A new synthetic approach to (+)-lactacystin based on radical cyclisation of enantiopure α-ethynyl substituted serine derivatives to 4-methylenepyrrolidinones†

Gerald Pattenden* and Gwenaëlla Rescourio

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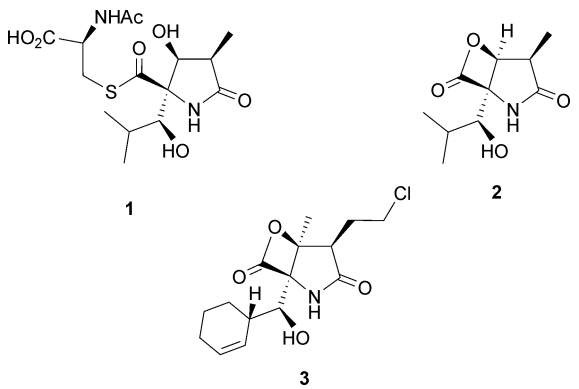
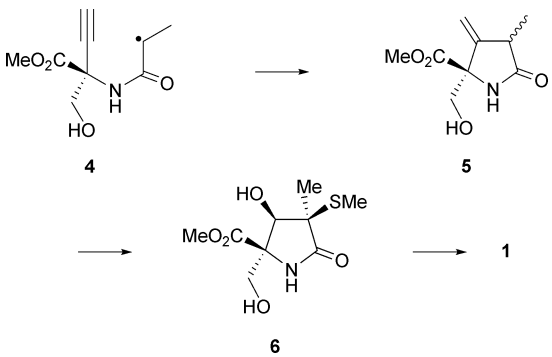
Treatment of the acetylenic bromoamide **42c**, derived from the enantiopure α-amino alcohol **40**, with Bu_3SnH–AlBN results in an efficient 5-*exo* dig radical cyclisation to the 4-methylenepyrrolidinone **43/44** (2 : 1). Cleavage of the alkene bond in **43/44**, using O_3–Me_2S, next gave the corresponding 4-ketopyrrolidinone **45/46**. α-Phenylsulfanylation of **45/46**, using *S*-methyl-*p*-toluenethiosulfonate–Et_3N, proceeded in a stereoselective manner and led to the methylsulfanyl derivative **48** (*ca.* 9 : 1 selectivity). Manipulation of the functionality in **48**, using two separate sequences, then led to the substituted pyrrolidinones **49b**, **50** and **53** which are advanced intermediates in a previous synthesis of (+)-lactacystin **1**. In related studies, the acetylenic bromoamide **28a** containing all the carbon atoms in lactacystin was synthesised, but this substrate failed to undergo an anticipated radical cyclisation to the 4-methylenepyrrolidinone **30**, analogous to **43/44**. Instead, only the product of reduction of **28a**, *i.e.* **28b**, was produced, possibly resulting from adventitious intramolecular hydrogen-abstraction processes from the carbon centred radical intermediate **29**, *i.e.* **32** to **33** and/or **31** to **34**.

1. Introduction

Lactacystin **1** is one of the most important biologically active pyrrolidinone-based natural products yet to be found in nature. It was isolated from the culture broth of a *Streptomyces* in 1991,[1] and since that time has generated an enormous interest as a consequence of its highly selective and irreversible inhibition of the 20S proteasome.[2] The 20S proteasome is involved in the turnover of cellular proteins and in removing damaged, misfolded and mistranslated proteins in cells.[3] The β-lactone omuralide **2** (also known as clasto-lactacystin β-lactone) is derived from lactacystin *in vivo*, and is the actual biological agent that acts by acylation of the amino terminal threonine residue of a proteasome unit.[4] A more recently isolated pyrrolidinone-based inhibitor of the 20S proteasome is salinosporamide A (**3**) found in the marine bacterium *Salinospora tropica*.[5] The three natural products **1**, **2** and **3**, have become important compounds in studies of protein biochemistry and cell biology, and to indicate that they have been attractive targets for synthetic and medicinal chemists would be an understatement! Indeed, the first synthesis of lactacystin **1** was described by Corey *et al.*[6] as early as 1992, and since then a range of ingenious synthetic approaches have been developed towards this exciting target.[7–10]



In this paper we describe a synthetic approach to lactacystin which hinges on a radical cyclisation from a chiral α-ethynyl substituted serine derivative, *viz* **4**, as a key step to a functionalised pyrrolidinone, *i.e.* **5**.[11] The pyrrolidinone **5** is then elaborated to the derivative **6** from which the natural product can be obtained in a few steps using a documented procedure.



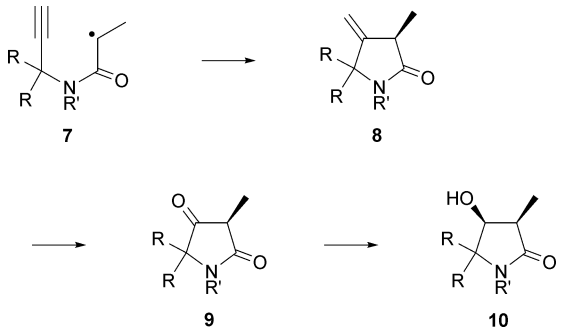
School of Chemistry, The University of Nottingham, University Park, Nottingham, England NG7 2RD

† Electronic supplementary information (ESI) available: Additional experimental procedures and data. CCDC reference number 226290. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b806681g

2. Results and discussions

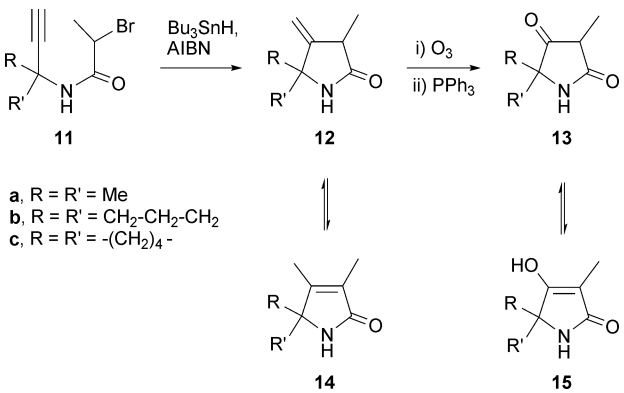
2.1 Synthetic strategy

Our synthetic approach to the pyrrolidinone ring in lactacystin was based on an initial 5-*exo* dig radical cyclisation of an acetylenic amide radical, *viz* **7**, leading to a 4-methylenepyrrolidinone, *i.e.* **8**. We then envisaged an oxidative cleavage of the alkene bond in **8**, producing the corresponding 4-ketopyrrolidinone **9** for subsequent elaboration to the 4-hydroxy derivative **10** and thence onwards to lactacystin.



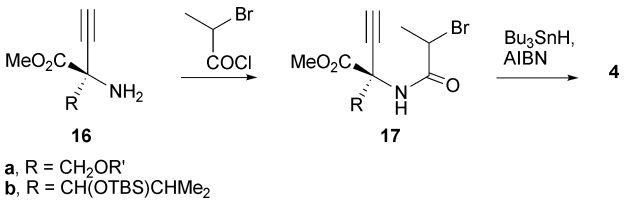
2.2 Radical approach to 4-methylenepyrrolidinones

The feasibility of the key radical cyclisation step **7** → **8** was demonstrated several years ago in our laboratories using a number of model acetylenic α-bromoamide substrates, *i.e.* **11**, which smoothly led to the corresponding 4-methylenepyrrolidinones **12** by way of 5-*exo*-dig radical cyclisations upon treatment with Bu_3SnH–AIBN in refluxing benzene.[12] Furthermore, the reactions and work-up procedures could be controlled such that only very small amounts of the isomeric δ-lactam products **14** were obtained concurrently. Equally satisfying was the finding that careful cleavage of the alkene bonds in the 4-methylenepyrrolidinones **12**, using ozone at −78 °C followed by reductive work-up at −78 °C to room temperature with Ph_3P or Me_2S, allowed the isolation of the corresponding 4-ketopyrrolidinones **13** with little contamination by the isomeric tetramic acid derivatives **15**.



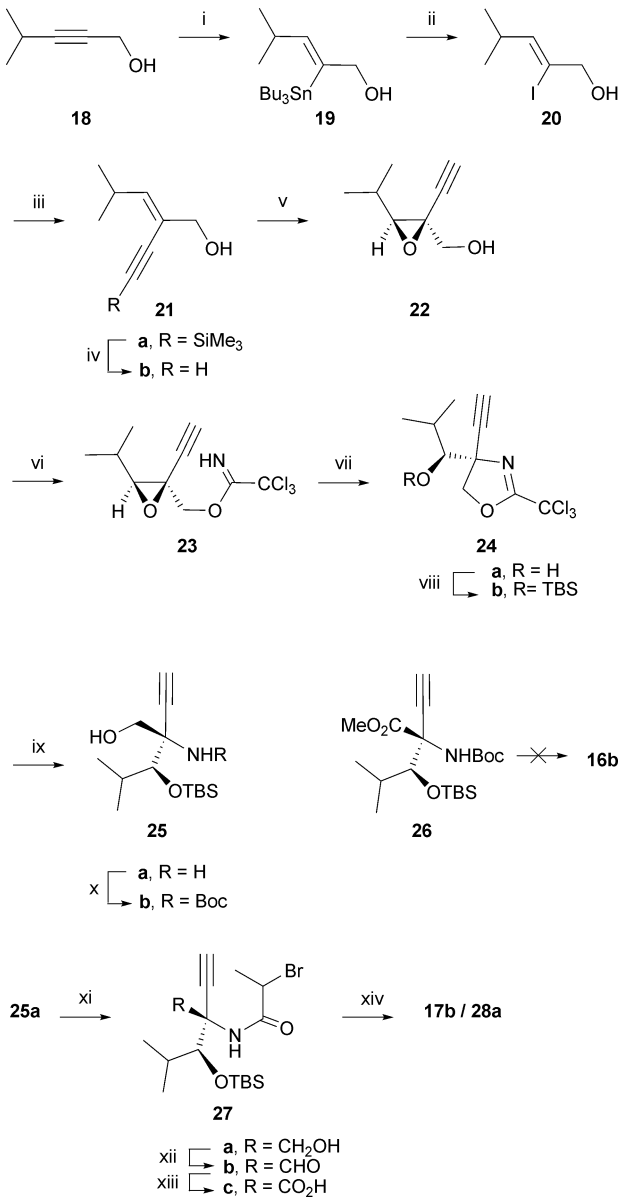
2.3 Synthesis of α-ethynyl-α′-substituted α-amino acids and the proposed lactacystin precursor 28a

With the model radical cyclisations studies complete we now required a practical synthetic route to an enantiopure α-ethynyl-α-substituted amino acid derivative, *viz* **16**, for elaboration to the bromoamide **17** *en route* to **4**, **5** and **6**, and beyond. In fact, a plethora of methods are available for the synthesis of α,α-disubstituted amino acid derivatives akin to **16**, and we evaluated the scope for several of these procedures.[13] In these investigations, which were carried out in parallel with our contemporaneous studies towards the natural products oxazolomycin and neooxazolomycin,[14] we found that the procedure of Schmidt and Hatakeyama[15] involving the ring-opening of 3,3-disubstituted 2-trichloromethyloxazolines derived from enantiopure 2-substituted glycidols (*i.e.* 2,3-epoxy-1-propanols) was particularly convenient for the synthesis of the 2-ethynyl serine derivatives **16**.



In our first synthetic approach to lactacystin we decided to prepare the acetylenic bromoamide radical precursor **28a** containing all the carbon atoms in the natural product. In turn, the bromoamide **28a** was to be made from the α,α-disubstituted amino alcohol derivative **25a** using the aforementioned Schmidt–Hatakeyama protocol (Scheme 1).

