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# Formal Total Synthesis of (+)-C9-Deoxyomuralide from L-Leucine Using a Double Sacrificial Chirality Transfer Approach

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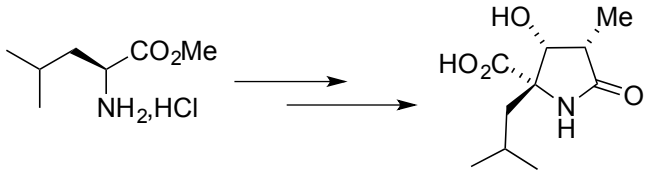



*Abstract:* Formal stereocontrolled syntheses of (±)- and (+)-C9-deoxyomuralide is reported, constituting one of the shortest routes to the full carbon skeleton reported to date.

## Introduction

The proteasome is a 28 protein complex responsible for the normal turnover of cellular proteins, the removal of damaged proteins, and control of cell growth and metabolism. It comprises a 20S catalytic core with additional subunits.[1] Selective proteasome inhibitors have great therapeutic potential for the treatment of inflammatory diseases and cancer.[2] In 1991 Omura reported the isolation of (+)-lactacystin **1**, a novel amino acid metabolite from *Streptomyces sp*. OM-6519.[3] The compound, and the corresponding β-lactone omuralide **2**, inhibit cancer cell growth and vascular smooth muscle cell proliferation,[4] suggesting that it may have therapeutic potential in vascular diseases and diabetes.[5] Several β-lactone-derived natural products (e.g. lactacystin **1**,[1] omuralide **2**, salinosporamides such as **3** [6] and cinnabaramides such as **4** [7]) have been identified with similar modes of activity as potent covalent inhibitors of the 20S proteasome (Figure 1). Due to the unique ability of compounds **1** and **2** to inhibit the activity of the 20S proteasome, several research groups have targeted this important biologically active structure,[8] and the area has been reviewed.[9] Retrosynthetic disconnection at the thiol ester linkage leads to the substituted pyroglutamic acid **5**. Corey has shown that this may be coupled with a suitably protected (*R*)-*N*-acetylcysteine in one step without hydroxyl group protection (Figure 1).[8] The convoluted chemical syntheses of such molecules, however, render them costly and limit accessibility to improved analogues.[8,9]

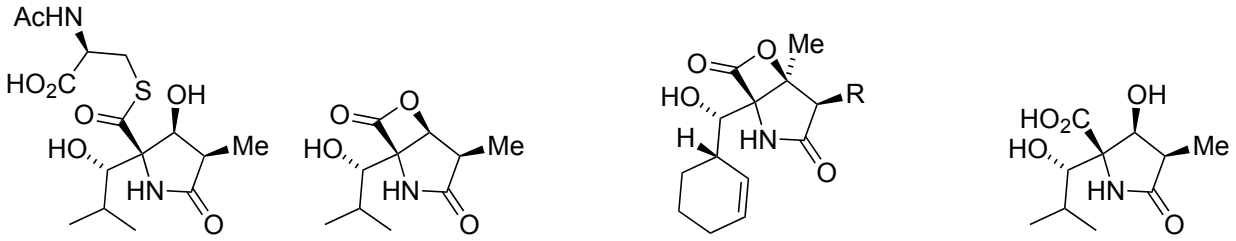
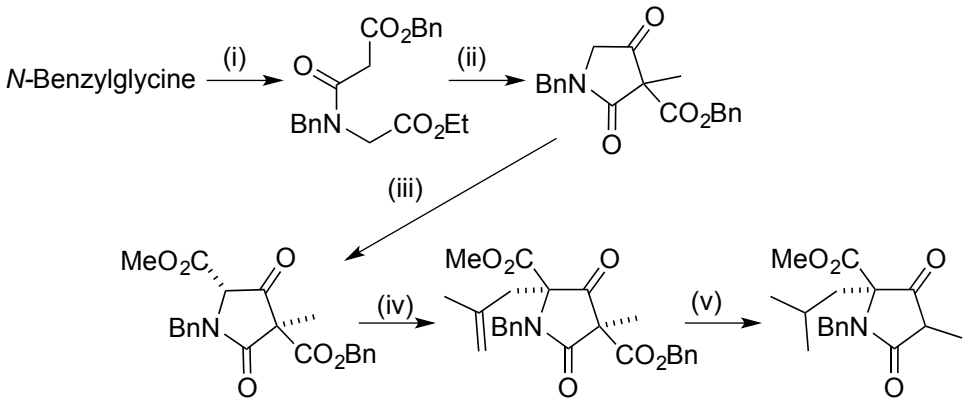



**Figure 1.** Omuralide and related structures

Our approach was informed by our original finding that the carbon framework of the (±)-lactacystin/omuralide nucleus could be achieved in as few as five steps from *N*-benzylglycine;[10] in this route, key steps were a Dieckmann cyclization,[11] followed by enolate functionalization, hydrogenolysis, and concomitant decarboxylation (Scheme 1).

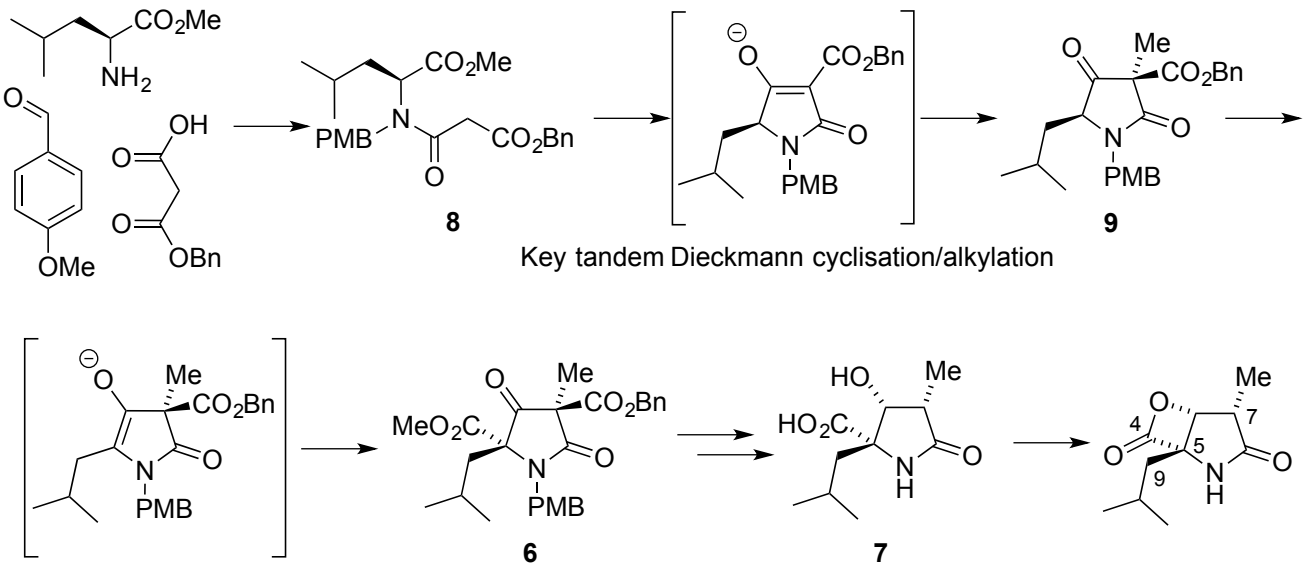



*Reagents and conditions*: (i) $BnOCOCH_2COCl$, pyridine, DMAP, $CH_2Cl_2$, rt, 24 h, 83%; (ii) a) TBAF, $Et_2O$, rt; b) MeI, THF, rt, 24 h, 53% over 2 steps; (iii) LiHMDS, $NCCO_2Me$, DMPU, THF, –78 °C, 2 h, 75%; (iv) NaH, $CH_2=C(CH_3)CH_2Br$, DMF, rt, 24 h, 75%; (v) $H_2$, Pd/C, 90%.

**Scheme 1.** Early approach to omuralide skeleton

We have now devised a stereocontrolled formal synthesis of (+)-C9-deoxyomuralide from L-leucine, using a double internal sacrificial chirality transfer approach (Scheme 2). This strategy hinges on preparation of the key fully functionalized intermediate **6** from protected leucine **8** through a tandem Dieckmann cyclisation/alkylation process to afford pyroglutamate **9**, and subsequent acylation using Mander's reagent. Reduction, decarboxylation and protecting group removal sequence would lead to known intermediate **7**.[12]

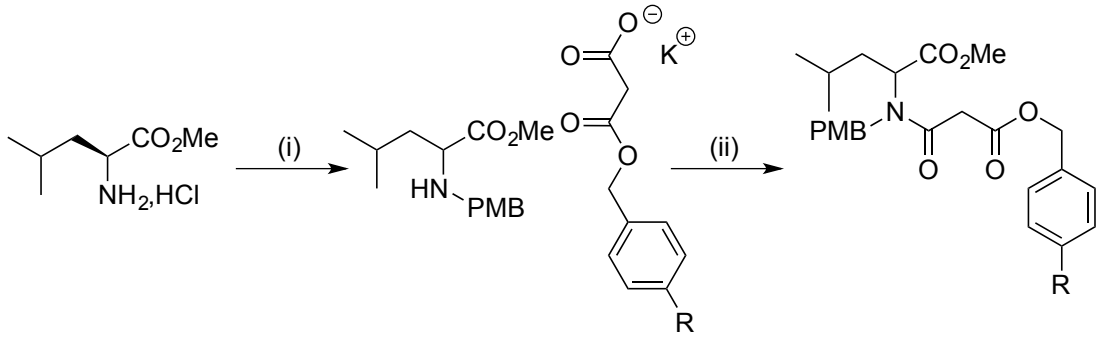
Stereochemistry is derived ultimately from L-leucine. The isobutyl group stereochemistry controls the asymmetric induction during the enolate methylation step to give **9**, but is then itself sacrificed during the subsequent enolization; the stereochemistry at this centre is then re-introduced under the control of the methylated centre, the stereochemistry of which is also subsequently sacrificed during decarboxylation.




**Scheme 2.** Synthetic approach towards (+)-C9-deoxyomuralide

## Results and Discussion

The synthesis began with the reductive amination of L-leucine methyl ester with 4-anisaldehyde and sodium cyanoborohydride under reflux to afford amine (±)**-10** as a racemic mixture in 96% yield (Scheme 2). It is known that complete racemization of amino acids can occur at high temperature in the presence of an aldehyde and acetic acid.[13] In this racemic series, coupling of (±)-**10** with the potassium salts of carboxylic acids (±)**-11** and (±)**-12** using EDAC·HCl afforded the corresponding amides (±)**-13** and (±)**-8** in 75% and 78% yields, respectively (Scheme 3).

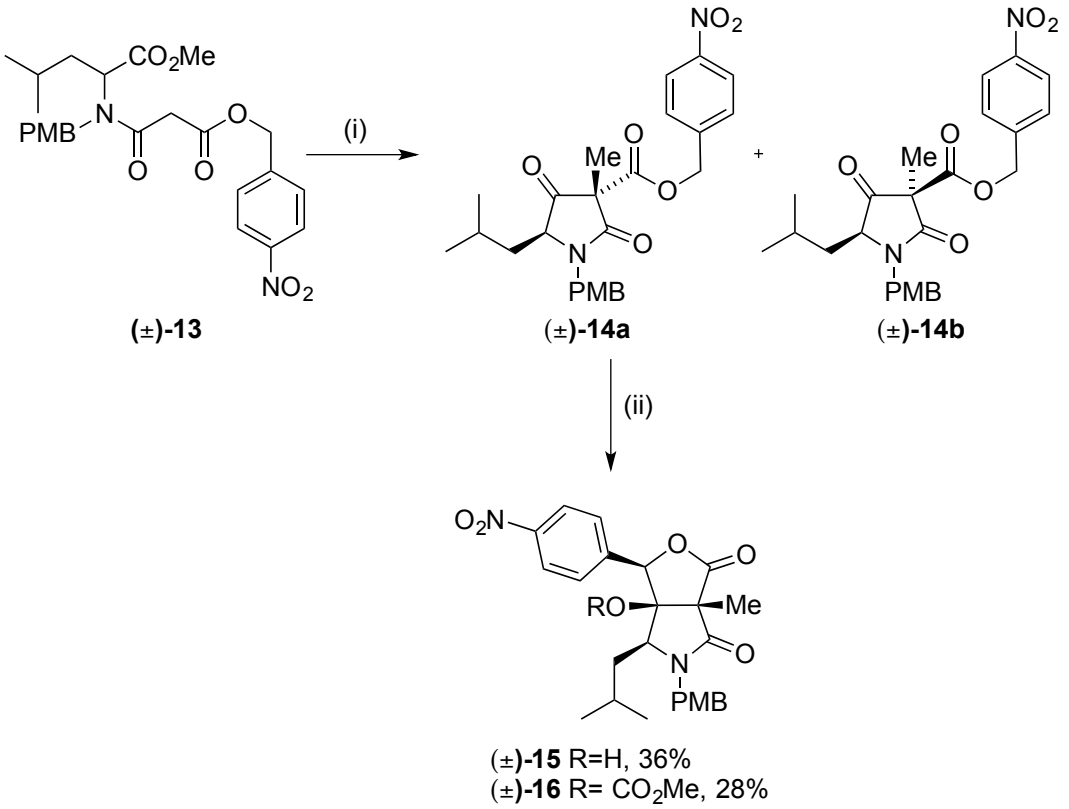



*Reagents and conditions*: (i) $CH_3CO_2H$, 4-methoxybenzaldehyde, toluene, reflux under Dean-Stark trap, 12 h; then $CH_3CO_2H$, $NaBH_3CN$ (2 equiv.), MeOH, 0 ºC to r.t., 5 h, 96%; (ii) NMM, EDAC·HCl, DMAP, $CH_2Cl_2$, r.t., 20 h.

**Scheme 3.** Preparation of Dieckmann cyclization substrates

The key Dieckmann cyclization step was initially studied using 4-nitrobenzyl ester (±)**-13**. Treatment of amide (±)**-13** with 2.5 equivalents of TBAF in diethyl ether induced cyclization followed by deprotonation to afford the cyclized enolate tetrabutylammonium salt. Removal of the solvent and dissolution of the residue in THF followed by addition of methyl iodide produced the two methylated pyroglutamate

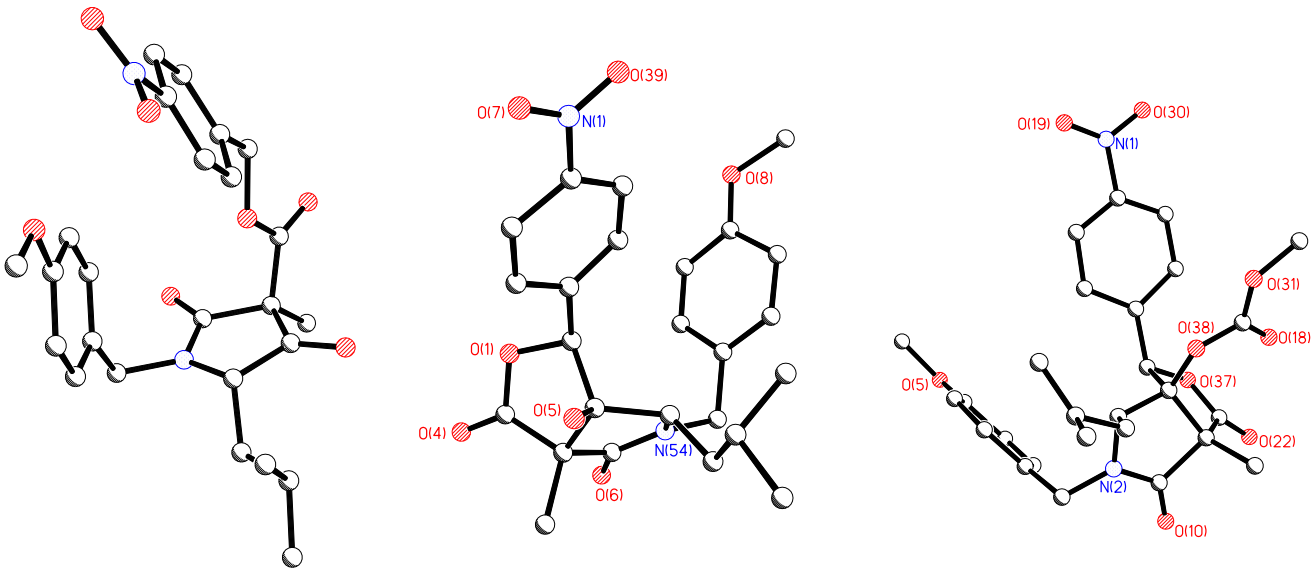
diastereoisomers (±)-**14a** and (±)-**14b** in an approximately 1:1 ratio, assessed by analysis of the $^1$H NMR spectrum of the reaction mixture. Column chromatography on silica gel afforded the first eluting diastereoisomer (±)-**14a** and the second eluting diastereoisomer (±)-**14b** in 37% and 25% yields, respectively. Compound (±)-**14a** was submitted to attempted enolate C-acylation α to the nitrogen atom using Mander's reagent,[14] and two products, (±)-**15** and (±)-**16,** were obtained in 36% and 28% yield, respectively (Scheme 4). Structural assignment of these two products and of (±)-**14a** was achieved through single crystal X-ray crystallography (Figure 2).




