A concise and straightforward total synthesis of (±)-salinosporamide A, based on a biosynthesis model†

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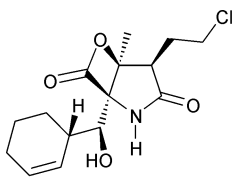
A 14-step total synthesis of (±)-salinosporamide A (**1**), a potent inhibitor of the 20S proteasome isolated from the marine bacterium *Salinospora tropica*, is described. The synthesis is based on a diastereoselective intramolecular aldolisation of a substituted β-keto amide intermediate, *i.e.* **13**, derived from a β-keto acid, *viz.* **21**, and an α-amino malonate, leading to the pyrrolidinone ring **24** in the natural product. This synthetic approach closely mimics the origin of the pyrrolidinone ring in salinosporamide A *in vivo.* Another key feature of the total synthesis is a regioselective reduction of the malonate derivative **31** to the key aldehyde intermediate **32**, using Super-hydride.

Introduction

Salinosporamide A (**1**), isolated from the marine bacterium *Salinospora tropica* by Fenical *et al.* in 2005, is a potent inhibitor of the 20S proteasome.[1] The metabolite is related to the β-lactone pyrrolidinone-based natural product omuralide (or *clasto*-lactacystin β-lactone) **2**, which is produced by lactonisation of the more familiar proteasome 20S inhibitor lactacystin **3**.[2] More recently, the homologue **4** of salinosporamide A, designated cinnabaramide A, has been isolated from the terrestrial streptomycete *S. cinnabarinus.*[3] The 20S proteasome inhibitors **1**–**4** and their relatives, together with a range of analogues, are currently in clinical trials for the treatment of cancer.[4] It is no surprise, therefore, that this family of natural products and salinosporamide A in particular, the most potent inhibitor of proteasome, have attracted a great deal of attention from synthetic and medicinal chemists.[5] In this paper we describe a total synthesis of salinosporamide A (**1**), which uses a strategy based, in part, on speculation of the origin of the pyrrolidinone ring in the metabolite, *in vivo*.



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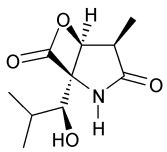

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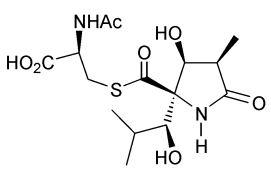

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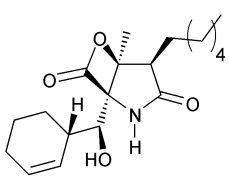

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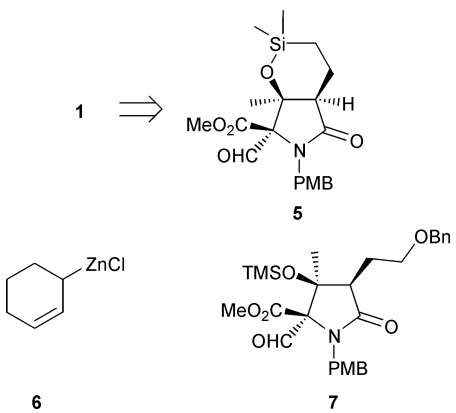
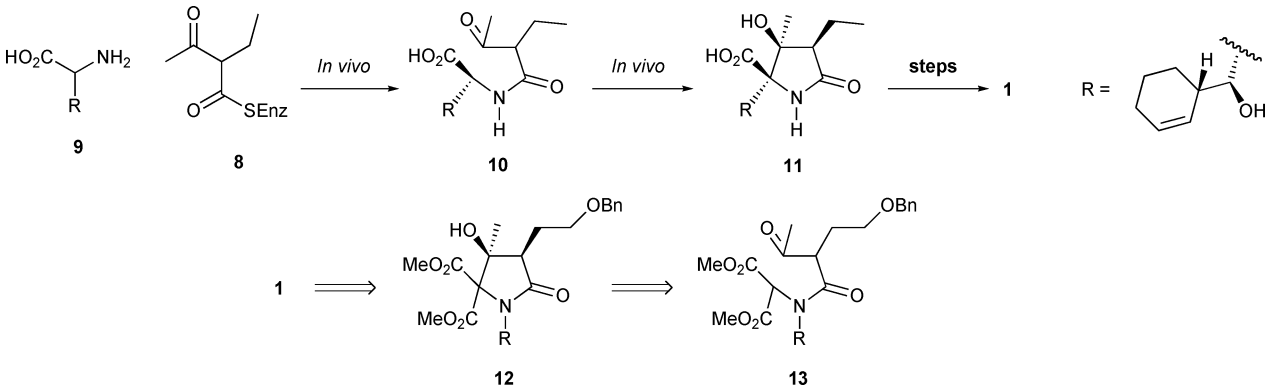
Discussion and synthetic strategy

The first synthesis of salinosporamide A (**1**) was described by Corey *et al.*,[6] starting from *S*-threonine, and featured the addition of 2-cyclohexenylzinc chloride **6** to the intermediate aldehyde **5** as a key step. A year later, Danishefsky *et al.*[7] presented an alternative synthesis of **1** starting from a chiral pool pyroglutamate derivative and proceeding *via* addition of the same zinc reagent **6** to a related bicyclic aldehyde intermediate. Almost simultaneously, in 2007 Macherla *et al.*,[8] Langlois *et al.*,[9] and Romo *et al.*[10] published additional syntheses of salinosporamide A, which also featured the addition of **6** to appropriate aldehyde intermediates, as key steps. Our own synthesis of salinosporamide A (**1**), which was presented in preliminary form in 2006,[11] proceeds *via* the pyrrolidinone aldehyde intermediate **7**, and also uses Corey's cyclohexenylzinc reagent **6** in a pivotal step.



Although until recently limited information was available,[12] at the outset of our studies it seemed likely to us that the pyrrolidinone ring core in salinosporamide A (**1**) is derived in nature *via* an intramolecular aldolisation process from a substituted β-keto amide intermediate, *viz.* **10**, derived from a β-keto ester **8** and a 2-cyclohexenemethanol-substituted amino acid, *e.g.* **9** (Scheme 1). In our design of a synthesis of salinosporamide A, we focussed our attention on the intramolecular aldolisation of the substituted



Scheme 1 Biosynthesis model, and retrosynthesis, for salinosporamide **1**.

β-keto amide intermediate **13** (*cf.* structure **10**) to the pyrrolidinone core in **1**, as the key biomimetic step.[11]

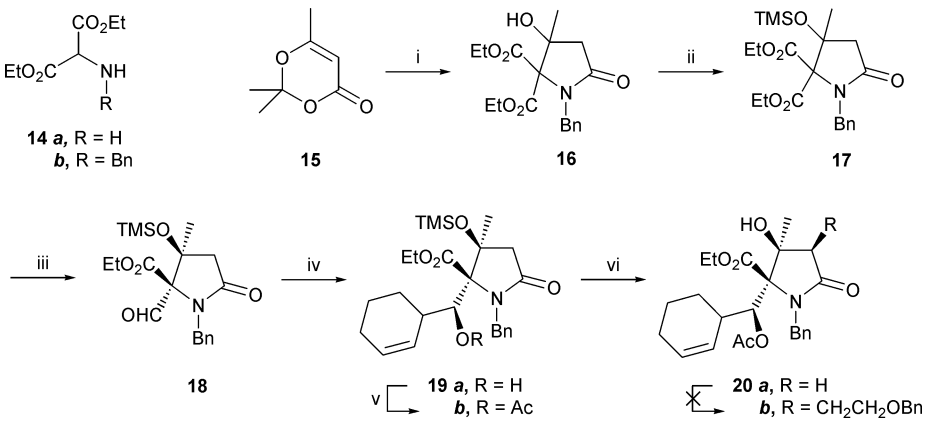
Synthesis of the pyrrolidinone 19 lacking substitution at C3

We began our investigation of the aforementioned intramolecular aldolisation approach to salinosporamide A by first preparing the amino malonate **14b**, and then reacting it with the dioxinone **15** (acting as an equivalent of diketene)[13] in the presence of acetic acid at 120 °C. This reaction gave rise to the known pyrrolidinone **16**[14] in a single step in 75% yield. Protection of the OH-group in **16** as its TMS ether **17**, followed by regioselective reduction of the ester group positioned *anti* to the bulky OTMS group in **17**, next led to the aldehyde **18** (Scheme 2).[15] The relative stereochemistry of the substituents in **18** followed from NOE studies (see Experimental).