Thus, 4-methylpent-2-yn-1-ol **18**[16] was first hydrostannylated in a regio- and stereo-selective manner, under free radical conditions (*i.e.* Bu_3SnH–AIBN)[17] leading to the *Z*-stannylpentenol **19** in 74% yield. Exchange of tin for iodide in **19**,[18] followed by a coupling reaction between the resulting iodide **20** and trimethylsilylacetylene under Sonogashira conditions[19] next led to the *Z*-enynol **21a** in excellent yield. Removal of the silyl protecting group in **21a**, followed by epoxidation of the resulting 2-ethynylpropenol **21b** using (+)-diethyl tartrate and *tert*-butyl hydroperoxide in the presence of catalytic calcium hydride and silica gel at −40 °C to −18 °C,[20] next gave the corresponding epoxide **22** which was obtained in 89% yield and with >95% ee (determined by ^{19}F NMR analysis of the corresponding Mosher ester derivative). Acetamidation of the epoxy alcohol **22**, using trichloroacetonitrile in the presence of catalytic DBU then gave the acetamidate **23** which produced the corresponding oxazoline **24a** on treatment with diethylaluminium chloride at 0–25 °C.[21] Protection of the alcohol group in **24a** as its silyl ether **24b** followed by cleavage of the oxazoline ring, using 1 M aqueous HCl now gave the α-ethynyl amino alcohol **25a** which was immediately converted into its carbamate derivative **25b**. Our plan now was to convert **25b** into the α-ethynyl amino acid ester **16b** in readiness for elaboration to **17b**. However, although we were able to elaborate the primary alcohol group in **25b** to the corresponding methyl ester **26**, we were not able to remove the Boc protecting group in **26** leading to **16b**. We therefore altered our strategy at this point, and instead treated the amino alcohol **25a** with 2-bromopropionoyl chloride under Schotten–Baumann[22] conditions (*i.e.* $NaHCO_3$–DCM) at pH 6.0–6.5, which led to the substituted α-ethynyl bromoamide **27a** in an excellent 80% yield. Sequential oxidation of the primary alcohol group in **27a**, followed by esterification of the carboxylic acid **27c** finally gave the methyl ester precursor **28a** for our projected



Scheme 1 *Reagents and conditions*: i) Bu_3SnH, AIBN, 85 °C, 74%; ii) NIS, DCM, 0 °C, 95%; iii) $Me_3SiC{\equiv}CH$, $Pd(PPh_3)_4$, CuI, Et_2NH, RT, 91%; iv) K_2CO_3, MeOH, 0 °C, 89%; v) L-(+)-DET, $Ti(O^iPr)_4$, TBHP, DCM, SiO_2, CaH_2, −40 °C to −18 °C, 89%, >95% ee; vi) Cl_3CCN, DBU, 0 °C, 85%; vii) Et_2AlCl, DCM, 0 °C to RT, 79%; viii) TBSOTf, 2,6-lutidine, DCM, 0 °C to RT, 93%; ix) 2 M HCl, THF, RT; x) $(Boc)_2O$, $NaHCO_3$, DCM, 74% over 2 steps; xi) $CH_3CH(Br)COCl$, $NaHCO_3$, DCM, pH 6–6.5, 80% over 2 steps; xii) Dess–Martin periodinane, DCM, 0 °C; xiii) $NaClO_4$, NaH_2PO_4, *t*-BuOH, 2-methyl-2-butene, RT; xiv) Me_3SiCHN_2, MeOH–benzene, RT, 74% over 3 steps.

radical cyclisation to the substituted 4-methylenepyrrolidinone **30**, *en route* to lactacystin.

Much to our frustration, treatment of **28a** under standard radical cyclisations conditions (*i.e.* slow addition of Bu_3SnH and catalytic AIBN in toluene) did not lead to the anticipated 4-methylenepyrrolidinone **30**. Instead, a complex mixture of products resulted, from which only the product of reduction of the carbon-to-bromide bond in **28a**, *i.e.* **28b**, could be characterised.

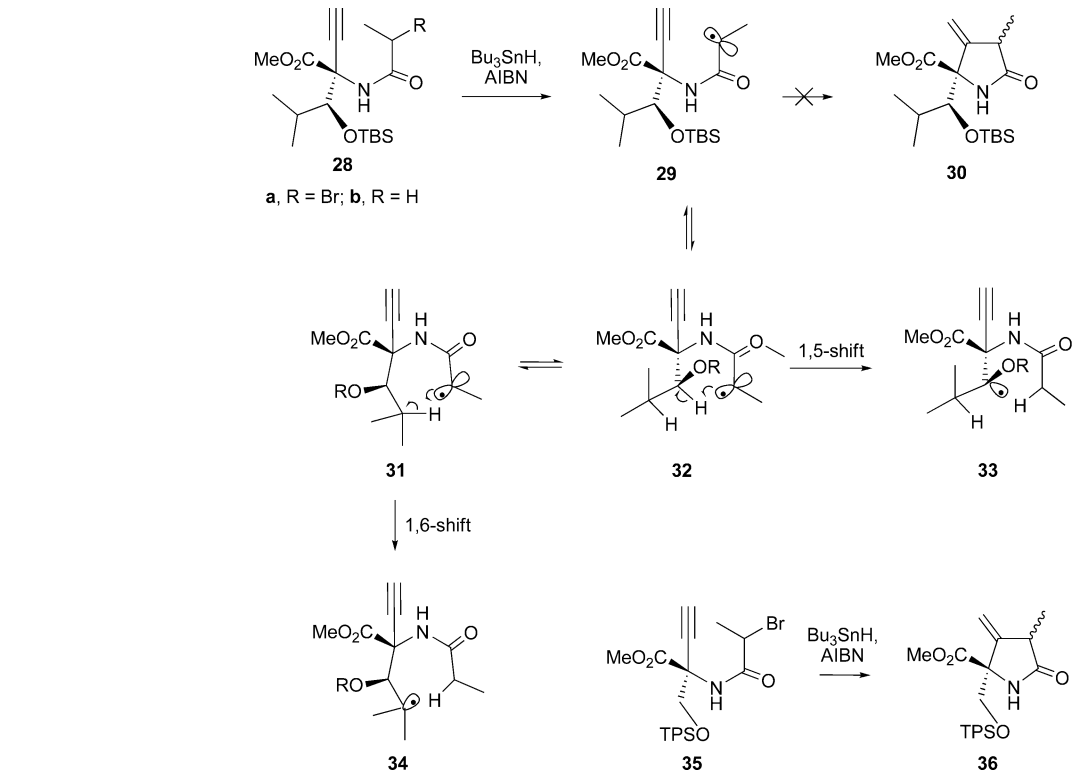
2.4 Synthesis of the 4-methylene and 4-keto pyrrolidinones 43/44 and 45/46 respectively

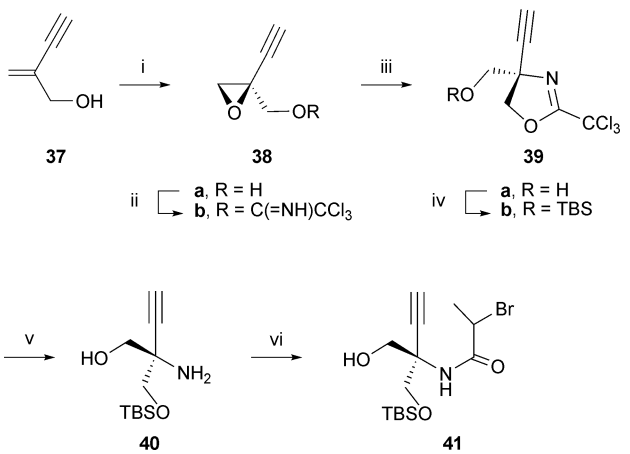
We reasoned that the failure of the radical intermediate **29** produced from the acetylenic bromoamide **28a** to undergo the anticipated 5-*exo*-dig radical cyclisation to **30** was due, in part, to a competing intramolecular 1,5-H abstraction process involving the same radical intermediate from its amide rotamer, *viz* **32** → **33**. Indeed, on this basis, we might expect the resulting radical centre **33** with its proximal oxy-centre to be quite stable (captodative effects). Interestingly, in contemporaneous studies[23] we showed that the substrate **35** which lacked the isopropyl appendage present in **28a** underwent a smooth 5-*exo* dig radical cyclisation when treated with Bu_3SnH–AlBN leading to the 4-methylenepyrrolidinone **36** in an excellent 80% yield. This contrasting result suggested that the isopropyl substituent in the substrate **28a** plays a significant role in inhibiting the desired cyclisation of **29** to **30**. Whether this effect is steric in nature, or due to an additional and competing 1,6-H abstraction process from **31** leading to the tertiary radical centre **34** is not clear. Whatever the rationale, we decided to capitalise on the difference and synthesise the enantiopure amino alcohol **40**, corresponding to the isopropyl-substituted compound **25a**, in an alternative approach to lactacystin.

Thus, a Sharpless epoxidation of 2-ethynylpropenol **37**[24] using (+)-diisopropyl tartrate, titanium tetraisopropoxide and cumene hydroperoxide[25] at −35 °C to −10 °C first gave the chiral epoxide **38a** in 66% yield and with 86% ee (Scheme 2). Interestingly, our attempts to epoxidise **37** applying the protocol used in the conversion of **21b** into **22** met with failure; this outcome reinforces the important differences in ease of epoxidation of *gem*-disubstituted and tri-substituted allylic alcohols using Sharpless procedures.[26] The epoxide **38a** was next converted into the oxazoline **39a** *via* the acetimidate **38b**, which was then protected as the crystalline TBS ether **39b**. X-Ray crystallographic analysis of **39b**, confirmed its absolute stereochemistry.[27] When the oxazoline **39b** was carefully treated with dilute (1 M) hydrochloric acid it was converted into the amino alcohol **40**, as its hydrochloride salt, which was reacted immediately with 2-bromopropionoyl chloride in the presence of sodium bicarbonate, to give the amide **41** as a 1 : 1 mixture of diastereoisomers.

The alcohol group in **41** was next converted into the corresponding methyl ester **42c** in three straightforward steps *via* the aldehyde **42a** and the carboxylic acid **42b**, in 62% overall yield. When a solution of the bromoamide **42c** in toluene under reflux was treated over 30 min with a solution of Bu_3SnH–AlBN, followed by heating under reflux for a further 2 h, work-up and chromatography gave a 2 : 1 mixture of C3 methyl epimers of the 4-methylenepyrrolidinone **43/44** in a satisfying 60% yield. The stereochemistries of the separated diastereoisomers **43** and **44** were established by NOE enhancement experiments in their ^1H NMR spectra. These data ascertained that the major diastereoisomer resulting from the 5-*exo* dig radical cyclisation of **42c** was the C3 α-Me epimer **43**.