*Reagents and conditions*: (i) TBAF in THF, $Et_2O$, r.t., overnight; then MeI, THF, 0 ºC to r.t., 16 h, 37% of (±)-**14a** and 25% of (±)-**14b**,; (ii) n-BuLi, Hexamethyldisilazane, DMPU, THF, −78 °C, 0.5 h, then $NCCO_2Me$, −78 °C 4h.

**Scheme 4.** Dieckmann cyclization and attempted acylation of **(±)-13**

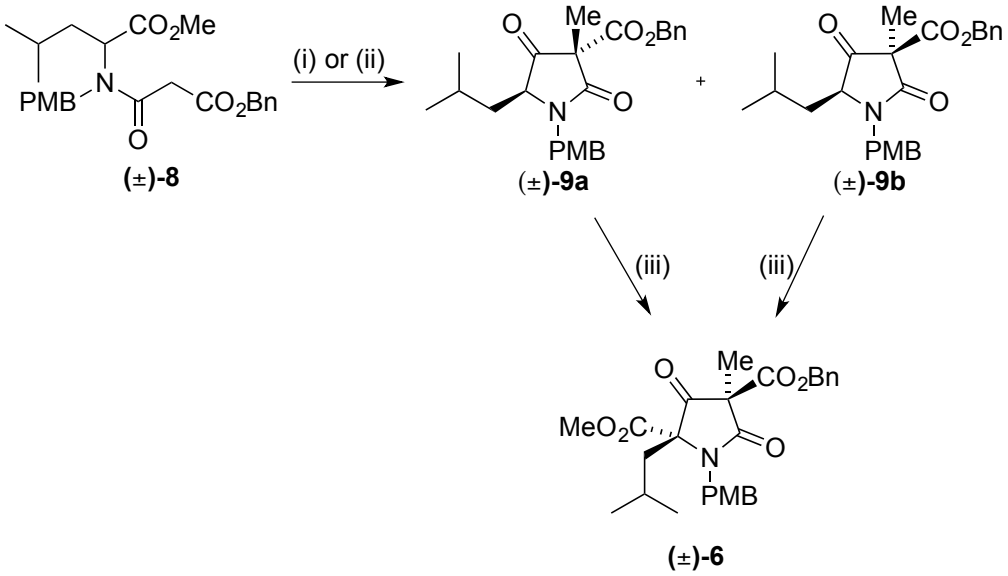
The structure of (±)-**14a** indicates that the compound has the methyl and *iso*-butyl groups in a *cis* relationship. The structure of (±)-**15** and (±)-**16** indicate the formation of a 5-membered ring lactone rather than the desired C-acylated material, presumably through deprotonation at the benzylic position of the 4-nitrobenzyl group followed by attack at the ketone moiety, giving the corresponding bicyclic alkoxide. Quench with a proton source or reaction with Mander's reagent would then yield (±)-**15** or (±)-**16**, respectively.




(±)-**14a** (±)-**15** (±)-**16**

**Figure 2**: Single crystal X-ray structures of compound (±)-**14a**, (±)-**15** and (±)-**16** (hydrogen atoms have been omitted for clarity)

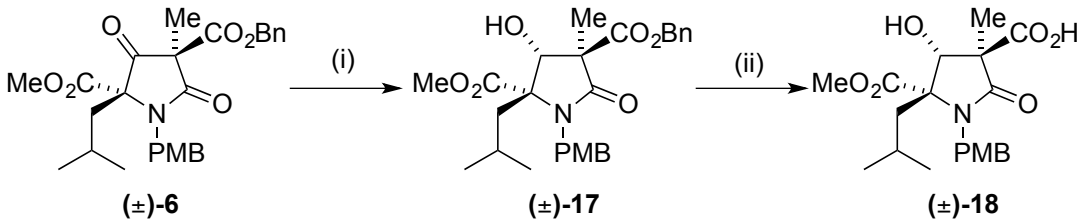
Starting from benzyl ester (±)-**8**, however, the two methylated pyroglutamate diastereoisomers (±)-**9a** and (±)-**9b** were obtained, also in an approximately 1:1 ratio as assessed by analysis of the $^{1}$H NMR spectrum of the reaction mixture. Column chromatography allowed the separation of these diastereoisomers, which were obtained in 30% and 29% yield, respectively, (±)-**9a** being the first eluting isomer. The two diastereoisomers were separately treated with base followed by Mander's reagent. Pleasingly, the desired acylation took place and was completely stereoselective; the same racemic diastereoisomer (±)-**6** was isolated after column chromatography when (±)-**9a** and (±)-**9b** were used separately, or in a mixture of (±)-**9a** and (±)-**9b**, as substrates, the approach of the reagent having occurred towards the opposite face of the five-membered ring to that bearing the benzyl ester group (Scheme 5). No competing cyclization to γ-lactone was observed, presumably due to reduced acidity at the benzylic position.




*Reagents and conditions*: (i) TBAF in THF, $Et_2O$, r.t., 16 h; then MeI, THF, 0 ºC to r.t., 16 h, 30% of (±)-**9a** and 29% of (±)-**9b**; (ii) TBAF in THF, THF, r.t., 0.5 h, then MeI, r.t., 16 h, (±)-**9a, 9b** (1:1) 57% (iii) LiHMDS, DMPU, THF, –78 °C, 0.5 h, then $NCCO_2Me$, –78 °C, 4 h, 88%.

**Scheme 5.** Dieckmann cyclization and acylation of **(±)-8**

Two possible two-step pathways were now available to obtain target compound (±)-**18**: ketone reduction followed by decarboxylation, or decarboxylation followed by ketone reduction. Sodium borohydride reduction of the ketone moiety in compound (±)-**6** afforded alcohol (±)-**17** as a single diastereoisomer according to analysis of the $^1H$ and $^{13}C$ NMR spectra (Scheme 6). Optimization of the reduction conditions led to the isolation of the desired product in 52% yield with 31% of starting material recovered. Other reducing agents such as sodium cyanoborohydride, sodium triacetoxyborohydride, DIBAL, and aluminium triisopropoxide/isopropanol only led to complete recovery of the starting material, perhaps due to the steric hindrance around the ketone moiety. Single crystal X-ray crystallography carried out on (±)-**17** showed that the relative stereochemistry is as desired with the methyl group, the hydroxyl group and the ester group in an all *cis* relationship (Figure 3). Subsequent hydrogenolysis was expected to proceed with concomitant decarboxylation of the resulting α-amidoacid, but only the corresponding carboxylic acid (±)-**18** could be isolated, most efficiently by treatment with palladium hydroxide and hydrogen.




*Reagents and conditions*: (i) $NaBH_4$, EtOH, –10 °C, 30 min, 52% of (±)-**17** and 31% of (±)-**6**; (ii) $H_2$, $Pd(OH)_2/C$, THF, quant.

**Scheme 6.** Reduction and hydrogenolysis of **(±)-6**

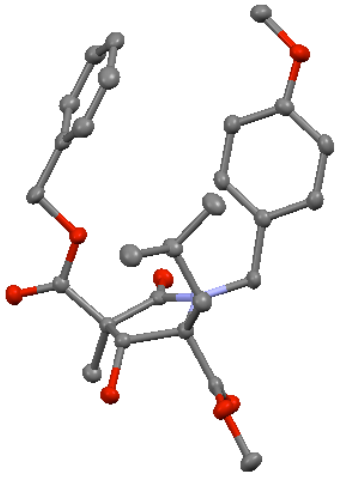
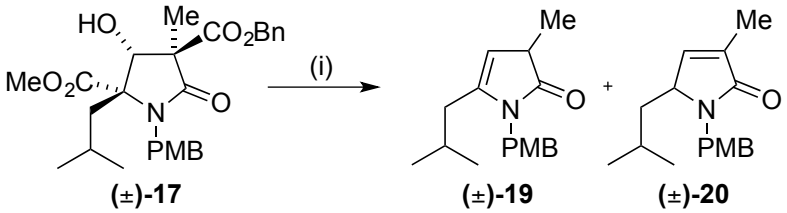


**Figure 3**: Single crystal X-ray structure of (±)-**17** (hydrogen atoms are omitted for clarity)

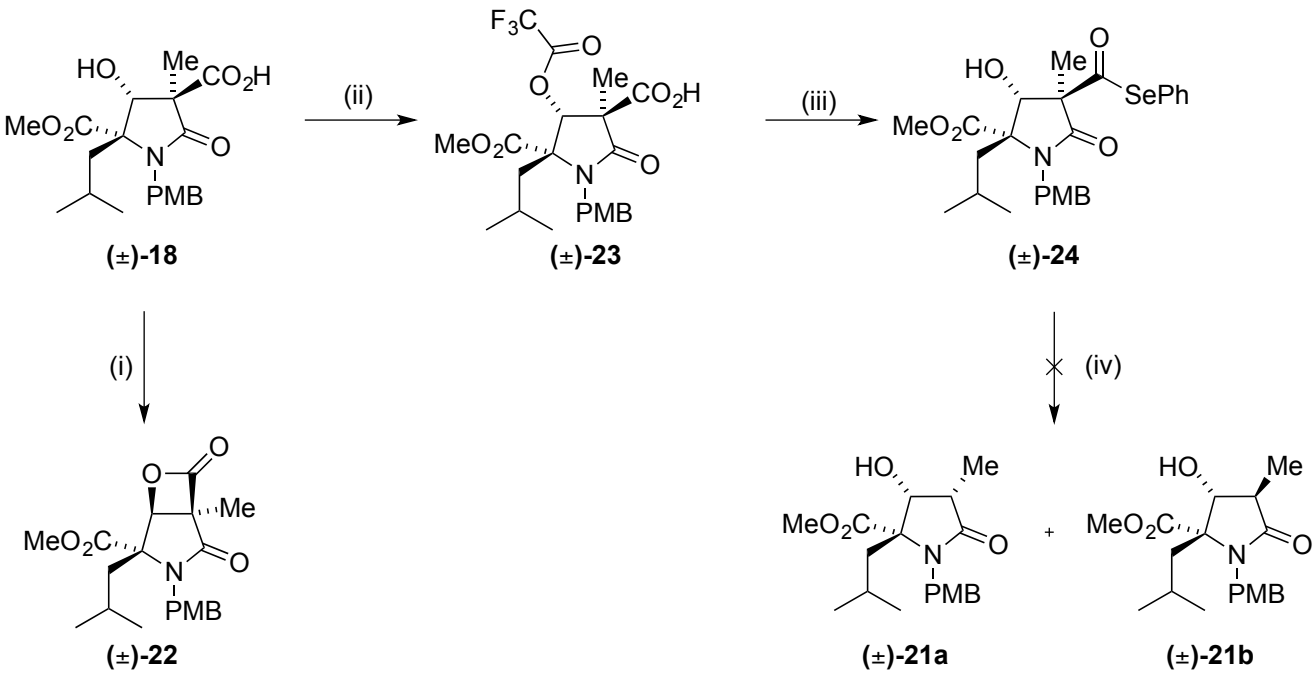
Decarboxylation of (±)-**17** was attempted using Krapcho conditions (Scheme 7),[15] but double decarboxylation and elimination occurred to give products (±)-**19** and (±)-**20** in 49% and 38% yields, respectively.




*Reagents and conditions*: (i) LiCl, DMF, 135°C, 4 h, (±)-**19**, 49% and (±)-**20**, 38%.

**Scheme 7.** Attempted decarboxylation of **(±)-17**

Radical-mediated decarbonylation of the corresponding acylselenide was also attempted (Scheme 8).



*Reagents and conditions*: (i) $(SePh)_2$, $Bu_3P$, $CH_2Cl_2$, 18 h, 43%; or oxalyl chloride, 2-mercaptopyridine *N*-oxide sodium salt, DMF, $CHCl_3$; or EDAC·HCl, NMM, DMAP, 2-mercaptopyridine *N*-oxide sodium salt, THF; (ii) TFAA, Pyridine, $Et_2O$, –10 °C, 4 h, 81%; (iii) $(SePh)_2$, $Bu_3P$, $CH_2Cl_2$, 18 h, 31%; (iv) $Bu_3SnH$, ABCN, toluene

**Scheme 8.** Attempted decarboxylation of **(±)-18**

Carboxylic acid (±)-**18** was dissolved in dichloromethane at 0 °C and tributylphosphine and diphenyl diselenide were added. Data for the major product did not, however, match the expected acyl selenide. β-Lactone (±)-**22** was identified as the product using mass spectrometry (*m/z* = 376.1756, corresponding to $[M+H]^+$) and IR spectroscopy (β-lactone signal at 1842 $cm^{-1}$), and its relative configuration was confirmed using NOESY NMR spectroscopy (Figure 4). The Barton decarboxylation methodology was investigated, [16] but attempted preparation of the thiolester using EDAC or oxalyl chloride yielded only β-lactone (±)-**22**.

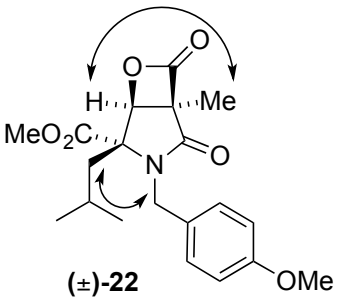
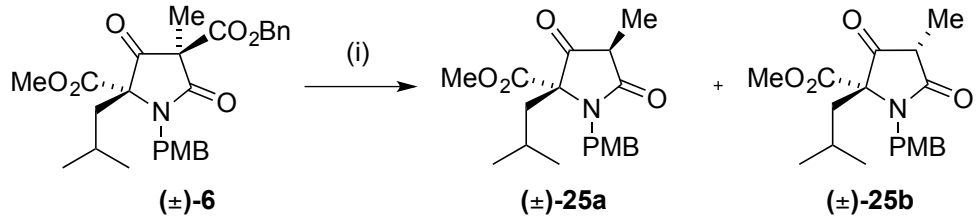



**Figure 4**: NOESY NMR spectrum analysis of (±)-**22**

The lactonization was partially circumvented by protection of the hydroxyl group; trifluoroacetylation proceeded in 81% yield to give (±)-**23** after an aqueous work-up. Trifluoroacetate (±)-**23** was used without further purification as it proved unstable to silica gel column chromatography. Treatment with diphenyl diselenide and tributylphosphine afforded the desired acyl selenide (±)-**24** in 31% yield alongside lactone (±)-**22** in 10% yield; the trifluoroacetate unit appears to be lost during the reaction process. Attempted radical-mediated decarboxylation of (±)-**24** using tributyltin hydride and ABCN (1,1'-azobis(cyclohexanecarbonitrile)) as the initiator failed to yield the desired products **21a**/**21b**. Tributylgermanium hydride and tris(trimethylsilyl)silane were tested in the reaction in place of tributyltin hydride, but both methods proved unsuccessful and resulted in complex mixtures, with neither the desired compound nor the starting material being isolated.

As this first route was unsuccessful, we investigated initial decarboxylation of (±)-**6**: hydrogenolysis of β-ketoamide (±)-**6** induced concomitant decarboxylation as expected, leading to a mixture of inseparable diastereoisomers (±)-**25a** and (±)-**25b** in a 1:1 ratio in quantitative yield (Scheme 9).



