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Regioselective synthesis of substituted piperidine-2,4-diones and their derivatives via Dieckmann cyclisations

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ARTICLE INFO

Article history:

Received 21 May 2015

Received in revised form 9 June 2015

Accepted 12 June 2015

Available online xxx

Keywords:

Dieckmann cyclisation

Piperidine-2,4-diones

Regioselective synthesis

Enantioselective synthesis

ABSTRACT

A flexible route to piperidine-2,4-diones variously substituted at the 6-, 5,6- and 2,6-positions, both with and without 1-substitution, is described; no *N*-protective group is required. A related regioselective Dieckmann cyclisation is also described that uses Davies' α -methylbenzylamine auxiliary and affords 6-substituted piperidine-2,4-diones enantioselectively.

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1. Introduction

The piperidine ring, a privileged scaffold in pharmaceutically active compounds,¹ is exemplified in the numerous piperidine alkaloids.^{2,3} Oxygenated forms of the piperidine ring such as substituted piperidin-2-ones are also present in a number of alkaloids³ and in other biologically active derivatives,⁴ and can confer advantages of increased stability and crystallinity compared with piperidine analogues. Diversely substituted piperidines and oxygenated piperidines find much use in drug development, but their synthesis is still challenging;⁵ general, scalable methods are in demand. Many oxopiperidines including piperidine-2,4-diones possess biological and pharmaceutical relevance (Fig. 1),^{6,7} some being key intermediates in the synthesis of kinase inhibitors^{6f} and modulators of glutamate receptors^{5g} but routes to 6-substituted piperidine-2,4-diones are limited.⁸ Enantiocontrolled strategies to substituted piperidines present a further challenge, although the work of Comins⁹ and Davis¹⁰ has addressed some of the limitations in the range or location of substituents. Enantioselective syntheses of 1-unsubstituted piperidine-2,4-diones include rearrangements of substituted 1,3-oxazinan-2-ones,⁸ and cyclisations of *N*-sulfinyl δ -amino- β -keto esters,¹⁰ δ -aryl- δ -amino- β -keto esters^{6d} and *N*-Boc- β -amino acids.¹¹ Herein, we describe the synthesis of variously substituted piperidine-2,4-diones prepared via a regioselective Dieckmann cyclisation, some being obtained enantioselectively.

2. Results and discussion

It was desired to investigate the scope of Dieckmann cyclisations for the synthesis of piperidine-2,4-diones in regard to substituent location, and in particular to achieve a succinct protocol for the preparation of *N*-unsubstituted piperidine-2,4-diones, since few such Dieckmann cyclisations have been described, and a cyclisation in THF that afforded 3-methoxycarbonyl-6-(2-phenethyl)piperidine-2,4-dione in 15% yield.¹² The proposed route (Scheme 1) began with β -keto esters **1**, which in the cases of **1b** and **1c** were prepared by Weiler alkylation¹³ of the dianion of methyl acetoacetate (**1a**), prepared in THF using NaH (1.1 equiv) and butyllithium (1.1 equiv), and reacted with methyl iodide or ethyl bromide, respectively (Scheme 2). Subsequent alkylation at the β -position was also possible, ester **1b** being converted into **1d**. Reaction of β -keto esters **1** with ammonium acetate in the presence of acetic acid afforded the vinylogous carbamates **2**, which were reduced with sodium triacetoxyborohydride prepared *in situ*¹⁴ to give the corresponding β -amino esters **3**. The latter were coupled with monomethyl malonate using EDC in the presence of HOBt to give the amidodiester **4**. Those underwent Dieckmann cyclisation upon treatment with sodium methoxide in methanol to give the keto esters **5**, which were hydrolysed (NaOMe in methanol) and decarboxylated using sodium methoxide in wet acetonitrile^{6b} in a one-pot process to give the corresponding piperidine-2,4-diones **6**.

For the 2,3-disubstituted β -amino esters **3**, a Blaise reaction¹⁵ (Scheme 3) with *in situ* reduction was investigated, and afforded **6e**; however, the poor yield suggested that the reductive amination of β -keto esters **1**, as in Scheme 1, would in general be preferable.

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<http://dx.doi.org/10.1016/j.tet.2015.06.052>

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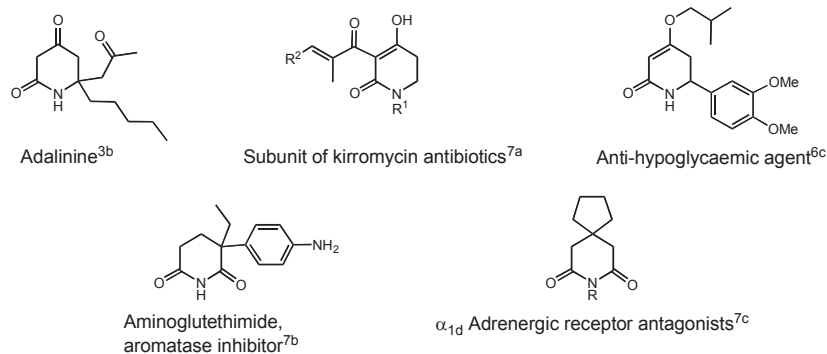
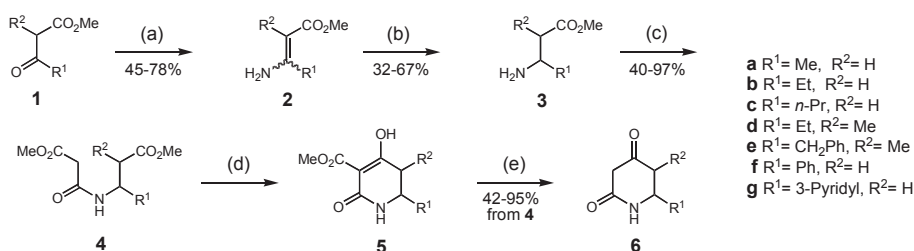
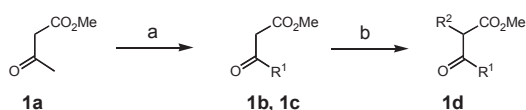


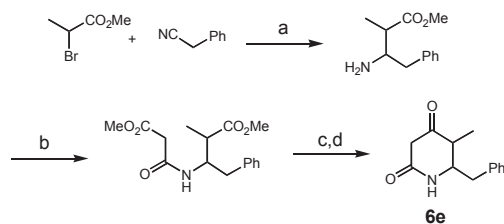
Fig. 1. Representative oxopiperidine derivatives with biological or pharmaceutical activity.



Scheme 1. Synthesis of substituted piperidine-2,4-diones and derivatives via Dieckmann cyclisations. Reagents and conditions: (a) NH₄OAc, AcOH, PhH, reflux, 18–72 h; (b) NaBH₄ (2.5 equiv) AcOH, 20 °C, 3 h; (c) monomethyl malonate, EDC (1 equiv), HOBT (1.5 equiv), (*i*-Pr)₂NEt, CH₂Cl₂, 20 °C, 2 h; (d) NaOMe (2 equiv), MeOH, reflux, 1 h; (e) MeCN, 1% H₂O, reflux, 1 h.



Scheme 2. Synthesis of β -keto esters via Weiler dialkylation. Reagents and conditions: (a) NaH (1.1 equiv), BuLi (1.1 equiv), THF, MeI or EtBr (1.1 equiv) EtOH, 20 °C, 3 h, 97% (**1b**), 85%, (**1c**); (b) MeI (1.0 equiv), K₂CO₃ (1.5 equiv), Me₂CO, 0 °C, 2 h, 88% (**1d**).

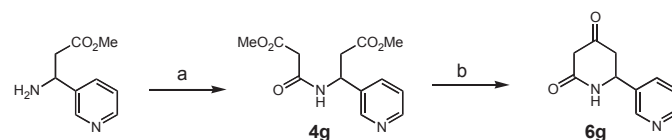


Scheme 3. Synthesis of 2,3-disubstituted piperidine-2,4-diones. Reagents and conditions: (a) Zn (4 equiv), TMSCl (12 equiv), CH₂Cl₂, THF, reflux, 2 h then NaBH₄ (0.55 mol equiv) EtOH, 20 °C, 3 h, 15%; (b) monomethyl malonate, EDC (1.0 equiv), HOBT (1.5 equiv), (*i*-Pr)₂NEt, CH₂Cl₂, 20 °C, 2 h, 67%; (c) NaOMe (1.3 equiv), MeOH, reflux, 1 h, then MeCN, 1% H₂O, reflux, 1 h, 56%.

These results show that a variety of 6-monosubstituted piperidine-2,4-diones can be prepared by the protocol of Scheme 1, and that in all of the examples studied cyclisation proceeded satisfactorily and usually in good yields. 5,6-Disubstituted piperidine-2,4-diones can also be prepared, although not with high diastereoselectivity in the examples studied herein. Alkylation of **6f** with MeI (3 equiv) in acetone at 50 °C in the presence of potassium carbonate afforded the 3,3,6-trisubstituted piperidine-2,4-dione **6h** (65%); no monomethyl product could be isolated, even when 1 equiv of MeI was used. Accordingly, monomethylation of ester **5f** was attempted using the conditions above, but no **6i** was observed; however, using Page's procedure¹⁶ alkylation with MeI (2 equiv) in

THF at 20 °C was achieved, affording **6i** in 64% yield. Attempts to remove the methoxycarbonyl group from **6i**, including sodium chloride in DMSO,¹⁷ LiI in pyridine, wet acetonitrile, or hydrochloric acid (1.3 M), all at reflux, were not successful.

The scope of the 2-substituent appears to include 3-pyridyl, since the formation of **6g** (Scheme 4) was confirmed by ¹H NMR spectroscopy, but the aqueous solubility of this piperidine-2,4-dione precluded isolation under the standard procedures attempted.



Scheme 4. Attempted cyclisation of diester **4g**. Reagents and conditions: (a) ClOCCCH₂CO₂Me (1.5 equiv), (*i*-Pr)₂NEt (4 equiv), 0 °C, then 20 °C, 1 h, 99%; (b) NaOMe (1.3 equiv), MeOH, reflux, 1 h, then MeCN, 1% H₂O, reflux, 1 h.

The present study has established a greater scope of Dieckmann cyclisations that afford substituted piperidine-2,4-diones (Fig. 2), notably *N*-unsubstituted compounds; the use of dimethyl ester precursors, cyclised in methanol (in the presence of sodium methoxide), followed by decarbomethoxylation in aqueous acetonitrile appears to be an improved procedure for obtaining such Dieckmann products; for example, using those procedures, cyclisation and decarbomethoxylation afforded 6-phenylpiperidine-2,4-dione (**6f**) in 66% yield, compared with 32% using previous conditions.^{6b} Convenient features of this synthetic approach include the ready preparation of a wide variety of β -amino esters from the corresponding β -keto esters, and the avoidance of *N*-protection followed by *N*-deprotection; the substituted piperidine-2,4-diones are obtained directly as *N*-unsubstituted compounds, as

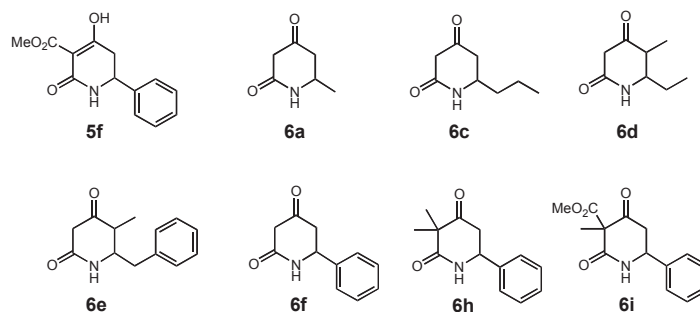


Fig. 2. Synthesis of substituted piperidine-2,4-diones and derivatives via Dieckmann cyclisations.

are all intermediates. The route is compatible with one or more substituents at the 3-, 5- and 6-positions.

