Synthesis of (*R*)- and (*S*)-2,3-methanovaline as the hydrochloride salts, through manipulation of the *N*-phthaloyl group of an (*S*)-leucine derivative for the recall of stereochemistry

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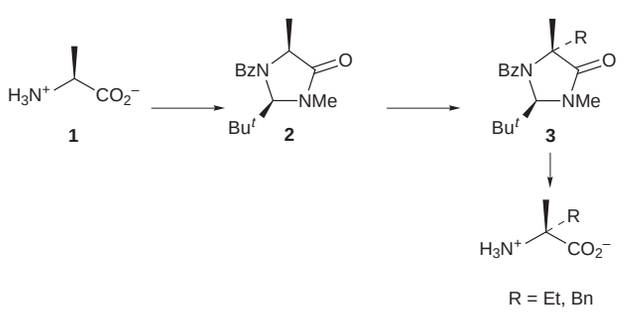
Received (in Cambridge) 17th August 1998, Accepted 21st September 1998

(*S*)-*N*-Phthaloyl-4-bromoleucine methyl ester was prepared from (*S*)-leucine. Treatment of the phthalimide with sodium borohydride in methanol gave the corresponding diastereomeric α-methoxyamides. The new stereochemical centre gave rise to diastereoselectivity in the base-induced cyclisation of the methoxyamides. It was also exploited to distinguish and separate the stereoisomers of the methanovaline derivatives produced in those reactions. Deprotection of the cyclised species then completed the synthesis of the hydrochloride salts of the enantiomers of methanovaline, illustrating the way in which an *N*-phthaloyl protecting group may be manipulated to recall the stereochemistry of an α-amino acid in asymmetric synthesis.

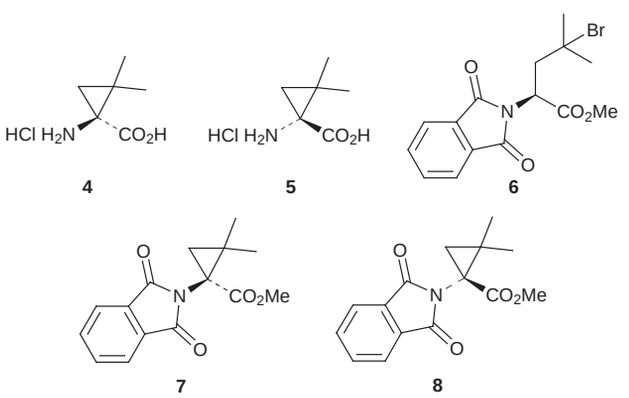
Introduction

α-Amino acids are important chiral starting materials for asymmetric synthesis,[1] however, in the absence of another chiral centre in the molecule, reactions at the α-carbon generally give rise to enantiomeric products which are difficult to separate.[2] To overcome this limitation, Seebach *et al.*,[3,4] developed the concept of 'self-reproduction of chirality', which was later referred to as 'self-regeneration of chirality'.[5] Originally this approach was applied to α-hydroxy- and α-mercapto-carboxylic acids,[3] but its later use with amino acids is illustrated in Scheme 1.[4] The new stereochemical centre of the