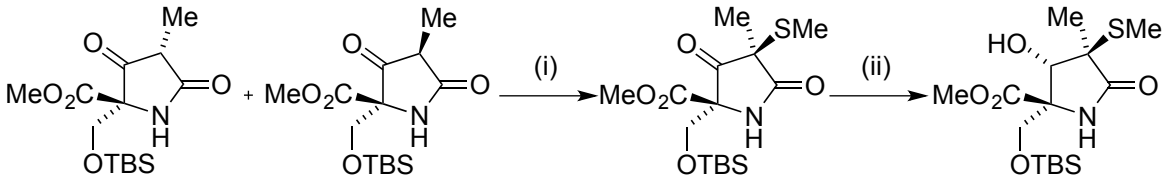

**(±)-6** **(±)-25a** **(±)-25b**

*Reagents and conditions*: (i) $H_2$, $Pd(OH)_2/C$, THF, 30 °C, 12 h, 100%

**Scheme 9.** Decarboxylation of **(±)-6**

The subsequent reduction of the ketone, however, proved much more challenging than expected. Attempted reduction using sodium borohydride, sodium triacetoxyborohydride, sodium cyanoborohydride, DIBAL, and Red-Al all proved unsuccessful under a variety of reaction conditions, perhaps due to ready enolization. These reactions all resulted in the recovery of the starting material, decomposition, or formation of complex mixtures.

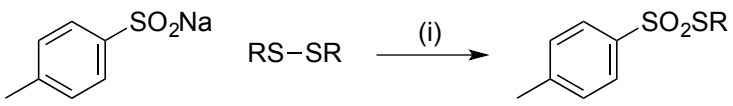
Noting that both Pattenden (Scheme 10) and Corey[8] had prepared C-thiomethyl derivatives prior to ketone reduction in related structures, we treated the mixture of (±)-**25a** and (±)-**25b** with *S*-methyl-*p*-toluenethiosulfonate **26**[17] and triethylamine in dichloromethane solution to give the desired thiomethyl product as an inseparable mixture of diastereoisomers (±)-**27a** and (±)-**27b** in 63% yield and a 1:2 ratio (Scheme 11).



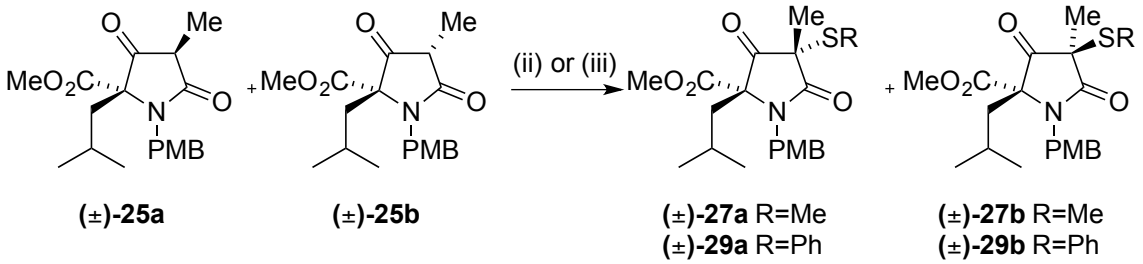

*Reagents and conditions*: (i) i) *p*-$MePhSO_2SMe$, $Et_3N$, $CH_2Cl_2$, r.t., 78%; (ii) $Zn(BH_4)_2$ (4.4 M in THF), THF, 0 °C, 79%.

**Scheme 10.** Approach to reduction in related systems

We also prepared the thiophenyl analogue using *S*-phenyl-*p*-toluenethiosulfonate **28**.[8] Despite a slightly decreased overall yield, incorporation of the thiophenyl group increased the yield of the desired diastereoisomer (±)-**29a**: the (±)-**29a**/(±)-**29b** mixture was obtained in 60% yield and 1:1 ratio; the diastereoisomers were identified using NOESY spectroscopy (Figure 5).




**26** R=Me
**28** R=Ph




*Reagents and conditions*: i) Iodine, $CH_2Cl_2$, r.t., **26**: 76%; **28**: 67%; ii) **26**, $Et_3N$, $CH_2Cl_2$, r.t., (±)-**27a** and (±)-**27b**: 63%; iii) **28**, $Et_3N$, $CH_2Cl_2$, r.t., (±)-**29a** and (±)-**29b**: 60%.

**Scheme 11.** Introduction of thioether groups

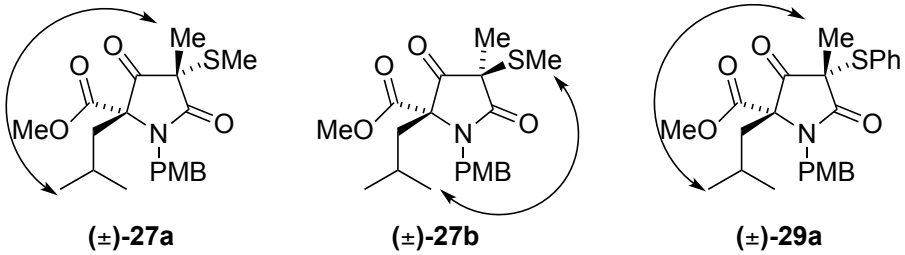
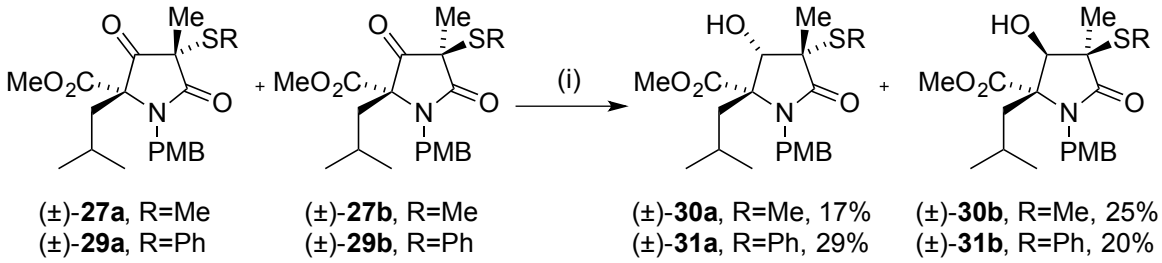



**Figure 5**: NOESY analysis of the relative configurations of (±)-**27a**, (±)-**27b** and (±)-**29a**

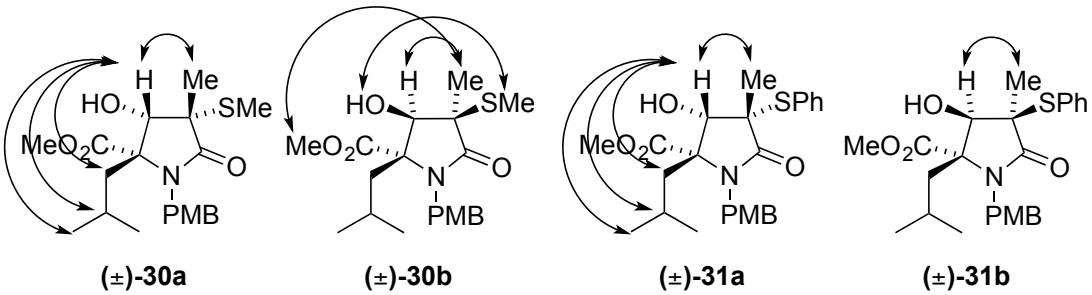
Reduction of the mixtures of diastereoisomers (±)-**27a/b** (thiomethyl) and (±)-**29a/b** (thiophenyl) using sodium borohydride was successful and completely stereoselective (Scheme 12). Only diastereoisomers (±)-**30a** and (±)-**30b** were isolated from the reaction of (±)-**27a/b**, in 17% and 25% yields, respectively, alongside recovered starting material (23%). The ratio of (±)-**27b** to (±)-**27a** in the recovered starting material increased from 2:1 to 6:1, suggesting a higher reactivity of isomer (±)-**27a**. Increased reaction times led to lower yields, presumably due to the reduction of the ester moiety. Reduction of (±)-**29a/b** took place to give only diastereoisomers (±)-**31a** and (±)-**31b** in 29% and 20% yields, respectively, alongside recovered starting material (15%). Similarly to the reduction of (±)-**27a/b**, the ratio of (±)-**29b** to (±)-**29a** in the recovered starting material increased from 0.9:1 to 6:1, suggesting a higher reactivity of isomer (±)-**29a**. Reduction of the thiophenyl isomers (±)-**29a/b** provided a higher isolated yield of (±)-**31a**, the desired product isomer, than was observed for (±)-**30a** in the reduction of the thiomethyl isomers (±)-**27a/b**.




*Reagents and conditions*: i) $NaBH_4$, EtOH, –10 °C, 30 min.

**Scheme 12.** Carbonyl group reduction

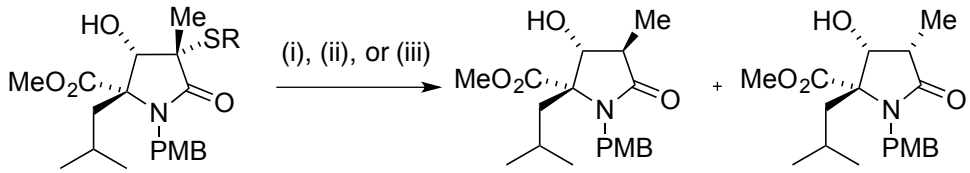
The relative configurations of compounds (±)-**30a/b** and (±)-**31a/b** were determined using NOESY spectroscopy (Figure 6).




(±)-**30a** (±)-**30b** (±)-**31a** (±)-**31b**

**Figure 6**: NOESY analysis of (±)-**30a**, (±)-**30b**, (±)-**31a** and (±)-**31b**

Treatment of (±)-**30a** with Raney nickel (Raney 2800) in ethanol at 0 °C did not induce desulfurization.[8r] When the reaction mixture was heated, a 3:1 mixture of diastereoisomeric products (±)-**21a/b** was obtained in just 7% yield. Similar treatment of (±)-**31a** led at best to a 3:1 mixture of (±)-**21a/b** in 42% yield (Scheme 13).




(±)-**30a**, R=Me
(±)-**31a**, R=Ph

(±)-**21a** (±)-**21b**

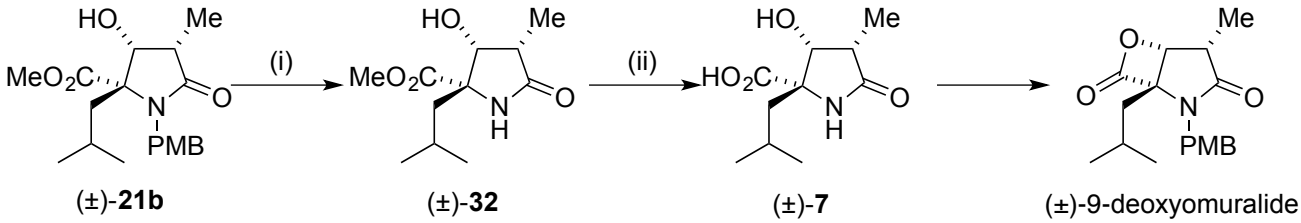
*Reagents and conditions*: i) Starting from (±)-**30a**, Raney nickel, ethanol, reflux, 4 h, (±)-**21a**:(±)-**21b** 3:1, 7%; starting from (±)-**31a**, Raney nickel, ethanol, reflux, 4 h, (±)-**21a**:(±)-**21b** 3:1, 42%; (ii) Starting from (±)-**31a**, tributyltin hydride, AIBN, acetone, reflux, 16 h, (±)-**21a**:(±)-**21b** 1:2, 93%; (iii) Starting from (±)-**31a**, tris(trimethylsilyl)silane, AIBN, acetone, reflux, 16 h, (±)-**21a**:(±)-**21b** 1:5, 88%.

**Scheme 13.** Desulfurization reactions

Inversion of the preferred stereochemical outcome in related desulfurization processes in an α-thiophenylamide was previously observed under Raney nickel-mediated and AIBN/tributyltin hydride-mediated reaction conditions.[18] We were pleased to observe that desulfurization with tributyltin hydride proceeded in 93% yield to give a 2:1 ratio in favour of the desired diastereoisomer (±)-**21b**. To our delight, replacing the radical propagator with the bulkier tris(trimethylsilyl)silane further improved this selectivity to 5:1 in 88% yield, allowing the isomers to be separated by column chromatography.

Removal of the PMB protecting group of **(±)-21b** led to the formation of **(±)-32** in 82% yield, the structure of which was confirmed by NOESY spectroscopy and single crystal X-ray analysis (Figure 7). Saponification of the methyl ester afforded **(±)-7** in good yield (Scheme 14). Compound **(±)-7** was

previously lactonized to produce (±)-9-deoxyomuralide in one step with BOP.Cl by Mereddy.[12] The formal synthesis of (±)-9-deoxyomuralide was thus complete at this point.




*Reagents and conditions*: i) CAN, MeCN/$H_2O$ (3:1), r.t., 82% (ii) NaOH (0.5M), 0-5 °C, 62%

**Scheme 14.** Generation of **(±)-7** and formal total synthesis of (±)-9-deoxyomuralide

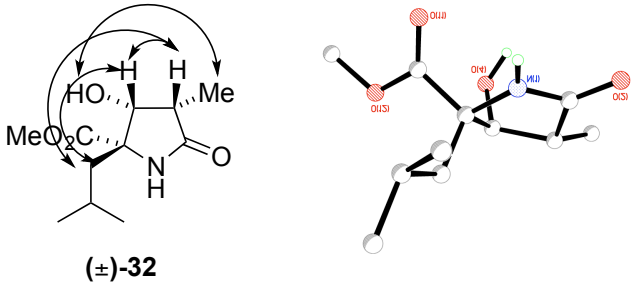
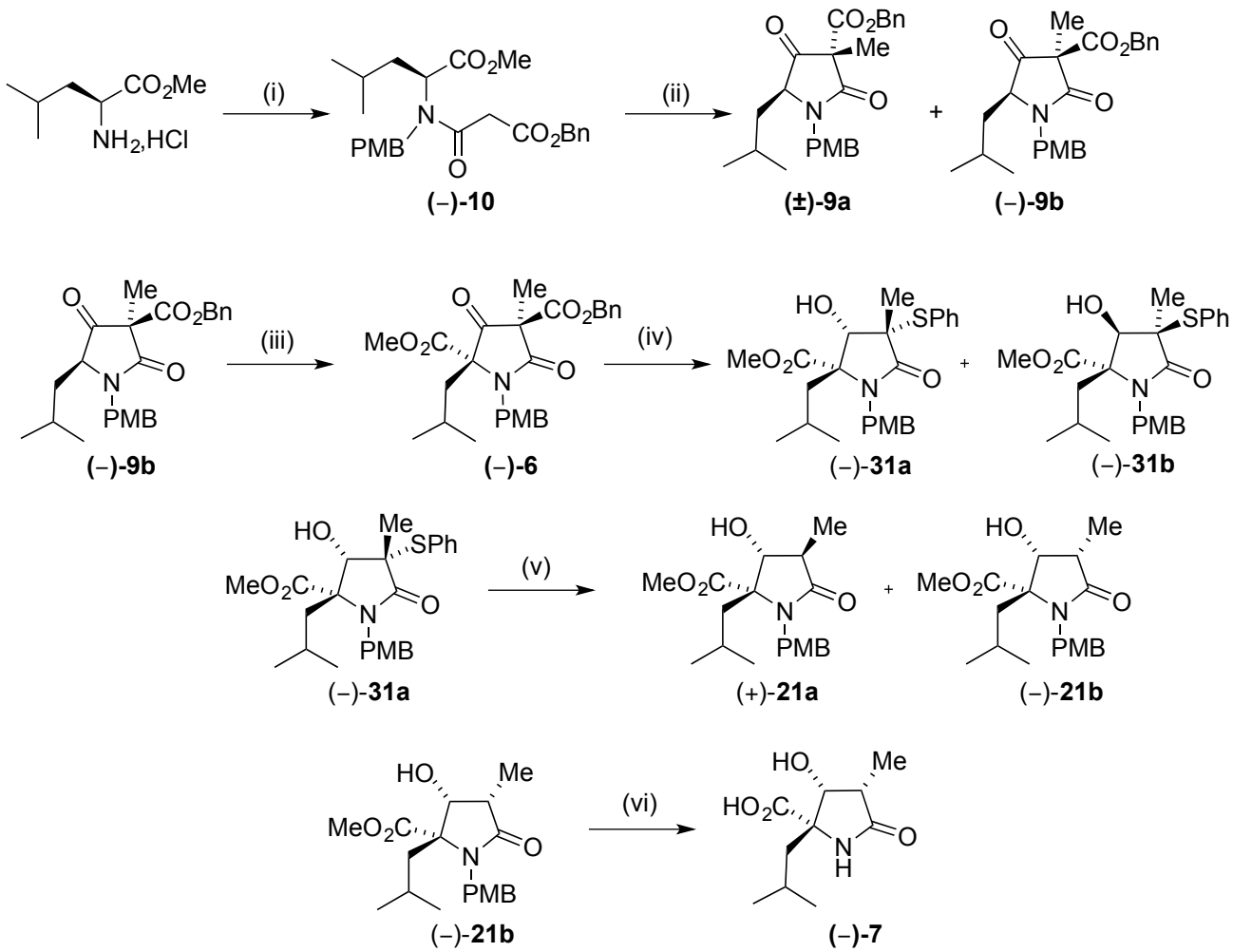



**Figure 7**: NOESY spectroscopy and single crystal X-ray structure of (±)-**32** (hydrogen atoms have been omitted for clarity)

With our methodology in place for the synthesis of (±)**-7,** we turned our attention to the corresponding enantioselective route. To obtain amine **10** as a chiral non-racemic mixture, a milder one-pot reductive amination procedure was attempted: *p*-methoxybenzaldehyde and L-leucine methyl ester hydrochloride were stirred in methanol in the presence of triethylamine and sodium borohydride, affording amine (–)-**10** in 71% yield. Peptide coupling proceeded as described above to form (–)-**8**. Analysis of both products using HPLC on chiral stationary phase confirmed that no racemization had occurred at this point. Compound (–)-**8** was subjected to the Dieckmann cyclization/alkylation reaction. Methylation in THF at 0 °C led to pyroglutamate diastereoisomers (+)-**9a** and (–)-**9b** in an improved 1:2 ratio. Upon separation and HPLC analysis, we found that both (+)-**9a** and (–)-**9b** had undergone partial epimerization; racemization has previously been observed during Dieckmann cyclization reactions.[19] Isomer (+)-**9a** was isolated in just 10% ee. The desired major isomer (–)-**9b**, however, was isolated in 79% ee (and up to 86% ee on a small scale). Isomer (–)-**9b** was then used to complete the synthesis as described above. The fully diastereoselective acylation using Mander's reagent led to the formation of (–)-**6** in 70% yield and 79% ee. Decarboxylation of (–)-**6** followed by thiophenylation and reduction of the ketone moiety afforded (–)-**31a** and (–)-**31b** in 30% and 35% yield over the three steps, respectively. Desulfurization of (–)-**31a** using the conditions described above led to the formation of (–)-**21b** and (+)-**21a** in a 5:1 ratio (**21b**: 83% yield). Successive protecting group removal on substrate (–)-**21b** gave compound (–)-**7** in 53% yield over two steps, completing the first synthesis of **7** in non-racemic form. The complete sequence is shown for clarity in Scheme 15.