An enantioselective route to substituted piperidine-2,4-diones based on the regioselective Dieckmann cyclisation was then investigated (Scheme 5). The enantiomerically pure β -keto esters **8** were prepared by metalation of **7** and reaction with α,β -unsaturated esters, according to the Davies methodology.¹⁸ Deallylation of allyl amines **8** was achieved using Wilkinson's catalyst^{18b,19} via isomerisation to the corresponding enamides that are hydrolysed in situ.²⁰ However, in the case of **8g** several products were obtained; accordingly, allylic transfer was investigated, and was achieved using 1,3-dimethylbarbituric acid (3 equiv) with a catalytic quantity of $(\text{Ph}_3\text{P})_4\text{Pd}$ in dichloromethane, affording **9g** in 96% yield. Acylation of β -amino esters **9** using monomethyl malonate and EDC or, where that proved unsatisfactory, methyl malonyl chloride and Et_3N afforded the corresponding malonamides **10**, which underwent ring closure upon treatment with sodium methoxide in ethanol; in two cases the intermediate sodium salts **11** were isolated, but since those were only needed to confirm the course of the reaction, direct ester hydrolysis and decarboxylation was otherwise achieved, either using warm dilute hydrochloric acid at reflux or in wet acetonitrile at reflux, affording the enantiopure 6-piperidine-2,4-diones **12** in a one-pot procedure from diesters **10**. Using methanesulfonic acid (0.9 equiv) in toluene

at reflux,²¹ several of the *N*-alkylated products **12** were cleaved to the corresponding enantiopure piperidine-2,4-diones **6** lacking a 1-substituent (Fig. 3). 3,3-Dimethylation of **6i** with methyl iodide (3 equiv) in methanol in the presence of potassium carbonate afforded the 3,3,6-trisubstituted piperidine-2,4-dione **13**. The route can also be used to prepare enantiomerically pure 4-hydroxypiperidinones, as illustrated by the reduction of (*R*)-**6f** to **14** using zinc borohydride.²² The 3-pyridyl derivative **12f** could be a useful building block for the enantioselective synthesis of novel substituted piperidines related to the alkaloid anabasine.

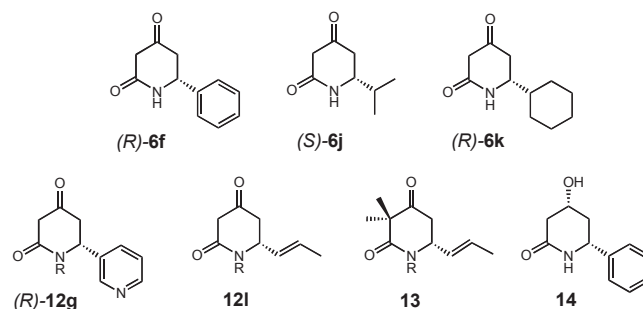
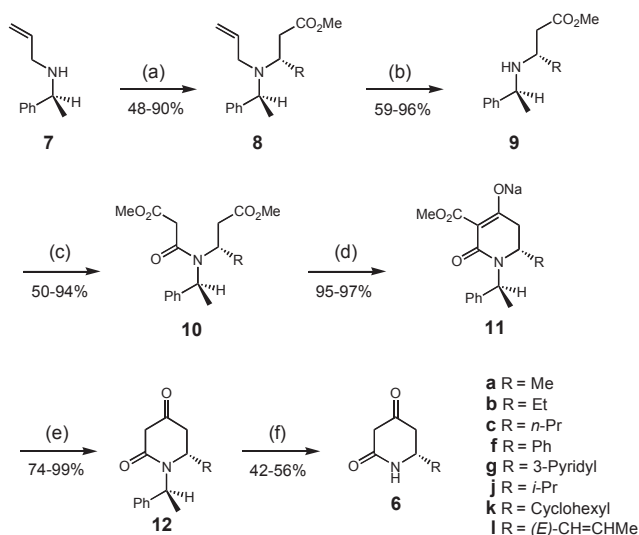


Fig. 3. Enantioselective synthesis of substituted piperidine-2,4-diones and derivatives via Dieckmann cyclisations (R=(*S*)-1-phenylethyl).



Scheme 5. Enantioselective synthesis of substituted piperidine-2,4-diones and derivatives via Dieckmann cyclisations (R=(*S*)-1-phenylethyl). Reagents and conditions: (a) BuLi (1 equiv), THF, -78°C , 30 min; RCH=CHCO₂Me (1 equiv), -78°C , 30 min; (b) $(\text{Ph}_3\text{P})_3\text{RhCl}$ (5 mol %), aq MeCN, reflux, 16 h; (c) methyl 3-chloro-3-oxopropanoate (1.1 equiv), Et_3N (1.2 equiv), 0°C – 20°C , 1 h; (d) NaOMe (1.1 equiv), reflux 1 h, then dil. HCl; (e) 1% water in MeCN, reflux 1 h; (f) MsOH (0.9 equiv), toluene, reflux, 3 h.

This study shows that a variety of substituted piperidine-2,4-diones, in which 1-substitution may be present or absent, can be conveniently prepared by Dieckmann cyclisation. Use of the Davies¹⁸ conjugate addition of (*S*)-*N*-(α -methylbenzyl)allylamine (**7**) to α,β -unsaturated esters afforded enantiopure β -amino esters that also underwent Dieckmann cyclisation to give, after hydrolysis and decarboxylation, the corresponding substituted piperidine-2,4-diones; the chiral auxiliary was cleaved using methanesulfonic acid, thereby achieving some enantioselective syntheses of substituted piperidine-2,4-diones without 1-substitution. Synthesis of substituted piperidine-2,4-diones can be used to access to a variety of congeners of alkaloids or other pharmacologically active compounds, including 4-hydroxypiperidin-2-ones, the corresponding substituted piperidin-2-ones and piperidines; examples herein include the piperidine-2,4-dione **12g**, an analogue of anabasine, and (4*R*,6*R*)-4-hydroxy-6-phenylpiperidin-2-one (**14**) prepared by reduction of **6f** with LiAlH_4 .

3. Experimental section

3.1. General

All moisture-sensitive reactions were performed under a nitrogen atmosphere and the glassware was pre-dried in an oven

(130 °C). Evaporation refers to the removal of solvent under reduced pressure. Melting points were measured by a microscope hot-stage Electrothermal 9100 apparatus. Infra-red (IR) spectra were recorded on a Perkin–Elmer PE-983 spectrophotometer; absorptions are quoted in wavenumbers. ¹H NMR spectra were recorded on a Bruker AC300 (300 MHz) spectrometer or a Bruker AMX 500 (125 MHz) spectrometer; data are reported in parts per million (δ). Coupling constants (J) are given in Hertz (Hz). The following abbreviations were used in signal assignments: singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), and multiplet (m). ¹³C NMR spectra were recorded on a Bruker AC300 (300 MHz) spectrometer or a Bruker AMX 500 (125 MHz) spectrometer; data are reported in parts per million (δ), with CHCl₃ as an internal standard. Mass spectra were recorded on a VG7070H mass spectrometer with Finigan Incos II data system at University College London. Optical rotations were measured using a Perkin–Elmer 343 digital polarimeter. Thin-layer chromatography was performed on Merck 0.2 mm aluminium-backed silica gel 60 F₂₅₄ plates and visualised by UV (254 nm) or by staining with potassium permanganate with subsequent heating. Flash column chromatography was performed using Merck 0.040–0.063 mm, 230–400 mesh silica gel. Temperatures below 0 °C were obtained using various mixtures of water, salt and ice, or acetone and dry ice.

The following compounds were prepared according to the literature: methyl 2-methyl-3-oxopentanoate (**1d**);²³ methyl 3-amino-3-phenylpropanoate hydrochloride (**3f**);²⁴ methyl 3-(2-methoxycarbonylacetylamino)-3-phenylpropanoate (**4f**);²⁵ (*S*)-*N*-(α -methylbenzyl)allylamine (**7**);²⁶ (*E*)-methyl 4-methylpent-2-enoate;²⁷ (*E,E*)-methyl hexa-2,4-dienoate;²⁸ methyl (2*E*)-3-cyclohexyl-2-propenoate;²⁹ (*E*)-methyl 3-(pyridin-3-yl)propenoate.³⁰

3.1.1. General procedure A. Preparation of amidodiester 4 and 10. Anhydrous 1-hydroxybenzotriazole (1.5 equiv) and *N,N*-diisopropylethylamine (4.0 equiv) were added to a stirred solution of the β -amino ester **3** (1.0 equiv) in dichloromethane at 0 °C, under nitrogen. Monomethyl malonate (3.0 equiv) in dichloromethane was added dropwise; *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.0 equiv) was added and the mixture was then allowed to warm to 20 °C and stirred for 2 h. Saturated aqueous sodium hydrogen carbonate was then added and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried (MgSO₄) and evaporated. The residue was purified as described under the given product.

3.1.2. General procedure B. Preparation of amido diesters 4. Triethylamine (1.3 equiv) and methyl 3-chloro-3-oxopropanoate (1.2 equiv) were added to a stirred solution of the β -amino ester **3** (1 equiv) in dichloromethane at 0 °C, under nitrogen. The mixture was then allowed to warm to 20 °C and stirred for 1 h. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium hydrogen carbonate. The aqueous layer was extracted twice with dichloromethane and the combined organic layers were dried (MgSO₄) and evaporated. The residue was purified as described under the given product.

3.1.3. General procedure C for Dieckmann cyclisations. Sodium methoxide (1.2 equiv) in methanol was added to a stirred solution of the diester (1.0 equiv) in methanol at 20 °C under nitrogen. The mixture was then heated under reflux for 1 h. After allowing to cool to 20 °C, the mixture was acidified with hydrochloric acid (1 M) to pH 6. The aqueous layer was extracted with dichloromethane, dried (MgSO₄), and evaporated. A solution of 1% water in acetonitrile was added to the oily residue, and the mixture was heated under reflux

for 1 h. The mixture was allowed to cool, then evaporated, and the residue was purified as described under the given product.

3.1.4. General procedure D for Michael addition.¹⁸ *n*-Butyllithium (1.55 equiv) in THF was added dropwise via a syringe to a stirred solution of (*S*)-*N*-(α -methylbenzyl)allylamine (**7**) (1.6 equiv) in anhydrous THF at –78 °C under nitrogen. The mixture was stirred at –78 °C for a further 30 min. A solution of the α,β -unsaturated ester (1.0 equiv) in anhydrous THF was added dropwise via syringe at –78 °C and the mixture was stirred for further 3 h at the same temperature. The mixture was then quenched with aqueous saturated ammonium chloride and allowed to warm to 20 °C over about 15 min. Evaporation gave a pale yellow liquid that was partitioned between dichloromethane and aqueous 10% citric acid. The aqueous layer was extracted with dichloromethane (3 \times 10 mL) and all of the organic layers were combined, washed with saturated aqueous sodium hydrogen carbonate then brine, dried (MgSO₄), and evaporated. The residue was purified as described under the given product.

3.1.5. General procedure E for *N*-deallylation.^{18b,19} Tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst, 5 mol%) was added in one portion to a stirred solution of the β -amino ester (1.0 equiv) in acetonitrile–water (85:15) at 20 °C. The mixture was then heated under reflux for 16 h. After allowing to cool, the mixture was extracted with dichloromethane, and the combined organic layers were dried (MgSO₄) and evaporated. The residue was purified as described under the given product.

3.1.6. Methyl 3-amino-2-methylpent-2-enoate (2d). Ammonium acetate (2.60 g, 33.8 mmol) and acetic acid (0.1 mL) were added to a stirred solution of methyl 2-methyl-3-oxopentanoate (**1d**) (0.98 g, 6.77 mmol) in benzene (50 mL). The mixture was heated under reflux for 72 h with the azeotropic removal of water. After allowing to cool to 20 °C, ethyl acetate (50 mL) was added and the mixture was washed with saturated aqueous sodium hydrogen carbonate (15 mL), dried (Na₂SO₄), and evaporated to give **2d** (0.51 g, 52%) as an orange oil; IR ν_{\max} 3303, 2924, 1744, 1656, 1610, 1462, 1161 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.72 (3H, s) 2.25 (2H, q, $J=7.6$ Hz) 1.75 (3H, s) 1.15 (3H, t, $J=7.6$ Hz); m/z (Cl, %) 144 ([M+H]⁺, 65). HRMS C₇H₁₄NO₂ calcd 144.1025, found 144.1019.

