Asymmetric syntheses of moiramide B and andrimid

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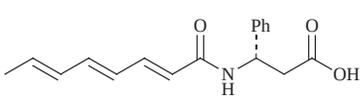
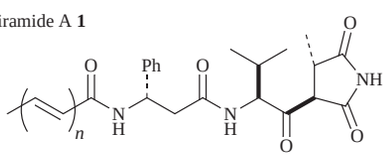
The first highly diastereoselective asymmetric syntheses of moiramide B **2** and andrimid **3** have been achieved using lithium amide (*R*)-**6** and pyrrolidinone auxiliary (*R*)-**9**. Pyrrolidinone auxiliary (*R*)-**9** was used to create the novel (*S*)-3-methyl-*N*-benzyloxysuccinimide (*S*)-**11** which was subsequently acylated with the highly reactive *tert*-butoxycarbonyl-protected *N*-carboxy anhydride of L-valine (Boc-val-NCA) (*S*)-**19** under strongly basic conditions, without racemisation. Lithium amide (*R*)-**6** was used to synthesise homochiral D-β-phenylalanine *tert*-butyl ester **25**.

Introduction

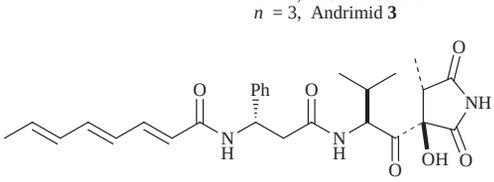
Andrimid **3**, a pseudopeptide antibiotic, was first discovered in 1987 from the culture broth of an intracellular symbiont of *Nilaparvata lugens* (brown planthopper) by Komura and co-workers.[1] More recently it was isolated alongside a family of related antibiotics, moiramide A **1**, B **2** and C **4**, from the



Moiramide A **1**



n = 2, Moiramide B **2**
n = 3, Andrimid **3**



Moiramide C **4**

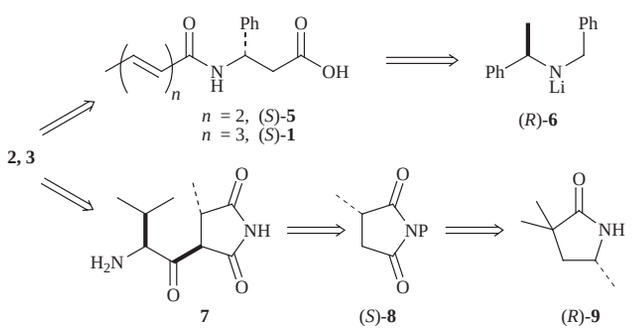
marine bacterium *Pseudomonas fluorescens*.[2] Of the four related compounds only andrimid **3** and moiramide B **2** were found to exhibit potent *in vitro* antibacterial activity against methicillin resistant *Staphylococcus aureus* and a range of other antibiotic-resistant human pathogens.

As part of their structural make-up, andrimid **3** and moiramide B **2** share a D-β-phenylalanine fragment and an acyl succinimide unit bearing a (4*S*)-methyl substituent, which is essential for the observed antimicrobial activity.[3] These interesting structural motifs, combined with the potential to exploit the chiral auxiliaries and methodologies developed within our laboratory, made both **2** and **3** attractive synthetic targets.

Herein, and in conjunction with our recent communication,[4] we wish to report the full experimental details of the first highly diastereoselective asymmetric syntheses of these interesting natural products.

Logical retrosynthetic disconnection of **2** and **3** reveal acyl succinimide fragment **7**, common to both compounds and D-β-phenylalanine derivatives **5** and **1** differing only in the length of the *N*-acyl grouping.

Previous work in our laboratory confirmed that the synthesis of **5** and **1**, using as the key step the highly diastereoselective Michael addition[5] of homochiral lithium amide (*R*)-**6** to a cinnamate ester, would be trivial relative to that of acyl succinimide fragment **7**. However, we envisioned that a successful route to **7** would incorporate the treatment of the kinetic enolate of a suitably *N*-protected (*S*)-2-methyl succinimide **8** with a suitably reactive cationic L-valine source. In turn, it was forecast that homochiral **8** would be readily obtained using the 'Quats' pyrrolidinone auxiliary (*R*)-**9**.[6]



n = 2, (*S*)-**5**
n = 3, (*S*)-**1**

(*R*)-**6**

2, 3

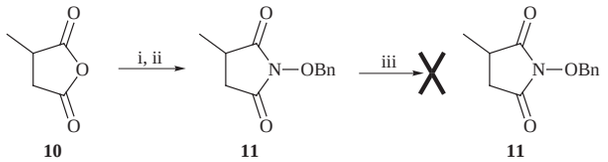
7 (*S*)-**8** (*R*)-**9**

Results and discussion

Our initial attention was focused on the asymmetric synthesis of **7**. However, before this was realised, preliminary studies were performed on a model system. These studies were essential in order to probe enolate formation, stability, reactivity and protecting group compatibility. An extensive review of the literature revealed that succinimide protecting groups compatible with the functionality of the acyl succinimide fragment **7** included *N*-allyl,[7] *N*-*p*-methoxybenzyl,[8] *N*-benzyloxy[9] and *N*-benzyloxymethyl.[10]

Silvie *et al*. recently demonstrated the non-racemising nature of the deprotection conditions required for the removal of the *N*-benzyloxy group in their asymmetric synthesis of (*S*)- and (*R*)-thalidomide.[9] Accordingly, this imide protecting group was chosen for our system. Thus, gram quantities of racemic 2-methyl-*N*-benzyloxysuccinimide **11** were synthesised in 92% yield by the sequential treatment of methylsuccinic anhydride **10** with *O*-benzyl hydroxylamine followed by 1,1′-carbonyldiimidazole (CDI). Treatment of **11** with LiHMDS at −78 °C followed by protic quench after 5 min and aqueous work-up revealed that no starting material remained in the reaction mixture (Scheme 1).

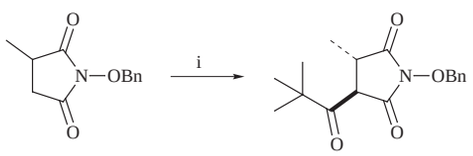
Clearly, the lithium enolate of **11** was decomposing rapidly at −78 °C. Accordingly, the possibility of an *in situ* quench protocol was investigated using trimethylacetyl chloride as the electrophilic component. Thus a concentrated solution of **11** and trimethylacetyl chloride (2.0 equiv.) in THF was slowly



10 **11** **11**

Scheme 1 *Reagents*: i, *O*-benzyl hydroxylamine; ii, CDI; iii, LiHMDS.

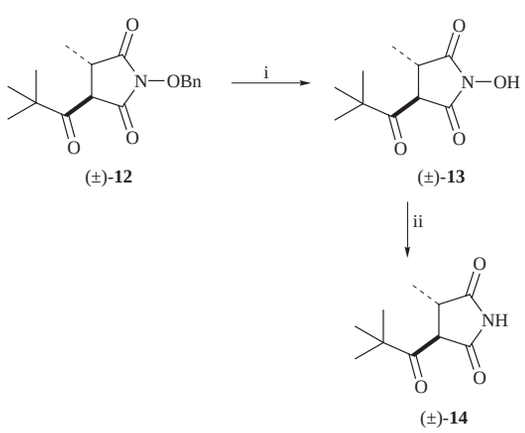
added to a preformed, concentrated solution of LiHMDS (2.3 equiv.) in THF at −78 °C *via* cannula. After 5 min, protic quench and aqueous work-up followed by purification by a single recrystallisation gave the desired *C*-acylated material **12** in a pleasing 93% yield. In $CDCl_3$ at room temperature **12** existed as an 82 : 18 equilibrium mixture of *trans*- and *cis*-forms respectively (Scheme 2).



11 (±)-**12**

Scheme 2 *Reagents*: i, trimethylacetyl chloride, then LiHMDS.

To complete the studies on the model system, efficient removal of the succinimide *N*-benzyloxy group was required. This was achieved by a modification of the two step literature procedure.[9] First, subjection of **12** to standard hydrogenolysis conditions afforded the *N*-hydroxysuccinimide **13** in quantitative yield. Treatment of this material with 2′-bromoacetophenone and triethylamine in acetonitrile at room temperature for 14 h effectively reduced the N–O bond to afford the fully deprotected acyl succinimide **14** in 80% yield. In $CDCl_3$, at room temperature **14** existed as a 94 : 6 equilibrium mixture of *trans*- and *cis*-forms respectively (Scheme 3).

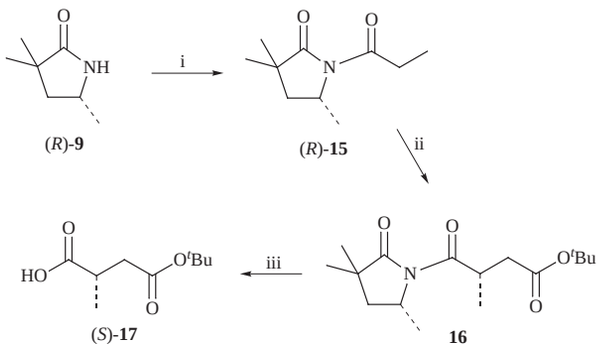


(±)-**12** (±)-**13** (±)-**14**

Scheme 3 *Reagents*: i, H_2, Pd-C; ii, 2′-bromoacetophenone, Et_3N.

The success of the studies on the model system were very encouraging and suggested that our proposed route to the acylsuccinimide fragment **7** was indeed viable. Therefore, an efficient route to homochiral (*S*)-2-methyl-*N*-benzyloxysuccinimide **11** was required to allow investigations into the possibility of a diastereoselective acylation with a suitably reactive electrophilic valine source.