*Reagents and conditions:* (i) 1) *p*-Methoxybenzaldehyde, $Et_3N$, MeOH, $NaBH_4$, 0 ° C to r.t., 71%; 2) **12**, NMM, EDAC·HCl, DMAP, $CH_2Cl_2$, r.t., 16 h, 93%; (ii) TBAF in THF, THF, r.t., 0.5 h, then MeI, 0 °C to r.t., 16 h, **9a/b** 57%; (iii) LiHMDS, DMPU, THF, –78 °C, 0.5 h, then $NCCO_2Me$, –78 °C, 4 h, 70%; (iv) 1) $H_2$, $Pd(OH)_2/C$, THF, 30 °C, 12 h, quant.; 2) **28**, $Et_3N$, $CH_2Cl_2$, r.t., mixture of **29a-b**, 67%; 3) $NaBH_4$, EtOH, –10 °C, 0.5 h, 30% of (–)-**31a** and 35% of (–)-**31b**; (v) Acetone, reflux, AIBN, 16 h, tris(trimethylsilyl)silane, 83% of **21b**; (vi) 1) CAN, $MeCN/H_2O$ (3:1), r.t., 62%; 2) NaOH (0.5M), 0-5 °C, 86%.

**Scheme 15.** Synthesis of **(–)-7** and formal total synthesis of (+)-9-deoxyomuralide

## Experimental Detail

### General experimental detail

Infrared spectra were acquired using a Perkin-Elmer Spectrum 100 FT-IR spectrophotometer. Solid samples were run as thin films of their solution in $CH_2Cl_2$ on sodium chloride plates. Liquid samples were run neat. $^1H$ and $^{13}C$ NMR spectra were measured respectively at 500 and 126 MHz using a Bruker Ascend 500, or at 400 and 100 MHz using a Bruker Ultrashield 400 Plus instrument. The solvent used for NMR spectroscopy was deuteriated chloroform unless stated otherwise, using tetramethylsilane as the internal reference. Chemical shifts are given in parts per million (ppm) and *J* values are given in Hertz (Hz). Mass spectra were recorded by the EPSRC Mass Spectrometry Service at the University of Swansea; ionization technique is stated alongside the data. HPLC was carried out on a VWR Elite Lachrom instrument. Separation was achieved by an AD-H Chiralpak column (4.6mm x 250mm 5μm) under the stated conditions. Melting points

were recorded using a Büchi B-545 melting point instrument and are reported uncorrected. Optical rotation values were measured with a Bellingham and Stanley ADP-440 instrument, operating at λ=589 nm, corresponding to the sodium D line, at the temperatures indicated. Spectrophotometric grade chloroform was used for these measurements unless otherwise stated; solutions for these measurements were prepared in volumetric flasks for maximum accuracy of the volume of solvent used. Reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere unless otherwise stated, using flame dried glassware. Reaction solvents were obtained commercially anhydrous, except for the following. Light petroleum (b.p. 40-60 ºC) was distilled prior to use. Dichloromethane was distilled over calcium hydride. Tetrahydrofuran and diethyl ether were distilled under an argon atmosphere from the sodium/benzophenone ketyl radical. All chromatographic manipulations used silica gel as the adsorbent. Reactions were monitored using thin layer chromatography (TLC) on aluminium-or glass-backed plates with Merck Kieselgel 60 F254 silica gel. TLC plates were visualized by UV radiation at a wavelength of 254 nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid or aqueous potassium permanganate, followed by charring where appropriate. Purification by column chromatography used Material Harvest silica gel 60.

**(±)-2-(N-(4-Methoxybenzylimino))-4-methylpentanoic acid methyl ester** [20]

*L*-Leucine methyl ester hydrochloride (5.0 g, 28 mmol), acetic acid (1.0 mL, 17 mmol, 0.6 equiv) and *p*-anisaldehyde (3.4 mL, 28 mmol, 1 equiv) were heated under reflux in toluene (250 mL) using a Dean-Stark apparatus for 24 h. The solvent was removed under reduced pressure and the corresponding racemized imine was collected as a mustard coloured oil (7.3 g, quant.), which was used for the next experiment without further purification. $\nu_{max}$ (thin film)/cm$^{-1}$ 2956 and 1739. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta_H$: 8.20 (s, 1H), 7.73 (d, 2H, *J* = 8.8 Hz), 6.92 (d, 2H, *J* = 8.8 Hz), 4.05 (dd, 1H, *J* = 8.7, 5.7 Hz), 3.84 (s, 3H), 3.73 (s, 3H), 1.77-1.86 (m, 2H), 1.52-1.63 (m, 1H), 0.94 (d, 3H, *J* = 6.6 Hz), 0.89 (d, 3H, *J* = 6.6 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta_C$: 173.3, 162.6, 162.2, 130.4, 128.8, 114.1, 71.7, 55.6, 52.3, 42.3, 24.6, 23.3, 21.6.

**(±)-2-(4-Methoxybenzylamino)-4-methylpentanoic acid methyl ester** (±)-**10** [20]

(±)-2-(N-(4-Methoxybenzylimino))-4-methylpentanoic acid methyl ester (8.26 g, 31 mmol) was dissolved in methanol (150 mL), followed by addition of acetic acid (2.0 mL, 35 mmol, 1.2 equiv). The mixture was cooled to 0 °C, sodium cyanoborohydride (3.9 g, 62 mmol, 2 equiv) added in portion, and the mixture stirred for 30 min at 0 °C, then allowed to reach room temperature while stirring for 20 h under an atmosphere of nitrogen. The reaction was quenched with a few drops of water and the solvents removed under reduced pressure to give a colourless residue that was suspended in water (25 mL) and washed with dichloromethane (2 x 25 mL). The combined organic layers were washed with water (2 x 30 mL), brine (2 x 30 mL), and sodium carbonate (2 x 30 mL), and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue purified by column chromatography on silica gel using 10% ethyl acetate in petroleum ether (40-60 °C) as eluent to give the product **10** as a pale yellow oil (8.2 g, 97%).

**(±)-2-(4-Methoxybenzylamino)-4-methylpentanoic acid methyl ester** (±)-**10**

One step procedure: Leucine methyl ester hydrochloride (9.96 g, 55 mmol) and p-methoxybenzaldehyde (7.4 ml, 61 mmol) were dissolved in toluene (100 mL). Acetic acid (2 mL, 35 mmol) was added, and the solution vigorously refluxed with a well-insulated Dean-Stark apparatus overnight. The resulting solution was evaporated to dryness to produce a thick red/brown oil, which was dissolved in methanol (130 mL). Acetic acid was added (2.8 mL, 50 mmol, 0.9 equiv.) and the reaction mixture cooled to 0 °C. Sodium cyanoborohydride (6.9 g, 110 mmol, 2 equiv.) was added in small portions and the reaction stirred for 30 min. The solution was allowed to reach room temperature and stirred for a further 5 h. A few drops of water were added, and the solution was evaporated to dryness. The resulting oil was dissolved in dichloromethane (150 mL) and washed twice each with equal amounts of water, brine and aqueous sodium carbonate. The organic layer was then dried over magnesium sulfate, filtered, and evaporated to dryness to produce compound ±**10** as a red/brown oil (14g, 96%), which was used without further purification.

**(–)-2-(4-Methoxy-benzylamino)-4-methyl-pentanoic acid methyl ester (–)-10** [20]

Leucine methyl ester hydrochloride (0.19 g, 1.05 mmol) was dissolved in methanol (10 mL). $Et_3N$ (0.15 mL, 1.0 mmol), and *p*-methoxybenzaldehyde (0.15 mL, 1.2 mmol) added. The solution was stirred for 90 min, cooled to 0 °C, and sodium borohydride (0.82 g, 2.0 mmol) added over 30 min. The mixture was stirred for a further 30 min. The solvents were removed under reduced pressure and the resulting oil was dissolved in ethyl acetate (50 mL). The organic solution was washed twice each with equal amounts of water, brine, and aqueous sodium carbonate. The aqueous layer was washed with ethyl acetate, and the organic fractions were combined, dried over magnesium sulfate, filtered and the solvents removed under reduced pressure. The residue was purified by column chromatography on silica gel using petroluem ether-ethyl acetate (2:1) as eluent to afforded (**–**)-**10** as a colourless oil (0.212g, 76%). $\nu_{max}$ (neat)/$cm^{-1}$: 2953, 2869, 2836, 1733, 1612, 1511, 1244, 1170, 1149, 824; $[\alpha]_D^{25}$ = –40.3 (*c* 1.3, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta_H$: 0.82 (d, 3H, *J*= 6.6 Hz), 0.90 (d, 3H, *J*= 6.6 Hz), 1.46 (t, 2H, *J*= 7.2 Hz), 1.71-1.79 (m, 2H), 3.29 (t, 1H, *J*= 7.3 Hz), 3.54 (d, 1H, *J*= 12.6 Hz), 3.68 (d, 1H, *J*= 12.6 Hz), 3.71 (s, 3H), 3.78 (s, 3H), 6.84 (d, 2H, *J*= 8.6 Hz), 7.23 (d, 2H, *J*= 8.3 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta_C$: 176.7, 158.8, 132.2, 129.6, 113.9, 59.2, 55.4, 51.8, 51.7, 43.0, 25.0, 23.0, 22.3. HRMS (ESI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{15}H_{24}NO_3]^+$ 266.1751; Found 266.1745.

**(±)-2-{N-(4-Methoxybenzyl)-[2-(4-nitrobenzyloxycarbonyl)-acetyl]-amino}-4-methyl-pentanoic acid methyl ester (±)-13**

Amine (±)-**10** (4.36 g, 16 mmol), *N*-methylmorpholine (2 mL, 18 mmol), *p*-nitrobenzyl malonic half ester **11** (4.31 g, 18 mmol), EDAC.HCl (4.60 g, 24 mmol) and 4-dimethylaminopyridine (0.39 g, 3 mmol) were stirred in dichloromethane (100 mL) for 20 h under a nitrogen atmosphere. Aqueous HCl (1M, 5 mL) was added, and the reaction mixture stirred for a further 30 min. The reaction mixture was washed with water (2

x 50 mL), and the organic layer dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue purified by column chromatography on silica gel using 30% ethyl acetate in petroleum ether (40-60 ºC) as eluent to give the product **12** as a dark brown oil (5.65 g, 75%). $\nu_{max}$ (neat)/cm$^{-1}$: 2957, 1747, 1651, 1611, 1515, 1435, 1348, 1252, 1176, 1033; Major conformation: $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.33 – 5.24 (m, 2H), 4.89 (t, *J* = 6.9 Hz, 1H), 4.59 (d, *J* = 17.2 Hz, 1H), 4.45 (d, *J* = 17.3 Hz, 1H), 3.80 (s, 3H), 3.62 (s, 3H), 3.51 (d, *J* = 5.6 Hz, 2H), 1.90 – 1.80 (m, 1H), 1.65 – 1.52 (m, 2H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 6.4 Hz, 3H).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.8, 167.3, 167.1, 159.4, 147.9, 142.9, 129.6, 128.5, 127.9, 123.9, 114.4, 65.6, 56.4, 55.5, 52.3, 50.1, 41.7, 38.5, 25.3, 22.7, 22.4; HRMS (ESI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{25}H_{31}N_2O_8]^+$ 487.2075; Found 487.2066.

***trans* and *cis* (±)-5-Isobutyl-1-(4-methoxybenzyl)-3-methyl-2,4-dioxopyrrolidine-3-carboxylic acid 4-nitrobenzyl ester (±)-14a and (±)-14b**

*tert*-Butylammonium fluoride (1 M solution in THF, 19.0 mL, 19 mmol) was added to a solution of the ester-amide (±)-**13** (3.65 g, 7.5 mmol) in diethyl ether (80 mL) at room temperature under a nitrogen atmosphere, and the reaction mixture stirred overnight. The solvents were removed under reduced pressure, and the residue was suspended in THF (80 mL) and cooled to 0 °C. Methyl iodide (1.44 mL, 23 mmol) was added, and the mixture stirred at room temperature overnight under a nitrogen atmosphere. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (50 mL) and washed with water (50 mL). The organic layer was dried over magnesium sulfate, and the solvents removed under removed pressure. The residue was purified by column chromatography on silica gel using 20% acetone in petroleum ether (40-60 °C) as eluent to afford (±)-**14a** as colourless crystals (1.3 g, 2.8 mmol, 37%) and (±)-**14b** as a pale yellow oil (0.9 g, 1.9 mmol, 25 %).

**First eluting diastereoisomer** (±)-**14a:** $\nu_{max}$ (solid)/cm$^{-1}$: 2959, 1780, 1749, 1696, 1610, 1348, 1248, 1123; $^{1}$H NMR ($CDCl_3$, 400 MHz) $\delta_H$: 0.82 (3H, d, *J*= 8.0 Hz), 0.92 (3H, d, *J*= 8.0 Hz), 1.60 (3H, s), 1.64-1.86 (3H, m), 3.74 (3H, s), 3.85 (1H, d *J*= 16.0 Hz), 3.90 (1H, dd, *J*= 8.0, 7.92 Hz), 5.19 (1H, d *J*= 14.0 Hz), 5.26 (1H, d *J*= 14.0 Hz), 5.40 (1H, d *J*= 16.0 Hz), 6.69 (2H, d, *J*=8.0 Hz), 7.11 (2H, d, *J*= 8.0 Hz), 7.33 (2H, d, *J*= 8.0 Hz), 8.19 (2H, d, *J*= 8.0 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta_C$: 16.4, 22.6, 23.5, 24.8, 38.2, 43.5, 55.4, 58.8, 62.8, 66.5, 114.3, 124.1, 126.5, 128.3, 129.8, 142.1, 148.0, 159.6, 165.6, 169.4, 205.9; HRMS (ESI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{25}H_{29}N_2O_7]^+$ 469.1969; Found 469.1966.