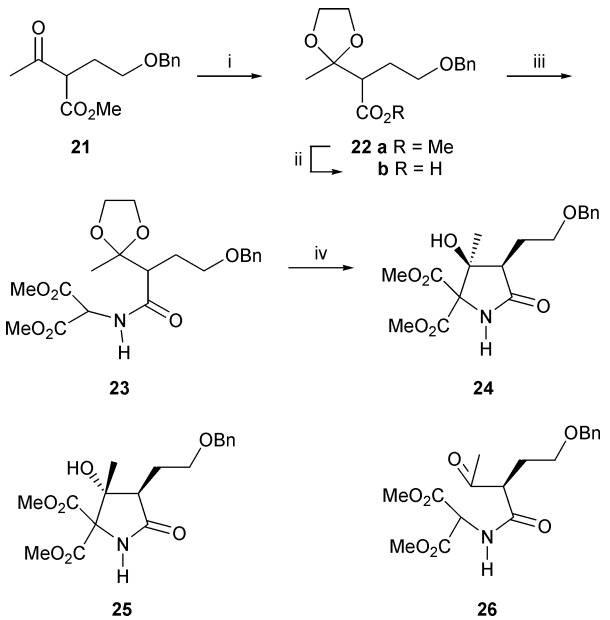
When the aldehyde **18** was now treated with 2-cyclohexenylzinc chloride **6**, using Corey's conditions,[6] the desired adduct **19a** was obtained in 82% yield. The stereoselectivity observed in the zincate addition to **18** was shown to be 15 : 1 by analysis of the ^{1}H NMR data, and the relative stereochemistry of **19a** was tentatively assigned by comparison of the NMR data with those recorded for analogous adducts prepared by Corey and Danishefsky in their approaches to salinosporamide A. Based on precedent from other laboratories,[7,16] we had hoped to complete a synthesis of salinosporamide A by effecting a diastereoselective alkylation of the acetate **20a** derived from **19a**, following deprotonation at C3, and reaction with 2-iodoethyl benzyl ether, leading to **20b**. Unfortunately however, all our attempts to alkylate at the C3 position of **20a** met with failure.

Synthesis of the pyrrolidinone core 33 in salinosporamide A

We next decided to employ an intramolecular aldolisation strategy to the pyrrolidinone core in salinosporamide A, using **14a** and the β-keto ester **21** already containing a benzyl-protected ethanol (C2) substituent.[17] Thus, protection of the β-keto ester **21** as its dioxolane **22a**, followed by saponification of the ester group in **22a** and treatment of the resulting carboxylic acid **22b** with **14a**, first gave the substituted amide **23** in 97% yield (Scheme 3). When a solution of **23** in 4 : 1 acetic acid–water[18] was heated at 65 °C for 2 days, it underwent simultaneous deprotection of the dioxolane and *in situ* intramolecular aldol reaction, leading to a single diastereoisomer of the (±)-pyrrolidinone **24** in 71% yield. The correct choice of temperature in this deprotection–aldolisation sequence was found to be critical. If the temperature was too high, the *trans*-diastereoisomer **25** was produced as an inseparable by-product, as well as some of the methyl ketone **26**. If the temperature was less than 65 °C, the reaction rate was too low and only the methyl ketone **26** was instead isolated. The *anti*-arrangement of



Scheme 2 *Reagents and conditions*: (i) **14b**, HOAc, PhH, reflux (75%); (ii) TMSCl, CH_2Cl_2, Et_3N, DMAP, 0 °C, 1 h (93%); (iii) Super-hydride, CH_2Cl_2, −78 °C, 0.5 h, (69%); (iv) 2-cyclohexenylzinc chloride, THF, −78 °C, 3.5 h, (82%); (v) Ac_2O, pyridine, DMAP, 25 °C, (87%); (vi) KF, MeOH, HOAc, 16 h, 25 °C (78%).



Scheme 3 *Reagents and conditions*: (i) ethylene glycol, *p*-TSA, PhH, 110 °C, 20 h (99%); (ii) 2 N NaOH, EtOH, 70 °C, 3 h (82%); (iii) dimethyl aminomalonate.HCl, HOBt, EDC.HCl, CH_2Cl_2, NMM, 0 °C to 25 °C (97%); (iv) 4 : 1 AcOH–H_2O, 65 °C, 4 days (71%).

the C3–C4 alkyl substituents in **24** followed from NOE studies, and was confirmed by X-ray crystallographic analysis.[19]

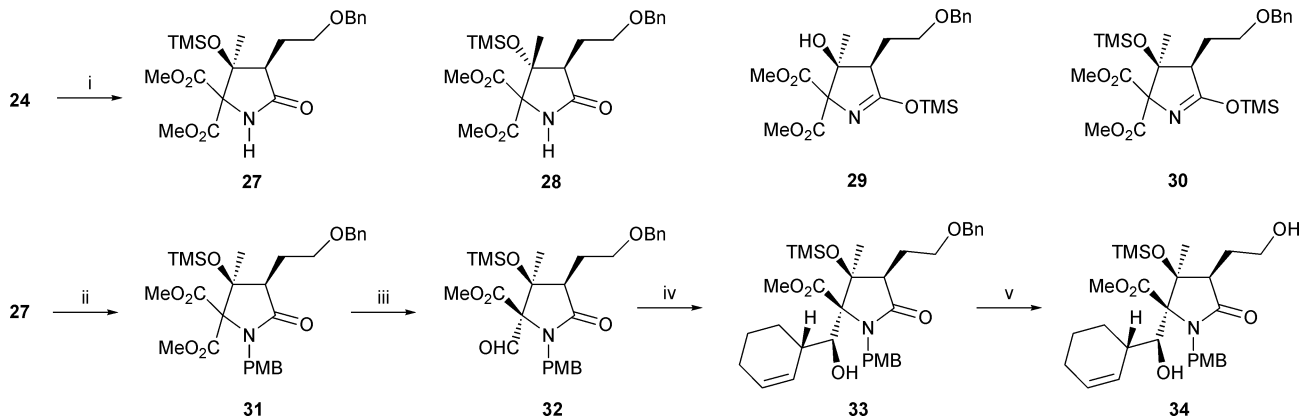
Our plan now was to protect the OH and NH groups in **24**, prior to regioselective reduction of one of the ester groups to the corresponding aldehyde **32**, followed by reaction with 2-cyclohexenylzinc chloride **6**. The protection of the tertiary OH group in **24** proved problematic. The use of TMSCl–DMAP–Et_3N proved ineffective, and when **24** was treated with TMSCl–imidazole in DMF, a 1 : 1 mixture of C3-epimers (**27** and **28**) of the required OTMS ether resulted. We presume that the unwanted C3-epimer **28** is produced by way of a retro-aldol–realdolisation sequence in **24** prior to the OH group protection. At a lower temperature, *i.e.* −20 – 0 °C, the ratio of diastereoisomers was improved to 3 : 1 in favour of the required product **27**. Interestingly, treatment of **24** with TMS cyanide in hot CH_2Cl_2, or with TMS triflate in the presence of 2,6-lutidine at −78 °C, led to the silyl imidate **29** exclusively (Scheme 4). This observation provided a solution to the problem of epimerisation in **24** under the previously used silylation conditions. The tertiary alcohol **24** was therefore treated with excess TMS triflate in the presence of 2,6-lutidine at −78 °C, leading to **27** *via* **30**, and the solution was then allowed to very slowly warm-up to room temperature over 14 h, where it was quenched with 1 M HCl. Using this procedure we were able to obtain the pure diastereoisomer **27** in 91% yield. The nitrogen centre in **27** was next protected as its PMB derivative **30** in a straightforward manner using NaH and freshly prepared 4-methoxybenzyl bromide.