3.1.7. Methyl 3-aminohexanoate (3c). Ammonium acetate (30.0 g, 0.39 mol) and acetic acid (0.1 mL) were added to a stirred solution of methyl 3-oxohexanoate (**1c**) (11.2 g, 77.7 mmol) in benzene (160 mL). The mixture was heated under reflux for 72 h with the azeotropic removal of water. After allowing to cool to 20 °C, the mixture was diluted with ethyl acetate (150 mL), washed with saturated aqueous sodium hydrogen carbonate (15 mL), dried (Na₂SO₄), and evaporated to give the crude β -enamino ester as an oil. Sodium borohydride (7.15 g, 0.19 mmol) was added in portions to a stirred solution of glacial acetic acid (200 mL) maintaining the temperature at near 20 °C. The mixture was stirred for 30 min until there was no more hydrogen was evolved. The β -enamino ester was then added in one portion and the mixture was stirred at 20 °C for 3 h. The acetic acid was removed under reduced pressure and the residue was dissolved in ethyl acetate (100 mL). The mixture was extracted with water (4 \times 100 mL), and the pH of the combined aqueous layers was adjusted to pH 12 by potassium carbonate. The solution was extracted with chloroform (3 \times 150 mL) and the combined organic layers were dried (MgSO₄), and evaporated to give **3c** (3.61 g, 32%) as an orange oil; IR ν_{\max} 3272, 2957, 1736, 1553, 1436, 1379, 1174 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.73 (3H, s) 3.18 (1H, m) 2.46 (1H, dd, $J=15.7, 4.0$ Hz) 2.25 (1H, dd, $J=15.7, 9.0$ Hz) 2.03 (2H, br s) 1.36–1.33 (4H, m) 0.91 (3H, t, $J=2.5$ Hz); ¹³C NMR (300 MHz, CDCl₃) δ 173.1, 51.5, 48.0, 42.3,

39.7, 19.2, 14.0; m/z (CI, %) 146 ($[M+H]^+$, 100). HRMS $C_7H_{16}NO_2$ calcd 146.1181, found 146.1183.

3.1.8. Methyl 3-amino-2-methylpentanoate (3d). Sodium borohydride (0.64 g, 16.8 mmol) was added in small portions to a stirred solution of glacial acetic acid (11 mL), maintaining the temperature near 20 °C. The mixture was then stirred for 30 min until no more hydrogen was evolved. Ester **2d** (0.93 g, 6.47 mmol) was then added in one portion and the mixture was stirred at 20 °C for 3 h. The acetic acid was removed under reduced pressure and the residue was dissolved in ethyl acetate (10 mL). The solution was extracted with water (4×10 mL), and the pH of the combined aqueous layers was adjusted to pH 12 using potassium carbonate. The aqueous mixture was extracted with chloroform (3×15 mL) and the combined organic layers were dried ($MgSO_4$), and evaporated to give **3d** (0.63 g, 67%) as an orange oil, IR ν_{max} (cm^{-1}) 3321, 2961, 1731, 1569 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 3.67 (3H, s) 2.90–2.43 (2H, m) 1.53 (2H, br s) 1.42–1.16 (2H, m) 1.14–1.11 (3H, m) 0.96–0.90 (3H, m). m/z (CI, %) 146 ($[M+H]^+$, 100). HRMS $C_7H_{16}NO_2$ calcd 146.1181, found 146.1179.

3.1.9. Methyl 3-amino-2-methyl-4-phenylbutanoate (3e). Trimethylsilyl chloride (0.26 mL, 2.0 mmol) was added to a stirred mixture of zinc dust (2.60 g, 39.3 mmol) in dichloromethane (13 mL) at 20 °C under nitrogen, and the mixture was stirred for 30 min. Tetrahydrofuran (8 mL) was then added and the mixture was heated to 42 °C. A mixture of benzyl cyanide (1.00 g, 8.54 mmol) and methyl 2-bromopropanoate (2.85 g, 17.1 mmol) was added and the reaction mixture was then heated under reflux for 2 h. After allowing to cool the mixture was filtered, and sodium borohydride (0.60 g, 15.4 mmol) and ethanol (2.5 mL) were added cautiously to the filtrate. The mixture was stirred for 3 h, then hydrochloric acid (2 M, 9 mL) was then added and the aqueous layer was extracted with dichloromethane (2×10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. Toluene (4 mL) was added to the residue and the mixture was made alkaline with 0.880 aqueous ammonia (3 mL). The aqueous layer was extracted with toluene (2×4 mL), and the organic layers were combined, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (20% ethyl acetate/hexane) to give **3e** (0.27 g, 15%) as a yellow oil; IR ν_{max} 3368 (N–H), 2948 (C–H), 1726, 1664 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) (1:1 mixture of diastereoisomers) δ 7.38–7.30 (5H, m, Ph) 3.69 (3H, s) 3.30 (1H, m) 2.82 (1H, m) 2.60–2.40 (2H, m) 1.65 (2H, br s) 1.26–1.18 (3H, m); ^{13}C NMR (500 MHz, $CDCl_3$) δ 176.1, 175.9, 139.1, 139.1, 129.4, 129.3, 129.1, 128.6, 126.5, 55.5, 54.4, 51.7, 51.6, 45.7, 44.6, 41.8, 41.6, 14.5, 11.7; m/z (CI, %) 208 ($[M+H]^+$, 100). HRMS $C_{12}H_{18}NO_2$ calcd 208.1338, found 208.1335.

3.1.10. Dihydrochloride salt of methyl 3-amino-3-(pyridin-3-yl)propanoate (3g). 3-Amino-3-(pyridin-3-yl)propanoic acid was prepared as previously described³¹ and directly treated with thionyl chloride in methanol to give the dihydrochloride salt of **3g**. To a stirred solution of pyridine-3-carboxaldehyde (8.24 g, 76.8 mmol) in ethanol (15 mL) were added malonic acid (8.0 g, 76.8 mmol) and ammonium acetate (12.0 g, 0.156 mmol). The mixture was heated under reflux for 6 h. After allowing to cool, the mixture was filtered and the filtrate evaporated. The residue was dissolved in methanol (150 mL) and the solution cooled to 0 °C. To the stirred solution thionyl chloride (2.7 mL, 99.8 mmol) was added dropwise; the mixture was stirred at 0 °C for an additional 30 min, then stirred at 20 °C for 3 h. The mixture was then heated at reflux for 1 h. After allowing to cool, diethyl ether (200 mL) was added and the precipitate filtered to give the dihydrochloride salt of **3g** (5.42 g, 43%)

as a white solid, mp 202–205 °C (lit.³² mp 197.5–199 °C); IR ν_{max} 3296, 2953, 1737, 1657 cm^{-1} ; 1H NMR (500 MHz, D_2O) δ 8.54 (1H, m) 8.50 (1H, m) 7.90 (1H, m) 7.47 (1H, m) 4.74 (1H, dd, $J=7.9, 6.6$ Hz) 3.70 (3H, s) 2.88 (1H, dd, $J=16.3, 7.9$ Hz) 2.80 (1H, dd, $J=16.3, 6.6$ Hz).

3.1.11. Methyl 3-(2-methoxycarbonylacetylamino)butanoate (4a). Following general procedure A, reaction of methyl 3-aminobutanoate hydrochloride (0.50 g, 3.3 mmol) in dichloromethane (7 mL), 1-hydroxybenzotriazole (0.66 g, 4.9 mmol), *N,N*-diisopropylethylamine (2.3 mL, 13 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.59 g, 3.3 mmol), and monomethyl malonate (1.52 g, 9.8 mmol) in dichloromethane (10 mL) gave a pale yellow solid that was purified by flash chromatography (60% ethyl acetate/hexane) to give **4a** (0.33 g, 46%) as a yellow gum; IR ν_{max} 3293, 2956, 1730, 1650 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 7.26 (1H, br s) 4.35 (1H, m) 3.63 (3H, s) 3.58 (3H, s) 3.19 (2H, s) 2.51–2.36 (2H, m) 1.13 (3H, d, $J=6.7$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.7, 169.4, 164.3, 52.3, 51.6, 42.2, 41.3, 39.8, 19.8; m/z (CI, %) 218 ($[M+H]^+$, 100). HRMS $C_9H_{16}NO_5$ calcd 218.1023, found 218.1022.

3.1.12. Methyl 3-(2-methoxycarbonylacetylamino)-hexanoate (4c). Following general procedure A, reaction of methyl 3-aminohexanoate **3c** (0.47 g, 3.3 mmol) in dichloromethane (7 mL), 1-hydroxybenzotriazole (0.66 g, 4.9 mmol), *N,N*-diisopropylethylamine (2.3 mL, 13 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.59 g, 3.3 mmol), and monomethyl malonate (1.52 g, 9.8 mmol) in dichloromethane (10 mL) gave a pale yellow solid that was purified by flash chromatography (55:45 ethyl acetate/hexane) to give **4c** (0.32 g, 40%) as a colourless gum; IR ν_{max} 3292, 2956, 1734, 1649 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 7.22 (1H, br s) 4.38 (1H, m) 3.74 (3H, s) 3.69 (3H, s) 3.31 (2H, s) 2.56–2.54 (2H, m) 1.56–1.49 (2H, m) 1.35 (2H, m) 0.91 (3H, t, $J=7.3$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.1, 169.7, 164.3, 52.4, 51.7, 46.0, 41.2, 38.4, 36.1, 19.3, 13.8; m/z (CI, %) 246 ($[M+H]^+$, 100). HRMS $C_{11}H_{20}NO_5$ calcd 246.1336, found 246.1332.

3.1.13. Methyl 3-(2-methoxycarbonylacetylamino)-2-methylpentanoate (4d). Following general procedure B, reaction of ester **3d** (0.30 g, 2.07 mmol), triethylamine (0.38 mL, 2.7 mmol), and methyl 3-chloro-3-oxopropanoate (0.27 mL, 2.48 mmol) in dichloromethane (8 mL) gave a pale yellow oil that was purified by flash chromatography (40:60 ethyl acetate/hexane) to give **4d** (0.20 g, 40%) as a pale yellow oil; 1H NMR (300 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 7.35 (1H, m) 4.17 (1H, m) 3.75 (3H, s) 3.67 (3H, s) 3.34–3.30 (2H, m) 2.68 (1H, m) 1.61–1.55 (2H, m) 1.16 (3H, d, $J=6.0$ Hz) 0.92 (3H, t, $J=7.2$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.7, 174.8, 169.6, 169.3, 165.0, 164.8, 52.8, 52.7, 52.4, 52.3, 51.7, 48.6, 43.3, 42.0, 41.5, 41.2, 26.4, 24.7, 14.7, 12.8, 10.6; m/z (CI, %) 246 ($[M+H]^+$, 100). HRMS $C_{11}H_{20}NO_5$ calcd 246.1342, found 246.1345.

3.1.14. Methyl 3-(2-methoxycarbonylacetylamino)-2-methyl-4-phenylbutanoate (4e). Following general procedure B, reaction of amine **3e** (0.13 g, 0.60 mmol), *N,N*-diisopropylethylamine (0.21 mL, 1.21 mmol), and methyl 3-chloro-3-oxopropanoate (0.10 mL, 0.90 mmol) in dichloromethane (4 mL) afforded an oil that was purified by flash chromatography (40:60 ethyl acetate:hexane) to give **4e** (0.13 g, 67%) as a colourless oil; IR ν_{max} 3301, 2953, 1733, 1657 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 7.29–7.16 (5H, m) 4.51–4.13 (1H, m) 3.72 (3H, s) 3.66 (3H, s) 3.27–3.12 (2H, m) 2.84–2.67 (3H, m) 1.22–1.18 (3H, m); ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.9, 174.8, 169.8, 169.4, 164.8, 164.3, 137.8, 137.6, 129.3, 129.2, 128.5, 128.4, 126.7, 126.6, 53.1, 52.4, 52.3, 51.9, 42.9, 42.6, 41.5, 41.0, 40.7, 39.9, 37.8, 37.7, 13.2, 12.9; m/z (EI, %)

308 ($[M+H]^+$, 5), 276 ($[M-CH_4O]^+$, 12). HRMS $C_{16}H_{22}NO_5$ calcd 308.1498, found 308.1491.