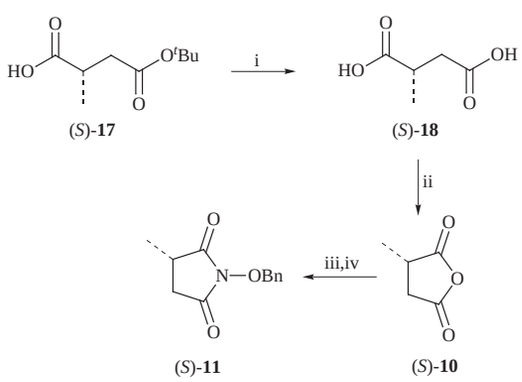
The pyrrolidinone auxiliary (*R*)-**9** has been shown to induce high diastereoselectivities in enolate reactions of attached acyl side chains.[11] This, combined with the mild, non-racemising conditions required to cleave the chiral side chain from the auxiliary, made (*R*)-**9** ideally suited for the synthesis of homochiral (*S*)-2-methyl-*N*-benzyloxysuccinimide (*S*)-**11**. Acylation of the pyrrolidinone auxiliary (*R*)-**9** with butyllithium followed by propionyl chloride afforded the *N*-propionyl pyrrolidinone **15** in 95% yield. Subsequent treatment with LDA at −78 °C and *tert*-butyl bromoacetate afforded the succinate derivative **16** in 92% yield and high diastereoselectivity (>95% de). Hydrolysis of **16** with LiOH led to the synthesis of succinic acid derivative (*S*)-**17** in 89% yield (Scheme 4).



(*R*)-**9** (*R*)-**15** (*S*)-**17** **16**

Scheme 4 *Reagents*: i, BuLi, then propionyl chloride; ii, LDA, then *tert*-butyl bromoacetate; iii, LiOH.

Treatment of (*S*)-**17** with trifluoroacetic acid afforded (*S*)-methylsuccinic acid (*S*)-**18** in quantitative yield. This material was then cyclised to (*S*)-methylsuccinic anhydride (*S*)-**10** $[\alpha]_D^{24}$ −36.3 (*c* 1.77, $CHCl_3$) {lit.,[12] [for (*R*)-enantiomer] $[\alpha]_D^{30}$ +32.6 (*c* 1.77, $CHCl_3$)} with refluxing acetyl chloride in 99% yield. Finally, treatment of (*S*)-**10** with *O*-benzylhydroxylamine followed by 1,1′-carbonyldiimidazole (CDI) afforded (*S*)-2-methyl-*N*-benzyloxysuccinimide (*S*)-**11**, in 95% yield. A ^1H NMR (300 MHz, $CDCl_3$) chiral shift experiment[13] with $Eu(hfc)_3$ showed the ee of (*S*)-**11** to be >98% (Scheme 5).

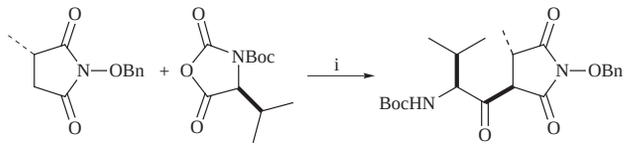


(*S*)-**17** (*S*)-**18** (*S*)-**11** (*S*)-**10**

Scheme 5 *Reagents*: i, TFA; ii, acetyl chloride; iii, *O*-benzylhydroxylamine; iv, CDI.

The desired acylation of (*S*)-**11** was possible using the highly reactive *tert*-butoxycarbonyl-protected *N*-carboxy anhydride of L-valine (Boc-val-NCA)[14] (*S*)-**19** as the electrophilic valine source. Under the optimal reaction conditions investigated, an almost saturated solution of equimolar quantities of (*S*)-**11** and (*S*)-**19** in THF at room temperature was slowly added to a concentrated solution of lithium hexamethyldisilazide (2.5 equiv.) in THF at −78 °C. After stirring for 5 min at this temperature the intense yellow solution was quenched and aqueous work-up afforded a crude yellow solid. Inspection of the crude ^1H NMR spectrum (500 MHz, $CDCl_3$) indicated that the reaction had occurred with minimal racemisation (>98% de) and to ~80% conversion. Purification by chromatography on silica gel afforded the fully protected acylsuccinimide product **20** in 53% yield and the unreacted starting material (*S*)-**11** in 17% yield. In $CDCl_3$ at room temperature **20** existed as an 87 : 9 : 4 equilibrium mixture of *trans*-, enolic- and *cis*-forms respectively (Scheme 6).

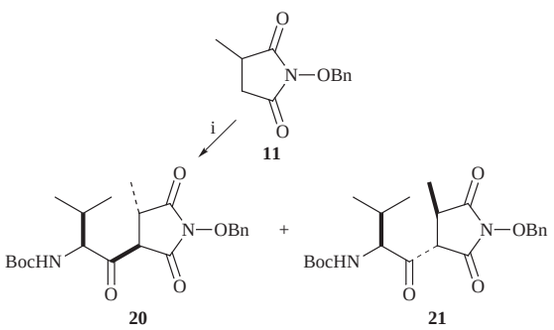
The diastereoselectivity in the above reaction was confirmed by the independent preparation of an authentic sample of the



(*S*)-**11** (*S*)-**19** **20**

Scheme 6 *Reagents*: i, LiHMDS.

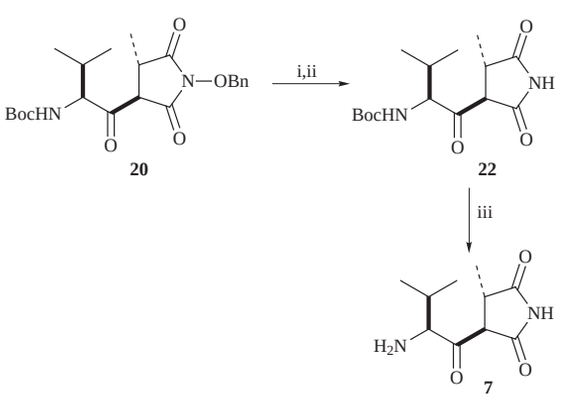
minor diastereoisomer in the acylation reaction. This was achieved in an analogous fashion to the above, using racemic **11**. In this case a 50 : 50 mixture of diastereoisomeric products **20** and **21** was obtained in 61% yield and a diastereomerically pure sample of **21** was isolated by fractional crystallisation. Interestingly, neither an enolic- or *cis*-form could be identified within the ^{1}H NMR spectrum of **21** in $CDCl_3$ at room temperature. This was in contrast to **12**, **14** and **20**, which existed in all cases in an equilibrium with a minor enol- and/or *cis*-form in $CDCl_3$ at room temperature (Scheme 7).



20 **21**

Scheme 7 *Reagents*: i, Boc-val-NCA, then LiHMDS.

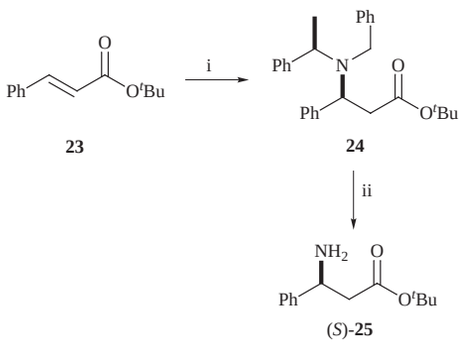
The modest yield in this acylation step was probably due to a competitive base-induced dimerisation reaction of the Boc-val-NCA.[15] However, with **20** in hand, removal of the succinimide protecting group was possible following the optimal conditions devised for the model system. Thus, hydrogenolysis of the benzyl group under standard conditions followed by treatment of the resultant *N*-hydroxy acylsuccinimide with 2′-bromoacetophenone and triethylamine afforded the acyl succinimide **22** in 69% yield over two steps. Finally, quantitative removal of the *tert*-butoxycarbonyl group with trifluoroacetic acid in dichloromethane afforded the desired acyl succinimide **7** as the trifluoroacetate salt (Scheme 8).



20 **22** **7**

Scheme 8 *Reagents*: i, H_2, Pd-C; ii, 2′-bromoacetophenone, Et_3N; iii, TFA.

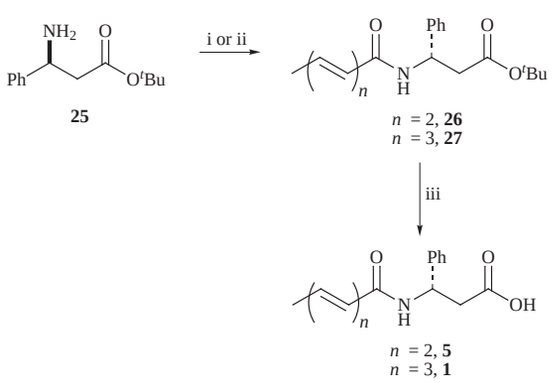
The highly diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-α-methylbenzylamide (*R*)-**6** to α,β-unsaturated esters has been described.[5] Using this protocol, D-β-phenylalanine *tert*-butyl ester (*S*)-**25** $[\alpha]_D^{23}$ −21.3 (*c* 1.0, $CHCl_3$) [lit.,[16] $[\alpha]_D^{20}$ −21.0 (*c* 1.0, $CHCl_3$)] was readily obtained in good overall yield (72%) by the conjugate addition (95% de) of this lithium amide (*R*)-**6** to *tert*-butyl cinnamate **23** and subsequent hydrogenolysis of the conjugate adduct **24**. Derivatisation as the Mosher's amide showed the ee of (*S*)-**25** to be 95% (Scheme 9).



23 **24** (*S*)-**25**

Scheme 9 *Reagents*: i, (*R*)-**6**; ii, H_2, $Pd(OH)_2$.

The syntheses of (*S*)-**5** and (*S*)-**1** were readily completed through the application of standard peptide coupling procedures. In the first case, acylation of (*S*)-**25** with commercially available hexadienoic acid using dicyclohexylcarbodiimide and hydroxybenzotriazole in tetrahydrofuran, followed by hydrolysis of the *tert*-butyl ester (*S*)-**26**, afforded **5** in 80% overall yield. In the second case, a similar sequence was followed using octatrienoic acid. Subsequent hydrolysis of (*S*)-**27** with TFA afforded the desired acid (*S*)-**1**, again in good overall yield (79%) (Scheme 10).



25

n = 2, **26**
n = 3, **27**

n = 2, **5**
n = 3, **1**

Scheme 10 *Reagents*: i, hexadienoic acid, DCC, HOBt; ii, octatrienoic acid, DCC, HOBt; iii, TFA.

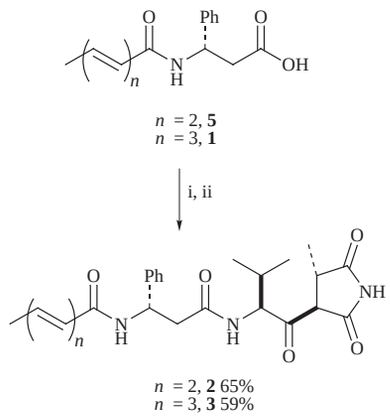
With all the desired fragments in hand the syntheses of moiramide B **2** and andrimid **3** were readily accomplished by employing standard peptide coupling procedures.