The reduction of one of the ester groups in **31** using Super-hydride at −78 °C, similar to the analogous diester **17**, was found to be completely regioselective and gave the aldehyde **32** in 78% yield. The stereochemistry of the aldehyde **32** followed from ^{1}H NMR nOe studies (see data in Experimental).

The aldehyde **32** was next treated with 2-cyclohexenylzinc bromide in THF at −78 °C, using the protocol of Corey *et al.*, to deliver the single diastereoisomer **33** of the adduct as colourless crystals, in 87% yield. The stereochemistry of **33** was confirmed by single-crystal X-ray diffraction analysis.[19] In our studies of the organozinc–aldehyde addition **32** → **33**, we found it preferable to prepare the zincate intermediate from commercial 3-bromocyclohexene and activated zinc in THF at 0 °C, instead of by transmetallation of 2-cyclohexyl-tri-*n*-butylstannane used earlier by Corey and others. This was a more straightforward preparation of the zincate, avoiding the use of toxic tin reagents, and simplified the purification of the adduct **33**.

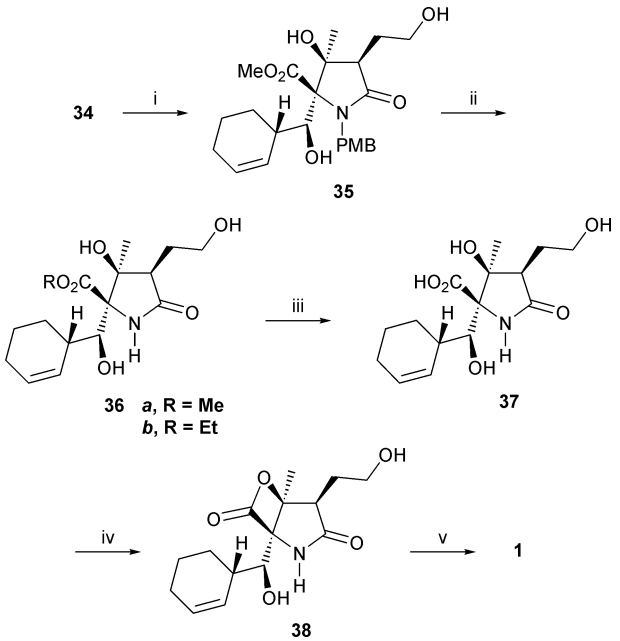
Completion of (±)-salinosporamide A

To complete the synthesis of salinosporamide A (**1**) from the adduct **33** required selective deprotection of the N- and O-protecting groups, β-lactone ring formation and introduction of the chloride group in the ethyl side chain. The deprotection of the *O*-benzyl group in **33** initially proved problematic. Transfer hydrogenation removed the benzyl group,[20] but also reduced the alkene bond in **33**, whereas DDQ was ineffective[21] and only starting material was recovered. Treatment of **33** with BCl_3·DMS complex in DCM at room temperature also returned starting



Scheme 4 *Reagents and conditions*: (i) excess TMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C to 0 °C, then 1 M HCl (91%); (ii) PMB-Br, NaH, DMF, 0 °C to 25 °C, 14 h (72%); (iii) Super-hydride (1.0 M in THF), CH_2Cl_2, −78 °C, 3 h (78%); (iv) 2-cyclohexenylzinc bromide, THF, −78 °C (87%); (v) BCl_3·DMS, CH_2Cl_2, 0 °C to 25 °C, 24 h (99%).

material.[22] After experimentation, however, use of 10 equivalents of BCl_3·DMS resulted in complete and selective removal of the *O*-benzyl ether group in **33**, giving the diol **34** in 99% yield. Deprotection of the TMS group in **34** using 48% aqueous HF in acetonitrile[23] next gave the triol **35**, which was then deprotected at nitrogen by oxidative cleavage of the PMB group using CAN,[6] leading to **36a** in excellent overall yield (Scheme 5). The triol **36b** is the same intermediate in Corey's synthesis of salinosporamide A.[6]



Scheme 5 *Reagents and conditions*: (i) 48% HF in H_2O–MeCN (1 : 9), 25 °C, 22 h; (ii) CAN, MeCN, H_2O (3 : 1), 0 °C, 1 h (87% over 2 steps); (iii) $[MeTeAlMe_2]_2$, PhMe, 25 °C, 24 h; (iv) BOP-Cl, CH_2Cl_2, pyridine, 25 °C, 3 h; (v) PPh_3Cl_2, MeCN, pyridine, 25 °C, 4 h (45% over 3 steps).

The hydrolysis of the ester group in **36a** to the corresponding carboxylic acid **37** turned out to be tiresome and difficult. Indeed, the ethyl ester **36b** corresponding to **36a** failed completely to undergo hydrolysis using LiOH in THF. Instead, total decomposition of **36b** took place, presumably by a retro-aldol process, and possibly as a consequence of the significant steric congestion and strain in the substrate. As described by Corey *et al.*,[6] the methyl ester **36a** did undergo hydrolysis in the presence of 3 M LiOH in THF at 4 °C, but in our hands a very poor yield (<10%) of the corresponding carboxylic acid **37** was obtained. Eventually, we used dimethylaluminium methyltelluride[24] in THF to hydrolyse the ester **36a**, which gave the carboxylic acid **37** in a satisfactory 60% yield. Treatment of the crude carboxylic acid **37** with BOP-Cl and pyridine resulted in smooth lactonisation to the pyrrolidinone β-lactone **38** which, on chlorination with Ph_3PCl_2 was then converted into (±)-salinosporamide A (**1**) in 45% yield over the three steps.

Salinosporamide A was obtained as colourless crystals, mp 169–172 °C, which displayed ^1H and ^{13}C NMR spectroscopic data identical to those presented for the natural product.

Summary

A conceptually straightforward and concise synthesis of (±)-salinosporamide has been developed, which has features in common with the most likely origin of the pyrrolidinone ring system in the natural product, *i.e.* an intramolecular aldolisation from a substituted β-keto amide intermediate derived from a β-keto acid and an α-amino acid, *cf.* Schemes 1 and 3.

Experimental

For general experimental details, see ref. 25.