**Second eluting diastereoisomer**(±)-**14b:** $\nu_{max}$ (neat)/cm$^{-1}$: 2959, 1778, 1748, 1694, 1610, 1515, 1454, 1416, 1347, 1248, 1177, 1124, 1034; $^{1}$H NMR ($CDCl_3$, 400 MHz) $\delta_H$: 0.76-0.82 (6H, m), 1.56 (3H, s), 1.51-1.60 (2H, m), 1.77-1.85 (1H, m), 3.72-3.77 (1H, dd, *J*= 8.0, 4.0 Hz), 3.80 (3H, s), 4.0 (1H, d *J*= 16.0 Hz), 5.20-5.30 (2H, m), 5.32 (1H, d *J*= 16.0 Hz), 6.86 (2H, d, *J*= 8.0 Hz), 7.16 (2H, d, *J*= 8.0 Hz), 7.45 (2H, d, *J*= 8.0 Hz), 8.22 (2H, d, *J*= 8.0 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta_C$: 17.0, 22.1, 23.4, 24.6, 39.0, 43.7, 55.5,

58.7, 62.4, 66.5, 114.6, 124.1, 127.0, 128.5, 129.7, 142.2, 148.0, 159.7, 165.7, 169.3, 205.6; HRMS (ESI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{25}H_{29}N_2O_7]^+$ 469.1969; Found 469.1965.

**(±)-(3R,3aS,4S,6aS)-3a-Hydroxy-4-isobutyl-5-(4-methoxybenzyl)-6a-methyl-3-(4-nitro phenyl)-tetrahydro-1H-furo[3,4-c]pyrrole-1,6(6aH)-dione (±)-15 and (±)- (3R,3aS,4S, 6aS)-4-isobutyl-5-(4-methoxybenzyl)-6a-methyl-3-(4-nitrophenyl)-1,6-dioxohexahydro-1H-furo[3,4-c]pyrrol-3a-yl methyl carbonate (±)-16**

Hexamethyldisilazane (0.27 mL, 1.3 mmol) was dissolved in anhydrous THF (20 mL) and the solution cooled to –78 °C. *n*-Butyllithium (2.5 M in THF, 0.51 mL, 1.3 mmol) was added. The solution was a stirred for 30 min and DMPU (0.08 mL, 0.6 mmol) added. Lactam (±)-**14a** (0.20 g, 0.4 mmol) was dissolved in anhydrous THF (5 mL), the resulting solution cooled to –78 °C, and DMPU (0.08 mL, 0.6 mmol) added. The solution of LHMDS was added dropwise using a cannula to the solution of the lactam. The mixture was stirred at –78 °C for 30 min. Methyl cyanoformate (0.17 mL, 2.13 mmol) was added and the reaction stirred for a further 4 h at –78 °C. A saturated aqueous solution of ammonium chloride was added at –78 °C. The mixture was allowed to reach room temperature and the solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate and the solution washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified using column chromatography on silica gel using petroleum ether (40-60 °C)/ethyl acetate (4:1) as eluent to yield (±)-**15** as an off-white solid (0.08 g, 36%) together with the methyl carbonate **(±)-16** (0.06g, 28%).

**Compound (±)-15**: $\nu_{max}$ (neat)/$cm^{-1}$ (thin film) 3390, 2958, 1791, 1679; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta_H$: 8.21 (d, 2H, *J*= 8.8 Hz), 7.28 (d, 2H, *J*= 8.8 Hz), 7.18 (d, 2H, *J*= 8.8 Hz), 6.97 (d, 2H, *J*= 8.8 Hz), 5.29 (d, 1H, *J*= 14.4 Hz), 4.82 (s, 1H), 3.84 (s, 3H), 3.77 (d, 1H, *J*= 14.4 Hz), 3.34 (dd, 1H, *J*= 8.6, 3.0 Hz), 1.68-1.74 (m, 1H), 1.58 (s, 3H), 1.37-1.47 (m, 2H), 0.84 (d, 6H, *J*= 6.0 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta_C$: 167.4, 160.1, 148.9, 139.7, 130.4, 127.8, 127.6, 124.3, 114.8, 84.6, 83.0, 58.3, 57.3, 55.5, 44.6, 37.3, 27.3, 26.3, 23.1, 22.0, 15.2; HRMS (NSI-FTMS) *m/z*: $[M+NH_4]^+$ Calcd for $[C_{25}H_{32}N_3O_7]^+$ 486.2224; Found 486.2235.

**Compound (±)-16**: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta_H$: 8.18 (d, 2H, *J*= 8.8 Hz), 7.28 (d, 2H, *J*= 8.8 Hz), 7.26 (d, 2H, *J*= 8.8 Hz), 6.93 (d, 2H, *J*= 8.8 Hz), 5.29 (d, 1H, *J*= 14.8 Hz), 4.96 (s, 1H), 3.85 (d, 1H, *J*= 14.8 Hz), 3.80 (s, 3H), 3.66-3.72 (m, 1 H), 3.47 (s, 3H), 1.70-1.82 (m, 2H), 1.62 (s, 3H), 1.46-1.50 (m, 1H), 0.97 (d, 3H, *J*= 6.4 Hz), 0.96 (d, 3H, *J*= 6.4 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta_C$: 171.5, 167.1, 160.1, 153.5, 148.3, 139.9, 130.2, 127.13, 127.09, 123.6, 114.8, 88.8, 83.7, 59.8, 56.4, 55.7, 55.4, 44.6, 38.5, 25.9, 23.1, 22.0, 15.9; HRMS (NSI-FTMS) *m/z*: $[M+NH_4]^+$ Calcd for $[C_{27}H_{34}N_3O_9]^+$ 544.2290; Found 544.2282.

**(±)-2-{(4-Methoxybenzyl)-[2-(benzyloxycarbonyl)-acetyl]-amino}-4-methylpentanoic acid methyl ester (±)-8**

Compound **(±)-10** (11.0 g, 41.5 mmol), *N*-methylmorpholine (5 mL, 45.7 mmol), benzyl malonic half ester (10.6 g, 45.7 mmol), EDAC.HCl (11.9 g, 62.3 mmol) and 4-dimethylaminopyridine (1.0 g, 8.3 mmol) were dissolved in dichloromethane (500 mL), and the mixture stirred for 20 h under a nitrogen atmosphere. Aqueous HCl (1M, 20 mL) was added and the reaction mixture stirred for further 30 minutes, washed with water (2 x 50 mL) and the organic layer dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue purified by column chromatography on silica gel using 30% ethyl acetate in petroleum ether (40-60 ºC) as eluent to give the product as a yellow oil (14.5 g, 79%).

**2-{(4-Methoxy-benzyl)-[2-(benzyloxycarbonyl)-acetyl]-amino}-4-methyl-pentanoic acid methyl ester (–)-8**

Compound **(–)-10** (1.38 g, 5.19 mmol), *N*-methylmorpholine (1.3 mL, 11.82 mmol), benzyl malonic half ester (2.54 g, 10.95 mmol), EDAC.HCl (2.63 g, 13.75 mmol) and 4-dimethylaminopyridine (0.16 g, 1.3 mmol) were dissolved in dichloromethane (40 mL), and the mixture stirred for 20 h under a nitrogen atmosphere. Aqueous HCl (1M, 1.5 mL) was added, and the reaction mixture stirred for a further 30 min, washed with water (2 x 50 mL), and the organic layer dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue purified by column chromatography on silica gel using 30% ethyl acetate in petroleum ether (40-60 ºC) as eluent to give the product as a yellow oil (2.128 g, 93%). $[\alpha]_D^{26}$ = –46.42 (*c* 1.12, $CHCl_3$) $\nu_{max}$ (neat)/$cm^{-1}$: 2956, 2870, 2838, 1740, 1655, 1613, 1515, 1456, 1249, 1176, 1033, 824, 699; $\delta_H$ $^1$H NMR (500 MHz, $CDCl_3$) Major conformation: δ 7.41 – 7.30 (m, 5H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.23 – 5.15 (m, 2H), 4.82 (t, *J* = 6.9 Hz, 1H), 4.55 (d, *J* = 17.1 Hz, 1H), 4.42 (d, *J* = 17.2 Hz, 1H), 3.79 (s, 3H), 3.58 (s, 3H), 3.50 – 3.46 (m, 2H), 1.90 – 1.79 (m, 1H), 1.61 – 1.50 (m, 2H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.80 (d, *J* = 6.4 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.8, 167.3, 159.3, 135.5, 128.7, 128.5, 128.1, 114.3, 67.3, 56.2, 55.5, 52.2, 50.1, 41.8, 38.4, 25.2, 22.7, 22.4; HRMS (ESI-FTMS) *m/z*: $[M–H]^+$ Calcd for $[C_{25}H_{31}NO_6]^+$ 442.2224; Found 442.2226.

**(±)-(3*S*,5*S*)-*N*-(4'-Methoxybenzyl)-3-methyl-5-(2'-methylpropyl)-pyrrolidin-2,4-dione-3-carboxylic acid benzyl ester (±)-9a and (±)-(3*R*,5*S*)-*N*-(4'-methoxybenzyl)-3-methyl-5-(2'-methylpropyl)-pyrrolidin-2,4-dione-3-carboxylic acid benzyl ester (±)-9b**

**Two-step synthesis:** Diester **(±)-8** (8.86 g, 0.02 mol) was dissolved in diethyl ether (50 mL) under a nitrogen atmosphere. Tetrabutylammonium fluoride (1 M solution in THF, 50 mL, 0.05 mol) was added and the reaction mixture was stirred overnight. The solvents were removed under reduced pressure and the residue dissolved in THF (50 mL) under an atmosphere of nitrogen. The solution was cooled to 0 °C, iodomethane (5.00 mL, 0.08 mol) added, and the mixture stirred overnight. The solvents were removed under reduced pressure and the residue dissolved in dichloromethane (50 mL). The solution was washed with water (2 x 50 mL), dried over anhydrous magnesium sulfate, filtered, and solvents removed under reduced pressure. The residue was purified by column chromatography on silica gel using 20% ethyl acetate

in light petroleum ether as eluent. The first eluting diastereoisomer **(±)-9a** was obtained as a pale yellow oil (2.59 g, 30%), and the second eluting diastereoisomer **(±)-9b** as a darker yellow oil (2.47 g, 29%).

**One-pot synthesis:** Diester **(±)-8** (4.915 g, 11.14 mmol) was dissolved in THF (250 mL). Tetrabutylammonium fluoride (1M in THF, 39 mL, 39 mmol) was added, and the solution stirred at room temperature for 0.5 h under static pressure of nitrogen. Iodomethane (2.9 mL, 46.58 mmol) was added, and the solution stirred overnight. Water (5 mL) was added, and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane, and the mixture washed with water (2 x 50 mL) and brine (2 x 50 mL), dried over magnesium sulphate, filtered, and the solvent removed under reduced pressure. The residue was purified using column chromatography on silica gel using 20% ethyl acetate in petroleum ether (40-60 °C) as eluent to obtain the diastereoisomers **(±)-9a** and **(±)-9b** in a 1:1 ratio (2.69 g, 57%).

**(+)-(3*S*,5*S*)-*N*-(4'-Methoxybenzyl)-3-methyl-5-(2'-methylpropyl)-pyrrolidin-2,4-dione-3-carboxylic acid benzyl ester (+)-9a and (–)-(3*R*,5*S*)-*N*-(4'-methoxybenzyl)-3-methyl-5-(2'-methylpropyl)-pyrrolidin-2,4-dione-3-carboxylic acid benzyl ester (–)-9b**

Tetrabutylammonium fluoride (1 M solution in THF, 11.5 mL, 11.5 mmol,) was added to a solution of the diester (–)-**8** (1.442 g, 3.2 mmol) in THF (72 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 30 min and cooled to 0 °C using an ice bath. Iodomethane (0.81 mL, 13 mmol) was added, and the reaction mixture stirred overnight. Water (4 mL) was added, and the solvent was removed under reduced pressure and the residue dissolved in dichloromethane (50 mL) and washed with water (50 mL). The organic layer was dried over magnesium sulfate and the solvent removed under reduced pressure. The residue was purified and partially separated by silica gel column chromatography using 10% ethyl acetate in petroleum ether (40-60°C) as eluent to afford the diastereoisomers in a 1:2 ratio (0.78 g, 57%).

For **(+)-(3*S*,5*S*)-*N*-(4'-Methoxybenzyl)-3-methyl-5-(2'-methylpropyl)-pyrrolidin-2,4-dione-3-carboxylic acid benzyl ester (+)-9a:** $[\alpha]_D^{26}$ = +14.54 (*c* 0.44, $CHCl_3$); $\nu_{max}$ (thin film)/$cm^{-1}$ 2958, 1778, 1747, 1697; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, 3H, *J* = 5.0, 1.9 Hz), 7.24 – 7.21 (m, 2H, Ar), 7.02 (d, 2H, *J* = 8.6 Hz), 6.59 (d, 2H, *J* = 8.6 Hz), 5.42 (d, 1H, *J* = 15.0 Hz), 5.19 (d, 1H, *J* = 12.3 Hz), 5.09 (d, 1H, *J* = 12.3 Hz), 3.85 (dd, 1H, *J* = 7.8, 3.9 Hz), 3.80 (d, 1H, *J* = 15.0 Hz), 3.73 (s, 3H), 1.82 – 1.73 (m, 1H), 1.67 – 1.61 (m, 1H), 1.58 (s, 3H), 1.56 – 1.48 (m, 1H), 0.87 (d, 3H, *J* = 6.6 Hz), 0.76 (d, 3H, *J* = 6.5 Hz); $^{13}C$ NMR (126 MHz, CDCl3) $\delta_C$: 205.9, 169.6, 165.6, 159.2, 134.8, 129.4, 128.7, 128.5, 128.2, 126.2, 114.1, 68.1, 62.4, 58.6, 55.2, 43.2, 37.9, 24.6, 23.2, 22.4, 16.1; HRMS (NSI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{25}H_{30}NO_5]^+$ 424.2124; Found 424.2110. Determined by HPLC to be 13% ee.

For **(–)-(3*R*,5*S*)-*N*-(4'-Methoxybenzyl)-3-methyl-5-(2'-methylpropyl)-pyrrolidin-2,4-dione-3-carboxylic acid benzyl ester (–)-9b:** $[\alpha]_D^{26}$ = –17.14 (*c* 0.98, $CHCl_3$); $\nu_{max}$ (thin film)/$cm^{-1}$ 2927, 1775, 1746, 1696; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 7.13 (d, 2H, *J* = 8.6 Hz), 6.83 (d, 2H, *J* = 8.6 Hz), 5.26 (d, 1H, *J* = 12.1 Hz), 5.19 (d, 1H, *J* = 14.9 Hz), 5.08 (d, 1H, *J* = 12.1 Hz), 4.01 (d, 1H, *J* = 14.9 Hz), 3.79 (s, 3H), 3.67 (t, 1H, *J* = 6.8 Hz, H5), 1.77 – 1.72 (m, 1H), 1.54 (s, 3H), 1.50 (dd, 2H, *J* = 7.4, 6.5 Hz), 0.73 (d,

3H, *J* = 6.5 Hz), 0.70 (d, 3H, *J* = 6.5 Hz); $^{13}$C NMR (126 MHz, CDCl3) δ: 205.6, 169.3, 165.6, 159.4, 134.7, 129.4, 128.7, 128.6, 128.4, 127.1, 114.3, 68.2, 62.4, 58.6, 55.3, 43.5, 38.9, 24.4, 23.0, 21.9, 16.6; HRMS (NSI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{25}H_{30}NO_5]^+$ 424.2124; Found 424.2108. Determined by HPLC to be 79% ee.

**(±)-(3R,5R)-*N*-(4'-Methoxybenzyl)-3-methyl-5-(2'-methylpropyl)-pyrrolidin-2,4-dione-3,5-dicarboxylic acid-3-benzyl ester-5-methyl ester (±)-6**

**From the first eluting diastereoisomer** (±)-**9a**. Hexamethyldisilazane (0.24 mL, 1.1 mmol) was dissolved in anhydrous THF (10 mL) and the solution cooled to –78 °C. *n*-Butyllithium (2.5 M in THF, 0.46 mL, 1.1 mmol) was added. The mixture was stirred for 30 min and DMPU (0.07 mL, 0.5 mmol) added. Compound (±)-**9a** (0.16 g, 0.3 mmol) was dissolved in anhydrous THF (5 mL), the solution was cooled to –78 °C, and DMPU (0.07 mL, 0.5 mmol) added. The solution of LHMDS was added dropwise using a cannula to the solution of the lactam. The mixture was stirred at –78 °C for 30 min. Methyl cyanoformate (0.15 mL, 1.9 mmol) was added, and the mixture was stirred for a further 4 h at –78 °C. Saturated aqueous ammonium chloride was added (0.2 mL), the mixture was allowed to reach room temperature, and the organic solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate and the solution washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel using light petroleum ether (40-60 °C)/ethyl acetate (2:1) as eluent to yield (±)-**6** as an off-white solid (0.13 g, 73%).