Moiramide B **2** was completed by coupling equimolar amounts of fragment (*S*)-**5** and **7** using the BOP reagent (1.0 equiv.) and DMAP (3.0 equiv.) in DMF at 0 °C for 30 min. Purification by chromatography on Sephadex LH-20, reversed-phase silica gel and finally silica gel afforded pure **2** as a colourless amorphous solid in 65% yield.

In an analogous manner to that described above, (*S*)-**1** (1.0 equiv.) and acyl succinimide **7** (1.1 equiv.) were coupled together using the BOP reagent (1.05 equiv.) in DMF at room temperature. Purification by HPLC using ODS as the stationary phase and methanol–water (60 : 40) as the mobile phase afforded pure andrimid **3** as a colourless amorphous solid in 59% yield (Scheme 11).

The ^{1}H NMR (500 MHz, d_6-DMSO), ^{13}C NMR (125 MHz, d_6-DMSO) and CD spectra of synthetic **2** and **3** were in good agreement with the reported data.[2]

In conclusion, the first highly diastereoselective asymmetric syntheses of moiramide B **2** and andrimid **3** have been achieved



Scheme 11 *Reagents*: i, BOP reagent, DMAP; ii, **7**.

using lithium amide (*R*)-**6** and pyrrolidinone auxiliary (*R*)-**9** as two sources of chirality. Also, the highly reactive Boc-val-NCA (*S*)-**19** has for the first time been demonstrated as a useful cationic valine source under strongly basic conditions, with negligible racemisation.

Experimental

Optical rotations were recorded using a Perkin-Elmer 241 which has a thermally jacketed 10 cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. CD spectra were recorded using a JASCO J720 Spectropolarimeter and were performed at ambient temperature and are given in units of deg L mol^{-1} cm^{-1}. Elemental analyses were obtained by the Dyson Perrins analytical department using a Carlo Erba 1106 analyser. Melting points were recorded using a Gallenkamp hot stage apparatus and are uncorrected. Infra-red spectra were obtained using a Perkin-Elmer 1750 spectrophotometer; solid samples as KBr discs and liquid samples as a thin film between sodium chloride plates. NMR spectra were recorded using either a Bruker AM500 (^{1}H; 500.13 MHz and ^{13}C; 125.8 MHz), WH 300 (^{1}H; 300.13 MHz), AM200 (^{1}H; 200 MHz and ^{13}C; 50.3 MHz) or Varian Gemini 200 (^{1}H; 200 MHz and ^{13}C; 50.32 MHz) spectrometer. All spectra were recorded using deuteriochloroform as solvent and internally referenced to residual protiochloroform (δ_H 7.27 and δ_C 77.0) unless otherwise stated. ^{1}H NMR spectra were run on a Bruker WH 300 spectrometer unless otherwise stated. ^{13}C NMR were obtained with DEPT editing or assigned by analogy with spectra so recorded. All chemical shifts are given in parts per million relative to tetramethylsilane (δ_H 0.00) and coupling constants (*J*) are given in Hz. Mass spectra were obtained in the Dyson Perrins analytical department using chemical ionisation (CI) or electronic ionisation (EI) on a VG MASSLAB VG 20-250 or on a Open Linx Micromass Platform 1 using APCI$^+$ or APCI$^-$. High resolution mass spectra were recorded using chemical ionisation (CI) on a VG-AutoSpec Instrument. Flash chromatography was carried out using silica gel (Kieselgel 60), Sephadex LH-20 or octadeca silane (ODS). High performance liquid chromatography (HPLC) was performed using a Waters 600E with a Waters 490E programmable multiwavelength detector set at 219 nm, using octadeca silane as the stationary phase with the mobile phase and flow rate as described. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Acetonitrile and dichloromethane were heated at reflux for 1 h over calcium hydride prior to distillation. Methanol was distilled from glass. *N*,*N*-Dimethylformamide was distilled under reduced pressure prior to use and stored over 4 Å molecular sieves. Petroleum ether refers to that fraction of petroleum ether boiling between 40 and 60 °C and was redistilled before use. All other solvents were used as received. Reactions were performed under an atmosphere of dry nitrogen unless otherwise stated.

2-Methyl-*N*-benzyloxysuccinimide (±)-11

To a solution of methylsuccinic anhydride (±)-**10** (1.200 g, 10.53 mmol) and *O*-benzylhydroxylamine hydrochloride (1.764 g, 11.05 mmol) in dichloromethane (100 mL) at room temperature was added *N*-methylmorpholine (2.50 mL, 11.58 mmol) dropwise *via* pipette. The reaction mixture was stirred overnight at room temperature before 1,1′-carbonyldiimidazole (1.878 g, 11.58 mmol) was added in one portion. After stirring for 2 h, the reaction mixture was heated at reflux for 30 min, cooled to room temperature, washed with aqueous hydrochloric acid (10%, 2 × 50 mL) then brine (40 mL), dried (magnesium sulfate), filtered and finally concentrated *in vacuo* to afford a white solid residue. Recrystallisation of this material from ethyl acetate–petroleum ether afforded the title compound (±)-**11** as fine colourless needles (2.125 g, 92%), mp 97–98 °C; ν_{max}(film)/cm^{-1} 1713s (C=O); δ_H 7.49–7.33 (5H, m, Ph), 5.12 (2H, s, PhCH_2), 2.83 (1H, dd, *J* 17.2 and 8.8, CH_2CO), 2.82–2.69 (1H, m, C*H*CH$_3$), 2.20 (1H, dd, *J* 17.2 and 3.4, CH_2CO), 1.24 (3H, d, *J* 7.1, CHCH_3); δ_C 175.0 and 171.0 (*C*=O), 133.5 (Ph:C$_{ipso}$), 130.2 (Ph:C), 129.6 (Ph:C$_{para}$), 128.7 (Ph:C), 78.5 (PhCH_2), 33.6 (CH_2CO), 31.8 (*C*HCH$_3$), 16.5 (CH*C*H$_3$); *m*/*z* (CI, NH$_3$) 237 (100%, MNH$_4^+$) 220 (13%, MH$^+$), 108 (30%).

Elemental analysis was obtained on homochiral (*S*)-**11**.

trans-1-Benzyloxy-3-(2′,2′-dimethyl-1′-oxopropyl)-4-methylpyrrolidine-2,5-dione (±)-12

To a stirred solution of hexamethyldisilazane (5.27 mL, 25.0 mmol) in THF (10 mL) at −78 °C was added butyllithium (15.03 mL, 23.0 mmol) *via* syringe. The resultant colourless solution was stirred at −78 °C (5 min), slowly warmed to 0 °C (10 min) and subsequently recooled to −78 °C. A solution of **11** (2.190 g, 10.0 mmol) and trimethylacetyl chloride (2.46 mL, 20 mmol) in THF (20 mL) was then added dropwise *via* cannula to the lithium amide solution. After stirring for 5 min at −78 °C the bright yellow reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (5 mL) and allowed to warm to room temperature. The reaction mixture was partitioned between dichloromethane (50 mL) and distilled water (30 mL) and further extracted with dichloromethane (2 × 50 mL). The combined organic portions were washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield the crude product as a yellow solid. A single recrystallisation of this material from diethyl ether–pentane afforded the title compound (±)-**12** as colourless plates (2.186 g, 93%), mp 84–85 °C (Found: C, 67.4; H, 6.8; N, 4.4. $C_{17}H_{21}NO_4$ requires C, 67.3; H, 7.0; N, 4.6%); ν_{max}(KBr)/cm^{-1} 1786s, 1727s and 1702s (C=O); δ_H 7.51–7.36 (5H, m, Ph), 5.09 (2H, s, PhCH_2), 3.85 (1H, d, *J* 4.1, COC*H*CO), 2.90 (1H, dq, *J* 7.5 and 4.1, C*H*CH$_3$), 1.26 (3H, d, *J* 7.5, CHCH_3), 1.22 [9H, s, C(CH_3)$_3$]; δ_C (50 MHz) 209.8, 173.9 and 168.0 (*C*=O), 133.3 (Ph:C$_{ipso}$), 130.3, 129.7 and 128.7 (Ph), 78.9 (Ph*C*H$_2$), 52.4 (CO*C*HCO), 45.0 [*C*(CH$_3$)$_3$], 37.6 (*C*HCH$_3$), 25.3 [C(*C*H$_3$)$_3$], 15.3 (CH*C*H$_3$); *m*/*z* (APCI$^-$) 302 (100%, M − H$^+$), 211 (6%), 194 (20%).

In CDCl$_3$ at room temperature, **12** existed in equilibrium with a minor *cis*-form (*trans*:*cis* = 82:18). Selected NMR data for minor *cis*-form; δ_H 4.40 (1H, d, *J* 8.1, COC*H*CO).

trans-3-(2′,2′-Dimethyl-1′-oxopropyl)-1-hydroxy-4-methylpyrrolidine-2,5-dione (±)-13

To a solution of (±)-**12** (1.118 g, 3.69 mmol) in degassed methanol–THF (1:1, 40 mL), under an inert atmosphere of nitrogen in a round-bottom flask, was cautiously added Pd-C (0.220 g, 20%). The flask was fitted with a balloon filled with hydrogen. The heterogeneous solution was vigorously stirred for 1 h at room temperature before the balloon was removed and the reaction mixture filtered through a short plug of

Celite®. The Celite® pad was washed with a small amount of methanol and the filtrate concentrated *in vacuo* to yield a white solid. Recrystallisation of this material from diethyl ether–petroleum ether afforded the title compound (±)-**13** as fine colourless needles (0.777 g, 99%), mp 94–95 °C (Found: C, 56.2; H, 7.2; N, 6.6. $C_{10}H_{15}NO_4$ requires C, 56.3; H, 7.1; N, 6.6%); ν_{max}(KBr)/cm^{-1} 3544m and 3454m (O–H), 1790m, 1719s and 1698s (C=O); δ_H (d_6-DMSO) 10.92 (1H, br s, O*H*), 4.39 (1H, d, *J* 4.2, COC*H*CO), 2.82 (1H, dq, *J* 7.2 and 4.2, C*H*CH$_3$), 1.24 (3H, d, *J* 7.4, CHC*H*$_3$), 1.13 [9H, s, C(C*H*$_3$)$_3$]; δ_C (d_6-DMSO) 212.0, 175.6 and 170.2 (*C*=O), 51.9 (CO*C*HCO), 45.0 [*C*(CH$_3$)$_3$], 37.8 (*C*HCH$_3$), 25.1 [C(*C*H$_3$)$_3$], 15.1 (CH*C*H$_3$); *m*/*z* (APCI$^-$) 212 (100%, M − H$^+$).