(2*R**,3*S**)-Ethyl-1-benzyl-2-((*R**)-(*S**)-cyclohex-2-enylhydroxymethyl)-3-methyl-5-oxo-3-(trimethylsilanyloxy)pyrrolidine-2-carboxylate (19a)

A pre-cooled (−78 °C) solution of the aldehyde **18** (818 mg, 2.17 mmol) in anhydrous THF (2.5 mL) was added *via* cannula to a freshly prepared solution of cyclohexenylzinc chloride (9.0 mL, 4.5 mmol, 0.5 M in THF)[7] at −78 °C, under a nitrogen atmosphere. The mixture was stirred at −78 °C for 5 h, then treated with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, using petroleum ether–diethyl ether (1 : 1) then diethyl ether as eluent, to give the *secondary alcohol* **19a** (819 mg, 82%) as a colourless solid; mp 128–130 °C (from diethyl ether); (Found: C 65.4; H, 8.2; N 3.1; $C_{25}H_{37}NO_5Si$ requires C, 65.3; H, 8.1; N, 3.0); ν_{max} ($CHCl_3$)/cm^{-1} 3572 (br), 2941, 1750, 1688; δ_H (400 MHz, $CDCl_3$) 7.36–7.15 (5H, m, C_6H_5), 6.06 (1H, m, CH_2CH=), 5.67 (1H, app. dd, *J* 2.9 and 10.3, CH_2CH=C*H*), 4.91 (1H, d, *J* 15.6, NC*H*HPh), 4.54 (1H, d, *J* 15.6 NCH*H*Ph), 4.14 (1H, dd, *J* 3.9 and 8.0, C*H*(OH)), 4.06 (2H, q, *J* 7.1, OCH_2CH_3), 2.88 (1H, d, *J* 16.6, C*H*HC(=O)NBn), 2.44 (1H, d, *J* 16.6, CH*H*C(=O)NBn), 2.30 (1H, br s, CH_2CH=CHC*H*), 2.04 (2H, br s, CH_2CH_2CH=), 1.88 (1H, d, *J* 8.0, O*H*), 1.78–1.72 (1H, m, =CHCH(R)C*H*H), 1.76 (3H, s,CCH_3), 1.55–1.47 (3H, m, C*H*HCH$_2$CH=, CH*H*CH$_2$CH=, =CHCH(R)CH*H*), 1.05 (3H, t, *J* 7.1, OCH_2CH_3), 0.18 (9H, s, OTMS); δ_C (100 MHz, $CDCl_3$) 175.2 (q), 168.9 (s), 138.4 (s), 134.3 (d), 127.7 (d) × 2, 126.4 (d) × 2, 126.1 (d), 124.1 (d), 82.9 (s), 82.1 (s), 76.7 (d), 61.0 (t), 48.1 (t), 46.7 (t), 38.0 (d), 29.2 (t), 25.0 (t), 22.6 (q), 20.5 (t), 13.6 (q), 2.1 (q) × 3; *m*/*z* (ES) 460.2518 (M + H$^+$, $C_{25}H_{38}NO_5Si$ requires 460.2519). ^1H NMR NOE experiments (360 MHz, $CDCl_3$): irradiation at δ 4.14 (C*H*OH) gave an enhancement of 7.6% at d 1.76 (C*Me*), and irradiation at δ 5.67 (CHC*H*=) gave enhancements of 3.4% at δ 2.44 (CH_2CO), and 3% at δ 2.30 (=CHC*H*CHOH).

2-(2-(Benzyloxy)ethyl)-3-oxobutyric acid methyl ester (21)

Potassium carbonate (33.1 g, 234 mmol) was added to a solution of 2-iodoethyl benzyl ether (25.1 g, 95.8 mmol) and methyl acetoacetate (15.5 mL, 144 mmol) in acetone (500 mL) and the mixture was then heated under reflux for 27 h under a nitrogen atmosphere. The mixture was cooled to room temperature and then evaporated *in vacuo*. The residue was diluted with water (200 mL) and extracted with diethyl ether (3 × 200 mL). The combined organic extracts were dried and then concentrated *in vacuo*, finally at 120 °C under high vacuum to leave the *β-ketoester* **21** (23.6 g, 99%) as a yellow oil which was used without further purification; ν_{max} ($CHCl_3$)/cm^{-1} 2954, 2865, 1742, 1715, 1360; δ_H (360 MHz, $CDCl_3$) 7.38–7.27 (5H, m, C_6H_5), 4.46 (2H, s, OCH_2Ph), 3.74–3.71 (2H, m, CH_2CH_2OBn), 3.70

(3H, s, CO_2CH_3), 3.51 (1H, t, *J* 7.2, $CH_3(C{=}O)CHCO_2CH_3$,), 2.24 (3H, s, $CH_3(C{=}O)$), 2.21–2.15 (2H, m, CH_2CH_2OBn); δ_C (90 MHz, $CDCl_3$) 203.0 (s), 170.2 (s), 138.1 (s), 128.2 (d) × 2, 127.8 (d) × 2, 127.7 (d), 73.0 (t), 67.5 (t), 56.4 (d), 52.4 (q), 29.3 (q), 28.3 (t); *m/z* (ES) 273.1096 ($M + Na^+$, $C_{14}H_{18}NaO_4$ requires 273.1097).

4-Benzyloxy-2-(2-methyl-1,3-dioxolan-2-yl)butyric acid methyl ester (22a)

A solution of the β-ketoester **21** (23.6 g, 95.6 mmol), *p*-toluenesulfonic acid (360 mg, 1.89 mmol) and ethylene glycol (7.5 mL, 130 mmol) in benzene (160 mL) was heated under reflux for 20 h using a Dean–Stark apparatus. The mixture was cooled to room temperature and then diluted with diethyl ether (500 mL). The solution was washed with aqueous saturated sodium hydrogen carbonate (160 mL), then dried and concentrated *in vacuo* to leave the *dioxolane* **22a** (26.5 g, 99%) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 2952, 2889, 1730; δ_H (360 MHz, $CDCl_3$) 7.38–7.27 (5H, m, C_6H_5), 4.48 (1H, br. s, OC*H*HPh), 4.47 (1H, br. s, OCH*H*Ph), 4.04–3.92 (4H, m, OCH_2CH_2O), 3.64 (3H, s, CO_2CH_3), 3.53–3.42 (2H, m, CH_2CH_2OBn), 2.88 (1H, dd, *J* 3.1 and 11.3, $CHCO_2CH_3$), 2.16–2.06 (1H, m, C*H*HCH$_2$OBn), 1.99–1.90 (1H, m, CH*H*CH$_2$OBn), 1.41 (3H, CCH_3); δ_C (90 MHz, $CDCl_3$) 173.1 (s), 134.3 (s), 128.3 (d) × 2, 127.6 (d) × 2, 127.5 (d), 109.6 (s), 72.8 (t), 68.4 (t), 64.8 (t) × 2, 51.7 (q), 51.1 (d), 28.4 (t), 21.5 (q); *m/z* (ES) 317.1369 ($M + Na^+$, $C_{16}H_{22}NaO_5$ requires 317.1365).