The 2 : 1 mixture **43/44** was next treated with ozone at −78 °C followed by a reductive work-up of the ozonide intermediate with dimethyl sulfide. This procedure led to a 2 : 1 mixture of α- and β-methyl epimers of the 4-ketopyrrolidinone **45/46**, in 75% yield, with no evidence for the co-formation of the tautomeric tetramic acid **47** (Scheme 3).[28] The diastereoisomer **46**, with a β-methyl at C3, has the correct stereochemistry for elaboration to lactacystin,





Scheme 2 *Reagents and conditions*: i) L-(+)-DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide, DCM, −10 °C, 66%, 86% ee; ii) Cl_3CCN, DBU, 0 °C, 66%; iii) Et_2AlCl, DCM, 0 °C to RT, 78%; iv) TBSOTf, 2,6-lutidine, DCM, 0 °C to RT, 97%; v) 1 M HCl, THF, RT; vi) $CH_3CH(Br)COCl$, $NaHCO_3$, DCM, RT, 76% over 2 steps.

and we were disappointed not to be able to produce further quantities of this diastereoisomer by selective epimerisation of the α-methyl diastereoisomer **45** using a range of conditions.[29]

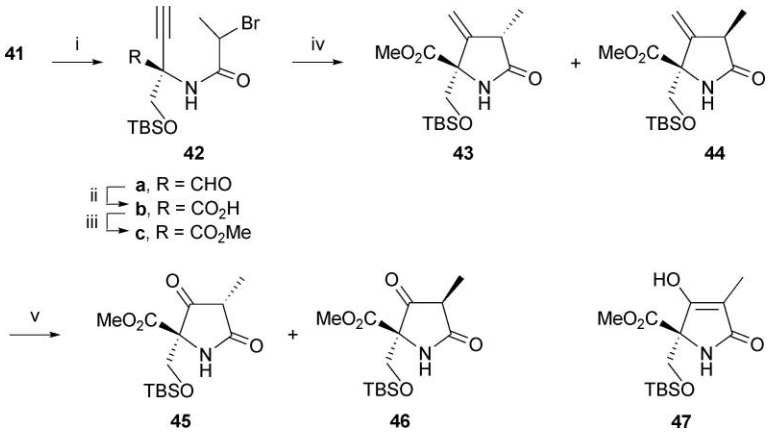
2.5 Elaboration of the 4-ketopyrrolidones 45/46 to the 3-methylsulfanyl derivatives 49 and 50, and completion of a formal synthesis of (+)-lactacystin

With our failure to epimerise the C3 centre in **45** to the β-methyl epimer **46** required for lactacystin, we decided to take advantage of an observation made earlier by Corey *et al.* and first convert **45/46** into the corresponding C3 methylsulfanyl derivative, *i.e.* **48**. In one of their syntheses of lactacystin Corey *et al.*[6d] had prepared the 3-methylsulfanyl derivative **53** as an advanced intermediate and showed that it could be desulfurised in a selective manner, using Raney nickel, producing the C3 β-methyl epimer of the resulting pyrrolidinone **54** in an excellent 82% yield (Scheme 4). We therefore treated the 2 : 1 mixture of diastereoisomers **45/46** with *S*-methyl-*p*-toluenethiosulfonate[30] in the presence of triethylamine and we were pleased to find that this procedure led to largely one diastereoisomer (ratio 87 : 13) of the C3 thiolated product **48** with the methylsulfanyl group *anti*-to the bulky CH_2OTBS group at C5. After protection of the nitrogen centre in **48** with a PMB group, deprotection of the primary alcohol group next led to the pyrrolidinone **49b**, which was found to undergo stereoselective reduction[6d] to the corresponding C4 β-hydroxy compound **50** using sodium triacetoxyborohydride, in 88% yield.

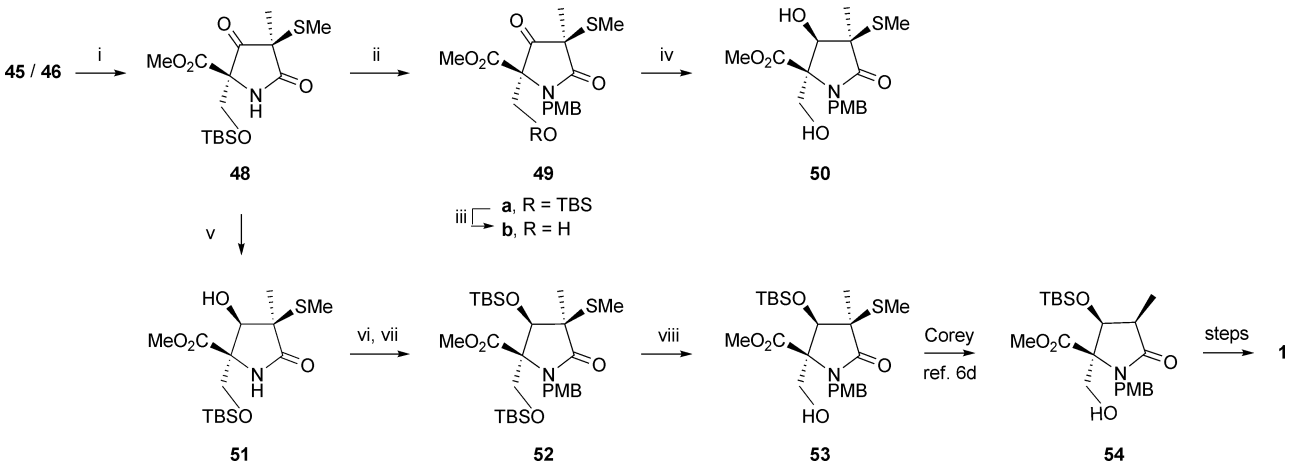
In a separate sequence, reduction of the 4-ketopyrrolidinone **48** with zinc borohydride in THF was also found to be stereoselective leading to the C4 β-alcohol **51** in 79% yield. Protection of the secondary alcohol and amine groups in **51** as their TBS and PMB groups respectively, followed by deprotection of the primary alcohol group in the product **52**, then led to the substituted pyrrolidinone **53**. The substituted pyrrolidinones **49b**, **50** and **53**, are all intermediates in one of Corey's total synthesis of lactacystin,[6d] and our synthetic **49b** displayed ^1H and ^{13}C NMR spectroscopic data which were identical to those reported in the literature.

3. Summary

We have developed a new, formal, synthesis of (+)-lactacystin **1** which is distinguished from other syntheses by elaboration of the pyrrolidinone ring system in the natural product *via* a novel 5-*exo*



Scheme 3 *Reagents and conditions*: i) Dess–Martin periodinane, DCM, 0 °C; ii) $NaClO_4$, NaH_2PO_4, *t*-BuOH, 2-methyl-2-butene, RT; iii) Me_3SiCHN_2, MeOH–benzene, RT, 62% over 3 steps; iv) Bu_3SnH, AIBN, toluene, reflux, 60%; v) O_3, MeOH, −78 °C, 15 min then Me_2S, −78 °C to RT, 75%.



Scheme 4 *Reagents and conditions*: i) *p*-$MeC_6H_4SO_2Me$, Et_3N, DCM, RT, 78%; ii) PMBBr, NaH, DMF, THF, 0 °C to RT; iii) HF–pyridine, THF, RT, 37% over 2 steps; iv) $NaBH(OAc)_3$, AcOH, RT, 88%. v) $Zn(BH_4)_2$ (4.4 M in THF), THF, 0 °C, 79%; vi) TBSOTf, 2,6-lutidine, DCM, 0 °C → RT, 80%; vii) PMBBr, NaH, DMF, 0 °C → RT, 73%; viii) HF–pyridine, pyridine, THF, RT → 40 °C, 89%.

dig radical cyclisation from the acetylenic bromoamide **42c**, produced from the enantiopure α-amino alcohol **40**, leading to **43/44**. Manipulation of the functionality in **43/44** ultimately led to the C3 methylsulfanyl derivative **48** which, by separate routes, could be converted into the pyrrolidinones **49b**, **50** and **53** used by Corey *et al.*[6d] in their total synthesis of (+)-lactacystin **1**.

4. Experimental

For general experimental details see ref. 31.

((*S*)-2-Ethynyl-oxiranyl)-methanol (38a)

L-(+)-Diisopropyl tartrate (437 µl, 2.1 mmol) was added dropwise over 1 min to a stirred solution of titanium tetraisopropoxide (471 µl, 1.6 mmol) and activated 3 Å molecular sieves (650 mg) in dry dichloromethane (26 ml) at −20 °C under an argon atmosphere, and the mixture was then stirred at −20 °C for 30 min. A solution of the allylic alcohol **37**[24] (650 mg, 7.9 mmol) in dry dichloromethane (0.65 ml), which had been dried over a small amount of activated 3 Å molecular sieves at room temperature for 20 min, was added dropwise over 1 min to the mixture at −20 °C. The mixture was stirred at −20 °C for a further 10 min and then cooled to −35 °C. Cumene hydroperoxide (4.39 ml, 24 mmol), which had been dried over a small amount of activated 3 Å molecular sieves at room temperature for 20 min, was added dropwise over 10 min. The mixture was stirred at −35 °C for 30 min and then at −10 °C overnight. The progress of the reaction was followed by ^{1}H NMR spectroscopy, and when complete, the mixture was quenched at −20 °C with citric acid monohydrate (333 mg, 1.6 mmol) in a 1 : 10 mixture of acetone and diethyl ether (47 ml), then allowed to warm to room temperature, and stirred for 30 min. The mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo* at 0 °C. The residue was purified by flash chromatography on silica, using pentane–diethyl ether (3 : 2 then 1 : 1) as eluent, to give the *epoxy alcohol* (513 mg, 66%) as a colourless liquid; $[a]_D^{23}$ −24.2 (*c* 1.02, $CHCl_3$); ν_{max}/cm^{-1} (film) 3286, 1631; δ_H (360 MHz, $CDCl_3$) 3.93 (1H, d, *J* 12.6, CH*H*O), 3.78 (1H, d, *J* 12.6, C*H*HO), 3.08 (1H, d, *J* 5.5, CH*H*OH), 3.05 (1H, d, *J* 5.5, C*H*HOH), 2.41 (1H, s, C≡C*H*), 2.01 (1H, br s, CH_2OH); δ_C (90 MHz, $CDCl_3$) 79.8 (s), 73.3 (d), 62.9 (t), 51.1 (t), 50.7 (s); *m*/*z* (EI) 98.0365 (M^+, $C_5H_6O_2$ requires 98.0368).

Mosher ester analysis of the epoxy alcohol (38a)

a) *R*-(+)-Methoxytrifluoromethylphenylacetic acid (6 μl, 0.030 mmol) was added in a single portion to a stirred solution of the epoxy alcohol **38a** (2.7 mg, 0.027 mmol), triethylamine (9 μl, 0.065 mmol) and DMAP (2.6 mg, 0.022 mmol) in chloroform (270 μl) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 h and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using pentane–diethyl ether (4 : 1) as eluent, to give a 6 : 1 mixture of diastereoisomers of the (*R*) *Mosher ester* (8 mg, 94%) as a colourless oil, which was not separated; δ_H (360 MHz, $CDCl_3$) 7.57 (2H, m, Ar*H*), 7.44 (3H, m, Ar*H*), 4.75 (1H, d, *J* 12.1, CH*H*OCO), 4.35 (1H, d, *J* 12.1, C*H*HOCO), 3.61 (3H, s, OCH_3), 3.10 (1H, d, *J* 5.4, CH*H*O), 2.98 (1H, d, *J* 5.4, C*H*HO), 2.41 (1H, s, C≡C*H*); δ_F (376 MHz, $CDCl_3$) −72.17 (ee = 86%).

b) *S*-(−)-Methoxytrifluoromethylphenylacetic acid (4 μl, 0.021 mmol) was added in a single portion to a stirred solution of the epoxy alcohol **38a** (1.9 mg, 0.019 mmol), triethylamine (6.3 μl, 0.046 mmol) and DMAP (1.85 mg, 0.015 mmol) in chloroform (190 μl) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 h and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using pentane–diethyl ether (4 : 1) as eluent, to give a 6 : 1 mixture of diastereoisomers of the (*S*) *Mosher ester* (5.7 mg, 95%) as a colourless oil, which was not separated; δ_H (360 MHz, $CDCl_3$) 7.55 (2H, m, Ar*H*), 7.42 (3H, m, Ar*H*), 4.64 (1H, d, *J* 12.0, CH*H*OCO), 4.39 (1H, d, *J* 12.0, C*H*HOCO), 3.58 (3H, s, OCH_3), 3.06 (1H, d, *J* 5.4, CH*H*O), 2.90 (1H, d, *J* 5.4, C*H*HO), 2.35 (1H, s, C≡C*H*); δ_F (376 MHz, $CDCl_3$) −72.24 (ee = 86%).