trans-3-(2′,2′-Dimethyl-1′-oxopropyl)-4-methylpyrrolidine-2,5-dione (±)-14

To a stirred solution of (±)-**13** (0.109 g, 0.51 mmol) in acetonitrile (25 mL) at room temperature was added 2-bromoacetophenone (0.101 g, 0.51 mmol) in one portion. A solution of triethylamine (0.057 g, 0.56 mmol) in acetonitrile (5 mL) was then added dropwise over 2 h and the reaction mixture was stirred at room temperature for a further 14 h before the volatiles were removed *in vacuo*. The residual material was partitioned between diethyl ether (20 mL) and aqueous hydrochloric acid (5%, 20 mL) and further extracted with diethyl (2 × 20 mL). The combined organic portions were washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield a yellow solid. In order to remove aromatic side products and impurities this material was repeatedly (×4) passed through a short plug of activated carbon, eluting with diethyl ether. Concentration *in vacuo* and further purification of the resulting colourless solid by recrystallisation from diethyl ether–petroleum ether afforded the title compound (±)-**14** as colourless crystals (0.102 g, 80%), mp 110–111 °C (Found: C, 61.2; H, 7.55; N, 6.8. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.7; N, 7.1%); ν_{max}(KBr)/cm^{-1} 1783s, 1746s and 1707s (C=O); δ_H 9.17 (1H, br s, N*H*), 4.02 (1H, d, *J* 5.0, COC*H*CO), 3.04 (1H, dq, *J* 7.4 and 5.0, C*H*CH$_3$), 1.32 (3H, d, *J* 7.4, CHC*H*$_3$), 1.20 [9H, s, C(C*H*$_3$)$_3$]; δ_C (50 MHz) 180.4 and 174.2 (*C*=O), 56.2 (CO*C*HCO), 45.0 [*C*(CH$_3$)$_3$], 41.8 (*C*HCH$_3$), 25.3 [C(*C*H$_3$)$_3$], 15.0 (CH*C*H$_3$); *m*/*z* (APCI$^-$) 196 (100%, M − H$^+$).

In $CDCl_3$ at room temperature, **14** existed in equilibrium with a minor *cis*-form (*trans*:*cis* = 94:6). Selected NMR data for minor *cis*-form; δ_H 4.48 (1H, d, *J* 8.5, COC*H*CO).

(5*R*)-1-(1′-Oxopropyl)-3,3,5-trimethylpyrrolidin-2-one (*R*)-15[17]

Butyllithium (26.3 mL, 39.4 mmol) was slowly added to a stirred solution of pyrrolidinone (*R*)-**9** (5.000 g, 39.37 mmol) in THF (120 mL) at −78 °C under a nitrogen atmosphere. Stirring was maintained at this temperature for a further 15 min before freshly distilled propionyl chloride (3.83 g, 41.34 mmol) was added dropwise *via* syringe. The reaction mixture was slowly warmed to room temperature (15 min), quenched with saturated aqueous ammonium chloride solution (~10 mL) and concentrated *in vacuo*. The residual material was partitioned between dichloromethane (80 mL) and distilled water (80 mL), and further extracted with dichloromethane (2 × 80 mL). The combined organic portions were washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield a crude yellow oil. Purification by silica gel chromatography [petroleum ether–diethyl ether (7:1)] afforded the title compound (*R*)-**15** as a colourless oil (6.869 g, 95%), $[\alpha]_D^{23}$ −101.0 (*c* 0.50, $CHCl_3$); lit.[17] $[\alpha]_D^{23}$ −101.0 (*c* 0.5, $CHCl_3$); δ_H (lit.[17]) 4.29–4.18 (1H, m, C*H*CH$_3$), 3.01–2.78 (2H, m, C*H*$_2$CH$_3$), 2.10 (1H, dd, *J* 13.2 and 8.5, C*H*$_2$CH), 1.56 (1H, dd, *J* 13.2 and 5.2, C*H*$_2$CH), 1.36 (3H, d, *J* 6.4, CHC*H*$_3$), 1.26 [3H, s, C(C*H*$_3$)$_2$], 1.17 [3H, s, C(C*H*$_3$)$_2$], 1.12 (3H, t, *J* 7.3, CH$_2$C*H*$_3$).

(2′*S*,5*R*)-1-{2′-[(*tert*-Butoxycarbonyl)methyl]propionyl}-3,3,5-trimethylpyrrolidin-2-one (2′*S*,5*R*)-16

To a stirred solution of diisopropylamine (2.71 mL, 19.35 mmol) in THF (60 mL) at −78 °C was added butyllithium (11.3 mL, 16.93 mmol) *via* syringe. The resultant colourless solution was stirred at −78 °C (5 min), slowly warmed to 0 °C (10 min) and subsequently recooled to −78 °C. A solution of (*R*)-**15** (2.951 g, 16.13 mmol) in THF (10 mL) was then added dropwise *via* cannula to the lithium amide solution. Stirring was maintained at this temperature for 1 h before *tert*-butyl bromoacetate (3.12 mL, 19.35 mmol) was added neat *via* syringe. The reaction mixture was slowly warmed to room temperature overnight, quenched with saturated aqueous ammonium chloride solution (5 mL) and concentrated *in vacuo*. The residual material was partitioned between dichloromethane (80 mL) and distilled water (80 mL), and further extracted with dichloromethane (2 × 80 mL). The combined organic portions were washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield a crude yellow oil. Inspection of the crude ^{1}H NMR spectrum (500 MHz, $CDCl_3$) indicated that the major reaction product had formed with a diastereomeric excess of >95%. An accurate assignment of the reaction diastereoselectivity was not possible due to the lack of an authentic sample of minor diastereoisomeric product. Purification by silica gel chromatography [petroleum ether–diethyl ether (9:1)] afforded the title compound (2′*S*,5*R*)-**16** as a mixture of diastereoisomers (>95% de) and as a colourless oil (4.412 g, 92%) (Found: C, 64.6; H, 9.0; N, 4.9. $C_{16}H_{27}NO_4$ requires C, 64.6; H, 9.15; N, 4.7%); $[\alpha]_D^{23}$ −29.1 (*c* 1.00, $CHCl_3$); ν_{max}(film)/cm^{-1} 1733s (OC=O), 1697s (NC=O); δ_H 4.28–4.17 (1H, m, C*H*N), 4.05–3.93 (1H, m, C*H*CO), 2.77 (1H, dd, *J* 16.5 and 9.4, C*H*$_2$CO$_2$), 2.31 (1H, dd, *J* 16.5 and 5.2, C*H*$_2$CO$_2$), 2.09 (1H, dd, *J* 13.0 and 8.5, C*H*$_2$CHN), 1.57 (1H, dd, *J* 13.0 and 5.5, C*H*$_2$CHN), 1.40 [9H, s, C(C*H*$_3$)$_3$], 1.35 (3H, d, *J* 6.2, CHC*H*$_3$), 1.28 [3H, s, (C*H*$_3$)$_2$C], 1.17 [3H, s, (C*H*$_3$)$_2$C], 1.12 (3H, d, *J* 6.8, CHC*H*$_3$); δ_C (50 MHz) 180.8 (N*C*=O), 178.1 (CH*C*=O), 171.5 (O*C*=O), 80.3 [*C*(CH$_3$)$_3$], 50.0 (*C*HN), 41.9 [(CH$_3$)$_2$*C*], 40.3 and 39.2 (*C*H$_2$), 36.1 (*C*HCO), 27.9 [C(*C*H$_3$)$_3$], 26.2 [C(*C*H$_3$)$_2$], 25.8 [C(*C*H$_3$)$_2$], 20.9 and 16.4 (CH*C*H$_3$); *m*/*z* (APCI$^+$) 320 (10%, MNa$^+$), 242 (20%, MH$^+$ − C$_4$H$_8$), 224 (15%), 128 (100%, C$_7$H$_{14}$NO).

(*S*)-2-[(*tert*-Butoxycarbonyl)methyl]propionic acid (*S*)-17

To a stirred solution of **16** (2.379 g, 8.01 mmol) in THF (45 mL) at 0 °C was added a solution of lithium hydroxide (0.840 g, 20.0 mmol) in distilled water (15 mL) dropwise *via* pipette. The reaction mixture was stirred at 0 °C for 5 h and at room temperature for 2 h before saturated aqueous sodium hydrogen carbonate solution (15 mL) was added. The aqueous layer was extracted with diethyl ether (4 × 40 mL) and the combined organic portions dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a white solid. This material was purified by sublimation (0.1 mmHg, 50 °C) to afford the pyrrolidinone auxiliary (*R*)-**9** (0.867 g, 85%) as colourless needles.

The aqueous layer was then acidified (pH 1) with concentrated aqueous hydrochloric acid and the resulting precipitate extracted with ethyl acetate (3 × 50 mL). The combined organic portions were washed with brine (40 mL), dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil. This material was purified by chromatography on silica gel [diethyl ether (100%)] to afford the title compound (*S*)-**17** (1.337 g, 89%) as a colourless oil which crystallised on standing, mp 52–54 °C; lit.[18] for the racemate, mp 38–40 °C (Found: C, 57.5; H, 8.8. $C_9H_{16}O_4$ requires C, 57.4; H, 8.6%); $[\alpha]_D^{23}$ −7.0 (*c* 0.86, $CHCl_3$); ν_{max}(film)/cm^{-1} 1729 and 1711 (OC=O); δ_H 2.96-2.84 (1 H, m, C*H*CH$_3$), 2.64 (1H, dd, *J* 16.4 and 8.0, C*H*$_2$CO$_2$), 2.36 (1H, dd, *J* 16.4 and 5.9, C*H*$_2$CO$_2$), 1.44 [9H, s, C(C*H*$_3$)$_3$], 1.24 (3H, d, *J* 7.2, CHC*H*$_3$); δ_C (50 MHz) 182.2 (CH*C*=O), 171.3 (CH$_2$*C*=O), 81.0 [*C*(CH$_3$)$_3$], 38.6 (*C*H$_2$CO$_2$), 35.8

(*C*HCH$_3$), 27.9 [C(*C*H$_3$)$_3$], 16.5 (CH*C*H$_3$); *m*/*z* (APCI$^-$) 173 (6%), 131 (100%, [M − H$^+$ − (C$_4$H$_8$)].