Scheme 1

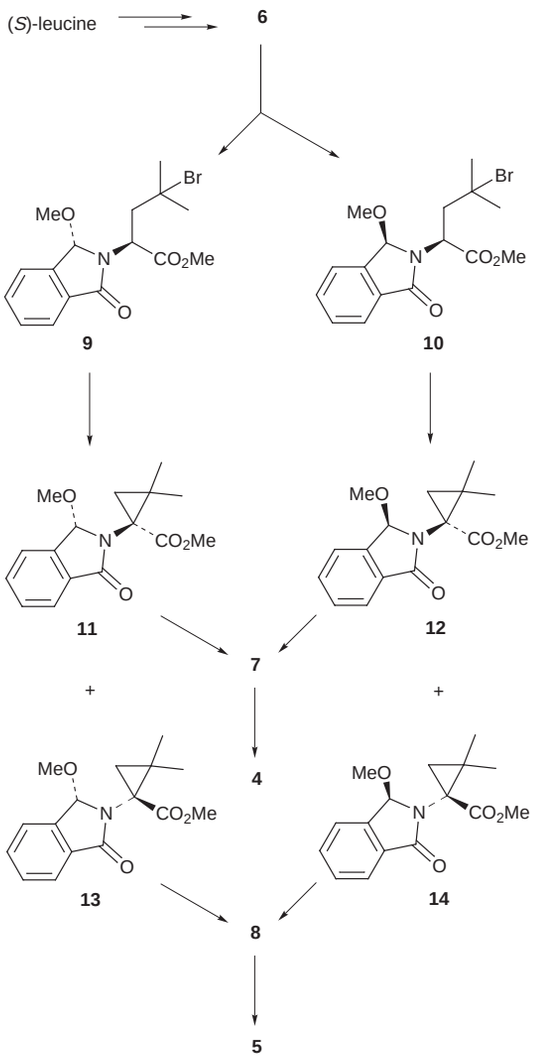
imidazolidinone **2** functions as a chiral auxiliary in reactions of that compound and it allows the product **3** to be distinguished from its diastereomer. The stereochemical distinction is derived from the starting α-amino acid **1**, even though the chiral integrity at the α-carbon of that species is not retained throughout the reaction sequence. In this report we describe the introduction of a stereochemical centre to the phthaloyl substituent of an amino acid derivative, as a related approach for the manipulation of stereochemistry. The methodology is illustrated through the synthesis of the enantiomers of methanovaline, as their hydrochloride salts **4** and **5**, from (*S*)-leucine. Consequently it complements procedures reported previously for the asymmetric synthesis of cyclopropylamino acids and their derivatives,[6] which are of interest as plant growth regulators and as enzyme inhibitors.



Results and discussion

Previously, we showed that treatment of *N*-phthaloyl-4-bromoleucine methyl ester with sodium hydride in tetrahydrofuran affords the corresponding methanovaline derivative,[7] however, this method is not directly applicable in asymmetric synthesis. When the bromide **6** was prepared from (*S*)-leucine, the cyclisation reaction gave a racemic mixture of the cyclopropane derivatives **7** and **8**, showing that reaction at the α-carbon occurred with complete loss of optical activity. Now, to obtain the enantiomers **7** and **8**, separately, we have used the methodology shown in Scheme 2.

The reduction and solvolysis of the phthalimide **6**[8] was carried out using the procedure reported by Speckamp *et al.*[9] Accordingly, treatment with sodium borohydride in methanol at −10 °C for 15 min, followed by acidification and stirring the mixture at room temperature for 16 h, afforded a *ca.* 1:1 mixture of the methoxyamides **9** and **10**, in 71% yield. These diastereomers were separated using normal phase preparative HPLC. The bromide **9** was treated with sodium hydride in tetrahydrofuran, to give a *ca.* 1:2 mixture of the cyclopropane derivatives **11** and **13**, which were separated using radial chromatography on silica, and isolated in yields of 34 and 58%, respectively. Similar treatment of the bromide **10** gave the cyclopropane derivatives **12** and **14**, in 10 and 84% yield,



Scheme 2

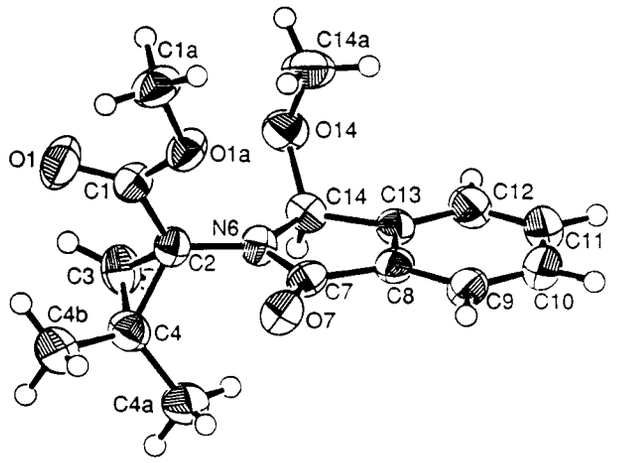


Fig. 1 Molecular structure and crystallographic numbering scheme employed for the α-methoxyamide **11**.