2′,2′,2′-Trichloro-acetimidic acid (*R*)-2-ethynyl-oxiranylmethyl ester (38b)

Trichloroacetonitrile (1.25 ml, 12 mmol), followed by DBU (187 μl, 1.2 mmol) were each added dropwise over 2 min to a stirred solution of the epoxy alcohol **38a** (1 g, 10 mmol) in dichloromethane (59.5 ml) at 0 °C, and the mixture was then stirred at 0 °C for 30 min. The mixture was diluted with diethyl ether (60 ml) and then washed with water (45 ml). The separated aqueous layer was extracted with diethyl ether (2 × 45 ml) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using petrol–diethyl ether (4 : 1) as eluent, to give the *trichloroacetimidate* (1.60 g, 66%) as a colourless liquid; $[\alpha]_D^{23}$ −22.2 (*c* 1.10, $CHCl_3$) (Found: C, 34.8; H, 2.4; N, 5.3; $C_7H_6Cl_3NO_2$ requires C, 34.9; H, 2.5; N, 5.8%); ν_{max}/cm^{-1} (film) 1670; δ_H (360 MHz, $CDCl_3$) 8.46 (1H, br s, N*H*), 4.60 (1H, d, *J* 12.0, CH*H*OC(NH)), 4.44 (1H, d, *J* 12.0, C*H*HOC(NH)), 3.13 (1H, d, *J* 5.5, CH*H*O), 3.10 (1H, d, *J* 5.5, C*H*HO), 2.41 (1H, s, C≡C*H*); δ_C (90 MHz, $CDCl_3$) 162.3 (s), 90.8 (s), 79.1 (s), 73.2 (d), 68.8 (t), 52.2 (t), 48.2 (s); *m*/*z* (CI) 242 (M + H^+, $C_7H_7Cl_3NO_2$ requires 242).

((*S*)-4-Ethynyl-2-trichloromethyl-4,5-dihydro-oxazol-4-yl)-methanol (39a)

Diethylaluminium chloride (1 M in hexanes, 4.7 ml, 4.7 mmol) was added dropwise over 10 min to a stirred solution of the epoxy trichloroacetimidate **38b** (2.29 g, 9.4 mmol) in dichloromethane (75 ml) at 0 °C under nitrogen atmosphere, and the mixture was then stirred at 0 °C for 20 min. The mixture was allowed to warm to room temperature and then stirred for a further 12 h. The solution was diluted with diethyl ether (150 ml) and then quenched with saturated aqueous sodium bicarbonate (75 ml). The separated aqueous layer was extracted with diethyl ether (3 × 75 ml) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using petrol–diethyl ether (4 : 1 then 7 : 3) as eluent, to give the *oxazoline* (1.77 g, 78%) as a colourless solid; mp 136–138 °C (petrol–diethyl ether); $[\alpha]_D^{23}$ 22.4 (*c* 1.00, $CHCl_3$) (Found: C, 34.7; H, 2.5; N, 5.55; $C_7H_6Cl_3NO_2$ requires C, 34.7; H, 2.5; N, 5.8%); ν_{max}/cm^{-1} (film) 3377, 3300, 1656; δ_H (360 MHz, $CDCl_3$) 4.82 (1H, d, *J* 8.4, CH*H*O), 4.70 (1H, d, *J* 8.4, C*H*HO), 3.97 (1H, dd, *J* 11.7, 6.0, CH*H*OH), 3.70 (1H, dd, *J* 11.7, 8.4, C*H*HOH), 2.63 (1H, s, C≡C*H*), 2.45 (1H, dd, *J* 8.4, 6.0, CH_2OH); δ_C (90 MHz, $CDCl_3$) 165.2 (s), 85.9 (s), 81.0 (s), 77.9 (t), 75.7 (d), 70.0 (s), 66.7 (t); *m*/*z* (ES) 241.9537 (M + H^+, $C_7H_7Cl_3NO_2$ requires 241.9542).

Mosher ester analysis of the oxazoline alcohol (39a)

a) *R*-(+)-Methoxytrifluoromethylphenylacetic acid (3.2 μl, 0.017 mmol) was added in a single portion to a stirred solution of the oxazoline **39a** (3.7 mg, 0.015 mmol), triethylamine (5 μl, 0.036 mmol) and DMAP (1.5 mg, 0.012 mmol) in chloroform (150 μl) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 h and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using pentane–diethyl ether (9 : 1 then 4 : 1) as eluent, to give a 6 : 1 mixture of diastereoisomers of the (*R*) *Mosher ester* (6.6 mg, 96%) as a colourless oil, which was not separated; δ_H (360 MHz, $CDCl_3$) 7.49 (2H, m, Ar*H*), 7.41 (3H, m, Ar*H*), 4.68 (1H, d, *J* 8.7, CH*H*O), 4.61 (1H, d, *J* 11.4, CH*H*OCO), 4.53 (1H, d, *J* 8.7, C*H*HO), 4.49 (1H, d, *J* 11.4, C*H*HOCO), 3.54 (3H, s, OCH_3), 2.66 (1H, s, C≡C*H*); δ_F (376 MHz, $CDCl_3$) −72.00 (ee = 86%).

b) *S*-(−)-Methoxytrifluoromethylphenylacetic acid (3.2 μl, 0.017 mmol, 0.015 mmol) was added in a single portion to a stirred solution of the oxazoline **39a** (3.7 mg, 0.015 mmol), triethylamine (5 μl, 0.036 mmol) and DMAP (1.5 mg, 0.012 mmol) in chloroform (150 μl) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 h and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using pentane–diethyl ether (9 : 1 then 4 : 1) as eluent, to give a 6 : 1 mixture of diastereoisomers of the (*S*) *Mosher ester* (6.5 mg, 94%) as a colourless oil, which was not separated; δ_H (360 MHz, $CDCl_3$) 7.51 (2H, m, Ar*H*), 7.41 (3H, m, Ar*H*), 4.70 (1H, d, *J* 8.9, CH*H*O), 4.64 (1H, d, *J* 8.9, C*H*HO), 4.56 (1H, d, *J* 11.3, CH*H*OCO), 4.53 (1H, d, *J* 11.3, C*H*HOCO), 3.54 (3H, s, OCH_3), 2.66 (1H, s, C≡C*H*); δ_F (376 MHz, $CDCl_3$) −72.12 (ee = 86%).

(*R*)-4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-ethynyl-2-trichloromethyl-4,5-dihydro-oxazole (39b)

tert-Butyldimethylsilyl trifluoromethanesulfonate (1.13 ml, 4.95 mmol) was added dropwise over 2 min to a stirred solution

of the oxazoline alcohol **39a** (0.8 g, 3.3 mmol) and 2,6-lutidine (0.8 ml, 6.6 mmol) in dichloromethane (3.3 ml) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min, then allowed to warm to room temperature and stirred for a further 4 h. The solution was diluted with dichloromethane (10 ml) and then quenched with saturated aqueous sodium bicarbonate (8 ml). The separated aqueous layer was extracted with dichloromethane (2 × 10 ml), and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by flash chromatography on silica, using petrol–diethyl ether (9 : 1 then 4 : 1) as eluent, to give the *silyl ether* (1.14 g, 97%) as a colourless solid; mp 56–58 °C (petrol–diethyl ether); $[\alpha]_D^{23}$ −1.81 (*c* 0.95, $CHCl_3$) (Found: C, 43.5; H, 5.6; N, 3.8; $C_{13}H_{20}Cl_3NO_2Si$ requires C, 43.8; H, 5.65; N, 3.9%); ν_{max} (film)/cm^{-1} 2126, 1660; δ_H (360 MHz, $CDCl_3$) 4.85 (1H, d, *J* 8.1, CH*H*O), 4.61 (1H, d, *J* 8.1, C*H*HO), 3.94 (1H, d, *J* 10.4, CH*H*OTBS), 3.75 (1H, d, *J* 10.4, C*H*HOTBS), 2.56 (1H, s, C≡C*H*), 0.89 (9H, s, SiC(CH_3)$_3$), 0.10 (3H, s, SiCH_3), 0.08 (3H, s, SiCH_3); δ_C (90 MHz, $CDCl_3$) 164.2 (s), 86.2 (s), 81.6 (d), 77.5 (t), 75.0 (s), 70.1 (s), 67.1 (t), 25.9 (3 × q), 18.3 (s), −5.1 (q), −5.5 (q); *m*/*z* (ES) 356.0393 (M + H$^+$, $C_{13}H_{21}Cl_3NO_2Si$ requires 356.0407). The absolute stereochemistry of this protected oxazoline was determined by X-ray crystallography.

2-Bromo-*N*-[(*R*)-1′-(*tert*-butyl-dimethyl-silanyloxymethyl)-1′-hydroxymethyl-prop-2′-ynyl]-propionamide (41)

Aqueous hydrochloric acid (1 M, 2.35 ml, 2.35 mmol) was added in a single portion to a stirred solution of the oxazoline **39b** (840 mg, 2.35 mmol) in THF (13.6 ml) at room temperature. The mixture was stirred at room temperature for 4 h and then saturated aqueous sodium bicarbonate (∼ 2.83 ml) was carefully added at room temperature until the pH = 7. The mixture was evaporated to dryness *in vacuo* and the residue, which consisted of the amino alcohol **40**, was then diluted with water (2.83 ml) and dichloromethane (1.49 ml). Saturated aqueous sodium bicarbonate (10 ml) was added in a single portion at room temperature and then 2-bromopropionyl chloride (242 μl, 2.35 mmol) was added dropwise over 1 min. The mixture was stirred at room temperature for 2 h and then the separated aqueous layer was extracted with dichloromethane (2 × 12 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by flash chromatography on silica, using petrol–diethyl ether (polarity increasing from 3 : 2 to 2 : 3) as eluent, to give a 1 : 1 mixture of diastereoisomers of the *acetylenic bromoamide* (651 mg, 76%) as a colourless solid; mp 66–68 °C (petrol–diethyl ether) (Found: C, 46.3; H, 7.0; N, 3.7; $C_{14}H_{26}BrNO_3Si$ requires C, 46.15; H, 7.2; N, 3.8%); ν_{max} (film)/cm^{-1} 3327, 3307, 1663; δ_H (400 MHz, $CDCl_3$) 7.14/7.14 (1H, br s, N*H*), 4.42/4.41 (1H, q, *J* 7.1/7.1, C*H*(Br)CH_3), 4.02/3.99 (1H, d, *J* 9.8/9.8, CH*H*OTBS), 3.93/3.93 (1H, dd, *J* 11.5/11.5, 4.9/4.9, CH*H*OH), 3.89/3.87 (1H, d, *J* 9.9/9.9, C*H*HOTBS), 3.83/3.82 (1H, dd, *J* 11.5/11.5, 9.0/9.0, C*H*HOH), 3.31/3.28 (1H, dd, *J* 9.0/9.0, 4.9/4.9, CH_2OH), 2.43/2.43 (1H, s, C≡C*H*), 1.90/1.90 (3H, d, *J* 7.1/7.1, CH(Br)CH_3), 0.94/0.94 (9H, s, SiC(CH_3)$_3$), 0.14/0.13 (3H, s, SiCH_3), 0.13/0.13 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 169.4/169.3 (s), 80.5/80.5 (s), 73.8/73.8 (d), 66.5/66.5 (t), 66.3/66.1 (t), 56.9/56.9 (s), 45.1/45.0 (d), 25.9/25.9 (3 × q), 23.0/23.0 (q), 18.3/18.3 (s), −5.3/−5.3 (q), −5.4/−5.4 (q); *m*/*z* (ES) 364.0940 (M + H$^+$, $C_{14}H_{27}BrNO_3Si$ requires 364.0944).