(*S*)-Methylsuccinic acid (*S*)-18[19]

To acid (*S*)-**17** (1.200 g, 6.383 mmol) in a round-bottomed flask at room temperature was added neat trifluoroacetic acid (10 mL) *via* pipette. The reaction mixture was stirred for 90 min before the volatiles were removed *in vacuo* to afford essentially pure title compound (*S*)-**18** (0.844 g, ~100%) as a white solid. A small amount of this material was sublimed (0.1 mmHg, 50 °C) for analysis, mp 109–111 °C; lit.[19] mp 116–117 °C; $[\alpha]_D^{23}$ −22.0 (*c* 0.20, acetone); lit.[19] $[\alpha]_D$-16.0 (*c* 4.4, EtOH); δ_H (300 MHz, d$_6$-DMSO) 12.16 (2H, s, O*H*), 2.72–2.60 (1H, m, C*H*CH$_3$), 2.49 (1H, dd, *J* 16.6 and 8.9, C*H*$_2$CO$_2$), 2.30 (1H, dd, *J* 16.6 and 5.6, C*H*$_2$CO$_2$), 1.10 (3H, d, *J* 7.2, CHC*H*$_3$).

(*S*)-Methylsuccinic anhydride (*S*)-10[12,20]

To succinic acid (*S*)-**18** (0.750 g, 5.68 mmol) in a round-bottomed flask at room temperature was added neat acetyl chloride *via* pipette. The flask was fitted with a condenser carrying a calcium chloride drying tube and the mixture was heated at reflux for 3.5 h. On cooling, the volatiles were removed *in vacuo* to afford essentially pure title compound (*S*)-**10** (0.640 g, 99%) as an off-white solid. A small amount of this material was sublimed (0.1 mmHg, 50 °C) for analysis, mp 61–63 °C; lit.[20] mp 65–66 °C; $[\alpha]_D^{24}$ −36.3 (*c* 1.77, CHCl$_3$); lit.[20] [for (*R*)-enantiomer] $[\alpha]_D^{20}$ +32.1 (*c* 3, CHCl$_3$); lit.[12] [for (*R*)-enantiomer] $[\alpha]_D^{30}$ +32.6 (*c* 1.77, CHCl$_3$); δ_H 3.26–3.12 (2H, m, C*H*CH$_3$ and C*H*$_2$CO$_2$), 2.70–2.58 (1H, m, C*H*$_2$CO), 1.45 (3H, d, *J* 6.7, CHC*H*$_3$).

(*S*)-2-Methyl-*N*-benzyloxysuccinimide (*S*)-11

To a solution of succinic anhydride (*S*)-**10** (0.557 g, 4.886 mmol) and *O*-benzylhydroxylamine hydrochloride (0.819 g, 5.130 mmol) in dichloromethane (50 mL) at room temperature was added *N*-methylmorpholine (0.59 mL, 5.375 mmol) dropwise *via* pipette. The reaction mixture was stirred overnight at room temperature before 1,1′-carbonyldiimidazole (0.871 g, 5.375 mmol) was added in one portion. After stirring for 1.5 h, the reaction mixture was heated at reflux for 30 min, cooled to room temperature, washed with aqueous hydrochloric acid (5%, 2 × 50 mL) then brine (40 mL), dried (magnesium sulfate), filtered and finally concentrated *in vacuo* to afford a white solid residue. Recrystallisation of this material from ethyl acetate–petroleum ether afforded the title compound (*S*)-**11** as fine colourless needles (1.017 g, 95%), mp 118–119 °C (Found: C, 65.8; H, 5.9; N, 6.5. C$_{12}$H$_{13}$NO$_3$ requires C, 65.7; H, 6.0; N, 6.4%); $[\alpha]_D^{23}$ −4.9 (*c* 0.72, CHCl$_3$).

(3*R*,4*S*,2′*S*)-*trans*-1-Benzyloxy-3-[2′-(*tert*-butoxycarbonyl)-amino-3′-methyl-1′-oxobutyl]-4-methylsuccinimide (3*R*,4*S*,2′*S*)-20

To a stirred solution of hexamethyldisilazane (1.77 mL, 8.397 mmol) in THF (4 mL) at −78 °C was added butyllithium (4.37 mL, 6.99 mmol) *via* syringe. The resultant colourless solution was stirred at −78 °C (5 min), slowly warmed to 0 °C (10 min) and subsequently recooled to −78 °C. A solution of (*S*)-**11** (0.613 g, 2.799 mmol) and Boc-val-NCA (*S*)-**19** (0.681 g, 2.799 mmol) in THF (7 mL) was then added dropwise *via* cannula to the lithium amide solution. After stirring for 5 min at −78 °C the bright yellow reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (5 mL) and allowed to warm to room temperature. The reaction mixture was partitioned between diethyl ether (20 mL) and distilled water (10 mL) and further extracted with diethyl ether (2 × 20 mL). The combined organic portions were washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield a white solid residue. Inspection of the crude ^{1}H NMR spectrum (500 MHz, CDCl$_3$) indicated the presence of two diastereoisomeric products **20** and **21**. Integration of the doublet of doublets resonance at δ 4.44 (1H, dd, *J* 8.7 and 4.8, C*H*N) for the major diastereoisomer **20** and comparison with that at δ 4.26 (1H, dd, *J* 8.3 and 5.4, C*H*N) for the minor diastereoisomer **21** indicated the reaction had occurred with a dr of 120:1 (>98% de). This material was purified by flash chromatography on silica gel [ethyl acetate–petroleum ether (1:3)] eluting first the less polar title compound **20** (0.621 g, 53%) followed by the more polar starting material (*S*)-**11** (0.104 g, 17%) as colourless solids, mp 120–121 °C (Found: C, 63.3; H, 7.4; N, 6.8. C$_{22}$H$_{30}$N$_2$O$_6$ requires C, 63.1; H, 7.2; N, 6.7%); $[\alpha]_D^{23}$ −33.9 (*c* 0.70, CHCl$_3$); ν_{max}(KBr)/cm^{-1} 3364s (N–H), 1786m, 1733s and 1698s (C=O); δ_H 7.44-7.36 (5H, m, Ph), 5.57 (1H, br d, *J* 8.1, N*H*), 5.10 (2H, s, PhC*H*$_2$), 4.44 (1H, dd, *J* 8.1 and 4.8, C*H*N), 3.70 (1H, d, *J* 4.4, COC*H*CO), 3.24 (1H, dq, *J* 7.4 and 4.4, C*H*CH$_3$), 2.36 [1H, m, C*H*(CH$_3$)$_2$], 1.46 [9H, s, (C(C*H*$_3$)$_3$], 1.24 (3H, d, *J* 7.4, CHC*H*$_3$), 1.00 [3H, d, *J* 6.6, CH(C*H*$_3$)$_2$], 0.78 [3H, d, *J* 6.8, CH(C*H*$_3$)$_2$]; δ_C (50 MHz) 201.9 (CH*C*OCH), 173.0, 166.6 and 156.0 (N*C*=O), 132.9 (Ph:C$_{ipso}$), 130.1, 129.6 and 128.5 (Ph), 80.3 [*C*(CH$_3$)$_3$], 78.7 (Ph*C*H$_2$), 65.1 (*C*HN), 55.1 (CO*C*HCO), 34.5 (*C*HCH$_3$), 29.7 [*C*H(CH$_3$)$_2$], 28.3 [C(*C*H$_3$)$_3$], 19.6, 17.2 and 15.5 (*C*H$_3$); *m*/*z* (APCI$^+$) 441 (4%, MNa$^+$), 319 [100%, MH$^+$ − (C$_4$H$_8$+CO$_2$)], 196 (12%).

In CDCl$_3$ at room temperature, **20** existed in equilibrium with minor enol- and *cis*-forms (*trans*:enol:*cis* = 87:9:4). Selected NMR data for minor enol-form; δ_H 11.02 (1H, br, O*H*), 3.98 (1H, t, *J* 9.5, C*H*N), 3.17 (1H, q, *J* 7.2, C*H*CH$_3$). Selected NMR data for minor *cis*-form; δ_H 4.18 (1H, d, *J* 8.8, COC*H*CO).

(3*S*,4*R*,2′*S*)-1-Benzyloxy-3-[2′-(*tert*-butoxycarbonyl)amino-3′-methyl-1′-oxobutyl]-4-methylsuccinimide (3*S*,4*R*,2′*S*)-21

To a stirred solution of hexamethyldisilazane (1.40 mL, 6.59 mmol) in THF (4 mL) at −78 °C was added butyllithium (2.35 mL, 5.80 mmol) *via* syringe. The resultant colourless solution was stirred at −78 °C (5 min), slowly warmed to 0 °C (10 min) and subsequently recooled to −78 °C. A solution of (±)-**11** (0.577 g, 2.635 mmol) and Boc-Val-NCA (*S*)-**19** (0.670 g, 2.757 mmol) in THF (5 mL) was then added dropwise *via* cannula to the lithium amide solution. After stirring for 5 min at −78 °C the bright yellow reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (5 mL) and allowed to warm to room temperature. The reaction mixture was partitioned between dichloromethane (20 mL) and distilled water (10 mL) and further extracted with dichloromethane (2 × 20 mL). The combined organic portions were washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield a white solid. Purification by silica gel chromatography [petroleum ether–ethyl acetate (3:1)] afforded the title compound **21** and **20** as a 1:1 mixture of diastereoisomers (0.672 g, 61%). Fractional recrystallisation of this material from ethyl acetate–petroleum ether afforded diastereomerically pure **21** (0.088 g) for analysis, mp 95–97 °C (Found: C, 63.1; H, 7.2; N, 6.6. C$_{22}$H$_{30}$N$_2$O$_6$ requires C, 63.1; H, 7.2; N, 6.7%); $[\alpha]_D^{23}$ −20.2 (*c* 0.51, CHCl$_3$); ν_{max}(KBr)/cm^{-1} 3354s (N–H), 1734s, 1713s and 1683s (C=O); δ_H 7.47–7.36 (5H, m, Ph), 5.11 (2H, s, PhC*H*$_2$), 4.93 (1H, d, *J* 8.2, N*H*), 4.26 (1H, dd, *J* 8.2 and 5.4, C*H*N), 3.70 (1H, d, *J* 4.3, COC*H*CO), 3.09 (1H, dq, *J* 7.4 and 4.3, C*H*CH$_3$), 2.34–2.26 [1H, m, CH(CH$_3$)$_2$], 1.43 [9H, s, (C(C*H*$_3$)$_3$], 1.28 (3H, d, *J* 7.4, CHC*H*$_3$), 1.00 [3H, d, *J* 6.7, C*H*(CH$_3$)$_2$], 0.87 [3H, d, *J* 6.9, CH(C*H*$_3$)$_2$]; δ_C (125 MHz) 201.7 (CH*C*OCH), 173.2, 166.9 and 155.9 (N*C*=O), 133.0 (Ph:C$_{ipso}$), 130.1, 129.5 and 128.5 (Ph), 80.6 [*C*(CH$_3$)$_3$], 78.7 (Ph*C*H$_2$), 64.7 (*C*HN), 56.2 (CO*C*HCO) 35.7 (*C*HCH$_3$), 28.2 [C(*C*H$_3$)$_3$], 27.8 [CH(CH$_3$)$_2$], 20.1, 17.1 and 15.8 (*C*H$_3$); *m*/*z* (APCI$^+$) 441 (10%, MNa$^+$), 363 (7%, MH$^+$ − C$_4$H$_8$), 319 [100%, MH$^+$ − (C$_4$H$_8$+CO$_2$)], 196 (16%), 168 (26%).