3.1.15. Methyl 3-(2-methoxycarbonylacetyl-amino)-4-(pyridin-3-yl)butanoate (4g). Following general procedure B, reaction of amine **3g** (0.50 g, 1.98 mmol), *N,N*-diisopropylethylamine (1.4 mL, 7.93 mmol), and methyl 3-chloro-3-oxopropanoate (0.32 mL, 2.98 mmol) in dichloromethane (12 mL) gave an oil was purified by flash chromatography (1:1 ethyl acetate:hexane) to give **4g** (0.54 g, 97%) as a yellow oil; IR ν_{max} 3273, 2954, 1733, 1656 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) (mixture of rotamers) δ 8.67 (1H, s) 8.53 (1H, m) 7.64–7.55 (1H, m) 7.22 (1H, m) 5.38 (1H, dd, $J=6.4, 5.3$ Hz) 3.67 (3H, s) 3.53 (3H, s) 3.26 (2H, s) 2.86 (1H, dd, $J=16.0, 6.4$ Hz) 2.79 (1H, dd, $J=16.0, 5.3$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.8, 169.3, 164.8, 148.8, 148.1, 136.2, 134.4, 123.6, 123.3, 52.5, 52.0, 47.9, 41.3, 39.6; m/z (EI, %) 281 ($[M+H]^+$, 51), 280 (M^+ , 88). HRMS $C_{13}H_{17}N_2O_5$ calcd 281.1137, found 281.1136.

3.1.16. 3-Methoxycarbonyl-6-phenylpiperidine-2,4-dione (5f). Sodium methoxide in methanol (2.0 M, 3.1 mL, 6.2 mmol) was added to a stirred solution of diester **4f**²⁵ (1.40 g, 5.0 mmol) in methanol (15 mL) at 20 °C under nitrogen. The mixture was then heated under reflux for 2 h. After allowing to cool to 20 °C, the mixture was diluted with diethyl ether and filtered. The white precipitate was dissolved in water, and the solution acidified to pH 2–3 by hydrochloric acid (1 M). After extraction with ethyl acetate (3×20 mL) the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated to give **5f** (0.86 g, 70%) as a white solid, mp 122–125 °C (lit.¹³ 128–130 °C); IR ν_{max} 3311 (O–H), 2952, 1713, 1638, 1571 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.14 (5H, m) 6.22 (1H, br s) 4.64 (1H, t, $J=7.5$ Hz) 3.68 (3H, s) 2.81 (2H, d, $J=7.5$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 183.5, 172.0, 164.8, 139.6, 129.1, 128.7, 126.5, 97.4, 52.7, 52.3, 37.8.

3.1.17. 6-Methylpiperidine-2,4-dione (6a). Following general procedure C, reaction of diester **4a** (0.30 g, 1.38 mmol), and sodium methoxide in methanol (1.84 M, 1.5 mL, 2.76 mmol) in methanol (2.0 mL) gave **6a** (74 mg, 42%) as a pale yellow solid, mp 124–128 °C; IR ν_{max} 3217, 2968, 1726, 1663, cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 3.88 (1H, m) 3.26 (2H, d, $J=19.8$ Hz) 3.19 (1H, d, $J=19.8$ Hz) 2.64 (1H, dd, $J=16.4, 4.0$ Hz) 2.30 (1H, dd, $J=16.4, 9.6$ Hz) 1.30 (3H, d, $J=6.5$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 203.4, 169.8, 47.0, 46.2, 44.6, 21.3; m/z (CI, %) 128 ($[M+H]^+$, 100). HRMS $C_6H_{10}NO_2$ calcd 128.0711, found 128.0714.

3.1.18. 6-Propylpiperidine-2,4-dione (6c). Following general procedure C, reaction of diester **4c** (0.17 g, 0.70 mmol), and sodium methoxide in methanol (2.0 M, 0.54 mL, 1.05 mmol) in methanol (1.0 mL) gave **6c** (63 mg, 58%) as a white solid, mp 112–116 °C; IR ν_{max} 3249, 2925, 1736, 1664 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 3.65 (1H, m) 3.25 (2H, m) 2.66 (1H, m) 2.33 (1H, m) 1.50–1.22 (4H, m) 0.93 (3H, m); ^{13}C NMR (500 MHz, $CDCl_3$) δ 208.0, 176.1, 36.9, 34.0, 29.7, 21.1, 18.4, 13.9; m/z (CI, %) 156 ($[M+H]^+$, 35). HRMS $C_8H_{14}NO_2$ calcd 156.1025, found 156.1022.

3.1.19. 6-Ethyl-5-methylpiperidine-2,4-dione (6d). Following general procedure C, reaction of diester **5d** (0.12 g, 0.48 mmol), and sodium methoxide in methanol (1.74 M, 0.53 mL, 0.92 mmol) in methanol (3.0 mL) gave **6d** (53 mg, 71%) as a yellow oil; IR ν_{max} 3280, 2925, 1725, 1661 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 7.95–7.79 (1H, br s) 3.75–3.69 (1H, m) 3.22 (2H, m) 2.67–2.36 (1H, m) 1.73–1.52 (2H, m) 1.19–1.05 (3H, m) 0.99–0.83 (3H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 205.7, 170.0, 55.6, 54.5, 46.4, 46.4, 46.0, 41.0, 26.2, 24.4, 11.6, 10.1, 10.0, 8.5; m/z (CI, %)

156 ($[M+H]^+$, 100). HRMS $C_8H_{14}NO_2$ calcd 156.2023, found 156.2021.

3.1.20. 6-Benzyl-5-methylpiperidine-2,4-dione (6e). Following general procedure C, reaction of diester **5e** (0.09 g, 0.30 mmol), and sodium methoxide in methanol (2.0 M, 0.2 mL, 0.38 mmol) in methanol (1.2 mL) gave **6e** (36 mg, 56%) as a yellow oil, IR ν_{max} 3245 (N–H), 2923, 1721, 1661 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 7.63–7.19 (5H, m) 3.92–3.83 (1H, m) 3.27–3.13 (2H, m) 2.90 (1H, m) 2.65–2.61 (1H, m) 2.51–2.46 (1H, m) 1.28–1.25 (3H, m); ^{13}C NMR (500 MHz, $CDCl_3$) δ 204.8, 204.7, 169.2, 168.4, 136.0, 135.5, 129.5, 129.4, 129.3, 129.1, 127.7, 127.4, 55.8, 54.5, 47.4, 46.6, 46.1, 46.0, 41.0, 37.9, 12.1, 10.5; m/z (CI, %) 218 ($M+H^+$, 100). HRMS $C_{13}H_{16}NO_2$ calcd 218.1181, found 218.1189.

3.1.21. 6-Phenylpiperidine-2,4-dione (6f). Diester **5f** (0.31 g, 1.25 mmol) was added to 1% water in acetonitrile (6 mL). The mixture was heated under reflux for 2 h, allowed to cool and then evaporated. The residue was purified by flash chromatography (1:99 methanol:chloroform) to give **6f** (0.25 g, 95%) as a white solid, mp 160–163 °C (lit.³³ 167–169 °C); IR ν_{max} 3248, 2927, 1722, 1664 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.28 (5H, m) 6.87 (1H, br s) 4.80 (1H, dd, $J=8.7, 4.5$ Hz) 3.34 (2H, s) 2.88 (1H, dd, $J=16.0, 4.5$ Hz) 2.88 (1H, dd, $J=16.0, 8.7$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 202.3, 169.0, 139.3, 129.4, 128.9, 126.0, 52.9, 47.2, 47.0; m/z (CI, %) 190 ($[M+H]^+$, 95). HRMS $C_{11}H_{12}NO_2$ calcd 190.0863, found 190.0859.

3.1.22. 3,3-Dimethyl-6-phenylpiperidine-2,4-dione (6h). Potassium carbonate (0.25 g, 1.84 mmol) and methyl iodide (0.11 mL, 1.84 mmol) were added to a solution of 6-phenylpiperidine-2,4-dione (**6f**) (0.12 g, 0.61 mmol) in acetone (3 mL). The mixture was stirred at 50 °C for 16 h. Filtration and evaporation of the filtrate gave a residue that was purified by flash chromatography (60:40 ethyl acetate/hexane) to give **6h** (0.09 g, 65%) as a white solid, mp 165–168 °C (lit.³⁴ 168–169 °C); IR ν_{max} 3200, 2978, 1714, 1649 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 7.60–7.26 (5H, m) 6.60 (1H, br s) 4.70 (1H, dd, $J=4.7, 2.5$ Hz) 2.92 (1H, dd, $J=15.5, 4.7$ Hz) 2.84 (1H, dd, $J=15.5, 2.5$ Hz) 1.39 (3H, s) 1.38 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 208.2, 175.8, 140.0, 129.3, 128.8, 126.0, 52.1, 52.0, 45.3, 23.1, 22.8.

3.1.23. 3-Methoxycarbonyl-3-methyl-6-phenylpiperidine-2,4-dione (6i). Tetrabutylammonium fluoride in THF (1 M, 0.8 mL) and methyl iodide (0.08 mL, 1.28 mmol) were added to 3-methoxycarbonyl-6-phenylpiperidine-2,4-dione (**5f**) (0.16 g, 0.64 mmol) in THF (2 mL). The mixture was stirred at 20 °C for 24 h. The solution was neutralised with hydrochloric acid (1 M), extracted with chloroform and evaporated. The residue that was purified by flash chromatography (55:45 ethyl acetate:hexane) to give **6i** (0.11 g, 64%) as a colourless solid; 1H NMR (300 MHz, $CDCl_3$) (1:1 mixture of diastereoisomers) δ 7.47–7.21 (5H, m) 6.60 (1H, br s) 4.82–4.49 (1H, m) 3.69 and 3.64 (3H, s) 3.04–2.73 (2H, m) 1.57 and 1.51 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 201.7, 201.6, 170.3, 169.6, 167.6, 167.5, 139.3, 139.2, 129.4, 129.3, 129.0, 128.9, 126.2, 126.1, 63.8, 63.7, 53.5, 53.4, 52.4, 52.0, 45.7, 45.6, 18.3, 18.2; m/z (CI, %) 262 ($[M+H]^+$, 100). HRMS $C_{14}H_{16}NO_4$ calcd 262.1074, found 262.1067.

3.1.24. Methyl (3*S*, α *S*)-3-[*N*-allyl-*N*-(α -methylbenzyl)]aminobutanoate (8a). Following general procedure D, butyllithium in hexanes (1.6 M, 8.0 mL, 12.9 mmol) and methyl but-2-enoate (0.83 g, 8.3 mmol) in anhydrous THF (9 mL) were added to (*S*)-*N*-(α -methylbenzyl)allylamine (**7**) (2.15 g, 13.3 mmol) in anhydrous THF (18 mL), affording an oil that was purified by flash chromatography (15:85 ethyl acetate:hexane) to give **8a** (1.85 g, 85%) as

a pale yellow oil; $[\alpha]_{\text{D}}^{21} +18.7$ (c 0.75, CHCl_3), lit.³⁵ for enantiomer $[\alpha]_{\text{D}}^{26} -14.2$ (c 1.85, CHCl_3); IR ν_{max} 2970, 1737 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.37–7.20 (5H, m) 5.85 (1H, m) 5.15 (1H, dd, $J=17.2, 10.4$ Hz) 5.04 (1H, dd, $J=17.2, 4.6$ Hz) 3.97 (1H, q, $J=6.8$ Hz) 3.56 (3H, s) 3.49 (1H, m) 3.18 (2H, d, $J=6.3$ Hz) 2.40 (1H, dd, $J=14.2, 7.0$ Hz) 2.19 (1H, dd, $J=14.2, 7.5$ Hz) 1.37 (3H, d, $J=6.8$ Hz) 1.07 (3H, d, $J=6.8$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 172.9, 145.2, 139.2, 128.1, 127.6, 126.8, 115.6, 57.7, 51.4, 50.6, 48.6, 40.4, 18.8, 17.5; m/z (CI, %) 262 ($[\text{M}+\text{H}]^+$). HRMS $\text{C}_{16}\text{H}_{24}\text{NO}_2$ calcd 262.1807, found 262.1803.