2-Bromo-*N*-[(*S*)-1′-(*tert*-butyl-dimethyl-silanyloxymethyl)-1′-formyl-prop-2′-ynyl]-propionamide (42a)

Dess–Martin periodinane (550 mg, 1.3 mmol) was added portionwise over 5 min to a stirred solution of the alcohol **41** (400 mg, 1.1 mmol) in dry dichloromethane (5.65 ml) at 0 °C under a nitrogen atmosphere, and the mixture was then stirred at 0 °C for 20 min. The mixture was allowed to warm to room temperature and then stirred at this temperature for a further 3 h. The mixture was quenched with saturated aqueous sodium bicarbonate (44 ml) followed by a saturated solution sodium bisulfite (44 ml), then diluted with diethyl ether (85 ml) and stirred at room temperature for 30 min. The separated aqueous layer was extracted with diethyl ether (2 × 90 ml) and the combined organic extracts were then washed with saturated aqueous sodium bicarbonate (130 ml) and brine (130 ml), dried ($MgSO_4$) and concentrated *in vacuo* to leave a 1 : 1 mixture of diastereoisomers of the *aldehyde* (396 mg, 99%) as a colourless solid (Found: C, 46.5; H, 6.5; N, 3.75; $C_{14}H_{24}BrNO_3Si$ requires C, 46.4; H, 6.7; N, 3.9%); ν_{max} (film)/cm^{-1} 1734, 1688; δ_H (400 MHz, $CDCl_3$) 9.38/9.38 (1H, s, C*H*O), 7.32/7.32 (1H, br s, N*H*), 4.45/4.43 (1H, q, *J* 7.1/7.1, C*H*(Br)CH_3), 4.19/4.17 (1H, d, *J* 10.2/10.2, CH*H*OTBS), 4.09/4.08 (1H, d, *J* 10.2/10.2, C*H*HOTBS), 2.60/2.59 (1H, s, C≡C*H*), 1.90/1.89 (3H, d, *J* 7.1/7.1, CH(Br)CH_3), 0.88/0.88 (9H, s, SiC(CH_3)$_3$), 0.08/0.08 (3H, s, SiCH_3), 0.07/0.07 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 191.5/191.4 (d), 168.9/168.8 (s), 76.5/76.5 (d), 76.4/76.4 (s), 64.4/64.3 (t), 62.2/62.2 (s), 44.1/44.0 (d), 25.7/25.7 (3 × q), 22.9/22.8 (q), 18.2/18.2 (s), −5.4/−5.4 (q), −5.5/−5.5 (q); *m*/*z* (ES) 362.0793 (M + H$^+$, $C_{14}H_{25}BrNO_3Si$ requires 362.0787), and was used without further purification.

(*S*)-2-(2′-Bromo-propionylamino)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-but-3-ynoic acid (42b)

A freshly prepared solution of sodium chlorite (1.22 g, 11 mmol) in aqueous sodium dihydrogen orthophosphate (20% w/v, 6.5 ml) was added dropwise over 5 min to a stirred solution of the aldehyde **42a** (390 mg, 1.1 mmol) in ^{t}BuOH (11.5 ml) and 2-methyl-2-butene (6.5 ml) at room temperature. The mixture was stirred vigorously at room temperature for 3 h and then diluted with ethyl acetate (43 ml). The separated aqueous layer was extracted with ethyl acetate (30 ml) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo.* The oily residue was taken up in ethyl acetate (16 ml), washed with aqueous sodium dihydrogen orthophosphate (8% w/v, 1.6 ml) and the aqueous layer was extracted with ethyl acetate (2 × 16 ml). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to leave a 1 : 1 mixture of diastereoisomers of the *acid* (363 mg, 87%) as a colourless solid; ν_{max} (film)/cm^{-1} 3385, 3308, 1733, 1628; δ_H (400 MHz, $CDCl_3$) 7.53/7.50 (1H, br s, N*H*), 4.47/4.46 (1H, q, *J* 7.1/7.1, C*H*(Br)CH_3), 3.82–3.74 (2H, m, C*HH*OTBS), 2.54/2.54 (1H, s, C≡C*H*), 1.91/1.90 (3H, d, *J* 7.1/7.1, CH(Br)CH_3), 0.90/0.90 (9H, s, SiC(CH_3)$_3$), 0.12/0.11 (3H, s, SiCH_3), 0.11/0.11 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 170.1/170.0 (s), 169.7/169.7 (s), 77.3/77.3 (s), 74.4/74.4 (d), 66.1/66.0 (t), 58.4/58.3 (s), 44.4/44.2 (d), 25.7/25.7 (3 × q),

23.0/22.8 (q), 18.2/18.2 (s), −5.4/−5.4 (q), −5.5/−5.5 (q); *m/z* (ES) 378.0771 (M + H^+, $C_{14}H_{25}BrNO_4Si$ requires 378.0736), and was used without further purification.

(*S*)-2-(2′-Bromo-propionylamino)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-but-3-ynoic acid methyl ester (42c)

Trimethylsilyl diazomethane (2 M in hexanes, 380 μl, 0.76 mmol) was added dropwise over 2 min to a stirred solution of the acid **42b** (263 mg, 0.69 mmol) in dry methanol (330 μl) and anhydrous benzene (600 μl) at room temperature. The mixture was stirred at room temperature for 20 min and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using petrol–diethyl ether (polarity increasing from 9 : 1 to 7 : 3) as eluent, to give a 1 : 1 mixture of diastereoisomers of the *ester* (194 mg, 72%) as a colourless solid; mp 57–59 °C (petrol-diethyl ether) (Found: C, 46.0; H, 6.5; N, 3.4; $C_{15}H_{26}BrNO_4Si$ requires C, 45.9; H, 6.7; N, 3.6%); ν_{max} (film)/cm^{-1} 1735, 1693; δ_H (400 MHz, $CDCl_3$) 7.44/7.42 (1H, br s, N*H*), 4.43/4.41 (1H, q, *J* 7.1/7.1, C*H*(Br)CH_3), 4.25/4.22 (1H, d, *J* 9.7/9.7, CH*H*OTBS), 4.04/4.03 (1H, d, *J* 9.7/9.7, C*H*HOTBS), 3.84/3.83 (3H, s, OCH_3), 2.50/2.49 (1H, s, C≡C*H*), 1.89/1.88 (3H, d, *J* 7.1/7.1, CH(Br)CH_3), 0.86/0.86 (9H, s, SiC(CH_3)$_3$), 0.05/0.04 (3H, s, SiCH_3), 0.03/0.03 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 168.5/168.4 (s), 168.2/168.1 (s), 77.5/77.5 (s), 73.7/73.7 (d), 66.3/66.1 (t), 58.8/58.8 (s), 53.8/53.8 (q), 44.6/44.4 (d), 25.6/25.6 (3 × q), 22.9/22.8 (q), 18.1/18.1 (s), −5.4/−5.5 (q), −5.6/−5.6 (q); *m/z* (ES) 392.0916 (M + H^+, $C_{15}H_{27}BrNO_4Si$ requires 392.0893).

(5*S*,3*S*)-5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-methyl-4-methylene-2-oxo-pyrrolidine-5-carboxylic acid methyl ester (43) and (5*S*,3*R*)-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-methyl-4-methylene-2-oxo-pyrrolidine-5-carboxylic acid methyl ester (44)

A solution of tri-butyltin hydride (291 μl, 0.98 mmol) and AIBN (29 mg, 20 mol%) in anhydrous degassed toluene (30 ml) was added dropwise over 30 min to a stirred solution of the ester **42c** (350 mg, 0.89 mmol) in anhydrous degassed toluene (280 ml) under reflux, and the mixture was then stirred under reflux for 2.5 h. The mixture was cooled and then evaporated to dryness *in vacuo.* The residue was partitioned between acetonitrile (118 ml) and hexane (82 ml), and the separated hexane layer was then extracted with acetonitrile (41 ml). The combined acetonitrile extracts were concentrated *in vacuo* to leave an oily residue which was purified by flash chromatography on silica, using petrol–diethyl ether (1 : 1 then 1 : 4) as eluent, to give: i, the C3 β-methyl epimer (70 mg, 22%) (eluted first) as a colourless oil (C, 57.8; H, 8.5; N, 4.3; $C_{15}H_{27}NO_4Si$ requires C, 57.5; H, 8.7; N, 4.5%) $[\alpha]_D^{23}$ +16.8 (*c* 0.15, $CHCl_3$), ν_{max} (film)/cm^{-1} 1715, 1662; δ_H (400 MHz, $CDCl_3$) 6.18 (1H, br s, N*H*), 5.51 (1H, app. d, *J* 2.9, C=CH*H*), 5.21 (1H, app. d, *J* 2.4, C=C*H*H), 4.16 (1H, d, *J* 9.4, C*H*HOTBS), 3.76 (3H, s, OCH_3), 3.55 (1H, d, *J* 9.4, C*H*HOTBS), 3.06–3.00 (1H, m, C*H*CH_3), 1.32 (3H, d, *J* 7.4, CHCH_3), 0.86 (9H, s, SiC(CH_3)$_3$), 0.05 (3H, s, Si CH_3), 0.04 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 177.1 (s), 171.2 (s), 145.2 (s), 111.7 (t), 70.1 (s), 69.6 (t), 53.0 (q), 40.5 (d), 25.7 (3 × q), 18.2 (s), 16.5 (q), −5.4 (q), −5.6 (q); *m/z* (ES) 355.2018 (M + H^+ + CH_3CN, $C_{17}H_{31}N_2O_4Si$ requires 355.2053); In an NOE experiment (400 MHz, $CDCl_3$) irradiation at δ_H 3.55 gave an enhancement at δ_H 3.03 (0.41%) and irradiation at δ_H 3.03 gave an enhancement at δ_H 3.55 (0.28%); and ii, C3 α-methyl epimer (120 mg, 38%) (eluted second) as a colourless oil; $[\alpha]_D^{23}$ −19.0 (*c* 0.19, $CHCl_3$), ν_{max} (film)/cm^{-1} 3230, 2954, 1714, 1662; δ_H (400 MHz, $CDCl_3$) 6.22 (1H, br s, N*H*), 5.45 (1H, app. d, *J* 2.9, C=CH*H*), 5.20 (1H, app. d, *J* 2.5, C=C*H*H), 4.23 (1H, d, *J* 9.4, C*H*HOTBS), 3.78 (3H, s, OCH_3), 3.47 (1H, d, *J* 9.4, C*H*HOTBS), 3.08–3.02 (1H, m, C*H*CH_3), 1.32 (3H, d, *J* 7.4, CHCH_3), 0.86 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 177.0 (s), 171.3 (s), 145.3 (s), 111.5 (t), 70.0 (s), 69.7 (t), 53.1 (q), 40.3 (d), 25.7 (3 × q), 18.2 (s), 15.8 (q), −5.4 (q), −5.6 (q); *m/z* (ES) 355.2081 (M + H^+ + CH_3CN, $C_{17}H_{31}N_2O_4Si$ requires 355.2053); In an NOE experiment (400 MHz, $CDCl_3$) irradiation at δ_H 3.47 gave an enhancement at δ_H 1.32 (0.40%) and irradiation at δ_H 1.32 gave an enhancement at δ_H 3.47 (0.14%).