(3*R*,4*S*,2′*S*)-3-[2′-(*tert*-Butoxycarbonyl)amino-3′-methyl-1′-oxobutyl]-4-methylsuccinimide (3*R*,4*S*,2′*S*)-22

To a solution of **20** (0.286 g, 0.684 mmol) in degassed methanol (25 mL), under an inert atmosphere of nitrogen in a round-bottom flask, was cautiously added palladium on carbon (0.057 g, 20%) and the flask was fitted with a balloon filled with hydrogen. The heterogeneous solution was vigorously stirred for 1 h at room temperature before the balloon was removed and the reaction mixture filtered through a short plug of Celite®. The Celite® pad was washed with a small amount of methanol and the filtrate concentrated *in vacuo* to yield a colourless oil (0.227 g).

This material was dissolved in acetonitrile (2 mL) and subsequently added to a stirred solution of 2-bromoacetophenone (0.125 g, 0.684 mmol) in acetonitrile (33 mL) at room temperature. A solution of triethylamine (0.104 g, 1.03 mmol) in acetonitrile (7 mL) was then added dropwise over 2 h and the reaction mixture was stirred at room temperature for a further 10 h before the volatiles were removed *in vacuo*. The residual material was partitioned between dichloromethane (20 mL) and aqueous hydrochloric acid (5%, 20 mL) and further extracted with dichloromethane (2 × 20 mL). The combined organic portions were washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield a yellow oil. In order to remove aromatic side products and impurities, this material was repeatedly passed through short plugs of activated carbon, eluting with diethyl ether. Concentration *in vacuo* and further purification of the resulting material by flash chromatography on silica gel [ethyl acetate–petroleum ether (1:1)] afforded a colourless oil which crystallised on standing. Recrystallisation of this material from diethyl ether–pentane afforded the title compound **22** as colourless needles (0.147 g, 69%), mp 105–106 °C (Found: C, 57.4; H, 7.9; N, 8.8. $C_{15}H_{24}N_2O_5$ requires C, 57.7; H, 7.7; N, 9.0%); $[\alpha]_D^{23}$ −41.8 (*c* 0.66, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1787m, 1736s, 1696s and 1672s (C=O); δ_H 8.09 (1H, br s, N*H*$_{imide}$), 5.58 (1H, br d, *J* 8.9, N*H*$_{carbamate}$), 4.55 (1H, dd, *J* 8.9 and 4.4, C*H*N), 3.90 (1H, d, *J* 5.4, COC*H*CO), 3.44 (1H, dq, *J* 7.4 and 5.4, C*H*CH$_3$), 2.47–2.30 [1H, m, C*H*(CH$_3$)$_2$] 1.46 [9H, s, C(C*H*$_3$)$_3$], 1.32 (3H, d, *J* 7.4, CHC*H*$_3$), 1.03 [3H, d, *J* 6.7, CH(C*H*$_3$)$_2$], 0.81 [3H, d, *J* 6.9, CH(C*H*$_3$)$_2$]; δ_C (125 MHz) 202.1 (CH*C*OCH), 179.9, 172.8 and 156.4 (N*C*=O), 80.3 [*C*(CH$_3$)$_3$], 64.8 (*C*HN), 58.9 (CO*C*HCO), 38.3 (*C*HCH$_3$), 29.6 [C(*C*H$_3$)$_3$], 28.2 [*C*H(CH$_3$)$_2$], 19.5, 16.7 and 15.1 (*C*H$_3$); *m*/*z* (APCI$^-$) 311 (100%, M − H$^+$), 211 [12%, M − H$^+$ − (C$_4$H$_8$+CO$_2$)].

(3*R*,4*S*,2′*S*)-3-(2′-Amino-3′-methyl-1′-oxobutyl)-4-methylsuccinimide trifluoroacetate salt (3*R*,4*S*,2′*S*)-7

To a stirred solution of **22** (0.100 g, 0.321 mmol) in dichloromethane (3 mL) at room temperature was added trifluoroacetic acid (3 mL) neat *via* pipette. The reaction mixture was stirred for 15 min before the volatiles were removed *in vacuo* to afford essentially pure title compound **7** (0.105 g, 100%) as a pink foam, $[\alpha]_D^{22}$ +18.5 (*c* 0.665, MeOH); ν_{max}(film)/cm^{-1} 3211br (NH), 1773m and 1696s (C=O); δ_H (500 MHz, d$_6$-DMSO) 11.50 (1H, br, N*H*$_{imide}$), 8.25 (3H, br, N*H*$_3$), 4.51–4.49 (1H, m, C*H*N), 4.28 (1H, d, *J* 6.2, COC*H*CO), 3.19 (1H, dq, *J* 7.4 and 6.2, C*H*CH$_3$), 2.59–2.53 [1H, m, C*H*(CH$_3$)$_2$], 1.20 (3H, d, *J* 7.4, CHC*H*$_3$), 1.09 [3H, d, *J* 7.0, CH(C*H*$_3$)$_2$], 0.82 [3H, d, *J* 7.0, CH(C*H*$_3$)$_2$]; δ_C (125 MHz, d$_6$-DMSO) 199.6 (CH*C*OCH), 179.6 and 173.1 (N*C*=O), 158.5 (q, *J* 36.1, *C*OCF$_3$), 115.8 (q, *J* 291.6, CO*C*F$_3$), 62.7 (*C*HN), 58.9 (CO*C*HCO), 37.5 (*C*HCH$_3$), 28.0 [*C*H(CH$_3$)$_2$], 19.3, 16.1 and 14.4 (*C*H$_3$); *m*/*z* (APCI$^+$) 213 (100%, M − H$^+$), 195 (90%).

***tert*-Butyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzyl)amino-3-phenylpropionate (3*S*,α*R*)-24**[16,21]

To a stirred solution of (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (5.064 g, 15.0 mmol) in THF (50 mL) at −78 °C was added butyllithium (14.06 mL, 22.5 mmol) *via* syringe. The resultant pink solution of (*R*)-**6** was slowly warmed to 0 °C (10 min) and subsequently recooled to −78 °C. A solution of *tert*-butyl cinnamate **23** (3.06 g, 15.0 mmol) in THF (15 mL) was then added dropwise *via* cannula to the lithium amide solution. After stirring for 1.5 h at −78 °C the reaction was quenched by the rapid addition of a saturated aqueous ammonium chloride solution (20 mL) *via* pipette, allowed to warm to room temperature and concentrated *in vacuo*. The residue was partitioned between dichloromethane (50 mL) and distilled water (50 mL) and further extracted with dichloromethane (2 × 50 mL). The combined organic portions were washed with aqueous citric acid solution (5%, 2 × 100 mL) and brine (50 mL), dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield a yellow oil. ^{1}H NMR (500 MHz) spectroscopic analysis of this crude product material indicated that the reaction had occurred in >95% de. Purification of this material by silica gel chromatography [diethyl ether (100%)] afforded the title compound **24** (5.982 g, 96%) as a mixture of diastereoisomers (>95% de) and as a colourless oil, δ_H (lit.[21]) 7.43–7.18 (15H, m, Ph), 4.40 (1H, dd, *J* 9.4 and 5.7, C*H*N), 4.00 (1H, q, *J* 6.9, C*H*CH$_3$), 3.68 (2H, s, PhC*H*$_2$), 2.56 (1H, dd, *J* 14.6 and 5.5, C*H*$_2$CO), 2.49 (1H, dd, *J* 14.6 and 9.7, C*H*$_2$CO), 1.26 (3H d, *J* 6.8, CHC*H*$_3$), 1.22 [9H, s, C(C*H*$_3$)$_3$].

***tert*-Butyl (*S*)-3-amino-3-phenylpropionate (*S*)-25**[16,22]

To a solution of (3*S*,α*R*)-**24** (4.391 g, 10.581 mmol) in methanol (20 mL) in a Fischer–Porter bottle was cautiously added Pearlman's catalyst (0.880 g, 20%). A pressure head was fitted and the flask was subsequently pressurised to 7 atm with hydrogen. The heterogeneous solution was stirred vigorously for 48 h at room temperature before the pressure was released and the reaction mixture filtered through a short plug of Celite®. The Celite® pad was washed with ethyl acetate and the filtrate concentrated *in vacuo* to yield a yellow oil. Purification of this material by silica gel chromatography [petroleum ether–ethyl acetate (2:1)] afforded the title compound (*S*)-**25** as a colourless oil (1.750 g, 75%); $[\alpha]_D^{23}$ −21.3 (*c* 1.0, $CHCl_3$); lit.[16] $[\alpha]_D^{20}$ −21.0 (*c* 1.0, $CHCl_3$); δ_H (lit.[22]) 7.38–7.22 (5H, m, Ph), 4.37 (1H, dd, *J* 7.0 and 7.0, C*H*N), 2.58 (2H, app d, *J* 7.0, C*H*$_2$CO$_2$), 1.74 (2H, br s, N*H*$_2$), 1.42 [9H, s, C(C*H*$_3$)$_3$].

The enantiomeric excess (>95%) of (*S*)-**25** was determined by derivatisation as the Mosher's amide.