3.1.25. Methyl (3*R*, α *S*)-3-[*N*-allyl-*N*-(α -methylbenzyl)amino]-4-methylpentanoate (8b**).** Following general procedure D, butyllithium in hexanes (2.5 M, 5.3 mL, 13.3 mmol) and methyl 4-methylpent-2-enoate (1.10 g, 8.58 mmol) in anhydrous THF (22 mL) were added to (*S*)-*N*-(α -methylbenzyl)allylamine (**7**) (2.22 g, 13.7 mmol) in anhydrous THF (28 mL), affording an oil that was purified by flash chromatography (12:88 ethyl acetate:hexane) to give **8b** (1.70 g, 69%) as a pale yellow oil; $[\alpha]_{\text{D}}^{21} +18.0$ (c 5.00, CHCl_3); IR ν_{max} 2970, 1736 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31–7.21 (5H, m) 5.90 (1H, m) 5.20 (1H, m) 5.07 (1H, m) 3.91 (1H, q, $J=7.1$ Hz) 3.58 (3H, s) 3.18 (1H, m) 3.09–3.06 (2H, m) 2.11 (1H, dd, $J=15.6, 7.8$ Hz) 2.02 (1H, dd, $J=15.6, 4.0$ Hz) 1.69 (1H, m) 1.43 (3H, d, $J=7.1$ Hz) 0.98 (3H, d, $J=6.7$ Hz) 0.81 (3H, d, $J=6.7$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 174.0, 143.9, 139.2, 128.3, 127.9, 126.8, 115.4, 59.8, 58.9, 51.4, 49.7, 35.0, 32.8, 21.0, 20.9, 19.8; m/z (CI, %) 290 ($[\text{M}+\text{H}]^+$, 40) 246 ($[\text{M}-\text{C}_3\text{H}_6]^+$, 100) 105 (C_8H_9^+ , 30). HRMS $\text{C}_{18}\text{H}_{28}\text{NO}_2$ calcd 290.2120, found 290.2123.

3.1.26. Methyl (3*R*, α *S*)-3-[*N*-allyl-*N*-(α -methylbenzyl)amino]hex-4-enoate (8c**).** Following general procedure D, butyllithium in hexanes (1.6 M, 11.3 mL, 18.0 mmol) and (*E*)-methyl hexa-2,4-dienoate (1.47 g, 11.6 mmol) in anhydrous THF (15 mL) were added to (*S*)-*N*-(α -methylbenzyl)allylamine (**7**) (3.00 g, 18.6 mmol) in anhydrous THF (15 mL), affording an oil that was purified by flash chromatography (1:9 ethyl acetate:hexane) to give **8c** (2.61 g, 78%) as a pale yellow oil; $[\alpha]_{\text{D}}^{21} +3.4$ (c 2.95, CHCl_3), lit.¹⁷ for enantiomer $[\alpha]_{\text{D}}^{13} -2.4$ (c 1.00, CHCl_3); IR ν_{max} 2970, 1736 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.35–7.17 (5H, m) 5.80 (1H, m) 5.51 (2H, m) 5.12–5.00 (2H, m) 4.02 (1H, q, $J=6.8$ Hz) 3.85 (1H, m) 3.56 (3H, s) 3.12 (2H, m) 2.51 (1H, dd, $J=14.3, 5.8$ Hz) 2.34 (1H, dd, $J=14.3, 7.5$ Hz) 1.69 (3H, d, $J=4.6$ Hz) 1.35 (3H, d, $J=6.8$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 172.5, 145.2, 138.8, 130.6, 128.0, 127.6, 127.1, 126.5, 115.7, 56.9, 56.8, 51.4, 49.6, 38.9, 18.1, 18.0; (EI, %) 288 ($[\text{M}+\text{H}]^+$, 20), 105 (C_8H_9^+ , 100). HRMS $\text{C}_{18}\text{H}_{26}\text{NO}_2$ calcd 288.1964, found 288.1961.

3.1.27. Methyl (3*R*, α *S*)-3-[*N*-allyl-*N*-(α -methylbenzyl)]-3-phenylpropanoate (8f**).** Following general procedure D, butyllithium in hexanes (2.5 M, 3.8 mL, 9.56 mmol) and methyl (*E*)-cinnamate (1.00 g, 6.17 mmol) in anhydrous THF (16 mL) to (*S*)-*N*-(α -methylbenzyl)allylamine (**7**) (1.59 g, 9.86 mmol) in anhydrous THF (20 mL), affording an oil that was purified by flash chromatography (10:9 ethyl acetate:hexane) to give **8f** (1.80 g, 90%) as a pale yellow oil; $[\alpha]_{\text{D}}^{21} +1.5$ (c 4.10, CHCl_3), lit.³⁵ for enantiomer $[\alpha]_{\text{D}}^{26} -3.6$ (c 0.85, CHCl_3); IR ν_{max} 2973, 1736 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.55–7.33 (10H, m) 5.80 (1H, m) 5.17 (1H, ddd, $J=17.2, 8.6, 1.4$ Hz) 5.08 (1H, ddd, $J=17.2, 10.1, 1.4$ Hz) 4.54 (1H, m) 4.08 (1H, q, $J=6.7$ Hz) 3.57 (3H, s) 3.22–3.18 (2H, m) 2.91 (1H, dd, $J=14.6, 5.6$ Hz) 2.69 (1H, dd, $J=14.6, 8.3$ Hz) 1.18 (3H, d, $J=6.7$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 172.5, 144.9, 141.5, 138.8, 128.4, 128.1, 127.7, 127.5, 127.3, 126.7, 116.0, 58.9, 56.3, 51.5, 49.8, 38.0, 16.6; m/z (CI, %) 324 ($[\text{M}+\text{H}]^+$, 18), 105 (C_8H_9^+ , 100). HRMS $\text{C}_{21}\text{H}_{26}\text{NO}_2$ calcd 324.1964, found 324.1958.

3.1.28. Methyl (3*R*, α *S*)-3-[*N*-allyl-*N*-(α -methylbenzyl)]-3-(3-pyridyl)propanoate (8g**).** Following general procedure D, butyllithium in

hexanes (2.5 M, 1.9 mL, 4.75 mmol) and methyl 3-(pyridin-3-yl)propanoate (0.50 g, 3.06 mmol) in anhydrous THF (5 mL) (*S*)-*N*-(α -methylbenzyl)allylamine (**7**) (0.95 g, 4.09 mmol) in anhydrous THF (10 mL) afforded an oil that was purified by flash chromatography (1:1 ethyl acetate:hexane) to give **8g** (0.52 g, 48%) as a yellow oil; $[\alpha]_{\text{D}}^{21} -0.6$ (c 1.70, CHCl_3); IR ν_{max} 2972, 1735 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.61 (1H, s) 8.50 (1H, m) 7.67 (1H, d, $J=7.9$ Hz) 7.37–7.22 (6H, m) 5.78 (1H, m) 5.16 (2H, ddd, $J=17.2, 4.8, 1.5$ Hz) 5.07 (2H, ddd, $J=17.2, 10.2, 1.5$ Hz) 4.54 (1H, m) 4.02 (1H, q, $J=6.8$ Hz) 3.55 (3H, s) 3.19–3.13 (2H, m) 2.81 (1H, dd, $J=15.2, 6.0$ Hz) 2.67 (1H, dd, $J=15.2, 9.0$ Hz) 1.23 (3H, d, $J=6.8$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 172.0, 149.7, 148.6, 144.2, 138.2, 137.2, 135.3, 128.3, 127.5, 127.0, 123.3, 116.4, 56.9, 56.6, 51.7, 49.8, 36.7, 17.6; m/z (EI, %) 325 ($[\text{M}+\text{H}]^+$, 15), 105 (C_8H_9^+ , 100). HRMS $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_2$ calcd 325.1916, found 325.1916.

3.1.29. Methyl (3*R*, α *S*)-3-[*N*-allyl-*N*-(α -methylbenzyl)amino]-3-cyclohexylpropanoate (8k**).** Following general procedure D, butyllithium in hexanes (2.5 M, 6.6 mL, 16.6 mmol) and methyl 3-cyclohexylpropanoate (1.80 g, 10.7 mmol) in anhydrous THF (27 mL) were added to (*S*)-*N*-(α -methylbenzyl)allylamine (**7**) (2.76 g, 17.1 mmol) in anhydrous THF (34 mL), affording an oil that was purified by flash chromatography (12:88 ethyl acetate:hexane) to give **8k** (2.40 g, 68%) as a pale yellow oil; $[\alpha]_{\text{D}}^{25} +11.0$ (c 6.69, CHCl_3); IR ν_{max} 2923, 1735 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.30–7.19 (5H, m) 5.85 (1H, m) 5.20 (1H, m) 5.07 (1H, m) 3.90 (1H, q, $J=7.0$ Hz) 3.57 (3H, s) 3.17–3.12 (2H, m) 3.06 (1H, m) 2.17–2.08 (2H, m) 2.00 (1H, dd, $J=15.7, 3.7$ Hz) 1.57–1.42 (4H, m) 1.39 (3H, d, $J=7.0$ Hz) 1.17–1.12 (4H, m) 0.88–0.76 (2H, m); ^{13}C NMR (500 MHz, CDCl_3) δ 174.0, 143.9, 139.2, 128.3, 127.9, 126.8, 115.4, 58.8, 51.4, 49.8, 42.7, 34.7, 31.1, 30.2, 27.0, 26.6, 21.0; m/z (CI, %) 330 ($[\text{M}+\text{H}]^+$, 20) 246 ($[\text{M}-\text{C}_7\text{H}_{10}]^+$, 100). HRMS $\text{C}_{21}\text{H}_{32}\text{NO}_2$ calcd 330.2433, found 330.2439.

3.1.30. Methyl (3*S*, α *S*)-3-[*N*-(α -methylbenzyl)]-butanoate (9a**).** Following general procedure E, reaction of amine **8a** (1.00 g, 3.83 mmol) and Wilkinson's catalyst (180 mg, 0.19 mmol) in acetonitrile–water (85:15, 20 mL) at 20 °C afforded an oil that was purified by flash chromatography (15:85 ethyl acetate:hexane) to give **9a** (0.73 g, 87%) as a pale brown oil; $[\alpha]_{\text{D}}^{21} -22.5$ (c 1.29, CHCl_3); IR ν_{max} (cm^{-1}) 2960, 2923, 1731 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.69–7.22 (5H, m) 3.87 (1H, q, $J=6.7$ Hz) 3.66 (3H, s) 3.00 (1H, m) 2.46 (1H, m) 2.37 (1H, m) 1.68 (1H, br s) 1.33 (3H, d, $J=6.7$ Hz) 1.05 (3H, d, $J=6.7$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 172.8, 132.0, 128.6, 127.0, 126.6, 55.3, 51.5, 47.8, 40.6, 24.6, 21.5; m/z (CI, %) 222 ($[\text{M}+\text{H}]^+$, 100). HRMS $\text{C}_{13}\text{H}_{20}\text{NO}_2$ calcd 222.1494, found 292.1491.

3.1.31. Methyl (3*R*, α *S*)-3-[*N*-(α -methylbenzyl)]-4-methylpentanoate (9b**).** Following general procedure E, reaction of amine **8b** (1.50 g, 5.18 mmol) and Wilkinson's catalyst (0.24 g, 0.26 mmol) in acetonitrile–water (85:15, 30 mL) at 20 °C afforded an oil that was purified by flash chromatography (18:82 ethyl acetate:hexane) to give **9b** (0.77 g, 59%) as a pale yellow oil; $[\alpha]_{\text{D}}^{21} -48.1$ (c 2.35, CHCl_3); IR ν_{max} 2957, 1733 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.20 (5H, m) 3.84 (1H, m) 3.67 (3H, s) 2.65 (1H, q, $J=6.3$ Hz) 2.45 (1H, dd, $J=14.6, 9.0$ Hz) 2.37 (1H, dd, $J=14.6, 5.5$ Hz) 1.67 (1H, m) 1.31 (3H, d, $J=6.3$ Hz) 0.87 (3H, d, $J=6.8$ Hz) 0.80 (3H, d, $J=6.8$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 173.5, 132.0, 128.3, 126.9, 126.5, 57.6, 55.5, 51.5, 35.9, 31.4, 24.9, 18.6, 18.5; m/z (CI, %) 250 ($[\text{M}+\text{H}]^+$, 100) 206 ($[\text{M}-\text{C}_3\text{H}_6]^+$, 53). HRMS $\text{C}_{15}\text{H}_{24}\text{NO}_2$ calcd 250.1807, found 250.1805.