(5*R*,3*S*)-5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-methyl-2,4-dioxo-pyrrolidine -5-carboxylic acid methyl ester (45) and (5*R*,3*R*)-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-methyl-2,4-dioxo-pyrrolidine-5-carboxylic acid methyl ester (46)

A stream of ozone was bubbled through a stirred solution of the 2 : 1 mixture of pyrrolidinone diastereoisomers **43** and **44** (189 mg, 0.60 mmol) in dry methanol (8.5 ml) at −78 °C until a persistent blue colour appeared (usually between 10 and 20 min). The mixture was purged with oxygen to remove the excess of ozone and then dimethyl sulfide was added. The mixture was stirred at −78 °C for 1 h, then at room temperature for 1 h and evaporated to dryness *in vacuo.* The oily residue was taken up in dichloromethane (5 ml) and the solution was washed with water (4 ml). The separated aqueous layer was extracted with dichloromethane (2 × 4 ml) and the combined organic extracts were then washed with brine (6 ml), dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by flash chromatography on silica, using petrol–diethyl ether (polarity increasing from 1 : 1 to 1 : 4) as eluent, to give a 2 : 1 mixture of diastereoisomers of the corresponding *ketone* (142 mg, 75%) as a colourless oil which was not separated; ν_{max} (film)/cm^{-1} 1784, 1741, 1666; δ_H (360 MHz, $CDCl_3$) (β-methyl epimer) 6.61 (1H, br s, N*H*), 4.15 (1H, d, *J* 10.2, C*H*HOTBS), 3.95 (1H, d, *J* 10.2, C*H*HOTBS), 3.80 (3H, s, OCH_3), 2.80 (1H, q, *J* 7.8, C*H*CH_3), 1.35 (3H, d, *J* 7.8, CHCH_3), 0.83 (9H, s, SiC(CH_3)$_3$), 0.03 (6H, 2 s, SiCH_3); (α-methyl epimer) 6.67 (1H, br s, N*H*), 4.05 (1H, d, *J* 10.2, C*H*HOTBS), 4.02 (1H, d, *J* 10.2, C*H*HOTBS), 3.80 (3H, s, OCH_3), 2.96 (1H, q, *J* 7.6, C*H*CH_3), 1.31 (3H, d, *J* 7.6, CHCH_3), 0.85 (9H, s, SiC(CH_3)$_3$), 0.04 (6H, s, SiCH_3); δ_C (90 MHz, $CDCl_3$) (β-methyl epimer) 203.8 (s), 174.1 (s), 166.5 (s), 75.1 (s), 65.6 (t), 53.6 (q), 44.6 (d), 25.7 (3 × q), 18.2 (s), 11.0 (q), −5.6 (2 × q); (α-methyl epimer) 203.0 (s), 173.7 (s), 166.5 (s), 75.3 (s), 65.1 (t), 53.6 (q), 44.3 (d), 25.7 (3 × q), 18.3 (s), 9.6 (q), −5.5 (q), −5.6 (q); *m/z* (ES) 316.1604 (M + H^+, $C_{14}H_{26}NO_5Si$ requires 316.1580).

(5*R*,3*R*)-5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-methyl-3-methylsulfanyl-2,4-dioxo-pyrrolidine-5-carboxylic acid methyl ester (48)

Triethylamine (66 μl, 0.48 mmol) and *S*-methyl-*p*-toluenethiosulfonate (80 mg, 0.40 mmol) were added successively to a stirred solution of a 2 : 1 mixture of C3-Me epimers of **45** and **46** (125 mg, 0.40 mmol) in dichloromethane (1.24 ml) at

room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature overnight and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using petrol–diethyl ether (polarity increasing from 4 : 1 to 2 : 3) as eluent, to give a 7 : 1 mixture of diastereoisomers of the *methylsulfanyl derivative* (113 mg, 78%) as a colourless oil (Found: C, 49.85; H, 7.35; N, 3.4; $C_{15}H_{27}NO_5SSi$ requires C, 49.8; H, 7.5; N, 3.9%); ν_{max} (film)/cm^{-1} 1731, 1713; δ_H (360 MHz, $CDCl_3$) (major α-methyl epimer) 6.54 (1H, br s, NH), 4.11 (1H, d, *J* 10.0, CHHOTBS), 3.97 (1H, d, *J* 10.0, CHHOTBS), 3.82 (3H, s, OCH_3), 2.08 (3H, s, SCH_3), 1.50 (3H, s, CH_3), 0.86 (9H, s, $SiC(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$); (minor β-methyl epimer) 6.62 (1H, br s, NH), 4.35 (1H, d, *J* 9.6, CHHOTBS), 4.00 (1H, d, *J* 9.6, CHHOTBS), 3.83 (3H, s, OCH_3), 2.16 (3H, s, SCH_3), 1.53 (3H, s, CH_3), 0.87 (9H, s, $SiC(CH_3)_3$), 0.08 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$); δ_C (90 MHz, $CDCl_3$) (major α-methyl epimer) 195.7 (s), 171.0 (s), 166.5 (s), 73.5 (s), 66.3 (t), 53.6 (q), 50.4 (s), 25.7 (3 × q), 18.2 (s), 15.0 (q), 12.0 (q), −5.5 (q), −5.6 (q); *m/z* (ES) 362.1461 (M + H$^+$, $C_{15}H_{28}NO_5SSi$ requires 362.1457).

(5*R*,3*R*)-5-Hydroxymethyl-1-(4-methoxybenzyl)-3-methyl-3-methylsulfanyl-2,4-dioxo-pyrrolidine-5-carboxylic acid methyl ester (49)

A solution containing a 7 : 1 mixture of diastereoisomers of the methylsulfanyl derivative **48** (10.2 mg, 0.028 mmol) in anhydrous DMF (45 μl) was added dropwise to a stirred dispersion of sodium hydride (60% in mineral oil, 1.4 mg, 0.034 mmol) in anhydrous DMF (105 μl) at 0 °C under an argon atmosphere. The mixture was stirred at 0 °C for 15 min and then *p*-methoxybenzyl bromide (9 mg, 0.045 mmol) in anhydrous DMF (60 μl) was added dropwise. 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 glacial acetic acid (30 μl) and ice water (0.25 ml), and then diluted with diethyl ether (0.4 ml). The separated aqueous layer was extracted with diethyl ether (3 × 0.4 ml) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using pentane and then pentane–diethyl ether (polarity increasing from 9 : 1 to 7 : 3) as eluent, to give the *N-PMB derivative* (5.4 mg, 40%) as a colourless oil; $[\alpha]_D^{22}$ +21.0 (*c* 0.21, $CHCl_3$); ν_{max} (film)/cm^{-1} 1738, 1704; δ_H (500 MHz, $CDCl_3$) 7.27 (2H, d, *J* 8.5, ArH), 6.83 (2H, d, *J* 8.5, ArH), 4.83 (1H, d, *J* 15.1, PhCHH), 4.41 (1H, d, *J* 15.1, PhCHH), 4.23 (1H, d, *J* 10.8, CHHOTBS), 4.03 (1H, d, *J* 10.8, CHHOTBS), 3.79 (3H, s, $PhOCH_3$), 3.48 (3H, s, OCH_3), 2.16 (3H, s, SCH_3), 1.55 (3H, s, CH_3), 0.82 (9H, s, $SiC(CH_3)_3$), 0.00 (3H, s, $SiCH_3$), −0.03 (3H, s, $SiCH_3$); δ_C (125 MHz, $CDCl_3$) 200.3 (s), 172.2 (s), 166.0 (s), 159.2 (s), 130.1 (2 × d), 128.3 (s), 113.9 (2 × d), 76.9 (s), 62.0 (t), 55.4 (q), 52.9 (q), 49.4 (s), 44.3 (t), 25.9 (3 × q), 18.4 (s), 17.2 (q), 12.5 (q), −5.6 (q), −5.7 (q); *m/z* (ES) Found 504.1834 (M + Na$^+$, $C_{23}H_{35}NO_6SSiNa$ requires 504.1852).

Pyridine (0.2 ml) was added to a stirred solution of HF·pyridine (0.12 ml) in anhydrous THF (0.49 ml) under a nitrogen atmosphere and the mixture was then added to a stirred solution of the above *N*-PMB derivative (8 mg, 0.016 mmol) in anhydrous THF (0.79 ml) at room temperature under a nitrogen atmosphere. The mixture was stirred overnight at room temperature, then carefully quenched with saturated aqueous sodium carbonate (2.7 ml) and diluted with dichloromethane (3.5 ml). The separated aqueous layer was extracted with dichloromethane (2 × 3.5 ml), and the combined organic extracts were then washed with brine (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using pentane–diethyl ether (polarity increasing from 3 : 2 to 2 : 3) as eluent, to give the *alcohol* (5.4 mg, 92%) as a colourless oil; $[\alpha]_D^{21}$ +76.2 (*c* 0.15, EtOAc) (Lit.[6d] $[\alpha]_D^{23}$ +94 (*c* 0.40, EtOAc)); δ_H (500 MHz, $CDCl_3$) 7.36 (2H, d, *J* 8.6, ArH), 6.88 (2H, d, *J* 8.6, ArH), 5.20 (1H, d, *J* 15.2, PhCHH), 4.28 (1H, d, *J* 15.2, PhCHH), 4.19 (1H, dd, *J* 12.2, 9.1, CHHOH), 3.80 (3H, s, $PhOCH_3$), 3.77 (1H, dd, *J* 12.2, 5.0, CHHOH), 3.73 (3H, s, OCH_3), 2.14 (3H, s, SCH_3), 1.56 (3H, s, CH_3), 1.03 (1H, dd, *J* 9.1, 5.0, CH_2OH); δ_C (125 MHz, $CDCl_3$) 198.8 (s), 172.1 (s), 165.7 (s), 159.7 (s), 129.8 (2 × d), 128.9 (s), 114.7 (2 × d), 77.7 (s), 61.9 (t), 55.4 (q), 53.4 (q), 49.6 (s), 44.3 (t), 16.8 (q), 12.4 (q); *m/z* (ES) 390.0979 (M + Na$^+$, $C_{17}H_{21}NO_6SNa$ requires 390.0987); In an NOE experiment (400 MHz, $CDCl_3$) irradiation at δ_H 4.19 gave an enhancement at δ_H 1.56 (1.57%) and irradiation at δ_H 3.73 gave an enhancement at δ_H 2.14 (0.11%).

(5*R*,4*S*,3*R*)-4-Hydroxy-5-hydroxymethyl-1-(4-methoxybenzyl)-3-methyl-3-methylsulfanyl-2-oxo-pyrrolidine-5-carboxylic acid methyl ester (50)

Sodium triacetoxyborohydride (1.8 mg, 0.008 mmol) was added in a single portion to a stirred solution of the 4-ketopyrrolidinone **49** (1.5 mg, 0.004 mmol) in acetic acid (100 μl) at room temperature. The mixture was stirred at room temperature for 1 h and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using pentane–diethyl ether (polarity increasing from 2 : 3 to 1 : 9) as eluent, to give the corresponding *alcohol* (1.3 mg, 88%) as a colourless solid; $[\alpha]_D^{22}$ −42.0 (*c* 0.13, $CHCl_3$) (Lit.[6d] $[\alpha]_D^{23}$ −41.8 (*c* 0.10, $CHCl_3$)); δ_H (500 MHz, $CDCl_3$) 7.31 (2H, d, *J* 8.6, ArH), 6.87 (2H, d, *J* 8.6, ArH), 5.16 (1H, d, *J* 15.3, PhCHH), 4.15 (1H, d, *J* 8.1, CHOH), 4.03 (1H, d, *J* 15.3, PhCHH), 3.82–3.80 (2H, m, CHHOH), 3.80 (3H, s, $PhOCH_3$), 3.79 (3H, s, OCH_3), 3.63 (1H, d, *J* 8.1, CHOH), 2.16 (3H, s, SCH_3), 1.63 (3H, s, CH_3), 1.06 (1H, dd, *J* 8.5, 5.7, CH_2OH); δ_C (125 MHz, $CDCl_3$) 173.5 (s), 171.6 (s), 159.5 (s), 129.7 (s), 129.5 (2 × d), 114.6 (2 × d), 76.7 (d), 72.4 (s), 62.5 (t), 55.4 (q), 53.4 (s), 52.9 (q), 44.8 (t), 22.9 (q), 12.4 (q); *m/z* (ES) 370.1310 (M + H$^+$, $C_{17}H_{24}NO_6S$ requires 370.1324); In an NOE experiment (400 MHz, $CDCl_3$) irradiation at δ_H 4.15 gave an enhancement at δ_H 1.63 (3.47%), and irradiation at δ_H 1.63 gave an enhancement at δ_H 4.15 (3.31%).