respectively. With sodium methoxide in methanol, instead of sodium hydride in tetrahydrofuran, reaction of the bromide **9** gave the cyclised products **11** and **13**, in 87 and 4% yield, respectively. The analogous reaction of the bromide **10** afforded the cyclopropane **12**, in 63% yield, and the diastereomer **14**, in 30% yield. The methoxyamides **11** and **12** each reacted with ceric ammonium nitrate and sodium bromate,[10] to give (*S*)-*N*-phthaloylmethanovaline methyl ester **7** in virtually quantitative yield, while oxidation of the corresponding enantiomers **14** and **13**, in similar fashion, afforded the (*R*)-methanovaline derivative **8**. Finally, the cyclopropylamino acid derivatives **7** and **8** were deprotected, by treatment with sodium borohydride in propan-2-ol and water, to remove the phthaloyl substituent,[11] then by refluxing in aqueous hydrochloric acid to hydrolyse the ester moiety. In this manner, the enantiomers of methanovaline hydrochloride **4** and **5** were obtained, in yields of 60 and 45%, respectively.

The chiral purity of the methanovaline derivatives **7** and **8** was confirmed through ^{1}H NMR spectroscopic analysis in the presence of the chiral shift reagent Eu(hfc)$_3$, whereby the corresponding racemate shows distinct duplicate signals for the cyclopropane methine protons and methyl substituents. The absolute stereochemistry of the methanovaline hydrochlorides **4** and **5** was determined by comparison of their optical rotations with literature data.[12] The structure and relative stereochemistry of the cyclopropylamino acid derivative **11** were determined through X-ray crystallographic analysis (Fig. 1). It was not possible to assign the absolute stereochemistry of this compound from the crystallography, as there were no significant differences between the refinements of the enantiomers. However, as the precursor of the (*S*)-methanovaline hydrochloride **4** and on the basis of the relative stereochemistry, compound **11** was determined to be the (1*S*,3′*S*)-stereoisomer. The relative and absolute stereochemistry of all the other compounds shown in Scheme 2 is then apparent from their chemical relationships to compounds **4**, **5** and **11**, and the starting material, (*S*)-leucine.

Presumably the reactions of the bromides **9** and **10** involve their deprotonation at the α-carbon, followed by cyclisation. If the corresponding intermediate anions attained conformational equilibrium, they would be enantiomers and produce identical ratios of the diastereomeric cyclopropanes **11** and **13**, and **14** and **12**. Clearly this is not the case, however, as the isolated product ratios, as percentage yields, were 34:58 and 84:10 from the reactions with sodium hydride in tetrahydrofuran, and 87:4 and 30:63 from those involving sodium methoxide in methanol. Therefore the anions must cyclise without complete equilibration, or with what has been referred to as 'memory of chirality' in reactions of related enolates.[13] The chiral centre introduced through reaction of the phthalimide **6** aids separation of the diastereomeric pairs of the cyclopropane derivatives **11** and **13**, and **12** and **14**. It also acts as a chiral auxiliary in the cyclisation reactions, with the diastereoselectivity being dependent on the choice of reagent and greatest in the respective reactions of the bromides **9** and **10** with sodium methoxide and sodium hydride.

Experimental

General

Melting points were determined on a Kofler hot stage melting point apparatus under a Reichert microscope and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Microanalyses were carried out by the Microanalytical Service of the Research School of Chemistry at the Australian National University, Canberra, Australia. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on a GEMINI 300 spectrometer and refer to deuteriochloroform solutions with chloroform as the internal standard measured at δ_H 7.26 ppm and δ_C 77.04 ppm, unless otherwise stated. Coupling constant values *J* between protons are given in Hz. Electron impact (EI) mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Radial chromatography was carried out using Merck Kieselgel 60 PF_{254}. HPLC was performed using a Waters μ-Porasil silica column (5 μm silica, 19 × 300 mm), eluting with hexane–ethyl

acetate (5:1). All solvents and reagents used were purified using standard methods and all organic extracts were dried over magnesium sulfate.