**From the second eluting diastereoisomer** (±)-**9b**: Hexamethyldisilazane (0.32 mL, 1.5 mmol) was dissolved in anhydrous THF (10 mL) and the solution cooled to –78 °C. *n*-Butyllithium (2.5 M in THF, 0.62 mL, 1.5 mmol) was added. The mixture was stirred for 30 min and DMPU (0.06 mL, 0.75 mmol) added. Compound (±)-**9b** (0.22 g, 0.5 mmol) was dissolved in anhydrous THF (5 mL), the solution was cooled to –78 °C, and DMPU (0.06 mL, 0.75 mmol) added. The solution of LHMDS was added dropwise using a cannula to the solution of the lactam. The mixture was stirred at –78 °C for 30 min. Methyl cyanoformate (0.20 mL, 2.6 mmol) was added, and the mixture stirred for a further 4 h at –78 °C. Saturated aqueous ammonium chloride (0.2 mL) was added, the mixture allowed to reach room temperature, and the solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate and the solution was washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and the organic solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel using light petroleum ether (40-60 °C)/ethyl acetate (2:1) as eluent to yield (±)-**6** as an off-white solid (0.19 g, 79%).

**From a mixture of diastereoisomers (±)-9a** and (±)-**9b**: A mixture of (±)-**9a-b** (0.34 g, 0.8 mmol) was dissolved in anhydrous THF (15 mL) and the solution cooled to –78 °C. DPMU (1.10 mL, 9.2 mmol) was added followed by LHMDS (1M in THF, 6.1 mL, 6.13 mmol), and the mixture stirred at –78 °C for 30 min.

Methyl cyanoformate (0.78 mL, 9.2 mmol) was added, and the mixture stirred for a further 4 h at –78 °C. Saturated aqueous ammonium chloride was added (0.4 mL) at –78 °C, the mixture allowed to reach room temperature, and the organic solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate and the solution washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel using light petroleum ether/ethyl acetate (2:1) as eluent to yield (±)-**6** as an off-white solid (1.26 g, 86%).

**(–)-(3R,5R)-*N*-(4'-Methoxybenzyl)-3-methyl-5-(2'-methylpropyl)-pyrrolidin-2,4-dione-3,5-dicarboxylic acid-3-benzyl ester-5-methyl ester (–)-6**

Compound (–)-**9b** (1.747 g, 4.125 mmol.) was dissolved in anhydrous THF (70 mL) and the solution cooled to –78 °C. DPMU (1.5 mL, 9.2 mmol) was added followed by LiHMDS (1M in THF, 8.5 mL, 8.5 mmol), and the mixture stirred at –78 °C for 30 min. Methyl cyanoformate (1.1 mL, 13 mmol) was added, and the mixture stirred for a further 4 h at –78 °C. Saturated aqueous ammonium chloride was added (2 mL) at –78 °C, the mixture allowed to reach room temperature, and the organic solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate and the solution washed with water (2 x 100 mL) and brine (2 x 100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel using light petroleum ether (40-60 C)/ethyl acetate (4:1) to yield (–)-**6** as an off-white solid (1.985 g, 70%). mp 79-82 °C; $[\alpha]_D^{21}$ = –20.35 (*c* 1.12, $CHCl_3$); $\nu_{max}$ (thin film)/$cm^{-1}$ 2958, 1782, 1751, 1699; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 7.19 (d, 2H, *J* = 8.7 Hz), 6.77 (d, 2H, *J* = 8.7 Hz), 5.20 (d, 1H, *J* = 12.1 Hz), 5.14 (d, 1H, *J* = 12.1 Hz), 4.89 (d, 1H, *J* = 15.0 Hz), 4.15 (d, 1H, *J* = 15.0 Hz), 3.77 (s, 3H), 3.23 (s, 3H), 2.15 (dd, 1H, *J* = 15.2, 5.4 Hz), 1.86 (dd, 1H, *J* = 15.2, 6.3 Hz), 1.72 (s, 3H), 1.47 – 1.41 (m, 1H), 0.65 (d, 3H, *J* = 6.6 Hz), 0.52 (d, 3H, *J* = 6.6 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 201.8, 170.8, 167.6, 165.2, 159.23, 134.5, 130.3, 128.7, 128.61, 128.64, 127.6, 113.8, 76.1, 68.5, 58.4, 55.3, 52.9, 43.9, 38.7, 24.2, 23.4, 23.1, 18.9; HRMS (NSI-FTMS) *m/z*: $[M+Na]^+$ Calcd for $[C_{27}H_{31}NO_7Na]^+$ 504.1993; Found 504.1979. Determined by HPLC to be 79% ee.

**(±)-(3R,4R,5R)-*N*-(4'-Methoxybenzyl)-3-methyl-4-hydroxy-5-(2'-methylpropyl)-pyrrolidin-2-one-3,5-dicarboxylic acid-3-benzyl ester-5-methyl ester (±)-17**

Compound (±)-**6** (0.21 g, 0.44 mmol) was dissolved in EtOH (10 mL). The mixture was cooled to –10 °C, and sodium borohydride (0.01 g, 0.22 mmol) added. The mixture was stirred at –10 °C for 30 min, and water added. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (10 mL). The mixture was washed with water (2 x 30 mL) and brine (2 x 30 mL), the organic layer dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel using light petroleum ether (40-60 °C)/ethyl acetate

(2:1) as eluent to afford (±)-**17** was isolated as a colourless foam (0.11 g, 52%). $n_{max}$ (thin film)/$cm^{-1}$ 3373, 1735, 1676; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41-7.33 (m, 5H), 7.11 (d, 2H, *J* = 8.7 Hz), 6.68 (d, 2H, *J* = 8.7 Hz), 5.25 (d, 2H, *J* = 1.5 Hz), 4.94 (d, 1H, *J* = 16.1 Hz), 4.69 (d, 1H, *J* = 8.4 Hz), 4.39 (d, 1H, *J* = 16.1 Hz), 3.75 (s, 3H), 3.70 (s, 3H), 3.14 (d, 1H, *J* = 8.4 Hz), 1.71-1.67 (m, 2H), 1.67-1.62 (m, 1H), 1.48 (s, 3H), 0.83 (d, 3H, *J* = 6.2 Hz), 0.70 (d, 3H, *J* = 6.2 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.8, 172.18, 170.8, 158.5, 135.1, 130.3, 128.7, 128.4, 128.3, 127.9, 113.8, 77.5, 72.1, 67.7, 56.2, 55.3, 52.5, 45.1, 40.3, 24.1, 24.1, 23.4, 19.2; HRMS (NSI-FTMS) *m/z*: $[M+Na]^+$ Calcd for $[C_{27}H_{33}NO_7Na]^+$ 506.2149; Found 506.2134.

**(±)-(3R,4R,5R)-*N*-(4'-Methoxybenzyl)-3-methyl-4-hydroxy-5-(2'-methylpropyl)-pyrrolidin-2-one-3,5-dicarboxylic acid 5-methyl ester (±)-18**

Compound (±)-**17** (1.29 g, 2.67 mmol) was dissolved in anhydrous THF (20 mL) and $Pd(OH)_2/C$ (0.65 g, 10 mol%) added. The mixture was purged with nitrogen, and treated with hydrogen under balloon pressure overnight at room temperature. The mixture was filtered through celite, and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate-petroleum ether (40-60°C) (1:2) as eluent to afford **(±)-18** as a colourless solid (0.89 g, 86%), mp 108-111 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3343, 1741, 1673; $^1$H NMR (500 MHz, $CDCl_3$) δ: 7.14 (d, 2H, *J*= 8.6 Hz), 6.85 (d, 2 H, *J*= 8.7 Hz), 4.98 (d, 1H, *J*= 16.2 Hz), 4.91 (s, 1H), 4.54 (d, 1H, *J*= 16.2 Hz), 3.79 (s, 3H), 3.77 (s, 3H), 1.89-1.84 (m, 1H), 1.70-1.64 (m, 2H), 1.44 (s, 3H), 0.90 (d, 3H, *J*= 6.4 Hz), 0.75 (d, 3H, *J*= 6.2 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 176.3, 172.3, 172.2, 158.8, 129.0, 127.9, 114.1, 74.4, 72.3, 55.6, 55.3, 52.7, 45.4, 39.4, 24.2, 24.0, 23.3, 20.9; HRMS (NSI-FTMS) *m/z*: $[M–H]^+$ Calcd for $[C_{20}H_{26}NO_7]^+$ 392.1715; Found 392.1704.

**(±)-(3R,4S,5R)-*N*-(4'-Methoxybenzyl)-3-methyl-5-(2'-methylpropyl)-3-azabicyclo[3.2.0] heptane-2,7-dione-5-carboxylic acid methyl ester (±)-22**

Compound (±)-**18** (0.13 g, 0.3 mmol) was dissolved in anhydrous dichloromethane (5 mL) under a nitrogen atmosphere, and diphenyldiselenide (0.16 g, 0.5 mmol) added. The mixture was cooled to 0 °C and tributylphosphine (0.16 mL, 0.7 mmol) added. The mixture was allowed to reach room temperature with stirring overnight, diluted with dichloromethane (2 mL), and washed with water (2 mL). The aqueous layer was extracted with dichloromethane (2ml), and the combined organic layers were washed with brine (2 mL), dried over anhydrous magnesium sulphate, and the solvents removed under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-petroleum ether (40-60 °C) (1:2) to yield (±)-**22** as an off-white solid (0.05 g, 43%), mp 104-109 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 1842, 1731, 1702. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, 2H, *J* = 8.7 Hz), 6.83 (d, 2H, *J* = 8.7 Hz), 5.15 (s, 1H), 4.51 (d, 2H, *J* = 1.8 Hz), 3.78 (s, 3H), 3.52 (s, 3H), 2.11 (dd, 1H, *J* = 13.4, 7.7 Hz), 1.77 – 1.71 (m, 1H), 1.67 (s, 3H), 1.62 (dd, 1H, *J* = 13.4, 5.5 Hz), 0.93 (d, 3H, *J* = 6.6 Hz), 0.86 (d, 3H, *J* = 6.6 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ

169.7, 168.4, 165.8, 159.0, 128.84, 128.82, 114.0, 76.0, 68.6, 64.9, 55.3, 52.7, 43.9, 37.3, 24.6, 23.8, 22.8, 11.7; HRMS (NSI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{20}H_{26}NO_6]^+$ 376.1755; Found 376.1756.

**(±)-(3R,4R,5R)-*N*-(4'-Methoxybenzyl)-3-methyl-4-trifluoroacetoxy-5-(2'-methylpropyl)-pyrrolidin-2-one-3,5-dicarboxylic acid 5-methyl ester (±)-23**

Compound (±)-**17** (0.30 g, 0.75 mmol) was dissolved in anhydrous diethyl ether (5 mL), and the solution cooled to 0 °C. Pyridine (0.15 mL, 1.88 mmol) and trifluoroacetic anhydride (0.26 mL, 1.88 mmol) were added. On completion of the reaction (TLC), pentane (3 mL) was added and the mixture filtered through celite to remove the pyridinium trifluoroacetate by-product. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane (3 mL), and the solution washed with water (2 x 10 mL) and brine (2 x 10 mL), and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to yield the product as a yellow oil (0.30 g, 81%), used without further purification. $\nu_{max}$ (thin film)/$cm^{-1}$ 1799, 1742, 1707 and 1676. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.7 Hz), 6.35 (s, 1H), 5.08 (d, 1H, *J* = 16.2 Hz), 4.57 (d, 1H, *J* = 16.2 Hz), 3.82 (s, 3H), 3.80 (s, 3H), 1.74 (dd, 1H, *J* = 13.9, 6.6 Hz), 1.56 (s, 3H), 1.54-1.48 (m, 2H), 0.72 (d, 3H, *J* = 6.5 Hz), 0.68 (d, 3H, *J* = 6.3 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 175.1, 170.7, 168.6, 159.1, 129.1, 128.4, 127.7, 114.6, 114.2, 77.9, 70.8, 55.3, 53.8, 53.3, 45.5, 40.3, 23.9, 23.3, 23.2, 21.1; HRMS (NSI-FTMS) *m/z*: $[M–COCF_3]^+$ Calcd for $[C_{20}H_{26}NO_7]^+$ 392.1709; Found 392.1701.

**(±)-(3R,4R,5R)-*N*-(4'-Methoxybenzyl)-3-methyl-4-hydroxy-5-(2'-methylpropyl)-pyrrolidin-2-one-3-phenylseleno ester-5-carboxylic acid methyl ester (±)-24**

Compound (±)-**23** (0.36 g, 0.7 mmol) was dissolved in anhydrous dichloromethane (5 mL) under a nitrogen atmosphere, and diphenyldiselenide (0.35 g, 1.0 mmol) added. The mixture was cooled to 0 °C and tributylphosphine (0.36 mL, 0.7 mmol) added. The mixture was allowed to reach room temperature and stirred overnight, and diluted with dichloromethane (3 mL) and water (3 mL). The aqueous layer was extracted with dichloromethane (3 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous magnesium sulphate, and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-petroleum ether (40-60 °C) (1:4) as eluent to yield the desired compound (±)-**24**, isolated as a yellow oil (0.12 g, 31%). Compound (±)-**22** was also isolated (0.03 g, 10%).

**For compound** (±)-**24**: $\nu_{max}$ (thin film)/$cm^{-1}$ 3423, 1736, 1690; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.44 – 7.37 (m, 3H), 7.22 (d, 2H, *J* = 8.6 Hz), 6.86 (d, 2H, *J* = 8.7 Hz), 4.98 (d, 1H, *J* = 16.1 Hz), 4.84 (d, 1H, *J* = 5.2 Hz), 4.49 (d, 1H, *J* = 16.1 Hz), 3.79 (s, 3H), 3.73 (s, 3H), 2.94 (d, 1H, *J* = 5.3 Hz), 1.85 – 1.77 (m, 1H), 1.72 – 1.64 (m, 2H), 1.51 (s, 3H), 0.87 (d, 3H, *J* = 6.4 Hz), 0.75 (d, 3H, *J* = 6.3 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 204.9, 172.6, 172.5, 158.6, 136.3, 136.2, 130.2, 129.3, 129.1, 128.1, 126.6, 113.9, 76.9, 71.5, 64.3, 55.3, 52.5, 45.0, 40.3, 24.1, 23.5, 21.4; $^{77}$Se NMR (95 MHz, $CDCl_3$) δ 700.24.

HRMS (NSI-FTMS) *m/z*: $[M–HSePh]^+$ Calcd for $[C_{20}H_{25}NO_6]^+$ 376.1760; Found 376.1758.

**(±)-N-(4'-Methoxybenzyl)-3-methyl-5-(2'-methylpropyl)-3,4-dehydropyrrolidin-2-one (±)-20 and (±)-N-(4'-Methoxybenzyl)-3-methyl-5-(2'-methylpropyl)-4,5-dehydropyrrolidin-2-one (±)-19**

Compound (±)-**18** (0.18 g, 0.4 mmol) was dissolved in DMF (5 mL), and lithium chloride (0.05 g, 1.1 mmol) added. The mixture was heated at 135 °C for 4 h, allowed to reach room temperature, and aqueous ammonium hydroxide (5%) added. The aqueous phase was extracted with diethyl ether (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography using 20% ethyl acetate in petroleum ether (40-60 °C) as eluent to give the first eluting compound (±)-**20** as a colourless oil (0.05 g, 49%) and the second eluting compound (±)-**19** as a colourless oil (0.04 g, 38%).

**(±)-20:** $\nu_{max}$ (thin film)/$cm^{-1}$: 1713, 1671; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.15 (d, 2H, *J* = 8.6 Hz), 6.82 (d, 2H, *J* = 8.6 Hz), 4.57 (d, 2H, *J* = 2.0 Hz), 4.51 (dt, 1H, *J* = 9.5, 2.2 Hz), 3.78 (s, 3H), 2.91 (ddd, 1H, *J* = 16.1, 9.7, 2.0 Hz), 2.72 – 2.61 (m, 1H), 2.39 – 2.31 (m, 1H), 2.22 (ddd, 1H, *J* = 16.1, 6.3, 2.4 Hz), 1.29 (d, 3H, *J* = 7.2 Hz), 0.92 (d, 3H, *J* = 4.9 Hz), 0.91 (d, 3H, *J* = 4.9 Hz); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 178.3, 158.7, 135.8, 128.7, 128.5, 113.8, 109.7, 55.2, 43.1, 35.1, 30.3, 26.8, 23.6, 23.5, 17.3; HRMS (NSI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{17}H_{24}NO_2]^+$ 274.1807; Found 274.1794.