(5*R*,4*R*,3*R*)-5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-hydroxy-3-methyl-3-methylsulfanyl-2-oxo-pyrrolidine-5-carboxylic acid methyl ester (51)

Zinc borohydride (4.4 M in THF, 14 μl, 0.062 mmol) was added dropwise to a stirred solution of a 7 : 1 mixture of diastereoisomers of the methylsulfanyl derivative **48** (22 mg, 0.061 mmol) in THF (0.6 ml) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 40 min, and then quenched with water (60 μl). The mixture was stirred for a further 40 min at 0 °C, then warmed to room temperature and diluted with dichloromethane (1.2 ml) and water (0.2 ml). The separated aqueous layer was extracted with dichloromethane (3 × 0.5 ml) and the combined organic

extracts were then washed with brine (1.5 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using pentane–diethyl ether (polarity increasing from 3 : 2 to 2 : 3) as eluent, to give: i, the secondary *alcohol* (17.6 mg, 79%) (eluted first) as a colourless solid, mp 147–149 °C (petrol–diethyl ether); $[\alpha]_D^{23}$ +30.1 (*c* 0.23, $CHCl_3$); ν_{max} (film)/cm^{-1} 3454, 3200, 1715, 1700; δ_H (400 MHz, $CDCl_3$) 6.23 (1H, br s, N*H*), 4.22 (1H, d, *J* 9.7, CH*H*OTBS), 4.17 (1H, d, *J* 8.2, CHO*H*), 3.97 (1H, d, *J* 8.2, C*H*OH), 3.80 (3H, s, OCH_3), 3.60 (1H, d, *J* 9.7, C*H*HOTBS), 2.13 (3H, s, SCH_3), 1.56 (3H, s, CH_3), 0.86 (9H, s, SiC(CH_3)$_3$), 0.05 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 173.3 (s), 172.9 (s), 79.2 (d), 68.4 (t), 66.3 (s), 53.4 (s), 53.0 (q), 25.6 (3 × q), 21.1 (q), 18.1 (s), 11.7 (q), −5.5 (q), −5.7 (q); *m/z* (ES) 364.1636 (M + H^+, $C_{15}H_{30}NO_5SSi$ requires 364.1614); In an NOE experiment (400 MHz, $CDCl_3$) irradiation at δ_H 3.97 gave enhancements at δ_H 3.60 (4.90%) and δ_H 1.56 (3.77%), irradiation at δ_H 3.60 gave an enhancement at δ_H 3.97 (6.14%), and irradiation at δ_H 1.56 gave an enhancement at δ_H 3.97 (2.29%); and ii, the minor β-methyl epimer (2.7 mg, 12%) (eluted second) as a colourless solid; $[\alpha]_D^{23}$ +23.4 (*c* 0.14, $CHCl_3$); ν_{max} (film)/cm^{-1} 3479, 3300, 1735, 1689; δ_H (400 MHz, $CDCl_3$) 6.11 (1H, br s, N*H*), 4.30 (1H, d, *J* 4.4, C*H*OH), 4.26 (1H, d, *J* 9.9, CH*H*OTBS), 4.07 (1H, d, *J* 9.9, C*H*HOTBS), 3.80 (3H, s, OCH_3), 3.02 (1H, d, *J* 4.4, CHO*H*), 2.19 (3H, s, SCH_3), 1.53 (3H, s, CH_3), 0.86 (9H, s, SiC(CH_3)$_3$), 0.06 (3H, s, SiCH_3), 0.04 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 173.3 (s), 172.6 (s), 78.4 (d), 68.4 (s), 65.7 (t), 54.9 (s), 53.0 (q), 25.7 (3 × q), 22.2 (q), 18.1 (s), 12.3 (q), −5.5 (q), −5.6 (q); *m/z* (ES) 364.1640 (M + H^+, $C_{15}H_{30}NO_5SSi$ requires 364.1614); In an NOE experiment (400 MHz, $CDCl_3$) irradiation at δ_H 4.30 gave an enhancement at δ_H 1.53 (3.52%), irradiation at δ_H 4.07 gave an enhancement at δ_H 2.19 (0.39%) and irradiation at δ_H 1.53 gave an enhancement at δ_H 4.30 (3.20%).

(5*R*,4*R*,3*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-1-(4-methoxybenzyl)-3-methyl-3-methylsulfanyl-2-oxo-pyrrolidine-5-carboxylic acid methyl ester (52)

tert-Butyldimethylsilyl trifluoromethanesulfonate (16.5 μl, 0.072 mmol) was added dropwise to a stirred solution of the secondary alcohol **51** (6.7 mg, 0.018 mmol) and 2,6-lutidine (17.5 μl, 0.144 mmol) in dichloromethane (70 μl) at 0 °C under a nitrogen atmosphere, and the mixture was then stirred at 0 °C for 30 min. The mixture was allowed to warm to room temperature and then stirred at this temperature for a further 18 h. The solution was diluted with dichloromethane (0.5 ml) and then quenched with saturated aqueous sodium bicarbonate (0.3 ml). The separated aqueous layer was extracted with dichloromethane (3 × 0.5 ml), and the combined organic extracts were then washed with saturated copper sulfate (2 × 2 ml) and water (4 × 1 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using petrol–diethyl ether (polarity increasing from 7 : 3 to 1 : 1) as eluent, to give the corresponding *TBS-ether* (6.9 mg, 80%) as a colourless oil; $[\alpha]_D^{22}$ +6.5 (*c* 0.62, $CHCl_3$); ν_{max} (film)/cm^{-1} 1738, 1706; δ_H (360 MHz, $CDCl_3$) 6.01 (1H, br s, N*H*), 4.18 (1H, d, *J* 9.4, CH*H*OTBS), 4.07 (1H, s, C*H*OTBS), 3.73 (3H, s, OCH_3), 3.53 (1H, d, *J* 9.4, C*H*HOTBS), 2.12 (3H, s, SCH_3), 1.51 (3H, s, CH_3), 0.95 (9H, s, SiC(CH_3)$_3$), 0.86 (9H, s, SiC(CH_3)$_3$), 0.15 (6H, s, Si(CH_3)$_2$), 0.06 (3H, s, SiCH_3), 0.04 (3H, s, SiCH_3); δ_C (90 MHz, $CDCl_3$) 174.0 (s), 169.9 (s), 79.6 (d), 69.1 (s), 67.9 (t), 53.0 (s), 52.3 (q), 25.7 (6 × q), 22.7 (q), 18.2 (2 s), 12.0 (q), −4.3 (q), −4.4 (q), −5.5 (q), −5.6 (q); *m/z* (ES) 478.2504 (M + H^+, $C_{21}H_{44}NO_5SSi_2$ requires 478.2479).

A solution of the TBS-ether (6.2 mg, 0.014 mmol) in anhydrous DMF (22 μl) was added dropwise to a stirred dispersion of sodium hydride (60% in mineral oil, 0.6 mg, 0.016 mmol) in anhydrous DMF (53 μl) at 0 °C under an argon atmosphere. The mixture was stirred at 0 °C for 15 min and then *p*-methoxybenzyl bromide (4.2 mg, 0.021 mmol) in anhydrous DMF (30 μl) was added dropwise. 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 glacial acetic acid (15 μl) and ice water (0.2 ml), and then diluted with diethyl ether (0.3 ml). The separated aqueous layer was extracted with diethyl ether (3 × 0.3 ml) and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using pentane and then pentane–diethyl ether (polarity increasing from 9 : 1 to 4 : 1) as eluent, to give the *N-benzyl derivative* (6.1 mg, 73%) as a colourless oil; $[\alpha]_D^{22}$ +12.0 (*c* 0.43, $CHCl_3$); ν_{max} (film)/cm^{-1} 2954, 1737, 1694, 1523; δ_H (400 MHz, $CDCl_3$) 7.23 (2H, d, *J* 8.7, Ar*H*), 6.80 (2H, d, *J* 8.7, Ar*H*), 4.60 (1H, d, *J* 15.2, PhCH*H*), 4.29 (1H, s, C*H*OTBS), 4.24 (1H, d, *J* 15.2, PhC*H*H), 4.03 (1H, d, *J* 11.1, CH*H*OTBS), 3.90 (1H, d, *J* 11.1, C*H*HOTBS), 3.78 (3H, s, PhOCH_3), 3.41 (3H, s, OCH_3), 2.18 (3H, s, SCH_3), 1.56 (3H, s, CH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.86 (9H, s, SiC(CH_3)$_3$), 0.15 (3H, s, SiCH_3), 0.10 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 174.8 (s), 169.3 (s), 158.8 (s), 130.0 (2 × d), 129.3 (s), 113.7 (2 × d), 78.2 (d), 73.1 (s), 61.7 (t), 55.4 (q), 51.9 (s), 51.5 (q), 44.6 (t), 25.9 (3 × q), 25.8 (3 × q), 24.0 (q), 18.2 (2 × s), 12.3 (q), −4.0 (q), −4.4 (q), −5.5 (q), −5.6 (q); *m/z* (ES) Found 598.3051 (M + H^+, $C_{29}H_{52}NO_6SSi_2$ requires 598.3054).

(5*R*,4*R*,3*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-5-hydroxymethyl-1-(4-methoxybenzyl)-3-methyl-3-methylsulfanyl-2-oxo-pyrrolidine-5-carboxylic acid methyl ester (53)

Pyridine (80 μl) was added to a stirred solution of HF·pyridine (50 μl) in anhydrous THF (0.2 ml) under a nitrogen atmosphere, and the resulting mixture was then added to a stirred solution of the *N*-protected derivative **52** (4.3 mg, 0.007 mmol) in anhydrous THF (0.31 ml) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature overnight, and then pyridine (40 μl), followed by a solution of HF·pyridine (25 μl) were each added dropwise and the mixture was stirred at 40 °C for 4 h. The mixture was quenched carefully with saturated aqueous sodium carbonate (2.6 ml) and then diluted with dichloromethane (3.4 ml). The separated aqueous layer was extracted with dichloromethane (2 × 3.4 ml), and the combined organic extracts were then washed with brine (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica, using pentane–diethyl ether (polarity increasing from 7 : 3 to 1 : 1) as eluent, to give the *alcohol*[6d] (3.0 mg, 89%) as a colourless oil; $[\alpha]_D^{23}$ −24.6 (*c* 0.28, $CHCl_3$); ν_{max} (film)/cm^{-1} 3410, 1737, 1674; δ_H (500 MHz, $CDCl_3$) 7.31 (2H, d, *J* 8.5, Ar*H*), 6.87 (2H, d, *J* 8.5, Ar*H*), 5.20 (1H, d, *J* 15.3, PhCH*H*), 4.36 (1H, s, C*H*OTBS), 3.83–3.76 (1H, m,

CH*H*OH), 3.79 (3H, s, PhOCH_3), 3.74 (1H, d, *J* 15.3, PhC*H*H), 3.72 (3H, s, OCH_3), 3.67 (1H, dd, *J* 13.0, 4.8, C*H*HOH), 2.19 (3H, s, SCH_3), 1.59 (3H, s, CH_3), 0.93 (9H, s, SiC(CH_3)$_3$), 0.80 (1H, dd, *J* 10.6, 4.8, CH_2OH), 0.15 (3H, s, SiCH_3), 0.11 (3H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 174.9 (s), 169.5 (s), 159.5 (s), 129.9 (s), 129.5 (2 × d), 114.7 (2 × d), 77.7 (d), 74.3 (s), 61.4 (t), 55.4 (q), 55.2 (q), 51.7 (s), 44.8 (t), 25.8 (3 × q), 23.7 (q), 18.2 (s), 12.1 (q), −4.2 (q), −4.5 (q); *m*/*z* (ES) 484.2203 (M + H^+, $C_{23}H_{38}NO_6SSi$ requires 484.2189).