Methyl (2*S*,3′*S*)-4-bromo-2-(2,3-dihydro-3-methoxy-1-oxo-1*H*-isoindol-2-yl)-4-methylpentanoate 9 and methyl (2*S*,3′*R*)-4-bromo-2-(2,3-dihydro-3-methoxy-1-oxo-1*H*-isoindol-2-yl)-4-methylpentanoate 10

Sodium borohydride (140 mg, 3.70 mmol) was added slowly to a solution of the phthalimide **6**[8] (1.09 g, 3.08 mmol) in dry methanol (50 cm^3), maintained at −10 °C. The mixture was stirred at that temperature for 15 min, then it was acidified, through the cautious addition of thionyl chloride (760 mg, 6.39 mmol). The resultant solution was allowed to warm to room temperature, then it was stirred for 16 h at room temperature, before it was poured into dilute aqueous ammonium chloride (50 cm^3). The solution was then extracted with dichloromethane and the extract was dried and concentrated under reduced pressure. Radial chromatography of the residual oil, eluting with hexane–ethyl acetate (3:1), afforded a *ca.* 1:1 mixture of the title compounds **9** and **10** (810 mg). HPLC of a portion (400 mg) of the mixture afforded the individual components. *Methyl* (2*S*,3′*S*)-4-*bromo*-2-(2,3-*dihydro*-3-*methoxy*-1-*oxo*-1*H*-*isoindol*-2-*yl*)-4-*methylpentanoate* **9** was obtained (138 mg, 25%) as a colourless clear oil (Found: C, 52.12; H, 5.60; N, 3.79. $C_{16}H_{20}BrNO_4$ requires C, 51.91; H, 5.44; N, 3.78%); HPLC R_t 31 min; δ_H 1.75 (3H, s, CCH_3), 1.78 (3H, s, CCH_3), 2.53 (1H, dd, *J* 5.5 and 15.5, C3-H), 2.90 (1H, dd, *J* 5.5 and 15.5, C3-H′), 3.06 (3H, s, OCH_3), 3.73 (3H, s, CO_2CH_3), 4.73 (1H, apparent t, *J* 5.5, C2-H), 6.13 (1H, s, C3′-H), 7.47–7.61 (3H, m, ArH) and 7.78 (1H, d, *J* 7.3, ArH); δ_C 34.15 (CCH_3), 34.78 (CCH_3), 46.60 (CH_2), 50.56 (OCH_3), 52.75 (OCH_3), 53.24 (C2), 66.28 (CHBr), 87.20 (C3′), 123.61 (Ar), 123.74 (Ar), 129.94 (Ar), 132.21 (Ar), 132.36 (Ar), 140.66 (Ar), 167.62 (C=O) and 171.00 (C=O); *m*/*z* 371 (M^+, ^{81}Br, 20%), 369 (M^+, ^{79}Br, 21%), 312 (79), 310 (80), 274 (44), 258 (64), 230 (100), 198 (100) and 132 (97). *Methyl* (2*S*,3′*R*)-4-*bromo*-2-(2,3-*dihydro*-3-*methoxy*-1-*oxo*-1*H*-*isoindol*-2-*yl*)-4-*methylpentanoate* **10** was obtained (110 mg, 20%) as a colourless clear oil (Found: C, 51.91; H, 5.41; N, 3.52. $C_{16}H_{20}BrNO_4$ requires C, 51.91; H, 5.44; N, 3.78%); HPLC R_t 32 min; δ_H 1.88 (3H, s, CCH_3), 1.90 (3H, s, CCH_3), 2.53 (1H, dd, *J* 6.6 and 15.8, C3-H), 2.91 (1H, dd, *J* 4.7 and 15.8, C3-H′), 3.01 (3H, s, OCH_3), 3.69 (3H, s, CO_2CH_3), 4.97 (1H, dd, *J* 4.7 and 6.6, C2-H), 5.99 (1H, s, C3′-H), 7.48–7.61 (3H, m, ArH) and 7.82 (1H, d, *J* 7.3, ArH); δ_C 33.93 (CCH_3), 34.98 (CCH_3), 45.09 (CH_2), 51.40 (OCH_3), 51.82 (C2), 52.57 (OCH_3), 64.72 (CHBr), 86.96 (C3′), 123.51 (Ar), 123.85 (Ar), 129.98 (Ar), 132.14 (Ar), 132.40 (Ar), 140.50 (Ar), 167.95 (C=O) and 171.08 (C=O); *m*/*z* 371 (M^+, ^{81}Br, 13%), 369 (M^+, ^{79}Br, 13%), 312 (98), 310 (100), 274 (20), 258 (65), 230 (94), 198 (95) and 132 (96).