**(±)-19:** $\nu_{max}$ (thin film)/$cm^{-1}$: 1675; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.15 (d, 2H, *J* = 8.6 Hz), 6.83 (d, 2H, *J* = 8.6 Hz), 6.70 – 6.66 (m, 1H), 5.09 (d, 1H, *J* = 15.0 Hz), 4.01 (d, 1H, *J* = 15.0 Hz), 3.78 (s, 4H), 1.92 (t, 3H, *J* = 1.7 Hz), 1.68 – 1.60 (m, 1H), 1.65 (d, 1H, *J* = 9.7 Hz), 1.25 (d, 1H *J* = 9.7 Hz), 0.89 (d, 3H, *J* = 6.1 Hz), 0.85 (d, 3H, *J* = 6.1 Hz); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 171.7, 158.9, 140.6, 134.5, 129.9, 129.3, 114.0, 58.1, 55.3, 43.3, 39.8, 25.1, 23.9, 22.3, 11.3; HRMS (NSI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{17}H_{24}NO_2]^+$ 274.1807; Found 274.1794.

**(±)-(3S,5R)-N-(4'-Methoxybenzyl)-3-methyl-5-(2'-methylpropyl)-pyrrolidin-2-one-5-carboxylic acid methyl ester (±)- 25a and (±)-(3R,5R)-N-(4'-Methoxybenzyl)-3-methyl-5-(2'-methylpropyl)-pyrrolidin-2-one-5-carboxylic acid methyl ester (±)-25b**

Compound (±)-**6** (0.33 g, 0.70 mmol) was dissolved in anhydrous THF (1.65 mL) $Pd(OH)_2/C$ (0.17 g) was added, and the mixture stirred under a static pressure of hydrogen at 35 °C overnight. The mixture was filtered through celite, and the solvent removed under reduced pressure. (±)-**25a** and (±)-**25b** were obtained as an inseparable mixture of diastereoisomers in a 1:1 ratio as a colourless oil (0.26 g, quant.). No further purification was carried out.

$\nu_{max}$ (thin film)/$cm^{-1}$: 2955, 1743, 1638; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.25 (d, 4H, *J* = 8.7 Hz), 6.82 (d, 4H, *J* = 8.7 Hz), 5.22 (d, 1H, *J* = 14.8 Hz), 4.97 (d, 1H, *J* = 14.8 Hz), 4.02 (d, 1H, *J* = 14.8 Hz), 3.84 (d, 1H, *J* = 14.8 Hz), 3.78 (s, 6H), 3.20 – 3.18 (m, 1H), 3.17 (s, 3H), 3.14 (s, 3H), 2.89 (q, 1H, *J* = 7.4 Hz), 2.17 – 2.08

(m, 4H), 1.45 (d, 3H, *J* = 7.6 Hz), 1.45 – 1.37 (m, 2H) 1.37 (d, 3H, *J* = 7.6 Hz), 0.92 (d, 3H, *J* = 6.8 Hz), 0.86 (d, 3H, *J* = 6.8 Hz), 0.78 (d, 3H, *J* = 6.6 Hz), 0.76 (d, 3H, *J* = 6.6 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 207.4, 206.0, 173.6, 173.2, 168.1, 167.9, 159.3, 159.3, 130.84, 130.81, 127.7, 127.5 113.8, 113.7, 75.7, 75.2, 55.3, 52.8, 44.5, 44.2, 43.7, 43.7, 38.1, 36.9, 23.9, 23.8, 23.7, 23.65, 23.62, 23.5, 12.5, 10.0;
HRMS (NSI-FTMS) m/z: [M+H]+ Calcd for [C19H26NO5]+ 348.1085; Found 348.1806.

**_S_-Methyl 4-methylbenzene-1-sulfonothioate 26** [17]

Sodium *p*-toluenesulfinate (3.23 g, 18.13 mmol) was dissolved in dichloromethane (50 mL), and dimethyl disulfide (0.50 mL, 5.7 mmol) was added. Iodine (2.81 g, 11.33 mmol) was added with vigorous stirring. The mixture was stirred and monitored by TLC until the dimethyl disulfide was consumed. The mixture was diluted with dichloromethane (30 mL) followed by the addition of aqueous sodium thiosulfate (1M) with stirring until the iodine colour disappeared. The organic layer was washed with water (2 x 50 mL), dried over anhydrous sodium sulfate, filtered, and the solvents removed under reduced pressure to yield **26** as an off-white solid (1.15 g, quant.), mp 56-57 °C; $\nu_{max}$ (thin film)/cm$^{-1}$: 2926, 1594; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, 2H, *J* = 8.3 Hz), 7.36 (d, 2H, *J* = 8.3 Hz), 2.50 (s, 3H), 2.46 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 144.9, 140.9, 129.9, 127.2, 21.7, 18.1. The product was sufficiently pure to be used without further purification.

**_S_-Phenyl 4-methylbenzene-1-sulfonothioate 28** [22]

Sodium *p*-toluenesulfinate (1.20 g, 6.7 mmol) and iodine (0.74 g, 2.9 mmol) were dissolved in $CH_2Cl_2$ (15 mL). Diphenyldisulfide (0.55 g, 2.9 mmol) was added with vigorous stirring, and the mixture stirred overnight. Aqueous sodium thiosulphate (1M) was added until the iodine colour was removed. The mixture was washed with water (100 mL) twice, dried over anhydrous sodium sulphate, filtered, and the solvents removed under reduced pressure to give an oil that crystallized on cooling to afford **28** as a colourless solid (1.0 g, 67%) mp 71-75 °C $\nu_{max}$ (thin film)/cm$^{-1}$: 3063, 1594; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.50-7.30 (m, 7H), 7.20 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 144.8, 140.5, 136.7, 131.4, 129.5, 129.5, 128.2, 127.8, 21.8. The product was sufficiently pure to be used without further purification.

**(±)-(3R,5R)-N-(4'-Methoxybenzyl)-3-methyl-3-methylsulfanyl-5-(2'-methylpropyl)-pyrrolidin-2,4-dione-5-carboxylic acid methyl ester (±)-27a and (±)-(3S,5R)-N-(4'-Methoxybenzyl)-3-methyl-3-methylsulfanyl-5-(2'-methylpropyl)-pyrrolidin-2,4-dione-5-carboxylic acid methyl ester (±)-27b**

A mixture of (±)-**25a-b** (0.30 g, 0.86 mmol) was dissolved in dichloromethane (5 mL) at room temperature under a nitrogen atmosphere. Triethylamine (0.2 mL, 1 mmol) and *S*-methyl *p*-toluenethiosulfonate (0.18 g, 0.8 mmol) were added. The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using 10% ethyl

acetate in petroleum ether (40-60 °C) as eluent to yield diastereoisomers (±)-**27a** and (±)-**27b** as an inseparable mixture in a 1:2 ratio (0.16 g, 47%).

**For the mixture (±)-27a-b:** $\nu_{max}$ (thin film)/cm$^{-1}$: 2960, 1769, 1745, 1698; HRMS (NSI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{20}H_{28}NO_5S]^+$ 394.1683; Found 394.1682.

**For (±)-(3*R*,5*R*)-*N*-(4'-Methoxybenzyl)-3-methyl-3-methylsulfanyl-5-(2'-methylpropyl)-pyrrolidin-2,4-dione-5-carboxylic acid methyl ester (±)-27a**

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, 2H, *J* = 8.7 Hz), 6.83 (d, 2H, *J* = 8.7 Hz), 4.80 (d, 1H, *J* = 15.2 Hz), 4.43 (d, 1H, *J* = 15.2 Hz), 3.78 (s, 3H), 3.45 (s, 3H), 2.25 (dd, 1H, *J* = 15.2, 6.8 Hz), 2.15 (s, 3H), 1.96 (dd, 1H, *J* = 15.2, 5.7 Hz), 1.58 (s, 3H), 1.38 – 1.29 (m, 1H), 0.75 (d, 3H, *J* = 4.5 Hz), 0.74 (d, 3H, *J* = 4.5 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 200.2, 171.7, 167.9, 159.0, 129.8, 128.5, 113.8, 75.4, 55.3, 52.9, 49.3, 44.9, 40.0, 24.0, 23.9, 23.5, 16.9, 12.3.

**For (±)-(3*S*,5*R*)-*N*-(4'-Methoxybenzyl)-3-methyl-3-methylsulfanyl-5-(2'-methylpropyl)-pyrrolidin-2,4-dione-5-carboxylic acid methyl ester (±)-27b**

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, 2H, *J* = 8.6 Hz), 6.82 (d, 2H, *J* = 8.6 Hz), 4.96 (d, 1H, *J* = 14.9 Hz), 4.03 (d, 1H, *J* = 14.9 Hz), 3.77 (s, 3H), 3.16 (s, 3H), 2.28 (s, 3H), 2.24 (dd, 1H, *J* = 15.25, 5.39 Hz), 1.98 (dd, 1H, *J* = 15.25, 6.15 Hz), 1.74 (dtd, 1H, *J* = 13.1, 6.6, 1.2 Hz), 1.67 (s, 3H), 0.93 (d, 3H, *J* = 6.6 Hz), 0.87 (d, 3H, *J* = 6.6 Hz); $^{13}$C NMR (126 MHz, CDCl3) δ 202.6, 172.4, 168.0, 159.3, 130.7, 127.5, 113.8, 75.2, 55.3, 52.8, 48.2, 43.7, 38.3, 24.6, 23.9, 23.7, 18.5, 11.6.

**(±)-(2S,4S)-methyl 2-isobutyl-1-(4-methoxybenzyl)-4-methyl-3,5-dioxo-4-(phenylthio)-pyrrolidine-2-carboxylate (±)-29a and (±)-(2S,4R)-methyl 2-isobutyl-1-(4-methoxybenzyl)-4-methyl-3,5-dioxo-4-(phenylthio)-pyrrolidine-2-carboxylate (±)-29b**

(±)-**25a/b** (0.21 g, 0.61 mmol) was dissolved in anhydrous dichloromethane (15 mL). Triethylamine (0.1 mL, 0.73 mmol) and *S*-phenyl 4-methylbenzene-1-sulfonothioate **28** (0.16 g, 0.67 mmol) were added. The mixture was stirred at room temperature for 6 h. The solvents were removed under reduced pressure, and the residue was purified by silica gel column chromatography using 10% ethyl acetate in petroleum ether (40-60 °C) as eluent to afford diastereoisomers (±)-**29a-b** as an inseparable mixture in a 0.95:1 ratio as an off-white solid (0.17 g, 60%).

**(2*S*,4*S*)-Methyl 2-isobutyl-1-(4-methoxybenzyl)-4-methyl-3,5-dioxo-4-(phenylthio)-pyrrolidine-2-carboxylate 29a and (2*S*,4*R*)-methyl 2-isobutyl-1-(4-methoxybenzyl)-4-methyl-3,5-dioxo-4-(phenylthio)-pyrrolidine-2-carboxylate 29b**

(–)-**6** (0.4377 g, 0.70 mmol) was dissolved in THF (2.2 mL). A catalytic amount of $Pd(OH)_2$/C was added the mixture was stirred overnight under a static pressure of hydrogen at 35 °C, filtered through celite, and the solvents removed under reduced pressure. The resulting oil was dissolved in anhydrous dichloromethane

(3.1 mL), and *S*-phenyl 4-methylbenzene-1-sulfonothioate **28** (0.481 g, 2 mmol) and triethylamine (0.15 mL, 1.1 mmol) added. The mixture was stirred under an atmosphere of nitrogen for 5 h, the solvents removed under reduced pressure, and the residue purified by column chromatography using petroleum ether (40-60 °C/ethyl acetate (9:1) as eluent, yielding diastereoisomers **(2*S*,4*S*)-29a** and **(2*S*,4*R*)-29b** as an inseparable mixture in 1:1 ratio as a pale yellow oil. (0.281 g, 67% over the two steps).

**For the mixture 29a-b:** $\nu_{max}$ (thin film)/cm$^{-1}$: 2957, 1771, 1745, 1700; HRMS (ASAP-TOF) *m/z*: $[M+H]^+$ Calcd for $[C_{25}H_{30}NO_5S]^+$ 456.1845; Found 456.1854.

**Compound 29a** $^1$H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.48-7.31 (m, 3H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.85 (d, *J* = 15.2 Hz, 2H), 4.41 (d, *J* = 15.2 Hz, 1H), 3.79 (s, 3H), 3.44 (s, 3H), 2.26 (dd, *J* = 15.2, 6.8 Hz, 1H), 1.95 (dd, *J* = 15.2, 5.6 Hz, 1H), 1.45 (s, 3H), 1.29 (d, *J* = 6.7 Hz, 1H), 0.73 (d, *J* = 6.7 Hz, 3H), 0.70 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 200.4, 171.8, 168, 159.2, 137.9, 130.6, 130.1, 129., 128.6, 128.2, 113.9, 75.7, 55.4, 53.1, 53, 45, 40.1, 24, 23.7, 18.3.

**Compound 29b** $^1$H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.0 Hz, 2H), 7.47-7.31 (m, 3H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.96 (d, *J* = 15.0 Hz, 1H), 4.04 (d, *J* = 15.0 Hz, 1H), 3.77 (s, 3H), 3.15 (s, 3H), 2.14 (dd, *J* = 15.0, 5.7 Hz, 1H), 1.74 (d, *J* = 6.5 Hz, 1H), 1.60 (dd, *J* = 15.0, 6.5 Hz, 1H), 1.54 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 204.2, 172.6, 168, 159.4, 137.8, 130.8, 130.4, 129, 128.3, 127.8, 113.9, 74.9, 55.4, 53.2, 52.9, 43, 38.4, 24.6, 23.9, 20.8.

**(±)-(3*S*,4*S*,5*R*)-*N*-(4'-Methoxybenzyl)-3-methyl-3-methylsulfanyl-4-hydroxy-5-(2'-methylpropyl)-pyrrolidin-2-one-5-carboxylic acid methyl ester (±)-30a and (±)-(3R,4R,5R)-N-(4'-Methoxybenzyl)-3-methyl-3-methylsulfanyl-4-hydroxy-5-(2'-methylpropyl)-pyrrolidin-2-one-5-carboxylic acid methyl ester (±)-30b**

A mixture of compounds (±)-**27a-b** (0.088 g, 0.22 mmol) was dissolved in ethanol (4.6 mL). Sodium borohydride (0.004 g, 0.11 mmol) was added and the mixture stirred at –10 °C for 30 min. Water (1 mL) was added, and the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate (5 mL), washed with water (2 x 5 mL) and brine (2 x 5 mL), and the organic layer dried over sodium sulfate, filtered, and the solvents removed under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether (40-60 °C/ethyl acetate (3:1) as eluent. The first eluting diastereoisomer (±)-**30a** was obtained as a yellow oil (0.015 g, 17%), and the second eluting diastereoisomer (±)-**30b** was obtained as a dark yellow oil (0.023 g, 25%). An inseparable mixture of compounds (±)-**27a-b** in a 1:6 ratio was recovered (0.020 g, 23%).

**For (±)-30a:** $\nu_{max}$ (thin film)/cm$^{-1}$: 3432, 2957, 2927, 1741, 1698; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, 2H, *J* = 8.7 Hz), 6.82 (d 2H, *J* = 8.7 Hz), 4.84 (d, 1H, *J* = 15.9 Hz), 4.47 (d, 1H, *J* = 10.0 Hz), 4.36 (d, 1H, *J* = 15.9 Hz), 4.03 (d, 1H, *J* = 10.0 Hz), 3.78 (s, 3H), 3.66 (s, 3H), 2.14 (s, 3H), 1.85 (dd, 1H, *J* = 14.5, 6.0 Hz), 1.77 – 1.72 (m, 1H), 1.65 (dd, 1H, *J* = 14.5, 4.5 Hz), 1.63 (s, 3H), 0.82 (d, 3H, *J* = 6.6 Hz), 0.71 (d, 3H, *J* = 6.6 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 174.6, 173.1, 158.7, 130.2, 128.7, 113.8, 81.3, 67.4, 55.3, 52.7,

51.5, 44.8, 44.0, 24.4, 23.9, 23.5, 21.8, 11.5; HRMS (NSI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{20}H_{30}NO_5S]^+$ 396.1839; Found 396.1830.