3.1.32. (4*E*)-Methyl (3*R*, α *S*)-3-[*N*-(α -methylbenzyl)]hex-4-enoate (9c**).** Following general procedure E, reaction of amine **8c** (5.10 g, 17.8 mmol) and Wilkinson's catalyst (0.82 g, 0.89 mmol) in acetonitrile–water (85:15, 120 mL) at 20 °C afforded an oil that was purified by flash chromatography (1:9 ethyl acetate:hexane) to give

9c (3.69 g, 84%) as a pale yellow oil; $[\alpha]_D^{21} -38.9$ (c 0.72, CHCl₃); IR ν_{\max} 3060, 2965, 1734 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.57–7.04 (5H, m) 5.55 (1H, m) 5.27 (1H, m) 3.83 (1H, q, *J*=6.5 Hz) 3.66 (3H, s) 3.48 (1H, m) 2.52–2.46 (2H, m) 1.63 (3H, dd, *J*=6.5, 1.4 Hz) 1.31 (3H, d, *J*=6.5 Hz); ¹³C NMR (500 MHz, CDCl₃) δ 172.5, 146.2, 132.7, 128.5, 127.1, 126.9, 126.7, 54.9, 54.7, 51.5, 40.5, 23.3, 17.8; (EI, %) 247 ([M+H]⁺, 5) 232 ([M-CH₃]⁺, 38), 105 (C₈H₉⁺, 100). HRMS C₁₅H₂₂NO₂ calcd 248.1650, found 248.1651.

3.1.33. Methyl (3*R*, α *S*)-3-[*N*-(α -methylbenzyl)]-3-phenylpropanoate (9f**).** Following general procedure E, reaction of amine **8f** (0.50 g, 1.55 mmol) and Wilkinson's catalyst (72 mg, 0.08 mmol) in acetonitrile–water (85:15, 10 mL) at 20 °C gave an oil that was purified by flash chromatography (1:4 ethyl acetate:hexane) to give **9f** (0.33 g, 76%) as a pale yellow oil; $[\alpha]_D^{21} -13.5$ (c 7.47, CHCl₃), lit.³⁶ $[\alpha]_D^{20} -16.3$ (c 1.00, CHCl₃); IR ν_{\max} 3050, 2964, 1732 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.33–7.21 (10H, m) 4.21 (1H, m) 3.66 (1H, q, *J*=6.6 Hz) 3.62 (3H, s) 2.77 (1H, m) 2.68 (1H, m) 1.85 (1H, br s) 1.23 (3H, d, *J*=6.6 Hz); ¹³C NMR (500 MHz, CDCl₃) δ 172.2, 132.0, 128.6, 128.5, 127.5, 127.1, 126.7, 56.9, 54.8, 51.6, 42.5, 22.2; *m/z* (CI, %) 284 ([M+H]⁺, 100). HRMS C₁₈H₂₂NO₂ calcd 284.1651, found 284.1648.

3.1.34. Methyl (3*R*, α *S*)-3-[*N*-(α -methylbenzyl)]-3-(pyridin-3-yl)propanoate (9g**).** Tetrakis(triphenylphosphine)palladium(0) (0.16 g, 0.01 mmol) and dimethylbarbituric acid (0.73 g, 2.98 mmol) were added to a stirred solution of amine **8g** (0.54 g, 1.51 mmol) in anhydrous dichloromethane (80 mL) at 30 °C under nitrogen. After stirring the solution at 30 °C for a further 3 h the mixture was washed with aqueous saturated sodium carbonate (2×10 mL), and the combined organic layers dried (MgSO₄) and evaporated to give an oil that was purified by flash chromatography (6:4 ethyl acetate:hexane) to give **9g** (0.41 g, 96%) as an orange oil; IR ν_{\max} 2982, 2920, 1732 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.47 (1H, s) 8.40 (1H, m) 7.65 (1H, m) 7.43–7.14 (6H, m) 4.17 (1H, dd, *J*=7.5, 6.3 Hz) 3.65 (1H, q, *J*=6.4 Hz) 3.58 (3H, s) 2.75 (1H, dd, *J*=15.5, 7.5 Hz) 2.63 (1H, dd, *J*=15.5, 6.3 Hz) 2.25 (1H, br s, NH) 1.33 (3H, d, *J*=6.4 Hz); ¹³C NMR (500 MHz, CDCl₃) δ 171.7, 149.3, 148.8, 145.4, 138.2, 133.7, 132.0, 128.9, 128.5, 127.1, 55.4, 54.9, 51.7, 41.8, 22.9; *m/z* (CI, %) 285 ([M+H]⁺, 100). HRMS C₁₇H₂₁N₂O₂ calcd 285.1603, found 285.1607.

3.1.35. Methyl (3*R*, α *S*)-3-[*N*-(α -methylbenzyl)]-3-cyclohexylpropanoate (9k**).** Following general procedure E, reaction of amine **8k** (1.86 g, 5.65 mmol) and Wilkinson's catalyst (0.30 g, 0.32 mmol) in 85:15 acetonitrile:water (35 mL) at 20 °C afforded an oil that was purified by flash chromatography (12:88 ethyl acetate:hexane) to give **9k** (0.79 g, 53%) as a yellow oil; $[\alpha]_D^{25} -35.2$ (c 1.90, CHCl₃); IR ν_{\max} 2985, 2922, 1732 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.35–7.20 (5H, m) 3.80 (1H, m) 3.67 (3H, s) 2.63 (1H, q, *J*=5.9 Hz) 2.49 (1H, dd, *J*=14.7, 5.5 Hz) 2.37 (1H, dd, *J*=14.7, 6.3 Hz) 1.79–1.62 (5H, m) 1.31 (3H, d, *J*=5.9 Hz) 1.17–1.08 (4H, m) 0.96–0.86 (2H, m); ¹³C NMR (500 MHz, CDCl₃) δ 173.5, 132.0, 128.3, 127.0, 126.9, 57.0, 55.5, 51.5, 41.8, 35.9, 29.3, 29.1, 26.6, 26.5; *m/z* (CI, %) 290 ([M+H]⁺, 100). HRMS C₁₈H₂₈NO₂ calcd 290.2120, found 290.2112.

3.1.36. Methyl (3*S*, α *S*)-3-[*N*-(α -methylbenzyl), *N*-(2-methoxycarbonylacetyl)]butanoate (10a**).** Following general procedure B, reaction of amine **9a** (0.30 g, 1.36 mmol), triethylamine (0.22 mL, 1.63 mmol) and methyl 3-chloro-3-oxopropanoate (0.16 mL, 1.5 mmol) in dichloromethane (6 mL) afforded an oil that was purified by flash chromatography (1:1 ethyl acetate:hexane) to give **10a** (0.25 g, 58%) as a colourless oil; $[\alpha]_D^{21} -2.5$ (c 0.80, CHCl₃); IR ν_{\max} 2952, 1736, 1646 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.38–7.22 (5H, m) 4.95 (1H, q, *J*=6.8 Hz) 3.78 (3H, s) 3.60 (3H, s) 3.46 (2H, s) 3.08 (1H, m) 2.42 (1H, m) 2.08 (1H, m) 1.66 (3H, d,

J=6.8 Hz) 1.43 (3H, d, *J*=6.7 Hz); ¹³C NMR (500 MHz, CDCl₃) δ 172.3, 168.3, 165.6, 139.0, 128.3, 128.1, 127.3, 56.9, 52.6, 51.4, 48.6, 42.9, 39.1, 18.7, 17.3; *m/z* (CI, %) 321 (M⁺, 5) 220 ([M-C₄H₅O₃]⁺, 85) 105 (C₈H₉⁺, 100). HRMS C₁₇H₂₃NO₅ calcd 321.1576, found 321.1571.

3.1.37. Methyl (3*R*, α *S*)-3-[*N*-(α -methylbenzyl)], *N*-(2-methoxycarbonylacetyl)-4-methylpentanoate (10b**).** Following general procedure B, reaction of amine **9b** (0.25 g, 1.0 mmol), triethylamine (0.18 mL, 1.30 mmol) and methyl 3-chloro-3-oxopropanoate (0.13 mL, 1.2 mmol) in dichloromethane (4 mL) afforded a pale yellow oil that was purified by flash chromatography (1:1 ethyl acetate:hexane) to give **10b** (0.18 g, 50%) as a pale yellow oil; $[\alpha]_D^{21} +74.3$ (c 0.35, CHCl₃); IR ν_{\max} 2953, 1738, 1647 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) (presence of rotamers) δ 7.35–7.22 (5H, m) 5.00 (1H, m) 3.95 (1H, d, *J*=15.7 Hz, rotamer A) 3.78 (3H, s) 3.72 (1H, d, *J*=15.2 Hz, rotamer B) 3.68 (1H, d, *J*=15.7 Hz, rotamer A) 3.60 (1H, d, *J*=15.2 Hz, rotamer B) 3.46 and 3.36 (3H, s) 3.27 (1H, m) 2.72 (1H, dd, *J*=18.0, 6.9 Hz) 2.24 (1H, dd, *J*=18.0, 2.5 Hz) 2.04 (1H, m) 1.88 and 1.65 (3H, d, *J*=7.0 Hz) 1.11 and 0.99 (3H, d, *J*=6.7 Hz) 0.92 and 0.81 (3H, d, *J*=6.8 Hz); ¹³C NMR (500 MHz, CDCl₃) δ 172.7, 171.9, 168.6, 168.4, 167.6, 165.9, 139.2, 128.8, 128.3, 127.9, 127.7, 126.8, 126.6, 62.3, 58.3, 56.6, 55.6, 52.6, 52.4, 51.9, 51.4, 43.0, 42.8, 39.6, 35.9, 31.2, 30.9, 21.4, 21.2, 20.7, 20.1, 19.9, 18.3; *m/z* (CI, %) 372 ([M+Na]⁺, 100). HRMS C₁₉H₂₇NO₅Na calcd 372.1787, found 372.1783.

3.1.38. (4*E*)-Methyl (3*R*, α *S*)-3-[*N*-(α -methylbenzyl)], *N*-(2-methoxycarbonylacetyl)hex-4-enoate (10c**).** Following general procedure B, reaction of amine **9c** (1.2 g, 4.85 mmol), triethylamine (0.80 mL, 5.8 mmol) and methyl 3-chloro-3-oxopropanoate (0.57 mL, 5.3 mmol) in dichloromethane (25 mL) afforded an oil that was purified by flash chromatography (3:7 ethyl acetate:hexane) to give **10c** (1.58 g, 94%) as a colourless oil; $[\alpha]_D^{21} +5.5$ (c 1.82, CHCl₃); IR ν_{\max} 3030 (N–H), 2952, 1733, 1641 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.21 (5H, m) 5.93 (1H, m) 5.65–5.56 (2H, m) 5.04 (1H, q, *J*=6.7 Hz) 3.78 (3H, s) 3.51 (2H, s) 3.45 (3H, s) 1.74 (2H, d, *J*=4.9 Hz) 1.64 (3H, d, *J*=6.7 Hz) 1.58 (3H, m); *m/z* (CI, %) 370 (M⁺, 100), 311 ([M-CO₂Me]⁺, 2). HRMS C₁₉H₂₅NO₅Na calcd 370.1630, found 370.1626.

3.1.39. Methyl (3*R*, α *S*)-3-[*N*-(α -methylbenzyl), *N*-(2-methoxycarbonylacetyl)]-3-phenylpropanoate (10f**).** Following general procedure B, reaction of amine **9f** (4.16 g, 14.7 mmol), triethylamine (2.7 mL, 19 mmol) and methyl 3-chloro-3-oxopropanoate (1.9 mL, 17.6 mmol) in dichloromethane (45 mL) afforded an oil that was purified by flash chromatography (35:65 ethyl acetate:hexane) to give **10f** (4.48 g, 80%) as a colourless oil; $[\alpha]_D^{21} +25.0$ (c 1.56, CHCl₃); IR ν_{\max} 2950, 1735, 1647 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) (presence of rotamers) δ 7.37–7.17 (10H, m) 5.32 and 5.24 (1H, m) 4.98 (1H, q, *J*=6.1 Hz) 3.71 (3H, s) 3.56 (2H, s) 3.51 (3H, s) 3.36–3.31 (2H, m) 2.96 (1H, m) 2.73–2.65 (1H, m) 1.25 (3H, *J*=6.1 Hz); ¹³C NMR (500 MHz, CDCl₃) δ 171.9, 171.1, 168.4, 168.2, 167.2, 166.5, 141.4, 140.4, 139.9, 139.0, 129.1, 129.0, 128.6, 128.5, 128.2, 128.0, 127.4, 127.2, 127.0, 126.6, 126.5, 56.8, 56.4, 55.2, 54.7, 52.6, 52.5, 52.1, 51.8, 43.0, 40.8, 38.9, 38.3 18.6; *m/z* (CI, %) 384 ([M-H]⁺, 100). HRMS C₂₂H₂₆NO₅Na calcd 384.1811, found 384.1803.