Methyl (1*S*,3′*S*)-2,2-dimethyl-1-(2,3-dihydro-3-methoxy-1-oxo-1*H*-isoindol-2-yl)cyclopropanecarboxylate 11 and methyl (1*R*,3′*S*)-2,2-dimethyl-1-(2,3-dihydro-3-methoxy-1-oxo-1*H*-isoindol-2-yl)cyclopropanecarboxylate 13

(a) Sodium hydride (45 mg, 1.90 mmol) was added slowly to a solution of the bromoleucine derivative **9** (138 mg, 0.37 mmol) in dry tetrahydrofuran (20 cm^3). The mixture was stirred at room temperature for 20 h, then it was poured cautiously into dilute aqueous hydrochloric acid (50 cm^3). The resultant solution was extracted with dichloromethane and the extract was dried and concentrated under reduced pressure. Radial chromatography of the residual oil, eluting with hexane–ethyl acetate (3:1), afforded *methyl* (1*R*,3′*S*)-2,2-*dimethyl*-1-(2,3-*dihydro*-3-*methoxy*-1-*oxo*-1*H*-*isoindol*-2-*yl*)*cyclopropanecarboxylate* **13** (62 mg, 58%) as a colourless solid, mp 82–84 °C (Found: C, 66.27; H, 6.69; N, 4.56. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84%); δ_H 1.41 (3H, s, CCH_3), 1.49 (3H, s, CCH_3) 1.49 (1H, d, *J* 5.0, C3-H), 1.62 (1H, d, *J* 5.0, C3-H′), 2.99 (3H, s, OCH_3), 3.61 (3H, s, CO_2CH_3), 5.83 (1H, s, C3′-H), 7.52–7.67 (3H, m, ArH) and 7.87 (1H, d, *J* 7.5, ArH); *m*/*z* 289 (M^+, 17%), 257 (48), 242 (25), 225 (41), 197 (100), 148 (28) and 133 (62). Continued elution afforded *methyl* (1*S*,3′*S*)-2,2-*dimethyl*-1-(2,3-*dihydro*-3-*methoxy*-1-*oxo*-1*H*-*isoindol*-2-*yl*)*cyclopropanecarboxylate* **11** (36 mg, 34%) as a colourless solid, mp 125–132 °C (Found: C, 66.17; H, 6.62; N, 4.68. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84%); δ_H 1.13 (1H, d, *J* 5.5, C3-H), 1.16 (3H, s, CCH_3), 1.43 (3H, s, CCH_3), 1.82 (1H, d, *J* 5.5, C3-H′), 3.09 (3H, s, OCH_3), 3.71 (3H, s, CO_2CH_3), 5.62 (1H, s, C3′-H), 7.49–7.62 (3H, m, ArH) and 7.84 (1H, d, *J* 7.4, ArH); *m*/*z* 289 (M^+, 15%), 257 (46), 242 (27), 225 (45), 197 (100), 148 (39) and 133 (74). The structure and relative stereochemistry of the cyclopropylamino acid derivative **11** were confirmed through X-ray crystallographic analysis (Fig. 1).

(b) A solution of methanolic sodium methoxide (1 cm^3, 0.5 mol dm^{-3}) was added to a solution of the bromoleucine derivative **9** (60 mg, 0.16 mmol) in dry methanol (20 cm^3) and the clear mixture was stirred at room temperature for 30 h, then it was poured cautiously into dilute aqueous hydrochloric acid (50 cm^3). The resultant solution was extracted with dichloromethane and the extract was dried and concentrated under reduced pressure. Radial chromatography of the residual oil, eluting with hexane–ethyl acetate (3:1), afforded the title compounds **13** (2 mg, 4%) and **11** (41 mg, 87%), which are identical in all respects to the samples obtained as described above.