**For (±)-30b:** $\nu_{max}$ (thin film)/$cm^{-1}$: 3484, 2957, 2928, 1738; 1682; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.15 (d, 2H, *J* = 8.7 Hz), 6.82 (d, 2H, *J* = 8.7 Hz), 4.89 (d, 1H, *J* = 16.0 Hz), 4.47 (d, 1H, *J* = 3.3 Hz), 4.43 (d, 1H, *J* = 16.0 Hz), 3.78 (s, 3H), 3.70 (s, 3H), 3.20 (d, 1H, *J* = 3.3 Hz), 2.15 (s, 3H), 1.88 (dd 1H, *J* = 13.7, 6.3 Hz), 1.80 (dd, 1H, *J* = 13.7, 5.3 Hz), 1.76 – 1.71 (m, 1H), 1.50 (s, 3H), 0.91 (d, 3H, *J* = 6.6 Hz), 0.77 (d, 3H, *J* = 6.6 Hz); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 173.2, 173.1, 158.5, 130.5, 128.2, 113.8, 75.9, 71.6, 57.5, 55.3, 52.4, 45.2, 40.7, 24.23, 24.20, 23.5, 21.9, 12.6; HRMS (NSI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{20}H_{30}NO_5S]^+$ 396.1839; Found 396.1832.

**(±)-(2S,3S,4S)-Methyl 3-hydroxy-2-isobutyl-1-(4-methoxybenzyl)-4-methyl-5-oxo-4-(phenylthio)pyrrolidine-2-carboxylate (±)-31a and (±)-(2S,3R,4R)-methyl 3-hydroxy-2-isobutyl-1-(4-methoxybenzyl)-4-methyl-5-oxo-4-(phenylthio)pyrrolidine-2-carboxylate (±)-31b**

A mixture of **(±)-29a-b** (0.36 g, 0.8 mmol) was dissolved in ethanol (16 mL), and the solution cooled to −10 °C. Sodium borohydride (0.02 g, 0.45 mmol) was added, and the mixture stirred for 30 min. Water (1 mL) was added, and the mixture allowed to reach room temperature. The solvents were removed under reduced pressure, and the residue dissolved in dichloromethane. The solution was washed twice with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether (40-60 °C)/ethyl acetate (6:1) as eluent, to give (±)-**31a** (0.11 g, 29%) and (±)-**31b** (0.075 g, 20%) as colourless oils.

**(−)-(2S,3S,4S)-Methyl 3-hydroxy-2-isobutyl-1-(4-methoxybenzyl)-4-methyl-5-oxo-4-(phenylthio)pyrrolidine-2-carboxylate (±)-31a and (±)-(2S,3R,4R)-methyl 3-hydroxy-2-isobutyl-1-(4-methoxybenzyl)-4-methyl-5-oxo-4-(phenylthio)pyrrolidine-2-carboxylate (−)-31b**

A mixture of **(2*S*,4*S*)-29a and (2*S*,4*R*)-29b** (0.2059, 0.45mmol) was dissolved in ethanol (9mL) and the solution cooled to −10 °C. Sodium borohydride (0.012g, 0.3mol) was added, and the mixture stirred for 30 min before being quenched by addition of water (1 mL). The solvents were removed under reduced pressure, and the residue dissolved in dichloromethane. The organic layer was washed with twice each with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulphate, filtered, and the solvents were removed under reduced pressure. The residue was purified by column chromatography using petroleum ether (40-60 °C)/ethyl acetate (6:1) as eluent to give (−)-**31a** and (−)-**31b** as colourless oils.

**The first eluting diastereoisomer** (−)-**31a:** (0.063 g, 30%); $\nu_{max}$ (thin film)/$cm^{-1}$: 3423, 2957, 1740, 1701; $[\alpha]_D^{22}$ = - 60.00 (*c* 0.34, $CHCl_3$); $^1H$ NMR (500 MHz, CDCl3) δ 7.55 (d, J = 6.9 Hz, 2H), 7.40 – 7.28 (m, 3H), 7.18 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 4.71 (d, J = 15.7 Hz, 1H), 4.52 – 4.45 (m, 2H), 4.09 (d, J = 10.3 Hz, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 1.95 (dd, J = 14.6, 6.1 Hz, 1H), 1.78 (d, J = 6.4 Hz, 1H),

1.66 (dd, J = 14.6, 5.0 Hz, 1H), 1.44 (s, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) $^{13}$C NMR (126 MHz, $CDCl_3$) δ 174.1, 173.6, 158.8, 137.5, 130.0, 129.5, 129.15, 129.09, 128.8, 113.8, 80.3, 68.0, 56.0, 55.4, 52.7, 44.8, 43.7, 24.5, 24.1, 23.6, 23.2; HRMS (ASAP-TOF) *m/z*: $[M+H]^+$ Calcd for $[C_{25}H_{32}NO_5S]^+$ 458.2001; Found 458.2003. Determined by HPLC to be 77% ee.

**The second eluting diastereoisomer** (–)-**31b:** (0.073 g, 35%); $\nu_{max}$ (thin film)/cm$^{-1}$: 3405, 2957, 2930, 1736, 1683; $[\alpha]_D^{19}$ = - 5.8 (*c* 13.1, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 6.7 Hz, 2H), 7.42 – 7.33 (m, 3H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.92 (d, *J* = 16.1 Hz, 1H), 4.44 (d, *J* = 16.1 Hz, 1H), 4.41 (d, *J* = 3.8 Hz, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.65 (d, *J* = 3.9 Hz, 1H), 1.93 – 1.86 (m, 1H), 1.81 – 1.72 (m, 2H), 1.29 (s, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.76 (d, *J* = 6.3 Hz, 3H).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 173.4, 173.2, 158.6, 136.4, 130.5, 129.5, 129.3, 128.7, 128.3, 113.9, 75.4, 71.8, 62.3, 55.4, 52.5, 45.4, 41.3, 24.3, 24.2, 23.7, 22.4; HRMS (ASAP-TOF) *m/z*: $[M–SPh]^+$ Calcd for $[C_{19}H_{26}NO_5]^+$ 348.1811; Found 348.1821.

**(±)-(2S,3R,4S)-Methyl 3-hydroxy-2-isobutyl-1-(4-methoxybenzyl)-4-methyl-5-oxopyrrolidine-2-carboxylate (±)-21a and (±)-(2S,3R,4R)-methyl 3-hydroxy-2-isobutyl-1-(4-methoxybenzyl)-4-methyl-5-oxopyrrolidine-2-carboxylate (±)-21b**

**Raney Nickel method:** Raney nickel 2800 grade was washed using ethanol and dried under an atmosphere of nitrogen. A catalytic quantity was added to a solution of (±)-**30a** (0.02 g, 0.05 mmol) in ethanol (2.3 mL). The mixture was heated under reflux for 4 h. After removal of the Raney nickel by filtration, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether (40-60 °C)/ethyl acetate (3:1) as eluent to give (±)-**21a** and (±)-**21b** as a 3:1 mixture of diastereoisomers (5.7 mg, 7%).

**AIBN method**: (±)-**31a** (0.064 g, 0.14 mmol) and AIBN (0.007 g, 0.043 mmol) were dissolved in anhydrous acetone (1 mL). Tris(trimethylsilyl)silane (0.14 mL, 0.45 mmol) was added and the mixture was heated under reflux under a nitrogen atmosphere overnight. The solvents were removed under reduced pressure, and the residue purified by column chromatography using ethyl acetate/petroleum ether (40-60 °C) (1:1) as eluent to afford (±)-**21a** as a colourless oil (0.007 g, 14%) and (±)-**21b** as a colourless oil (0.036 g, 74%).

**(+)-(2S,3R,4S)-Methyl 3-hydroxy-2-isobutyl-1-(4-methoxybenzyl)-4-methyl-5-oxopyrrolidine-2-carboxylate (+)-21a and (–)-(2S,3R,4R)-methyl 3-hydroxy-2-isobutyl-1-(4-methoxybenzyl)-4-methyl-5-oxopyrrolidine-2-carboxylate (–)-21b**

**Raney Nickel method:** Raney nickel 2800 grade was washed using ethanol and dried under an atmosphere of nitrogen. A catalytic quantity was added to a solution of **(–)-31a** (0.0237 g, 0.05 mmol) in ethanol (1 mL). The mixture was heated under reflux for 4 h. After removal of the Raney nickel by filtration, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica

gel using ethyl acetate/petroleum ether (40-60 °C) (1:1) as eluent, affording **(+)-21a** and **(–)-21b** as a 3:1 mixture of diastereoisomers (7.4 mg, 42%).

**AIBN method:** (–)-**31a** (0.0295 g, 0.064 mmol) and AIBN (0.0089g, 0.054 mmol) were dissolved in acetone (0.5 mL) from a previously unopened bottle. Tris(trimethylsilyl)silane (0.07 mL, 0.225 mmol) was added, and the mixture heated under reflux under a nitrogen atmosphere overnight. The solvents were removed under reduced pressure, affording **(+)-21a** and **(–)-21b** as a 1:5 mixture of isomers, which were purified by column chromatography using ethyl acetate/petroleum ether (40-60 °C) (1:1) as eluent, affording **(+)-21a** and **(–)-21b** (**21b**: 0.0186 g, 83%).

**First eluting diastereoisomer** (+)-**21a:** $[\alpha]_D^{19}$ = +7.4 (*c* 0.42, $CHCl_3$); $\nu_{max}$ (thin film)/$cm^{-1}$ 3356, 2957, 2918, 1741, 1673 δ 7.16 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.69 (d, *J* = 15.2 Hz, 1H), 4.17 (d, *J* = 15.4 Hz, 1H), 3.90 (t, *J* = 9.7 Hz, 1H), 3.78 (s, 3H), 3.34 (s, 3H), 2.84 (d, *J* = 9.9 Hz, 1H), 2.71 (dq, *J* = 9.6, 7.1 Hz, 1H), 2.15 (dd, *J* = 14.4, 7.5 Hz, 1H), 1.92 – 1.81 (m, 1H), 1.55 (dd, *J* = 14.5, 4.5 Hz, 1H), 1.32 (d, *J* = 6.9 Hz, 3H), 0.97 – 0.88 (m, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 175.5, 172.4, 159.0, 129.7, 129.4, 113.9, 79.4, 69.1, 55.4, 52.1, 43.4, 43.3, 41.9, 24.7, 24.0, 23.5, 13.7; HRMS (NSI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{19}H_{28}NO_5]^+$ 350.1962; Found 350.1964.

**Second eluting diastereoisomer** (–)-**21b:** $[\alpha]_D^{22}$ = –27 (*c* 0.67, $CHCl_3$); $\nu_{max}$ (thin film)/$cm^{-1}$ 3374, 2956, 1742, 1672; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.67 (d, *J* = 15.4 Hz, 1H), 4.47-4.36 (m, 2H), 3.77 (s, 3H), 3.46 (s, 3H), 3.03 (d, *J* = 7.7 Hz, 1H), 2.76 (d, *J* = 7.5 Hz, 1H), 1.99 (dd, *J* = 14.4, 6.1 Hz, 1H), 1.77-1.67 (m, *J* = 12.9, 6.5 Hz, 1H), 1.61 (dd, *J* = 14.3, 6.0 Hz, 1H), 1.27 (d, *J* = 7.5 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 176.6, 172.3, 158.7, 130.1, 128.9, 113.8, 73.4, 72.5, 55.4, 52.2, 44.7, 43.3, 39.9, 24.3, 24.1, 24.0, 9.5; HRMS (NSI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{19}H_{28}NO_5]^+$ 350.1962; Found 350.1964.

**(±)-(2S,3R,4S)-Methyl 3-hydroxy-2-isobutyl-4-methyl-5-oxopyrrolidine-2-carboxylate (±)-32**

**(±)-21b** (0.032 g, 0.09 mmol) was dissolved in acetonitrile/water (3:1, 0.9 mL). CAN (0.26 g, 0.47 mmol) was added, and the mixture stirred at room temperature until TLC showed the reaction to be complete. The mixture was extracted using ethyl acetate (3 x 10 mL), and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and the solvents removed under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate-petroleum ether (40-60 °C) (9:1) as eluent, affording **(±)-32** as a colourless solid (0.017 g, 82%), mp 147-156 °C.

**(–)-(2S,3R,4S)-Methyl 3-hydroxy-2-isobutyl-4-methyl-5-oxopyrrolidine-2-carboxylate (–)-32** [12a]

**(–)-21a** (0.036 g, 0.10 mmol) was dissolved in a 3:1 mixture of acetonitrile/water (1 mL). CAN (0.287 g, 0.52 mmol) was added, and the mixture stirred at room temperature until TLC showed the reaction was complete. The mixture was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and the solvents removed under reduced

pressure. The residue was purified by column chromatography using ethyl acetate/petroleum ether (40-60 °C) (9:1) as eluent, affording **(–)-32** as a colourless solid (0.023 g, 62%), $\nu_{max}$ (thin film)/cm$^{-1}$ 3434, 2959, 2079, 1725, 1641; $[\alpha]_D^{23}$ = – 2.85 (*c* 0.42, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 5.09 (d, 1H, *J* = 11.6 Hz), 4.06 (dd, 1H, *J* = 11.4, 5.1 Hz), 3.83 (s, 3H), 2.72 – 2.65 (m, 1H), 2.00 (dd, 1H, *J* = 13.8, 8.7 Hz), 1.78 – 1.68 (m, 1H), 1.51 (dd, 1H, *J* = 13.8, 5.1 Hz), 1.18 (d, 3H, *J* = 7.3 Hz), 0.96 (d, 3H, *J* = 6.7 Hz), 0.87 (d, 3H, *J* = 6.6 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 178.1, 174.2, 78.9, 72.0, 52.8, 43.5, 40.1, 25.0, 24.0, 21.9, 7.7; HRMS (NSI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{11}H_{20}NO_4]^+$ 230.1387; Found 230.1388.

**(±)-(2S,3R,4S)-3-Hydroxy-2-isobutyl-4-methyl-5-oxopyrrolidine-2-carboxylic acid (±)-7**

**(±)-32** (0.011 g 0.05 mmol) was dissolved in aqueous sodium hydroxide (0.5 M, 1 mL) and kept at 4 °C. The progress of the reaction was monitored by TLC. When all the starting material was consumed (approximately 24 h), the solution was acidified to pH 3 using HCl (1M), and the solvents were removed under reduced pressure. The residue was dissolved in hot THF, filtered through cotton wool, and the solvents were removed under reduced pressure to afford the desired product as a pale brown residue. The residue was purified by column chromatography using a dichloromethane, methanol, acetic acid (90:9:1) mixture as eluent, affording (±)-7 as a pale brown residue (0.0064 g, 62%).

**(–)-(2S,3R,4S)-3-Hydroxy-2-isobutyl-4-methyl-5-oxopyrrolidine-2-carboxylic acid (–)-7** [3]

(–)-**32** (0.01 g 0.04 mmol) was dissolved in aqueous sodium hydroxide (0.5 M, 0.86 mL). and kept at 4 °C. The progress of the reaction was monitored by TLC. When all the starting material was consumed (approximately 24 h), the solution was acidified to pH 3 with HCl (1 M), and the solvents were removed under reduced pressure. The residue was dissolved in hot THF, filtered through cotton wool, and the solvents were removed under reduced pressure. The residue was purified by column chromatography using a dichloromethane, methanol, acetic acid (90:9:1) mixture as eluent, affording **(–)-7** as a pale brown solid (0.078 g, 86%). $\nu_{max}$ (thin film)/cm$^{-1}$ 3405, 2923, 1725, 1686; $[\alpha]_D^{20}$ = –10 (*c* 0.28, MeOH); $^1$H NMR (500 MHz, $CD_3OD$) δ 4.10 (d, 1H, *J* = 5.2 Hz), 2.79 – 2.71 (m, 1H), 1.94 (dd, 1H, *J* = 13.8, 8.3 Hz), 1.76 – 1.65 (m, 1H), 1.57 (dd, 1H, *J* = 13.8, 4.7 Hz), 1.11 (d, 3H, *J* = 7.2 Hz), 0.95 (d, 3H, *J* = 6.8 Hz), 0.92 (d, 3H, *J* = 6.6 Hz); $^{13}$C NMR (126 MHz, $CD_3OD$) δ 180.0, 175.4, 78.1, 45.2, 41.4, 25.9, 24.8, 23.0, 20.8, 8.4; HRMS (NSI-FTMS) *m/z*: $[M+H]^+$ Calcd for $[C_{10}H_{18}NO_4]^+$ 214.1084; Found 214.1085.

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**Supplementary Information**

Copies of $^{1}H$ and $^{13}C$ NMR spectra. Copies of HPLC traces. ORTEP diagrams and X-ray data.

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