***tert*-Butyl (3*S*)-(*E*,*E*)-3-(*N*-hexa-2′,4′-dienoyl)amino-3-phenylpropionate (*S*)-(*E*,*E*)-26**

To a stirred solution of hexadienoic acid (0.079 g, 0.706 mmol) and 1-hydroxybenzotriazole (0.190 g; 1.41 mmol) in THF (2 mL) at room temperature was added solid dicyclohexylcarbodiimide (0.160 g, 0.777 mmol) in one portion. The reaction mixture was stirred for 2 h before a solution of (*S*)-**25** (0.172 g, 0.777 mmol) in THF (2 mL) was added *via* pipette. Stirring was maintained for a further 16 h before the reaction mixture was filtered through Celite®. The Celite® pad was washed with a small amount of THF and the filtrate concentrated *in vacuo*. This residue was dissolved in dichloromethane (30 mL), washed with dilute aqueous hydrochloric acid (0.1 M, 30 mL), saturated aqueous sodium hydrogen carbonate solution (30 mL) and then brine (30 mL), dried (magnesium sulfate), filtered and finally concentrated *in vacuo* to afford a yellow oil. Purification by silica gel chromatography [petroleum ether–diethyl ether (1:1)] afforded the title compound (*S*)-(*E*,*E*)-**26** as a colourless oil which crystallised on standing (0.179 g, 80%), mp 80–83 °C (Found: C, 72.2; H, 8.1; N, 4.4. $C_{19}H_{25}NO_3$ requires C, 72.35; H, 8.0; N, 4.4%); $[\alpha]_D^{23}$ −65.9 (*c* 1.00, $CHCl_3$); ν_{max}(film)/cm^{-1} 3273br (N–H), 1730s (OC=O), 1659s, 1631s, 1614s and 1544s; δ_H 7.32–7.15 (6H, m, Ph and C*H*=CHCO), 6.77 (1H, br d, *J* 8.5, N*H*), 6.19–6.00 (2H, m, CH$_3$C*H*=CH and CH$_3$CH=C*H*), 5.80 (1H, d, *J* 15.1, CH=C*H*CO), 5.50–5.43 (1H, m, C*H*N), 2.85 (1H, dd,

J 15.2 and 6.1, CH_2CO$_2$), 2.74 (1H, dd, *J* 15.2 and 6.0, CH_2CO$_2$), 1.82 (3H, d, *J* 5.7, CH_3CH), 1.32 [9H, s, C(CH_3)$_3$]; δ_C (50 MHz, $CHCl_3$) 170.9 (O*C*=O), 165.9 (N*C*=O), 141.7 (*C*H=CHCO), 141.0 (Ph:C$_{ipso}$), 138.0 (CH$_3$*C*H=CH), 129.9 (CH$_3$CH=*C*H), 128.7 (Ph), 127.6 (Ph:C$_{para}$), 126.6 (Ph), 121.7 (CH=*C*HCO), 81.3 [*C*(CH$_3$)$_3$], 49.7 (*C*HN), 41.1 (*C*H$_2$CO$_2$), 27.8 [C(*C*H$_3$)$_3$], 18.4 (*C*H$_3$CH); *m*/*z* (CI, NH_3) 316 (45%, MH^+), 260 (98%, $MH^+ - C_4H_8$), 242 (35%, $C_{15}H_{16}NO_2$), 164 (60%, $C_9H_{10}NO_2$), 95 (100%, C_6H_7O).

(3*S*)-(*E*,*E*)-3-(*N*-Hexa-2′,4′-dienoyl)amino-3-phenylpropionic acid (*S*)-(*E*,*E*)-5

To solid (*S*)-**26** (0.101 g, 0.321 mmol) in a round-bottomed flask at room temperature was added trifluoroacetic acid (3 mL) neat *via* pipette. The reaction mixture was stirred for 1 h before the volatiles were removed *in vacuo* to afford essentially pure title compound (*S*)-(*E,E*)-**5** (0.082 g, 99%) as a colourless solid. A small amount of (*S*)-(*E,E*)-**5** was recrystallised from ethyl acetate for analysis, mp 193–194 °C (Found: C, 69.4; H, 6.6; N, 5.7. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%); $[\alpha]_D^{23}$ −113.3 (*c* 0.57, MeOH); ν_{max}(KBr)/cm^{-1} 3292br (N–H), 1697s (OC=O), 1655s, 1630s and 1544s; δ_H (300 MHz, d$_6$-DMSO) 8.49 (1H, d, *J* 8.4, N*H*), 7.35–7.29 and 7.25–7.21 (5H, m, Ph), 6.98 (1H, dd, *J* 15.1 and 11.0, C*H*=CHCO), 6.21 (1H, ddd, *J* 15.0, 11.0 and 1.1, CH$_3$CH=C*H*), 6.08 (1H, dq, *J* 15.0 and 6.6, CH$_3$C*H*=CH), 5.93 (1H, d, *J* 15.1, CH=C*H*CO), 5.29–5.24 (1H, m, C*H*N), 2.72 (1H, dd, *J* 15.6 and 8.2, CH_2CO$_2$), 2.68 (1H, dd, *J* 15.6 and 6.9, CH_2CO$_2$), 1.79 (3H, d, *J* 6.6, CH_3CH); δ_C (125 MHz, d$_6$-DMSO) 171.9 (O*C*=O), 164.6 (N*C*=O), 142.8 (*C*H=CHCO), 139.8 (Ph:C$_{ipso}$), 137.0 (CH$_3$*C*H=CH), 130.1 (CH$_3$CH=*C*H), 128.5 (Ph), 127.2 (Ph:C$_{para}$), 126.7 (Ph), 123.0 (CH=*C*HCO), 49.7 (*C*HN), 41.1 (*C*H$_2$CO$_2$), 18.5 (*C*H$_3$CH); *m*/*z* (APCI$^-$) 258 (100%, M − H$^+$).

tert-Butyl (3*S*)-(*E*,*E*,*E*)-3-(*N*-octa-2′,4′,6′-trienoyl)amino-3-phenylpropionate (3*S*)-(*E*,*E*,*E*)-27

To a stirred solution of octatrieneoic acid (0.060 g, 0.435 mmol) and 1-hydroxybenzotriazole (0.088 g; 0.652 mmol) in THF (2 mL) at room temperature was added solid dicyclohexylcarbodiimide (0.107 g, 0.522 mmol) in one portion. The reaction mixture was stirred for 1 h before a solution of (*S*)-**25** (0.115 g, 0.522 mmol) in THF (0.5 mL) was added *via* pipette. Stirring was maintained for a further 16 h before the reaction mixture was filtered through Celite®. The Celite® pad was washed with a small amount of THF and the filtrate concentrated *in vacuo*. This residue was dissolved in diethyl ether (100 mL), washed with dilute aqueous hydrochloric acid (0.1 M, 2 × 40 mL), saturated aqueous sodium hydrogen carbonate solution (40 mL) and then brine (40 mL), dried (magnesium sulfate), filtered and finally concentrated *in vacuo* to afford a yellow oil. Purification by silica gel chromatography [petroleum ether–ethyl acetate (3:1)] afforded the title compound (3*S*)-(*E*,*E*,*E*)-**27** as a colourless oil (0.141 g, 95%), $[\alpha]_D^{23}$ −64.4 (*c* 0.89, $CHCl_3$); ν_{max}(film)/cm^{-1} 3279br (N–H), 1729s (OC=O), 1638s, 1610s and 1541s; δ_H 7.29–7.14 (7H, m, Ph, C*H*=CHCO and N*H*), 6.41 (1H, dd, *J* 14.8 and 10.6, C*H*=CHCH=CHCO), 6.15–6.04 (2H, m, CH$_3$CH=C*H* and CH=C*H*CH=CHCO), 5.88 (1H, d, *J* 14.8, CH=C*H*CO), 5.84 (1H, dq, *J* 15.0 and 6.8, CH$_3$C*H*=CH), 5.48–5.41 (1H, m, C*H*N), 2.80 (1H, dd, *J* 15.2 and 6.5, CH_2CO$_2$), 2.69 (1H, dd, *J* 15.2 and 6.5, CH_2CO$_2$), 1.77 (3H, d, *J* 6.8, CH_3CH), 1.30 [9H, s, C(CH_3)$_3$]; δ_C (50 MHz, $CHCl_3$) 170.8 (O*C*=O), 165.8 (N*C*=O), 141.6 (*C*H=CHCO), 141.1 (Ph:C$_{ipso}$), 140.1 (*C*H=CHCH=CHCO), 134.2 (CH$_3$*C*H=CH), 131.5 (CH$_3$CH=*C*H), 128.7 (Ph), 128.0 (CH=*C*HCH=CHCO), 127.5 (Ph:C$_{para}$), 126.7 (Ph), 123.0 (CH=*C*HCO), 81.2 [*C*(CH$_3$)$_3$], 49.8 (*C*HN), 41.3 (*C*H$_2$CO$_2$), 27.8 [C(*C*H$_3$)$_3$], 18.4 (*C*H$_3$CH); *m*/*z* (APCI$^+$) 342 (52%, MH^+), 286 (100%, $MH^+ - C_4H_8$), 138 (8%, $C_8H_{12}NO$), 121 (18%); [Found (CI, NH_3): MH^+, 342.20816. $C_{21}H_{28}NO_3$ MH^+ requires, 342.20692].