Methyl (1*S*,3′*R*)-2,2-dimethyl-1-(2,3-dihydro-3-methoxy-1-oxo-1*H*-isoindol-2-yl)cyclopropanecarboxylate 12 and methyl (1*R*,3′*R*)-2,2-dimethyl-1-(2,3-dihydro-3-methoxy-1-oxo-1*H*-isoindol-2-yl)cyclopropanecarboxylate 14

(a) Treatment of the bromoleucine derivative **10** (110 mg, 0.30 mmol) with sodium hydride, as described above for reaction of the diastereomer **9**, afforded *methyl* (1*S*,3′*R*)-2,2-*dimethyl*-1-(2,3-*dihydro*-3-*methoxy*-1-*oxo*-1*H*-*isoindol*-2-*yl*)-*cyclopropanecarboxylate* **12** (9 mg, 10%) and *methyl* (1*R*,3′*R*)-2,2-*dimethyl*-1-(2,3-*dihydro*-3-*methoxy*-1-*oxo*-1*H*-*isoindol*-2-*yl*)-*cyclopropanecarboxylate* **14** (72 mg, 84%). The physical appearance, melting points and spectral properties of these compounds are identical to those reported above for the corresponding enantiomers **13** and **11**.

(b) Treatment of the bromoleucine derivative **10** (51 mg, 0.14 mmol) with sodium methoxide, as described above for reaction of the diastereomer **9**, afforded the title compounds **12** (25 mg, 63%) and **14** (12 mg, 30%), which are identical in all respects to the samples obtained as described above.

(*S*)-*N*-Phthaloyl-2,3-methanovaline methyl ester 7

Sodium bromate (46 mg, 0.30 mmol) and a catalytic amount of ceric ammonium nitrate (*ca.* 1 mg) were added to a solution of the α-methoxyamide **12** (77 mg, 0.27 mmol) in acetonitrile (7 cm^3) and water (3 cm^3), and the mixture was heated for 16 h at 80 °C, then it was cooled to room temperature and poured into water (50 cm^3). The resultant solution was extracted with dichloromethane and the extract was dried and concentrated under reduced pressure. Radial chromatography of the residual oil, eluting with hexane–ethyl acetate (3:1), afforded (*S*)-*N*-phthaloylmethanovaline methyl ester **7** as a colourless clear oil (70 mg, 96%) (Found: C, 65.99; H, 5.72; N, 5.31. $C_{15}H_{15}NO_4$ requires C, 65.93; H, 5.53; N, 5.13%); δ_H 1.10 (3H, s, CCH_3), 1.50 (3H, s, CCH_3), 1.53 (1H, d, *J* 5.9, C4-H), 1.93 (1H, d, *J* 5.9, C4-H′), 3.61 (3H, s, CO_2CH_3), 7.73–7.81 (2H, m, ArH) and 7.84–7.92 (2H, ArH); *m*/*z* 273 (M^+, 24%), 242 (40), 241 (100), 213 (20), 132 (31) and 104 (30). The spectroscopic properties of this compound are identical to those reported earlier[7] for the corresponding racemate.

The methanovaline derivative **7** was also prepared through oxidation of the α-methoxyamide **11**, using the procedure employed for reaction of the diastereomer **12**.

(*R*)-*N*-Phthaloyl-2,3-methanovaline methyl ester 8

Oxidation of the α-methoxyamide **14** (85 mg, 0.29 mmol) with sodium bromate and ceric ammonium nitrate, as described above for reaction of the diastereomer **12**, afforded (*R*)-*N*-phthaloylmethanovaline methyl ester **8** as a colourless clear oil (78 mg, 97%) (Found: C, 65.59; H, 5.75; N, 4.89. $C_{15}H_{15}NO_4$ requires C, 65.93; H, 5.53; N, 5.13%). The spectroscopic properties of this compound are identical to those reported above for the enantiomer **7**.

The methanovaline derivative **8** was also prepared through oxidation of the α-methoxyamide **13**, using the procedure employed for reaction of the enantiomer **12**.

