100), 270 (61), 258 (78), 200 (35), 132 (42), 104 (73), 76 (37); Found *m*/*z* (EI): $M^{+\bullet}$ 389.1113. $C_{19}H_{19}NO_8$ requires 389.1111.

*(E)-Dimethyl 5-methoxycarbonyl-3-methyl-2-phthalimido-hex-2-ene-1,6-dicarboxylate* (**35**) and *(Z)-dimethyl 5-methoxycarbonyl-3-methyl-2-phthalimidohex-2-ene-1,6-dicarboxylate* (**36**) were obtained as separate species but were not distinguished on the basis of their relative stereochemistry. The minor isomer was obtained as colourless crystals, mp 118–119 °C (Found: C, 58.45; H, 5.12; N, 3.53%. $C_{19}H_{19}NO_8$ requires: C, 58.61; H, 4.92; N, 3.60%); $\nu_{max}/cm^{-1}$ 3482, 3005, 2956, 2848, 1787, 1724, 1640, 1436, 1386, 1278, 1224, 1117, 885, 722, 670; $\delta_H$ (300 MHz) 7.95–7.75 (4 H, m), 3.67 (6 H, s), 3.66 (3 H, s), 3.64 (1 H, t, *J* 7.0), 2.79 (2 H, d, *J* 7.0), 2.39 (3 H, s); $\delta_C$ (75 MHz) 167.8, 166.2, 162.2, 153.9, 133.4, 131.1, 122.8, 118.0, 102.6, 52.0, 51.3, 48.1, 34.4, 18.5; *m*/*z* (EI) 389 ($M^{+\bullet}$, 7%), 357 (87), 325 (24), 270 (85), 210 (8), 132 (66), 104 (100), 76 (43), 59 (15). The major isomer was obtained as colourless crystals, mp 93–95 °C. (Found: C, 58.58; H, 4.92; N, 3.54%. $C_{19}H_{19}NO_8$ requires: C, 58.61; H, 4.92; N, 3.60%); $\nu_{max}/cm^{-1}$ 3483, 3003, 2955, 2848, 1786, 1725, 1640, 1436, 1387, 1225, 1116, 1061, 885, 722; $\delta_H$ (300 MHz) 7.90–7.75 (4 H, m), 3.86 (1 H, t, *J* 8.0), 3.77 (6 H, s), 3.68 (3 H, s), 3.38 (2 H, d, *J* 8.0), 1.85 (3 H, s); $\delta_C$ (75 MHz) 169.3, 166.9, 163.2, 155.4, 134.7, 132.2, 124.1, 119.8, 53.0, 52.7, 50.6, 33.7, 22.0; *m*/*z* (EI) 390.1 ($MH^+$, 8%), 357 (93), 325 (31), 270 (82), 210 (10), 132 (80), 104 (100), 76 (50), 59 (15).

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