4-Benzyloxy-2-(2-methyl-[1,3]dioxolan-2-yl)butyric acid (22b)

A solution of the methyl ester **22a** in ethanol (100 mL) and aqueous sodium hydroxide (200 mL, 2 M), was heated at 70 °C for 3 h. The mixture was allowed to cool to room temperature and then concentrated *in vacuo* to approximately 200 mL. The solution was washed with diethyl ether (50 mL), then acidified to pH 1–2 with HCl (2 M) and extracted with diethyl ether (3 × 150 mL). The combined organic extracts were dried and concentrated *in vacuo* to leave the *carboxylic acid* **22b** (22.0 g, 82%) as a colourless solid, which was used in the next step without further purification. A small portion was recrystallised from diethyl ether; mp 52–56 °C; Found: C 64.3; H, 7.2; $C_{15}H_{20}O_5$ requires C, 64.6; H, 7.2; ν_{max} ($CHCl_3$)/cm^{-1} 3504, 3212 (br.), 2889, 1749, 1709; δ_H (400 MHz, $CDCl_3$) 7.34–7.27 (5H, m, C_6H_5), 4.50 (2H, s, OCH_2Ph), 4.07–3.94 (4H, m, OCH_2CH_2O), 3.59–3.47 (2H, m, CH_2CH_2OBn), 2.89 (1H, dd, *J* 3.1 and 10.8, $CHCO_2H$), 2.14–1.92 (2H, m, CH_2CH_2OBn), 1.43 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 177.4 (s), 138.2 (s), 128.3 (d) × 2, 127.6 (d) × 2, 127.5 (d), 109.4 (s), 72.8 (t), 68.2 (t), 64.8 (t) × 2, 50.7 (d), 28.1 (t), 21.4 (q); *m/z* (ES) 279.1225 ($M - H^+$, $C_{15}H_{19}O_5$ requires 279.1238).

2-[4-Benzyloxy-2-(2-methyl-1,3-dioxolan-2-yl)butyrylamino]malonic acid dimethyl ester (23)

Triethylamine (6.5 mL, 46 mmol) was added dropwise over 5 min to a stirred solution of the carboxylic acid **22b** (5.4 g, 19 mmol) in dichloromethane (80 mL) at 0 °C under a nitrogen atmosphere. 1-Hydroxybenzotriazole (3.1 g, 23 mmol) was added followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (4.45 g, 23 mmol). After a further 10 min dimethyl aminomalonate hydrochloride **14a** (4.3 g, 23 mmol) was added in one portion and the mixture was then allowed to warm to room temperature over 22 h. Dichloromethane (80 mL) was added, and the mixture was then washed with saturated sodium hydrogen carbonate (40 mL) and 10% aqueous citric acid (40 mL), dried and concentrated *in vacuo* to leave the *amide* **23** (7.90 g, 97%) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 3380, 2956, 2889, 1761, 1745, 1674; δ_H (360 MHz, $CDCl_3$) 7.36–7.25 (6H, m, C_6H_5, N*H*), 5.16 (1H, d, *J* 6.7, $NHCH(CO_2CH_3)_2$), 4.49 (2H, s, OBn), 4.07–3.97 (4H, m, OCH_2CH_2O), 3.82 (3H, s, CO_2CH_3), 3.81 (3H, s, CO_2CH_3) 3.60–3.45 (2H, m, CH_2CH_2OBn), 2.80 (1H, dd, *J* 4.9 and 9.3, C*H*(CO)NH), 2.09–1.98 (2H, m, CH_2CH_2OBn), 1.37 (3H, s, CH_3); δ_C (90 MHz, $CDCl_3$) 171.6 (s), 166.8 (s), 166.7 (s), 138.5 (s), 128.3 (d) × 2, 127.7 (d) × 2, 127.4 (d), 109.5 (s), 72.8 (t), 68.2 (t), 64.9 (t), 64.8 (t), 56.3 (d), 53.3 (q) × 2, 51.4 (d), 27.5 (t), 21.7 (q); *m/z* (ES) 432.1625 ($M + Na^+$, $C_{20}H_{27}NNaO_8$ requires 432.1629).

(3*S**,4*R**)-4-(2-(Benzyloxy)ethyl)-3-hydroxy-3-methyl-5-oxopyrrolidine-2,2-dicarboxylic acid dimethyl ester (24)

A solution of the amide **23** (4.0 g, 9.8 mmol) in acetic acid–water (4 : 1, 100 mL) was heated at 65 °C for 2 days. The mixture was concentrated *in vacuo* to leave a residue which was purified by flash chromatography using petroleum ether–diethyl ether (1 : 1), then ether as eluent to give the *pyrrolidinone* **24** (2.6 g, 71%) as a colourless solid; mp; 82–85 °C (from ether); (Found: C, 59.0; H, 6.3; N, 4.1; $C_{18}H_{23}NO_7$ requires C, 59.2; H, 6.3; N, 3.8); ν_{max} ($CHCl_3$)/cm^{-1} 3429, 3401 (br), 2956, 1722; δ_H (400 MHz, $CDCl_3$) 7.35–7.26 (5H, m, C_6H_5), 7.12 (1H, br. s, N*H*), 4.76 (1H, s, O*H*), 4.51 (2H, s, OCH_2Ph), 3.88 (3H, s CO_2CH_3), 3.76 (3H, s, CO_2CH_3), 3.75 (1H, ddd, *J* 5.6, 6.6 and 9.4, CH_2CHOBn) 3.67 (1H, ddd, *J* 5.3, 7.3 and 9.4, CH_2CHOBn), 2.89 (1H, app. t, *J* 6.4, C*H*C(=O)NH), 2.10–2.01 (1H, m, C*H*HCH$_2$OBn), 1.99–1.89 (1H, m CH*H*CH$_2$OBn), 1.56 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 177.9 (s), 168.8 (s), 167.8 (s), 138.2 (s), 128.3 (d) × 2, 127.6 (d) × 2, 127.5 (d), 81.1 (s), 76.2 (s), 72.8 (t), 67.7 (t), 53.5 (q), 53.3 (q), 47.4 (d), 23.7 (t), 21.3 (q); *m/z* (ES) 366.1555 $C_{18}H_{24}NO_7$ ($M + H^+$, requires 366.1553). ^1H NMR NOE experiments (400 MHz, $CDCl_3$): irradiation at δ 2.89 (C*H*C(=O)NH) gave an enhancement of 3.6% at δ 1.56 (C*Me*), and irradiation at δ 1.56 gave a corresponding enhancement of 4.5% at δ 2.89 ppm.

(3*S**,4*R**)-4-(2-(Benzyloxy)ethyl)-3-methyl-5-oxo-3-(trimethylsilanyloxy)pyrrolidine-2,2-dicarboxylic acid dimethyl ester (27)

Trimethylsilyl trifluoromethanesulfonate (4.8 mL, 27 mmol) was added dropwise over 25 min to a stirred solution of the alcohol **24** (2.6 g, 6.7 mmol) and 2,6-lutidine (6.2 mL, 54 mmol) in anhydrous dichloromethane (70 mL) at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 3 h, and then allowed to warm to room temperature very slowly overnight. The mixture was quenched with 1 M aqueous HCl (30 mL), and the separated aqueous layer was then extracted with dichloromethane (3 × 30 mL). The combined extracts were dried and concentrated *in vacuo* to leave a residue which was purified by flash chromatography, using petroleum ether–diethyl ether (1 : 1) as eluent, to give the *silyl ether* **27** (2.65 g, 91%) as a colourless solid; mp 90–92 °C (from

petroleum ether–diethyl ether); Found: C, 58.0; H, 7.1; N, 3.4; $C_{21}H_{31}NO_7Si$ requires C, 57.6; H, 7.1; N, 3.2; ν_{max} ($CHCl_3$)/cm^{-1} 3700, 3352, 2956, 1716, 1602; δ_H ((360 MHz, $CDCl_3$) 7.37–7.27 (5H, m, C_6H_5), 6.12 (1H, br. s, N*H*), 4.55 (1H, app. s, OC*H*HPh), 4.51 (1H, app. s, OCH*H*Bn), 3.85 (3H, s CO_2CH_3), 3.77 (3H, s, CO_2CH_3), 3.80–3.67 (2H, m, CH_2CH_2OBn), 2.84 (1H, dd, *J* 4.0 and 8.6, C*H*C(=O)NH), 1.96 (1H, m, CH*H*CH_2OBn), 1.70 (1H, m, C*H*HCH_2OBn), 1.68 (3H, s, CCH_3), 0.10 (9H, s, OTMS); δ_C (90 MHz, $CDCl_3$) 177.0 (s), 168.1 (s), 166.7 (s), 138.6 (s), 128.3 (d) × 2, 127.6 (d) × 2, 127.5 (d), 85.8 (s), 76.1 (s), 73.0 (s), 68.2 (t), 53.3 (q), 52.9 (q), 48.6 (d), 24.9 (t), 21.5 (q), 2.6 (q) × 3; *m*/*z* (ES) 438.1942 ($M + H^+$, $C_{21}H_{32}NO_7Si$ requires 438.1948).