(*S*)-2,3-Methanovaline hydrochloride 4

Sodium borohydride (87 mg, 2.35 mmol) was added slowly to a solution of the cyclopropylamino acid derivative **7** (88 mg, 0.32 mmol) in propan-2-ol (10 cm^3) and water (2 cm^3), and the mixture was stirred for 16 h at room temperature, then it was acidified to pH 5 through the dropwise addition of acetic acid. The resultant clear solution was heated at 80 °C for 48 h, then it was cooled to room temperature and poured into water (50 cm^3). This mixture was washed with dichloromethane, basified with dilute aqueous sodium hydroxide, and extracted with dichloromethane. The extract was dried and concentrated under reduced pressure to give a clear oil, to which aqueous hydrochloric acid (20 cm^3, 2 mol dm^{-3}) was added. The mixture was heated at reflux for 3 days, then it was cooled and concentrated under reduced pressure. The residual solid was washed with dichloromethane and dried, to give (*S*)-methanovaline hydrochloride **4** as a colourless solid (32 mg, 60%); δ_H (D_2O) 1.17 (1H, d, *J* 6.5, C4-H), 1.18 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.52 (1H, d, *J* 6.5, C4-H′); $[\alpha]_D^{21}$ −72 (*c* 0.78 in H_2O) (lit.,[12] $[\alpha]_D^{23}$ −72 (*c* 1.1 in H_2O). The spectroscopic properties of this compound are consistent with those reported earlier[14] for the corresponding racemate.

(*R*)-2,3-Methanovaline hydrochloride 5

Deprotection of the cyclopropylamino acid derivative **8** (78 mg, 0.29 mmol), as described above for reaction of the enantiomer **7**, afforded (*R*)-methanovaline hydrochloride **5** as a colourless solid (21 mg, 45%); $[\alpha]_D^{21}$ +73 (*c* 0.71 in H_2O) (lit.,[12] $[\alpha]_D^{23}$ +75 (*c* 0.6 in H_2O). The spectroscopic properties of this compound are consistent with those reported earlier[14] for the corresponding racemate.

Crystallography

Intensity data for a colourless crystal (0.19 × 0.21 × 0.24 mm) of the α-methoxyamide **11** were collected at room temperature on a Rigaku AFC6R diffractometer employing Cu-Kα radiation ($\lambda = 1.5418$ Å) and the $\omega/2\theta$ scan technique to $2\theta_{max}$ of 150.0°. The data set was corrected for Lorentz and polarisation effects[15] and data that satisfied the $I \geqslant 3.0\sigma(I)$ criterion of observability were used in the subsequent analysis. Crystal data and refinement details are given in Table 1.

The structure was solved using direct methods[16] and the model was refined using a full-matrix least-squares procedure based on *F*.[15] Non-hydrogen atoms were refined with anisotropic displacement parameters and hydrogen atoms were included in the model at their calculated positions (C–H 0.97 Å). The refinement was continued until convergence employing sigma weights, *i.e.*, $1/\sigma^2(F)$. As there were no significant differences between the refinements of the enantiomers, the absolute structure was assigned on the basis of the chemistry. The crystallographic numbering scheme employed is shown in Fig. 1 which was drawn with ORTEP at 50% probability ellipsoids.[17]

Table 1 Crystallographic data for the α-methoxyamide **11**

Formula	$C_{16}H_{19}NO_4$
M	289.3
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a/Å	14.232(3)
b/Å	18.168(2)
c/Å	5.916(2)
V/Å^3	1529.5(5)
Z	4
D_c/g cm^{-3}	1.256
F(000)	616
μ/cm^{-1}	7.44
No. data measured	3023
Range *hkl*	−3 to 17, −20 to 21, −6 to 7
No. unique data	1786
No. observed data [$I \geqslant 3.0\sigma(I)$]	1495
R	0.047
R_w	0.063
Residual ρ_{max}/e Å^{-3}	0.16

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/264.

Acknowledgements

The award of an Australian Postgraduate Award to N. L. F. is gratefully acknowledged. This work was supported by the Australian Research Council.

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