(3*S*)-(*E*,*E*,*E*)-3-(*N*-Octa-2′,4′,6′-trienoyl)amino-3-phenylpropionic acid (3*S*)-(*E*,*E*,*E*)-1[2]

To (3*S*)-(*E*,*E*,*E*)-**27** (0.101 g, 0.321 mmol) in a round-bottomed flask at room temperature was added trifluoroacetic acid (3 mL) neat *via* pipette. The reaction mixture was stirred for 30 min before the volatiles were removed *in vacuo* to afford a brown solid. This material was dissolved in aqueous potassium hydroxide solution (0.1 M, 10 mL) and the solution extracted with ethyl acetate (2 × 20 mL). On acidification of the aqueous layer with aqueous hydrochloric acid (10%) a white precipitate formed. Filtration and drying of this material afforded the title compound (3*S*)-(*E*,*E*,*E*)-**1** as a white amorphous solid (0.082 g, 83%), $[\alpha]_D^{23}$ −122.2 (*c* 0.315, MeOH); CD (lit.;[2] MeOH) λ_{max}-($\Delta\varepsilon$) 212.0 (+4.56), 244.5 (−12.02), 292.0 (−7.46); ν_{max}(KBr)/cm^{-1} 3285br (N–H), 1696s (OC=O), 1648s, 1612s and 1542s; δ_H (lit.;[2] 500 MHz, d$_6$-DMSO) 8.51 (1H, d, *J* 8.6, NH), 7.33–7.29 and 7.25–7.21 (5H, m, Ph), 7.01 (1H, dd, *J* 15.0 and 11.3, C*H*=CHCO), 6.55 (1H, dd, *J* 14.9 and 10.8, C*H*=CHCH=CHCO), 6.27 (1H, dd, *J* 14.9 and 11.3, CH=C*H*CH=CHCO), 6.19 (1H, ddd, *J* 14.9, 10.8 and 1.6, CH$_3$CH=C*H*), 6.01 (1H, d, *J* 15.0, CH=C*H*CO), 5.90 (1H, dq, *J* 14.9 and 6.7, CH$_3$-C*H*=CH), 5.28–5.24 (1H, m, C*H*N), 2.71 (1H, dd, *J* 15.6 and 8.1, CH_2CO$_2$), 2.67 (1H, dd, *J* 15.6 and 6.8, CH_2CO$_2$), 1.77 (3H, d, *J* 6.7, CH_3CH); δ_C (lit.;[2] 125 MHz, d$_6$-DMSO) 171.8 (O*C*=O), 164.4 (N*C*=O), 142.8 (Ph:C$_{ipso}$), 139.6 (*C*H=CHCO), 139.1 (*C*H=CHCH=CHCO), 133.5 (CH$_3$*C*H=CH), 131.6 (CH$_3$CH=*C*H), 128.4 (Ph), 128.2 (CH=*C*HCH=CHCO), 127.1 (Ph:C$_{para}$), 126.7 (Ph), 124.3 (CH=*C*HCO), 49.7 (*C*HN), 41.0 (*C*H$_2$CO$_2$), 18.4 (*C*H$_3$CH); *m*/*z* (APCI$^+$) 286 (68%, MH^+), 138 (22%, $C_8H_{12}NO$), 121 (100%, C_8H_9O).

Moiramide B 2[2]

To a stirred mixture of (*S*)-(*E,E*)-**5** (0.0190 g, 0.073 mmol) and BOP reagent (0.0324 g, 0.073 mmol) in a 5 mL round-bottomed flask at room temperature was added DMF (0.5mL) *via* syringe. The reaction mixture was stirred at room temperature for 30 min before DMAP (0.032 g, 0.265 mmol) was added in one portion. After a further 10 min at room temperature, the reaction mixture was cooled to 0 °C and a solution of (3*R*,4*S*,2′*S*)-**7** (0.024 g, 0.073 mmol) in DMF (0.5 mL) was then added *via* pipette. The reaction mixture was stirred at 0 °C for 30 min, diluted with ethyl acetate (30 mL), washed with aqueous hydrochloric acid (1%, 3 × 40 mL) and brine (40 mL), dried (magnesium sulfate), filtered and finally concentrated *in vacuo* to afford a colourless solid. This material was purified first by chromatography on Sephadex LH-20 eluting with ethyl acetate–methanol–water (8:2:1), secondly by chromatography on reversed-phase silica eluting with methanol–water (65:35) and finally by chromatography on silica gel eluting with ethyl acetate to afford the title compound **2** as a colourless solid (0.0215 g, 65%), mp 150–155 °C (decomp.); $[\alpha]_D^{25}$ −96.6 (*c* 0.28, MeOH); CD (lit.;[2] MeOH) λ_{max}($\Delta\varepsilon$) 214.0 (+6.40), 237.0 (−14.56), 288.5 (−0.31), 311.5 (−1.91); ν_{max}(KBr)/cm^{-1} 3306br (N–H), 1728s, 1711s, 1654s, 1630s and 1534m; δ_H (lit.;[2] 500 MHz, d$_6$-DMSO) 11.34 (1H, br s, NH_{imide}), 8.37 (1H, d, *J* 8.4, NH_{amide}), 8.08 (1H, d, *J* 8.5, NH_{amide}), 7.32–7.19 (5H, m, Ph), 6.96 (1H, dd, *J* 15.1 and 10.8, C*H*=CHCO), 6.20 (1H, dd, *J* 15.0 and 10.8, CH=C*H*CH=CHCO), 6.07 (1H, dq, *J* 15.0 and 6.7, CH$_3$C*H*=CH), 5.92 (1H, d, *J* 15.1, CH=C*H*CO), 5.30–5.25 (1H, m, C*H*NPh), 4.63 (1H, dd, *J* 8.4 and 5.4, C*H*NCO), 3.92 (1H, d, *J* 5.5, COC*H*CO), 2.91 (1H, dq, *J* 7.4 and 5.5, C*H*CH$_3$), 2.76 (1H, dd, *J* 14.5 and 8.6, CH_2CO), 2.64 (1H, dd, *J* 14.5 and 6.1, CH_2CO), 2.29 [1H, m, C*H*(CH$_3$)$_2$], 1.79 (3H, d, *J* 6.7, CH_3CH=CH), 1.08 (3H, d, *J* 7.4, CHCH_3), 0.80 (3H, d, *J* 6.8, CHCH_3), 0.75 (3H, d, *J* 6.8, CHCH_3); δ_C (lit.;[21] 125 MHz, d$_6$-DMSO) 203.5 (CH*C*OCH), 180.1 and 173.9 (*C*O$_{imide}$), 170.0 (CH$_2$*C*O), 164.5 (CH=CH*C*O), 143.0 (Ph:C$_{ipso}$), 139.6 (*C*H=CHCO), 136.8 (CH$_3$*C*H=CH), 130.0 (CH$_3$CH=*C*H), 128.4 (Ph), 127.0 (Ph:C$_{para}$), 126.6 (Ph), 123.1 (CH=*C*HCO),

63.2 (N*C*HCO), 58.0 (CO*C*HCO), 50.1 (N*C*HPh), 42.1 (*C*H_2CO), 39.2 (*C*HCH$_3$), 28.3 [*C*H(CH$_3$)$_2$], 19.5, 18.4, 17.4 and 14.7 (CH*C*H$_3$).

Andrimid 3[2]

To a stirred mixture of (*S*)-(*E,E,E*)-**1** (0.015 g, 0.053 mmol) and BOP reagent (0.0246 g, 0.056 mmol) in a 5 mL round-bottomed flask at room temperature was added DMF (0.5 mL) *via* syringe. The reaction mixture was stirred at room temperature for 30 min before DMAP (0.032 g, 0.265 mmol) was added in one portion. After a further 10 min a solution of (3*R*,4*S*,2′*S*)-**7** (0.019 g, 0.058 mmol) in DMF (0.7 mL) was then added *via* pipette. The reaction mixture was stirred at room temperature for 30 min, diluted with ethyl acetate (30 mL), washed with aqueous hydrochloric acid (1%, 3 × 30 mL) and brine (30 mL), dried (magnesium sulfate), filtered and finally concentrated *in vacuo* to afford a yellow solid.This material was purified by HPLC using an analytical column (4.6 mm × 250 mm) with ODS as the stationary phase and methanol–water (60 : 40) as the mobile phase at a flow rate of 1.5 mL min^{-1} (retention time, 15 min 10 s) to afford the title compound **3** as a white solid (0.015 g, 59%), mp 153–157 °C (decomp.); $[\alpha]_D^{24}$ −75.7 (*c* 0.53, MeOH); CD (lit.;[2] MeOH) $\lambda_{max}(\Delta\varepsilon)$ 215.1 (+6.14), 240.0 (−5.82), 276.2 (+0.03), 308.7 (−6.22); δ_H (lit.;[2] 500 MHz, d$_6$-DMSO) 11.35 (1H, br s, N*H*$_{imide}$), 8.39 (1H, d, *J* 8.4, N*H*$_{amide}$), 8.09 (1H, d, *J* 8.5, N*H*$_{amide}$), 7.31–7.21 (5H, m, Ph), 7.00 (1H, dd, *J* 15.0 and 11.2, C*H*=CHCO), 6.54 (1H, dd, *J* 14.8 and 10.8, C*H*=CHCH=CHCO), 6.26 (1H, dd, *J* 14.8 and 11.2, CH=C*H*CH=CHCO), 6.18 (1H, dd, *J* 14.8 and 10.8, CH$_3$CH=C*H*), 6.01 (1H, d, *J* 15.0, CH=C*H*CO), 5.90 (1H, dq, *J* 14.8 and 7.0, CH$_3$C*H*=CH), 5.28 (1H, m, NC*H*Ph), 4.62 (1H, dd, *J* 8.4 and 5.4, NC*H*CO), 3.92 (1H, d, *J* 5.6, COC*H*CO), 2.91 (1H, dq, *J* 7.4 and 5.6, C*H*CH$_3$), 2.76 (1H, dd, *J* 14.5 and 8.5, C*H*$_2$CO), 2.65 (1H, dd, *J* 14.5 and 6.1, C*H*$_2$CO), 2.29 [1H, m, C*H*(CH$_3$)$_2$], 1.78 (3H, d, *J* 7.0, C*H*$_3$CH=CH), 1.08 (3H, d, *J* 7.4, CHC*H*$_3$), 0.80 (3H, d, *J* 6.8, CHC*H*$_3$), 0.75 (3H, d, *J* 6.8, CHC*H*$_3$); δ_C (lit.;[2] 125 MHz, d$_6$-DMSO) 203.5 (NCH*C*O), 180.1 and 173.9 (*C*O$_{imide}$), 170.0 (CH$_2$*C*O), 164.4 (CH=CH*C*O), 143.0 (Ph : C$_{ipso}$), 139.6 (*C*H=CHCO), 139.1 (*C*H=CHCH=CHCO), 133.5 (CH$_3$*C*H=CH), 131.6 (CH$_3$CH=*C*H), 128.4 (Ph), 128.3 (CH=*C*HCH=CHCO), 127.0 (Ph : C$_{para}$), 126.6 (Ph), 124.4 (CH=*C*HCO), 63.2 (N*C*HCO), 58.0 (CO*C*HCO), 50.0 (N*C*HPh), 42.1 (*C*H$_2$CO), 39.2 (*C*HCH$_3$), 28.3 [*C*H(CH$_3$)$_2$], 19.6, 18.4, 17.4 and 14.7 (CH*C*H$_3$).

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