(3*S**,4*R**)-4-(2-(Benzyloxy)ethyl)-1-(4-methoxy-benzyl)-3-methyl-5-oxo-3-(trimethylsilanyloxy)pyrrolidine-2,2-dicarboxylic acid dimethyl ester (31)

Sodium hydride (60% in mineral oil, 110 mg, 2.75 mmol) was added in one portion to a stirred solution of the pyrrolidinone **27** (1.1 g, 2.5 mmol) in anhydrous DMF (10 mL) at 0 °C, under an argon atmosphere. The mixture was stirred at 0 °C for 15 min then *p*-methoxybenzyl bromide (550 μL, 3.75 mmol) was added dropwise over 3 min. The mixture was stirred at 0 °C for 1.5 h, then allowed to warm to room temperature and stirred overnight. The mixture was quenched with water (60 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with water (30 mL), then dried and concentrated *in vacuo*. The resiude was purified by flash chromatography, using petroleum ether–diethyl ether (4 : 1) as eluent, to give the *N-PMB pyrrolidinone* **31** (1.14 g, 72%) as a colourless soild; mp 80–82 °C (from diethyl ether-hexane); Found: C, 62.45; H, 7.1; N, 2.5; $C_{29}H_{39}NO_8Si$ requires; C, 62.48; H, 7.0; N, 2.5; ν_{max} ($CHCl_3$)/cm^{-1} 2955, 1741, 1698, 1613; δ_H (360 MHz, $CDCl_3$) 7.36–7.27 (5H, m, C_6H_5), 7.15 (2H, d, *J* 8.7 PMB Ar*H*), 6.79 (2H, d, *J* 8.7, PMB Ar*H*), 5.04 (1H, d, *J* 15.1, NC*H*H(C_5H_4)OCH_3), 4.57 (1H, d, *J* 15.1, NCH*H*(C_5H_4)OCH_3), 4.57 (1H, app. s, OCH*H*Ph), 4.56 (1H, app. s, OC*H*HPh), 3.88–3.83 (2H, m, CH_2CH_2OBn), 3.81 (3H, s, CO_2CH_3), 3.77 (3H, s, $OCH_2(C_5H_4)OCH_3$), 3.22 (3H, s, CO_2CH_3), 2.91 (1H, dd, *J* 4.1, 8.6, C*H*C(=O)NPMB), 2.02 (1H, m, CH*H*CH_2OBn), 1.76 (1H, m, C*H*HCH_2OBn), 1.61 (3H, s, CCH_3), 0.12 (9H, s, OTMS); δ_C (90 MHz, $CDCl_3$) 176.7 (s), 167.7 (s), 166.7 (s), 158.6 (s), 138.6 (s), 129.8 (d), 128.8 (d), 128.3 (d) × 2, 127.6 (d) × 2, 127.4 (d), 113.4 (d) × 2, 83.7 (s), 8.01 (s), 77.4 (s), 72.9 (t), 68.4 (t), 55.2 (q), 52.5 (q), 52.4 (q), 48.4 (d), 45.2 (t), 25.5 (t), 21.3 (q), 2.7 (q) × 3; *m*/*z* (ES) 558.2542 ($M + H^+$, $C_{29}H_{40}NO_8Si$ requires 558.2523).

(2*S**,3*S**,4*R**)-4-(2-(Benzyloxy)ethyl)-2-formyl-1-(4-methoxybenzyl)-3-methyl-5-oxo-3-(trimethylsilanyloxy)-pyrrolidine-2-carboxylic acid methyl ester (32)

A solution of Super-hydride® (3.8 mL, 3.8 mmol, 1.0 M in THF) was added dropwise over 15 min to a stirred solution of the diester **31** (1.73 g, 3.10 mmol) in anhydrous dichloromethane (15 mL) at −78 °C under a nitrogen atmosphere. The solution was stirred at −78 °C for 3 h, then brine–water (40 mL, 1 : 1) was added, and the mixture was extracted with ethyl acetate (3 × 80 mL). The combined organic extracts were dried, and concentrated *in vacuo*. The residue was purified by flash chromatography, using petroleum ether–diethyl ether (1 : 1) as eluent, to give the *aldehyde* **32** (1.28 g, 78%) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 2954, 1764, 1724, 1698, 1303, 1097; δ_H (360 MHz, $CDCl_3$) 9.70 (1H, s, CHO), 7.36–7.27 (5H, C_6H_5), 7.11 (2H, d, *J* 8.7, PMB Ar*H*), 6.80 (2H, d *J* 8.7, PMB Ar*H*), 4.56 (1H, d, *J* 12.0, NC*H*H(C_5H_4)OCH_3), 4.56 (2H, s, OCH_2Ph), 4.50 (1H, d, *J* 12.0 NCH_2PMB), 3.78–3.75 (2H, m, CH_2CH_2OBn), 3.78 (3H, s, $ArOCH_3$), 3.75 (3H, s, CO_2CH_3) 2.44 (1H, dd, *J* 4.5 and 8.4, C*H*C(=O)N), 2.06–1.95 (1H, m, C*H*HCH_2OBn), 1.78–1.67 (1H, m, CH*H*CH_2OBn), 1.50 (3H, s, CCH_3), 0.13 (9H, s, OTMS); δ_C (90 MHz, $CDCl_3$) 196.7 (d), 176.0 (s), 167.4 (s), 158.8 (s), 138.5 (s), 130.6 (d), 129.9 (s) 128.8 (d) × 2, 128.3 (d), 127.5 (d) × 2, 127.4 (d), 113.7 (d) × 2, 83.9 (s), 83.7 (s) 73.0 (t), 68.2 (t), 55.2 (q), 52.5 (q), 48.4 (d), 45.9 (t), 25.6 (t), 22.7 (q), 2.5 (q) × 3; *m*/*z* (ES) 550.2221 ($M + Na^+$, $C_{28}H_{37}NO_7SiNa$ requires 550.2232). ^1H NMR NOE experiments (360 MHz, $CDCl_3$): irradiation at δ 9.70 (C*H*O) gave an enhancement of 2.3% at δ 1.50 (C*Me*), and irradiation at δ 1.50 gave a corresponding enhancement of 5.3% at δ 9.70 ppm. In addition, irradiation at δ 1.50 (C*Me*) gave an enhancement of 6.7% at δ 2.44 (C*H*C(=O)N), and irradiation at δ 2.44 gave an enhancement of 4% at δ 1.50 ppm,

(2*R**,3*S**,4*R**)-4-(2-(Benzyloxy)ethyl)-2-((*R**)-(*S**)-cyclohex-2-enylhydroxymethyl)-1-(4-methoxybenzyl)-3-methyl-5-oxo-3-(trimethylsilanyloxy)pyrrolidine-2-carboxylic acid methyl ester (33)