3.1.40. Methyl (3*R*, α *S*)-3-[*N*-(α -methylbenzyl), *N*-(2-methoxycarbonylacetyl)]-3-(pyridin-3-yl)propanoate (10g**).** Following general procedure B, reaction of amine **9f** (0.16 g, 0.56 mmol), triethylamine (0.11 mL, 0.73 mmol) and methyl 3-chloro-3-oxopropanoate (0.07 mL, 0.67 mmol) in dichloromethane (3 mL) afforded an oil that was purified by flash chromatography (1:1 ethyl acetate:hexane) to give **10g** (0.16 g, 75%) as a colourless oil; $[\alpha]_D^{21} +15.0$ (c 1.00, CHCl₃); IR ν_{\max} 2952, 1735, 1648,

1496 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) (presence of rotamers) δ 8.57 (1H, s) 8.40 (1H, m) 7.82 (1H, d, $J=7.3$ Hz) 7.64 (1H, m) 7.45–7.17 (5H, m) 5.08 (1H, q, $J=6.5$ Hz) 4.86 (1H, dd, $J=7.7, 5.6$ Hz) 3.74 (3H, s) 3.58 (2H, s) 3.43 (3H, s) 2.60 (1H, dd, $J=17.1, 7.7$ Hz) 2.27 (1H, dd, $J=17.1, 5.6$ Hz) 1.60 (3H, d, $J=6.5$ Hz); ¹³C NMR (500 MHz, CDCl₃) δ 171.6, 168.1, 166.2, 149.0, 148.5, 136.1, 135.7, 132.1, 132.0, 129.1, 128.8, 128.4, 127.2, 123.3, 57.3, 53.3, 52.6, 51.8, 42.7, 38.7, 18.4; m/z (CI, %) 385 ([M+H]⁺, 100) 279 ([M–C₈H₈]⁺, 55). HRMS C₂₁H₂₅N₂O₅ calcd 385.1764, found 385.1761.

3.1.41. Methyl (3*R*, α S)-3-[N-(α -methylbenzyl), N-(2-methoxycarbonylacetyl)]-3-cyclohexylpropanoate (10k). Following general procedure B, reaction of amine **9k** (0.25 g, 0.86 mmol), triethylamine (0.16 mL, 1.12 mmol) and methyl 3-chloro-3-oxopropanoate (0.11 mL, 1.04 mmol) in dichloromethane (4 mL) afforded a pale yellow oil that was purified by flash chromatography (1:1 ethyl acetate:hexane) to give **10k** (0.22 g, 66%) as a pale yellow oil, $[\alpha]_D^{25} +22.5$ (c 1.00, CHCl₃); IR ν_{\max} 2925, 1737, 1648 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) (presence of rotamers) δ 7.32–7.16 (5H, m) 4.99–4.95 and 4.30–4.28 (1H, m) 3.77 (3H, s) 3.65 (1H, s) 3.60 (1H, s) 3.40 (3H, s) 2.72 and 2.46 (1H, d, $J=7.0$ Hz) 2.45–2.02 (2H, m) 1.84 (3H, d, $J=7.0$ Hz) 1.73–1.61 (5H, m) 1.29–0.82 (6H, m); ¹³C NMR (500 MHz, CDCl₃) δ 173.5, 172.7, 168.7, 168.4, 167.6, 165.8, 142.6, 139.3, 128.7, 128.3, 128.2, 127.9, 126.9, 126.8, 61.4, 57.2, 57.0, 55.5, 52.5, 51.5, 51.3, 50.0, 43.0, 42.8, 41.8, 40.8, 35.9, 31.5, 30.6, 30.1, 29.2, 29.1, 26.6, 26.5, 26.4, 26.3, 26.1, 26.0, 25.0, 21.2; m/z (CI, %) 412 ([M+Na]⁺, 100). HRMS C₂₂H₃₁NO₅Na calcd 412.2100, found 412.2115.

3.1.42. (1*S*,6*R*)-1-(α -Methylbenzyl)-3-methoxycarbonyl-6-phenylpiperidine-2,4-dione sodium salt (11f). Sodium methoxide in methanol (1.97 M, 0.2 mL, 0.38 mmol) was added to a stirred solution of diester **10f** (0.13 g, 0.34 mmol) in methanol (0.70 mL) at 20 °C, under nitrogen. The mixture was then heated under reflux for 1 h, allowed to cool to 20 °C, then diluted with diethyl ether and filtered to give **11f** (0.12 g, 97%) as a white solid, mp 230 °C (decomp.); IR ν_{\max} 3220, 2972, 1671, 1650, 1589 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.38–7.14 (10H, m) 6.21 (1H, q, $J=7.2$ Hz) 4.33 (1H, dd, $J=6.9, 1.3$ Hz) 3.67 (3H, s) 2.64 (1H, dd, $J=15.7, 6.9$ Hz) 2.15 (1H, dd, $J=15.7, 1.3$ Hz) 1.24 (3H, d, $J=7.2$ Hz); ¹³C NMR (500 MHz, CDCl₃) δ 186.6, 171.8, 170.6, 144.1, 143.9, 129.5, 129.2, 128.3, 128.1, 127.9, 127.7, 97.5, 53.6, 51.4, 50.5, 44.9, 17.0.

3.1.43. (1*S*,6*R*)-1-(α -Methylbenzyl)-3-methoxycarbonyl-6-(*E*)-propenylpiperidine-2,4-dione sodium salt (11i). Sodium methoxide in methanol (2.14 M, 2.3 mL, 5.0 mmol) was added to a stirred solution of diester **10i** (1.58 g, 4.6 mmol) in methanol (6 mL) at 20 °C, under nitrogen. The mixture was then heated under reflux for 1 h. After allowing to cool to 20 °C, the mixture was diluted with diethyl ether and filtered to give **11i** (1.46 g, 95%) as a white solid, mp 203–207 °C; IR ν_{\max} 3064, 2974, 1660 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.35–7.22 (5H, m) 6.04 (1H, q, $J=7.2$ Hz) 5.66 (1H, m) 5.53 (1H, m) 3.66 (3H, s) 3.60 (1H, m) 2.33 (1H, dd, $J=15.7, 6.2$ Hz) 2.18 (1H, dd, $J=15.7, 2.4$ Hz) 1.61 (3H, d, $J=6.2$ Hz) 1.49 (3H, d, $J=7.2$ Hz); ¹³C NMR (500 MHz, CDCl₃) δ 188.1, 170.8, 170.7, 144.1, 132.7, 129.4, 128.2, 128.2, 127.3, 96.4, 51.8, 51.4, 50.4, 43.4, 17.8, 17.3. HRMS C₁₈H₂₁NO₄Na calcd 338.1368, found 338.1360.

3.1.44. (1*S*,6*S*)-1-(α -Methylbenzyl)-6-methylpiperidine-2,4-dione (12a). Following general procedure C, reaction of diester **10a** (0.23 g, 0.70 mmol), and sodium methoxide in methanol (2.0 M, 0.70 mL, 1.4 mmol) in methanol (5 mL) gave **12a** (0.16 g, 97%) as a pale yellow oil, $[\alpha]_D^{21} -198.1$ (c 3.09, CHCl₃); IR ν_{\max} 2975, 1730, 1642 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.36–7.25 (5H, m) 6.10 (1H, q, $J=6.9$ Hz) 3.55 (1H, m) 3.41–3.29 (2H, m) 2.24 (1H, dd, $J=16.5, 8.6$ Hz) 2.17 (1H, dd, $J=16.5, 5.0$ Hz) 1.59 (3H, d, $J=6.9$ Hz) 1.25 (3H,

d, $J=6.7$ Hz); ¹³C NMR (500 MHz, CDCl₃) δ 204.6, 166.2, 140.0, 128.8, 128.1, 127.2, 50.9, 47.4, 46.5, 45.1, 22.7, 16.9; m/z (CI, %) 232 ([M+H]⁺, 100) 105 (C₈H₉⁺, 35). HRMS C₁₄H₁₈NO₂ calcd 232.1338, found 232.1334.

3.1.45. (1*S*,6*R*)-1-(α -Methylbenzyl)-6-phenylpiperidine-2,4-dione (12f). The piperidine-2,4-dione sodium salt **11f** (0.10 g, 0.28 mmol) was added to hydrochloric acid (1.3 M, 5 mL). The mixture was heated under reflux for 1 h, then allowed to cool to 20 °C and extracted with dichloromethane (2×5 mL). The combined organic layers were dried (MgSO₄) and evaporated, and the residue was purified by flash chromatography (1:1 ethyl acetate:hexane) to give **12f** (69 mg, 85%) as pale yellow solid, mp 104–107 °C; $[\alpha]_D^{21} +103.4$ (c 2.95, CHCl₃); IR ν_{\max} 2923, 1730, 1648 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.39–7.11 (10H, m) 6.31 (1H, q, $J=7.2$ Hz) 4.65 (1H, dd, $J=6.1, 2.2$ Hz) 3.39 (2H, s) 2.68 (1H, dd, $J=16.4, 2.2$ Hz) 2.51 (1H, dd, $J=16.4, 6.1$ Hz) 1.35 (3H, d, $J=7.2$ Hz); ¹³C NMR (500 MHz, CDCl₃) δ 203.2, 167.4, 140.1, 140.0, 129.2, 128.9, 128.1, 128.0, 127.5, 125.7, 53.0, 51.6, 48.8, 47.9, 16.4; m/z (EI, %) 293 ([M+H]⁺, 100) 105 (C₈H₉⁺, 35) 77 (C₆H₅⁺, 10). HRMS C₁₉H₁₉NO₂ calcd 293.1416, found 293.1413.

3.1.46. (1*S*,6*R*)-1-(α -Methylbenzyl)-6-(pyridin-3-yl)piperidine-2,4-dione (12g). Following general procedure C, reaction of diester **10g** (0.25 g, 0.65 mmol), and sodium methoxide in methanol (2.0 M, 0.65 mL, 1.30 mmol) in methanol (3 mL) gave **12g** (0.19 g, 99%) as a brown oil, $[\alpha]_D^{25} -84.7$ (c 1.00, CHCl₃); IR ν_{\max} 2977, 1730, 1642 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.57 (1H, d, $J=4.5$ Hz) 8.48 (1H, s) 7.65 (1H, m) 7.53–7.26 (6H, m) 6.31 (1H, q, $J=7.2$ Hz) 4.66 (1H, dd, $J=6.0, 1.8$ Hz) 3.46 (1H, d, $J=20.6$ Hz) 3.35 (1H, d, $J=20.6$ Hz) 2.66 (1H, dd, $J=16.4, 1.8$ Hz) 2.56 (1H, dd, $J=16.4, 6.0$ Hz) 1.34 (3H, d, $J=7.2$ Hz); ¹³C NMR (500 MHz, CDCl₃) δ 202.1, 167.1, 149.6, 147.6, 139.5, 135.7, 133.2, 132.2, 129.1, 128.6, 128.3, 127.4, 123.8, 51.6, 51.1, 48.6, 47.7, 16.6; m/z (EI, %) 294 (M⁺, 15). HRMS C₁₈H₁₈N₂O₂ calcd 294.1368, found 294.1366.