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References

1 S. Omura, T. Fujimoto, K. Otoguro, K. Matsuzaki, R. Moriguchi, H. Tanaka and Y. Sasaki, *J. Antibiot.*, 1991, **44**, 113–116; S. Omura, K. Matsuzaki, T. Fujimoto, K. Kosuge, T. Furuya, S. Fujita and A. Nakagawa, *J. Antibiot.*, 1991, **44**, 117–118.

2 M. Bogyo and E. W. Wang, *Curr. Top. Microbiol. Immunol.*, 2002, **268**, 185–208; D. H. Lee and A. L. Goldberg, *Trends Cell Biol.*, 1998, **8**, 397–403.

3 G. Fenteany, R. F. Standaert, G. A. Reichard, E. J. Corey and S. L. Schreiber, *Proc. Natl. Acad. Sci. U. S. A.*, 1994, **91**, 3358–3362; A. Craiu, M. Gaczynska, T. Akopian, C. F. Gramm, G. Fenteany, A. L. Goldberg and K. L. Rock, *J. Biol. Chem.*, 1997, **272**, 13437–13445; G. Fenteany, R. F. Standaert, W. S. Lane, S. Choi, E. J. Corey and S. L. Schreiber, *Science*, 1995, **268**, 726–731; G. Fenteany and S. L. Schreiber, *J. Biol. Chem.*, 1998, **273**, 8545–8548.

4 G. Fenteany, R. F. Standaert, W. S. Lane, S. Choi, E. J. Corey and S. L. Schreiber, *Science*, 1995, **268**, 726–731.

5 R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen and W. Fenical, *Angew. Chem., Int. Ed.*, 2003, **42**, 355–357.

6 (*a*) E. J. Corey and G. A. Reichard, *J. Am. Chem. Soc.*, 1992, **114**, 10677–10678; (*b*) E. J. Corey, G. A. Reichard and R. Kania, *Tetrahedron Lett.*, 1993, **34**, 6977–6980; (*c*) E. J. Corey, W. D. Li and G. A. Reichard, *J. Am. Chem. Soc.*, 1998, **120**, 2330–2336; (*d*) E. J. Corey, W. D. Li and T. Nagamitsu, *Angew. Chem., Int. Ed.*, 1998, **37**, 1676–1679.

7 For total syntheses of lactacystin see: T. Sunazuka, T. Nagamitsu, K. Matsuzaki, H. Tanaka, S. Omura and A. B. Smith, *J. Am. Chem. Soc.*, 1993, **115**, 5302; H. Uno, J. E. Baldwin and A. T. Russell, *J. Am. Chem. Soc.*, 1994, **116**, 2139–2140; N. Chida, J. Takeoka, N. Tsutsumi and S. Ogawa, *J. Chem. Soc., Chem. Commun.*, 1995, 793–794; T. Nagamitsu, T. Sunazuka, H. Tanaka, S. Omura, P. A. Sprengeler and A. B. Smith, *J. Am. Chem. Soc.*, 1996, **118**, 3584–3590; N. Chida, J. Takeoka, K. Ando, N. Tsutsumi and S. Ogawa, *Tetrahedron*, 1997, **53**, 16287–16298; J. S. Panek and C. E. Masse, *Angew. Chem., Int. Ed.*, 1999, **38**, 1093–1095; F. Soucy, L. Grenier, M. L. Behnke, A. T. Destree, A. T. McCormack, J. Adams and L. Plamondon, *J. Am. Chem. Soc.*, 1999, **121**, 9967–9976; H. Ooi, N. Ishibashi, Y. Iwabuchi, J. Ishihara and S. Hatekeyama, *J. Org. Chem.*, 2004, **69**, 7765–7768; T. J. Donohoe, H. O. Sintim, L. Sisangia and J. D. Harling, *Angew. Chem., Int. Ed.*, 2004, **43**, 2293–2296; T. J. Donohoe, H. O. Sintim, L. Sisangia, K. W. Ace, P. M. Guyo, A. Cowley and J. D. Harling, *Chem.–Eur. J.*, 2005, **11**, 4227–4238; C. J. Hayes, A. E. Sherlock and M. D. Selby, *Org. Biomol. Chem.*, 2006, **4**, 193–195; N. Fukuda, K. Sasaki, T. V. R. S. Sastry, M. Kanai and M. Shibasaki, *J. Org. Chem.*, 2006, **71**, 1220–1225; E. P. Balskus and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2006, **128**, 6810–6812; C. H. Yoon, D. L. Flanigan, D. L. Yoo and K. W. Jung, *Eur. J. Org. Chem.*, 2007, 37–39; C. J. Hayes, A. E. Sherlock, M. P. Green, C. Wilson, A. J. Blake, M. D. Selby and J. C. Prodger, *J. Org. Chem.*, 2008, **73**, 2041–2051.

8 For reviews see: E. J. Corey and W. -D. Z. Li, *Chem. Pharm. Bull.*, 1999, **47**, 1–10; C. E. Masse, A. J. Morgan, J. Adams and J. S. Panek, *Eur. J. Org. Chem.*, 2000, 2513–2528.

9 For formal and partial syntheses of lactacystin see: S. H. Kang and H.-S. Jun, *Chem. Commun.*, 1998, **18**, 1929–1930; S. H. Kang, H.-S. Jun and J.-H. Youn, *Synlett*, 1998, 1045–1046; S. Iwama, W.-G. Gao, T. Shinada and Y. Ohfune, *Synlett*, 2000, 1631–1633; Y. Ohfune and T. Shinada, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 1115–1129; P. C. B. Page, A. S. Hamzah, D. C. Leach, S. M. Allin, D. M. Andrews and G. A. Rassias, *Org. Lett.*, 2003, **5**, 353–355; P. C. B. Page, D. C. Leach, C. M. Hayman, A. S. Hamzah, S. M. Allin and V. McKee, *Synlett*, 2003, 1025–1027; D. J. Wardrop and E. G. Bowen, *Chem. Commun.*, 2005, **40**, 5106–5108; J. -C. Legeay and N. Langlois, *J. Org. Chem.*, 2007, **72**, 10108–10113; C. B. Gilley, M. J. Buller and Y. Kobayashi, *Org. Lett.*, 2007, **9**, 3631–3634; see also reference 11.

10 For some syntheses of isomers and analogues of lactacystin see: E. J. Corey and S. Choi, *Tetrahedron Lett.*, 1993, **34**, 6969–6972; E. J. Corey and G. A. Reichard, *Tetrahedron Lett.*, 1993, **34**, 6973–6976; E. J. Corey and W. Li, *Tetrahedron Lett.*, 1998, **39**, 7475–7478; H. Uno, N. Mizobe, Y. Yamaoka and N. Ono, *Heterocycles*, 1998, **48**, 635–640.

11 Preliminary communication: C. J. Brennan, G. Pattenden and G. Rescourio, *Tetrahedron Lett.*, 2003, **44**, 8757–8760.

12 J. M. Clough, G. Pattenden and P. G. Wight, *Tetrahedron Lett.*, 1989, **30**, 7469–7472. For some other examples of 5-*exo* dig radical cyclisations in synthesis, and in the synthesis of pyrrolidinones see under references 18 and 19 in reference 14*a* below.

13 C. Cativiela and M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry*, 1998, **9**, 3517–3599.

14 (*a*) N. J. Bennett, J. C. Prodger and G. Pattenden, *Tetrahedron*, 2007, **63**, 6216–6231; (*b*) C. J. Brennan, PhD Thesis, The University of Nottingham, 2000.

15 (*a*) U. Schmidt, M. Respondek, A. Lieberknecht, J. Werner and P. Fischer, *Synthesis*, 1989, 256–261; (*b*) S. Hatakeyama, H. Matsumoto, H. Fukuyama, Y. Mukugi and H. Irie, *J. Org. Chem.*, 1997, **62**, 2275–2279.

16 S. Aoyagi, T. C. Wang and C. Kibayashi, *J. Am. Chem. Soc.*, 1993, **115**, 11393–11409.

17 H. E. Ensley, R. R. Buescher and K. Lee, *J. Am. Chem. Soc.*, 1982, **47**, 404–408.

18 P. Gamez, C. Ariente, J. Gore and B. Cazes, *Tetrahedron*, 1998, **54**, 14825–14834.

19 K. C. Nicolaou, R. E. Zipkin, R. E. Dolle and B. D. Harris, *J. Am. Chem. Soc.*, 1984, **106**, 3548–3551.

20 Z. -M. Wang, W. -S. Zhou and G. -G. Lin, *Tetrahedron Lett.*, 1985, **26**, 6221–6224; Z.-M. Wang and W. -S. Zhou, *Tetrahedron*, 1987, **43**, 2935–2944.

21 See reference 15*b*.

22 D. J. Chadwick, I. A. Cliffe, I. O. Sutherland and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1707–1717; M. C. Elliott and E. Kruiswijk, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3157–3166; N. S. Chandrakumar and J. Hajdu, *J. Org. Chem.*, 1983, **48**, 1197–1202; A. Marchand, A. Maxwell, B. Mootoo, A. Pelter and A. Reid, *Tetrahedron*, 2000, **56**, 7331–7338.

23 See reference 14.

24 K. C. Nicolaou, C. -K. Hwang, A. L. Smith and S. V. Wendeborn, *J. Am. Chem. Soc.*, 1990, **112**, 7416–7418.

25 Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765–5780.

26 A. Romero and C. -H. Wong, *J. Org. Chem.*, 2000, **65**, 8264–8268.

27 We thank Professor A. J. Blake of this School for the crystal structure determination. The CIF has been deposited with the Cambridge Crystallographic Data Centre as CCDC 226290.

28 For a synthesis of **47** starting from serine see: M. D. Andrews, A. G. Brewster, K. M. Crapnell, A. J. Ibbett, T. Jones, M. G. Moloney, K. Prout and D. Watkin, *J. Chem. Soc., Perkin Trans. 1*, 1998, 223–236.

29 For related epimerisation studies of 3-substituted pyrrolidinones, see: J. -D. Charrier, J. E. S. Duffy, P. B. Hitchcock and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2367–2371; C. M. Acevedo, E. F. Kogut and M. A. Lipton, *Tetrahedron*, 2001, **57**, 6353–6359; M. D. Andrews, A. G. Brewster and M. G. Moloney, *J. Chem. Soc., Perkin Trans. 1*, 2002, 80–90; H. Uno, J. E. Baldwin and A. T. Russell, *J. Am. Chem. Soc.*, 1994, **116**, 2139–2140.

30 J. H. Bateson, A. M. Quinn and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1986, 1151–1152; For a synthesis of *S*-methyl-*p*-toluenethiosulfonate and other thiosulfonates, see: K. Fujiki, N. Tanifuji, Y. Sasaki and T. Yokoyama, *Synthesis*, 2002, 343–348.

31 G. Pattenden, N. J. Ashweek, C. A. G. Baker-Glenn, J. Kempson, G. M. Walker and J. G. K. Yee, *Org. Biomol. Chem.*, 2008, **6**, 1478–1497.