2-Cyclohexenyl bromide (1.15 mL, 10 mmol) was added dropwise over 20 min to a stirred suspension of activated zinc[26] (780 mg, 12 mmol) in anhydrous THF (20 mL) at 0 °C under a nitrogen atmosphere. The solution was stirred at room temperature for 1 h to give a 0.5 M solution of 2-cyclohexenylzinc bromide. A pre-cooled (−78 °C) solution of the aldehyde **32** (1.18 g, 2.23 mmol) in anhydrous THF (5 mL) was added *via* cannula to the freshly prepared solution of cyclohexenylzinc bromide (14 mL, 7 mmol, 0.5 M in THF) at −78 °C, under a nitrogen atmosphere. The mixture was stirred at −78 °C for 3 h, then quenched with saturated aqueous ammonium chloride (70 mL) and extracted with ethyl acetate (3 × 70 mL). The combined organic extracts were dried and concentrated *in vacuo* to leave a pale yellow oil. The oil was purified by flash chromatography on silica gel, using petroleum ether–diethyl ether (2 : 1 then 1 : 1) as eluent, to give the *homoallylic alcohol* **33** (1.18 g, 87%) as a colourless solid; mp 157–160 °C (from petroleum ether–diethyl ether); (Found: C, 66.8; H, 7.8; N, 2.3; $C_{34}H_{47}NO_7Si$ requires C, 67.0; H, 7.7; N, 2.3); ν_{max} ($CHCl_3$)/cm^{-1} 3564, 2953, 1755, 1721, 1688, 1514; δ_H (360 MHz, $CDCl_3$) 7.34–7.26 (5H, m, C_6H_5), 7.23 (2H, d, *J* 8.7, PMB Ar*H*), 6.80 (2H, d, *J* 8.7, PMB Ar*H*), 6.05 (1H, app. d, *J* 10.2, CH_2CH=), 5.63 (1H, app. d, *J* 10.2, CH_2CH=C*H*), 4.80 (1H, d, *J* 15.3, NC*H*H(C_5H_4)OCH_3), 4.52 (2H, s, OCH_2Ph), 4.42 (1H, d, *J* 15.3 NCH*H*(C_5H_4)OCH_3), 4.20 (1H, dd, *J* 3.3 and 7.9, C*H*(OH)), 3.89–3.80 (2H, m, CH_2OBn), 3.79 (3H, s, CO_2CH_3), 3.62 (3H, s, $CH_2(C_5H_4)OCH_3$), 3.03 (1H, dd, *J* 3.8 and 9.4, C*H*C(=O)NPMB), 2.26 (1H, br s, CH_2CH=CHC*H*), 2.04 (2H, br s, CH_2CH_2CH=), 1.91–1.89 (1H, m, C*H*HCH_2OBn), 1.90 (1H, d, *J* 7.9, CH(O*H*)), 1.80–1.78 (3H, m, C*H*HCH_2OBn, C*H*HCH_2CH=, =CHCH(R)CH*H*), 1.76 (3H, s,CCH_3), 1.59–1.51 (2H, m, CH*H*CH_2CH=, =CHCH(R)C*H*H), 0.16 (9H, s, OTMS); δ_H (90 MHz, $CDCl_3$) 177.7 (s), 169.5 (s), 157.8 (s), 138.7

(s), 134.7 (d), 130.6 (s), 128.2 (d) × 2, 127.7 (d) × 2, 127.3 (d), 127.1 (d), 123.8 (d) × 2, 113.2 (d) × 2, 86.2 (s), 82.4 (s), 76.8 (d), 72.9 (t), 68.8 (t), 55.2 (q), 51.7 (q), 48.3 (d), 47.7 (t), 38.2 (d), 29.4 (t), 26.1 (t), 25.0 (t), 20.8 (q), 20.5 (t), 2.7 (q) × 3; *m/z* (ES) 632.3041 (M + Na^+, $C_{34}H_{47}NO_7SiNa$ requires 632.3014).

(2*R**,3*S**,4*R**)-2-((*R**)-(*S**)-Cyclohex-2-enylhydroxymethyl)-4-(2-hydroxyethyl)-1-(4-methoxybenzyl)-3-methyl-5-oxo-3-(trimethylsilanyloxy)pyrrolidine-2-carboxylic acid methyl ester (34)

A solution of boron trichloride–methyl sulfide complex (2.1 mL, 4.2 mmol, 2 M, dichloromethane) in was added dropwise over 15 min to a stirred solution of the benzyl ether **33** (255 mg, 0.418 mmol) in anhydrous dichloromethane (4.2 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h and then at room temperature for a further 18 h. The mixture was re-cooled to 0 °C, then carefully quenched with a saturated aqueous solution of sodium hydrogen carbonate (20 mL), and extracted with dichloromethane (4 × 20 mL). The combined organic extracts were dried and concentrated *in vacuo* to leave the crude product (216 mg) as a pale brown oil. A small portion was purified by flash chromatography on silica gel, using ethyl acetate–2-methylpentane (1 : 1) as eluent, to give the *diol* **34** as a colourless solid; mp 85–87 °C (from ethyl acetate–2-methylpentane); ν_{max} ($CHCl_3$)/cm^{-1} 3306 (br), 2954, 1756, 1725, 1673, 1514; δ_H (360 MHz, $CDCl_3$) 7.21 (2H, d, *J* 8.8, PMB Ar*H*), 6.80 (2H, d, *J* 8.8, PMB Ar*H*), 6.07–6.02 (1H, m, CH_2CH=), 5.63 (1H, dd, *J* 2.6 and 10.2, CH_2CH=C*H*) 4.84 (1H, d, *J* 15.4, NC*H*H(C_5H_4)OCH_3), 4.28 (1H, d, *J* 15.4, NCH*H*(C_5H_4)OCH_3), 4.21 (1H, dd, *J* 3.4, 7.6, C*H*(OH)), 3.95–3.86 (1H, m, CH_2CH*H*OH), 3.79 (3H, s, CO_2CH_3), 3.70 (1H, dt, J 2.5, 10.6, CH_2CH*H*OH), 3.60 (3H, s, $CH_2(C_5H_4)OCH_3$), 3.06 (1H, dd, *J* 2.6 and 10.5, C*H*C(=O)NPMB), 2.32 (1H, d, *J* 7.6, O*H*) 2.26 (1H, app. br. s, CH_2CH=CHC*H*) 2.04 (2H, app. br. s, CH_2CH=CHCH), 1.91–1.72 (4H, m, CH_2CH_2OH, =CHCH(R)CH*H*, CH*H*CH_2C(R)H), 1.72 (3H, s, CCH_3), 1.61–1.51 (2H, m, =CHCH(R)C*H*H, CH*H*CH_2C(R)H), 0.16 (9H, s, OTMS); δ_C (90 MHz, $CDCl_3$) 179.0 (s), 169.1 (s), 157.9 (s), 134.6 (d), 129.9 (s), 127.1 (d) × 2, 123.7 (d), 113.3 (d) × 2, 86.1 (s), 83.3 (s), 76.8 (d), 62.4 (t), 55.2 (q), 53.4 (d), 51.8 (q), 47.9 (t), 38.2 (d), 29.4 (t), 28.3 (t), 25.0 (t), 20.5 (t), 20.3 (q), 2.7 (q); *m/z* (ES) 542.2577 (M + Na^+, $C_{27}H_{41}NO_7SiNa$ requires 524.2545).