3.1.47. (1*S*,6*R*)-1-(α -Methylbenzyl)-6-isopropylpiperidine-2,4-dione (12j). Following general procedure C, reaction of diester **10j** (0.15 g, 0.47 mmol) and sodium methoxide in methanol (2.0 M, 0.50 mL, 1.0 mmol) in methanol (3 mL) afforded **12j** (0.12 g, 95%) as a pale yellow oil, $[\alpha]_D^{21} -177.9$ (c 1.31, CHCl₃); IR ν_{\max} 2968, 1726, 1644 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.37–7.26 (5H, m) 6.07 (1H, q, $J=7.1$ Hz) 3.42 (1H, d, $J=21.3$ Hz) 3.20 (1H, d, $J=21.3$ Hz) 3.16 (1H, m) 2.52 (1H, dd, $J=16.7, 5.0$ Hz) 2.02–1.96 (2H, m) 1.65 (3H, d, $J=7.1$ Hz) 0.90 (3H, d, $J=6.9$ Hz) 0.84 (3H, d, $J=6.9$ Hz); ¹³C NMR (500 MHz, CDCl₃) δ 208.2, 170.2, 142.5, 131.5, 130.7, 130.2, 58.3, 55.4, 50.1, 43.7, 35.9, 22.9, 20.4, 20.2; m/z (EI⁺) 259 (M⁺, 100) 216 ([M–C₃H₇]⁺, 99) 105 (C₈H₉⁺, 75) 77 (C₆H₅⁺, 40). HRMS C₁₆H₂₁NO₂ calcd 259.1572, found 259.1575.

3.1.48. (1*S*,6*R*)-1-(α -Methylbenzyl)-6-cyclohexylpiperidine-2,4-dione (12k). Following general procedure C, reaction of diester **10k** (0.22 g, 0.57 mmol) and sodium methoxide in methanol (2.0 M, 0.6 mL, 1.2 mmol) in methanol (3 mL) gave **12k** (0.13 g, 76%) as a colourless oil, $[\alpha]_D^{25} -133.1$ (c 3.40, CHCl₃); IR ν_{\max} 2926, 1726, 1640 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.46–7.25 (5H, m) 6.03 (1H, q, $J=7.2$ Hz) 3.38 (1H, d, $J=21.2$ Hz) 3.26 (1H, d, $J=21.2$ Hz) 3.13 (1H, m) 2.49 (1H, dd, $J=16.7, 3.6$ Hz) 1.95 (1H, dd, $J=16.7, 6.5$ Hz) 1.74 (2H, m) 1.61 (3H, d, $J=7.2$ Hz) 1.59–1.47 (3H, m) 1.14–0.80 (6H, m); ¹³C NMR (500 MHz, CDCl₃) δ 205.6, 169.5, 139.9, 128.8, 128.0, 127.5, 55.2, 52.8, 47.7, 43.6, 41.7, 30.7, 28.6, 26.6, 26.4, 26.0, 17.6; m/z (CI, %) 300 ([M+H]⁺, 100). HRMS C₁₉H₂₆NO₂ calcd 300.1964, found 300.1953.

3.1.49. (1*S*,6*R*)-1-(α -Methylbenzyl)-6-(*E*)-propenylpiperidine-2,4-dione (12l). The piperidine-2,4-dione sodium salt **11l** (1.0 g, 2.96 mmol) was added to hydrochloric acid (1.3 M, 30 mL). The

mixture was heated under reflux for 1 h, then allowed to cool to 20 °C and extracted with dichloromethane (2×30 mL). The combined organic layers were dried (MgSO₄) and evaporated to give **12l** (0.56 g, 74%) as a pale yellow oil, $[\alpha]_D^{21} -203.8$ (c 2.08, CHCl₃); IR ν_{\max} 3060, 2938, 1726, 1650 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.52–7.26 (5H, m) 6.14 (1H, q, *J*=7.2 Hz) 5.55 (1H, ddq, *J*=18.0, 6.2, 1.4 Hz) 5.41 (1H, dq, *J*=18.0, 1.7 Hz) 3.92 (1H, m) 3.41–3.24 (2H, m) 2.42 (1H, dd, *J*=17.0, 2.1 Hz) 2.16 (1H, dd, *J*=17.0, 5.1 Hz) 1.68 (3H, dd, *J*=6.2, 1.7 Hz) 1.54 (3H, d, *J*=7.2 Hz); ¹³C NMR (300 MHz, CDCl₃) δ 204.1, 166.6, 139.9, 129.8, 128.7, 128.0, 127.9, 127.3, 51.1, 50.2, 48.4, 44.9, 17.7, 16.5; *m/z* (Cl⁺) 257 (M⁺, 70) 105 (C₈H₉⁺, 39) 77 (C₆H₅⁺, 15). HRMS C₁₆H₁₉NO₂ calcd 257.1416, found 257.1428.

3.1.50. (6*R*)-Phenylpiperidine-2,4-dione (**R**)-(6*f*). Methanesulfonic acid (0.23 mL, 3.07 mmol) was added to a stirred solution of piperidine-2,4-dione **12f** (1.0 g, 3.41 mmol) in toluene (15 mL) at 20 °C, under nitrogen. The mixture was then heated under reflux for 3 h, allowed to cool to 20 °C, evaporated, and the residue was purified by flash chromatography (9:1 ethyl acetate:hexane) to give (**R**)-(6*f*) (0.36 g, 56%) as a white solid, mp 163–166 °C (lit.³⁷ 166–168 °C); $[\alpha]_D^{25} +119.1$ (c 1.00, CHCl₃) (lit.³⁷ $[\alpha]_D^{20} +124.3$ c 0.35, CHCl₃); IR ν_{\max} 3185, 2899, 1716, 1665 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.43–7.21 (5H, m) 7.13 (1H, br s) 4.89 (1H, m) 3.33 (2H, s) 2.85 (1H, dd, *J*=16.1, 4.5 Hz) 2.73 (1H, dd, *J*=16.1, 8.9 Hz); ¹³C NMR (500 MHz, CDCl₃) δ 202.5, 169.2, 139.4, 129.4, 128.9, 126.1, 52.9, 47.3, 47.0; *m/z* (EI, %) 189 (M⁺, 100). HRMS C₁₁H₁₁NO₂ calcd 189.0790, found 189.0787.

3.1.51. (6*R*)-Isopropylpiperidine-2,4-dione (**R**)-(6*j*). Methanesulfonic acid (0.02 mL, 0.26 mmol) was added to a stirred solution of piperidine-2,4-dione **12j** (76 mg, 0.29 mmol) in toluene (2 mL) at 20 °C, under nitrogen. The mixture was heated under reflux for 3 h, then allowed to cool, evaporated, and the residue was purified by flash chromatography (ethyl acetate) to give (**R**)-(6*j*) (22 mg, 48%) as a pale yellow oil; $[\alpha]_D^{21} +30.6$ (c 0.49, CHCl₃), lit.³⁸ $[\alpha]_D^{13} +35.3$ (c 1.00, MeOH); IR ν_{\max} 3212, 2922, 1722, 1665 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.05 (1H, br s) 3.49 (1H, m) 3.28 (2H, s) 2.63 (1H, dd, *J*=16.1, 4.4 Hz) 2.45 (1H, dd, *J*=16.1, 9.1 Hz) 1.82 (1H, m) 1.01–0.95 (6H, m); ¹³C NMR (500 MHz, CDCl₃) δ 203.5, 170.2, 54.3, 47.2, 41.6, 32.5, 18.2, 17.9; *m/z* (ES, %) 155 (M⁺, 50). HRMS C₈H₁₃NO₂ calcd 155.0946, found 155.0940.

3.1.52. (6*R*)-Cyclohexylpiperidine-2,4-dione (**R**)-(6*k*). Methanesulfonic acid (0.04 mL, 0.61 mmol) was added to a stirred solution of piperidine-2,4-dione **12k** (0.14 g, 0.47 mmol) in toluene (3 mL) at 20 °C, under nitrogen. The mixture was heated under reflux for 5 h, then allowed to cool to 20 °C, and evaporated to give an oil that was purified by flash chromatography (ethyl acetate) to give (**R**)-(6*k*) (38 mg, 42%) as yellow solid, mp 125–127 °C; $[\alpha]_D^{21} +14.2$ (c 1.26, MeOH); IR ν_{\max} 3223, 2925, 1724, 1665 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.10 (1H, br s) 3.55 (1H, m) 3.25 (2H, s) 2.61 (1H, dd, *J*=16.1, 4.8 Hz) 2.50 (1H, dd, *J*=16.1, 8.1 Hz) 1.80–1.74 (3H, m) 1.70–1.69 (2H, m) 1.60 (1H, m) 1.25–1.14 (3H, m) 1.00 (2H, m); ¹³C NMR (500 MHz, CDCl₃) δ 203.9, 169.4, 53.6, 47.3, 42.4, 41.7, 28.8, 28.5, 26.1, 25.9, 25.8; *m/z* (EI, %) 195 (M⁺, 2) 112 ([M–C₆H₁₁]⁺, 100). HRMS C₁₁H₁₇NO₂ calcd 195.1259, found 195.1255.

3.1.53. (1*S*,6*R*)-1-(α -Methylbenzyl)-3,3-dimethyl-6-(*E*)-propenylpiperidine-2,4-dione (**13**). To piperidine-2,4-dione **12l** (0.13 g, 0.51 mmol) in ethanol (2 mL) was added potassium carbonate (0.21 g, 1.52 mmol) and methyl iodide (0.1 mL, 1.52 mmol). The mixture was stirred at 40 °C for 16 h then filtered. The filtrate was evaporated and the residue was dissolved in chloroform (5 mL) and the solution was filtered. Evaporation afforded an oil that was purified by flash chromatography (15:85 ethyl acetate:hexane) to give

13 (0.11 g, 76%) as a colourless oil, $[\alpha]_D^{21} -142.9$ (c 0.35, CHCl₃); IR ν_{\max} 2923, 1724, 1640 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.36–7.24 (5H, m) 6.07 (1H, q, *J*=6.5 Hz) 5.48 (1H, m) 5.25 (1H, m) 3.82 (1H, m) 2.65 (1H, dd, *J*=13.8, 5.7 Hz) 2.30 (1H, dd, *J*=13.8, 2.5 Hz) 1.63 (3H, d, *J*=6.5 Hz) 1.51 (3H, dd, *J*=7.2, 1.8 Hz) 1.38 (3H, d, *J*=1.9 Hz) 1.35 (3H, d, *J*=1.9 Hz); ¹³C NMR (300 MHz, CDCl₃) δ 209.2, 174.0, 140.5, 131.1, 128.7, 128.3, 127.7, 127.3, 52.4, 52.1, 50.6, 44.4, 26.5, 21.7, 17.6, 16.8; *m/z* (EI, %) 286 (M⁺, 4); 105 (C₈H₉⁺, 100). HRMS C₁₈H₂₄NO₂ calcd 286.1807, found 286.1803.

3.1.54. (4*R*,6*R*)-4-Hydroxy-6-phenylpiperidin-2-one (**14**). Zinc borohydride (2.0 mL, 1.37 M, 2.74 mmol) was added to a stirred solution of the piperidine-2,4-dione (**R**)-(6*f*) (0.19 g, 0.98 mmol) in anhydrous dichloromethane (2 mL) at 0 °C, under nitrogen. The mixture was then stirred at 20 °C for 20 h. Water (5 mL) was added to the mixture, which was then extracted with ethyl acetate (2×10 mL). The combined organic layers were dried (MgSO₄) and evaporated. The residue was recrystallised from isopropanol–hexane to give **14** (0.08 g, 43%) as a white solid, mp 206–210 °C (lit.^{10b} 213 °C); $[\alpha]_D^{25} +53.3$ (c 1.20, MeOH), lit.^{10b} $[\alpha]_D^{20} +52.3$ (c 0.88, MeOH); IR ν_{\max} 3269, 2896, 1648 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) δ 7.38–7.28 (5H, m) 4.51 (1H, dd, *J*=11.6, 4.3 Hz) 4.11 (1H, m) 2.71 (1H, ddd, *J*=17.1, 5.6, 2.3 Hz) 2.33–2.26 (2H, m) 1.62 (1H, ddd, *J*=15.6, 11.6, 10.8 Hz); ¹³C NMR (500 MHz, CD₃OD) δ 174.1, 143.5, 129.8, 129.0, 127.4, 65.6, 56.2, 42.7, 41.4; *m/z* (CI, %) 192 (M⁺, 100). HRMS C₁₁H₁₄NO₂ calcd 192.1025, found 192.1028.

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