(2*R**,3*S**,4*R**)-2-((*R**)-(*S**)-Cyclohex-2-enylhydroxymethyl)-3-hydroxy-4-(2-hydroxyethyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid methyl ester (36a)

A solution of the crude diol **34** (216 mg, 0.418 mmol) in acetonitrile–48% aqueous HF (3.5 mL, 9 : 1) was stirred at room temperature for 16 h. The mixture was filtered through a plug of silica, eluting with ethyl acetate. The filtrate was concentrated *in vacuo* to leave a residue, which was triturated with ethyl acetate and concentrated *in vacuo* to leave the crude *triol* **35** (187 mg), ν_{max} ($CHCl_3$)/cm^{-1} 3316, 2936, 1750, 1674; δ_H (400 MHz, $CDCl_3$) 7.29 (2H, d, *J* 8.8, PMB ArH), 6.84 (2H, d, *J* 8.8, PMB ArH), 5.95–5.93 (1H, m, CH_2CH=), 5.66 (1H, dm, *J* ~10, CH_2CH=C*H*), 4.76 (1H, d, *J* 15.5, NC*H*H), 4.59 (1H, d, J 15.5, NCH*H*), 4.15 (1H, d, *J* 2.5), 3.80 (1H, m), 3.72 (3H, s, CO_2Me), 3.68 (3H, s, OMe), 3.40 (1H, br), 3.0 (1H, m), 2.22 (1H, m), 2.01 (2H, s), 1.9–1.8 (2H, m), 1.70 (2H, m), 1.65 (3H, s, C*Me*), 1.45 (2H, m); δ_C (90 MHz, $CDCl_3$) 178.7 (s), 169.8 (s), 158.3 (s), 131.7 (s), 130.1 (s), 128.0 (d), 125.9 (d), 113.7 (d), 81.9 (s), 80.6 (s), 77.0 (d), 61.5 (t), 55.2 (q), 51.1 (q), 47.8 (t), 38.7 (d), 27.7 (t), 26.9 (t), 24.9 (t), 21.6 (q), 21.1 (t); *m/z* (ES) 448.2325 (M + H^+, $C_{24}H_{34}NO_7$ requires 448.2335), which was used in the next step without further purification.

A pre-cooled (0 °C) solution of ceric ammonium nitrate (690 mg, 1.25 mmol) in water (1.0 mL) was added dropwise over 3 min to a stirred solution of the triol **35** (187 mg, 0.42 mmol) in acetonitrile (3 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, then diluted with ethyl acetate (30 mL). The separated organic layer was washed with brine (3 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography, using ethyl acetate as eluent, to give the *triol* **36a** (117 mg, 87% over three steps) as an almost colourless solid; mp 137–140 °C (from ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3304 (br), 2935, 1725, 1681; δ_H (400 MHz, $CDCl_3$) 8.37 (1H, br. s, N*H*), 6.10 (1H, br. d, *J* 10.1, CH_2CH=), 5.75 (1H, br. d, *J* 10.1, CH_2CH=C*H*), 4.13 (1H, dd, *J* 7.0, 14.3, C*H*(OH)), 3.85 (3H, s, CO_2Me), 3.85–3.74 (2H, m, CH_2CH_2OH), 2.87 (1H, app. d, *J* 9.2, C*H*C(=O)NH), 2.22 (1H, br. s, CH_2CH=CHC*H*), 2.02 (3H, m, CH_2CH=CHCH, C*H*HCH$_2$OH) 1.81–1.74 (3H, m, C*H*HCH$_2$OH, =CHCH(R)CH*H*, CH*H*CH_2C(R)H), 1.61–1.50 (1H, =CHCH(R)C*H*H,), 1.57 (3H, s, CCH_3), 1.27–1.27 (1H, m, C*H*HCH$_2$C(R)H); δ_C (100 MHz, $CDCl_3$) 180.7 (s), 172.5 (s), 135.0 (d), 123.6 (d), 81.8 (s), 79.8 (s), 76.7 (d), 62.1 (t), 52.9 (q), 51.7 (d), 38.7 (d), 28.5 (t), 26.2 (t), 24.8 (t), 20.5 (t), 19.8 (q); *m/z* (ES) 350.1566 (M + Na^+, $C_{16}H_{25}NO_6Na$ requires 350.1574).

(±)-Salinosporamide (1)

A solution of trimethylaluminium (2.5 mL, 5.0 mmol, 2 M in toluene) was added in one portion to a stirred suspension of tellurium powder (0.71 g, 5.5 mmol, 99.99% Alfa Aesar) in dry degassed toluene (2.5 mL) under an argon atmosphere. The mixture was heated under reflux for 6 h, then allowed to cool to room temperature and transferred *via* cannula to a flame-dried flask, to afford a 0.8 M solution of dimethylaluminium methyltellurolate in toluene. A solution of the freshly prepared methyltellurolate (500 μL, 0.4 mmol, 0.8 M in toluene) was added in one portion to a stirred solution of the methyl ester **35** (12.7 mg, 0.038 mmol) in dry dichloromethane (50 μL) at room temperature under an atmosphere of argon. The solution was stirred at room temperature for 24 h, then diluted with ethyl acetate (5 mL) and treated with 2 M HCl (5 mL). The mixture was stirred vigorously for 3 h at room temperature whilst open to the atmosphere. The separated aqueous layer was saturated with sodium chloride and then extracted with ethyl acetate–ethanol (4 × 5 mL, 95 : 5). The combined organic extracts were concentrated *in vacuo* to leave the corresponding carboxylic acid **37** as an almost colourless solid.

A solution of the carboxylic acid **37** in dry dichloromethane (400 μL), containing dry pyridine (50 μL), was stirred vigorously at room temperature for 5 min under an argon atmosphere. BOP-Cl (16 mg, 0.064 mmol) was added and the mixture was stirred at room temperature for a further 3 h. The solvent was removed under high vacuum and the residue was diluted with dry pyridine (0.2 mL). PPh_3Cl_2 (200 μL, 1.0 M in acetonitrile) was added and the mixture was stirred under an argon atmosphere for 4 h, then evaporated *in vacuo*. The residue was purified by

chromatography, using 2 : 3 ethyl acetate–pentane as eluent, to give salinosporamide A (3.6 mg, 45% over the three steps) as a colourless solid; mp 169–172 °C (from ethyl acetate–pentane); δ_H (360 MHz, C_5D_5N) 10.60 (1H, br s, N*H*), 6.41 (1H, d, *J* 10.5, C*H*=CHCH), 5.88 (1H, m, CH=C*H*CH), 4.91 (1H, br s, O*H*), 4.25 (1H, app. t, *J* 9.0, C*H*(OH)), 4.13 (1H, app. td, *J* 6.8 and 10.7, CH_2CH*H*Cl), 4.01 (1H, app. td, *J* 6.8 and 10.7, CH_2CH*H*Cl), 3.17 (1H, app. t, *J* 7.0, C*H*C(=O)NH), 2.84 (1H, br s, CH=CHC*H*), 2.48 (1H, m, CH*H*CH_2Cl), 2.37–2.26 (2H, m, C*H*HCH_2Cl and =CHCH(R)CH*H*), 2.07 (3H, s, CCH_3), 1.91 (2H, m, CH_2CH=CHCH), 1.73–1.64 (2H, CH*H*CH_2C(R)H, =CHCH(R)C*H*H), 1.36 (1H, m, C*H*HCH_2C(R)H); δ_C (90 MHz, C_5D_5N) 176.9 (s), 169.5 (s), 129.1 (d), 128.7 (d), 86.3 (s), 80.4 (s), 71.0 (d), 46.2 (d), 43.3 (t), 39.3 (d), 29.0 (t), 26.5 (t), 25.4 (t), 21.8 (t), 20.0 (q); *m*/*z* (ES) 336.0957 ($M + Na^+$, $C_{15}H_{20}ClNO_4Na$ requires 336.0973).

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