Utility of the Ammonia-Free Birch Reduction of Electron-Deficient Pyrroles: Total Synthesis of the 20S Proteasome Inhibitor, *clasto*-Lactacystin β-Lactone

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Abstract: A new synthesis of the 20S proteasome inhibitor *clasto*-lactacystin β-lactone is described. Our route to this important natural product involves the partial reduction of an electron deficient pyrrole as a key step. By judicious choice of enolate counterion, we were able to exert complete control over the stereoselectivity of the reduction/aldol reaction. Early attempts to complete the synthesis by using a C-4 methyl substituted pyrrole are described in full, together with our attempts to promote regioselective elimination of a tertiary alcohol. The lessons learnt from this first approach led us to develop another, and ultimately successful, route that introduced the C-4 methyl group at a late stage in the synthesis. Our successful route is then described and this contains several highly stereoselective steps including a *cis*-dihydroxylation and an enolate methylation. The final synthesis proceeds in just 13 steps and in 15% overall yield making it an extremely efficient route to this valuable compound.

Keywords: lactacystin · natural products · pyrroles · total synthesis

Introduction

Proteolysis by ATP-dependent enzymes (proteasomes and proteases) plays an important role in controlling levels of key regulatory proteins and in the degradation of abnormal polypeptides.[1] Intracellular protein degradation is a tightly regulated process and is crucial for (amongst others) cell cycle progression, apoptosis, antigen presentation and NF-κB activation.[1] Regulatory proteasomes and proteases, such as bleomycin hydrolase, tricon, HsIU and DegP are restricted to specific locations in the cell and can be accessed only by polypeptides destined for destruction.[2]

Proteasomes are large, hollow cylindrical protein structures (700–900 kD) composed of four stacked rings of seven protein subunits and are indispensable to living cells.[3] All chemical agents that specifically inhibit the proteasome could be of great pharmacological relevance. In this regard, the natural products lactacystin (**3**),[4] which is a prodrug of *clasto*-lactacystin β-lactone (**1**),[5–8] salinosporamide A (**2**),[9] and epoxomicin (**4**)[10] (Figure 1) are examples of potent and selective inhibitors of the proteasome.

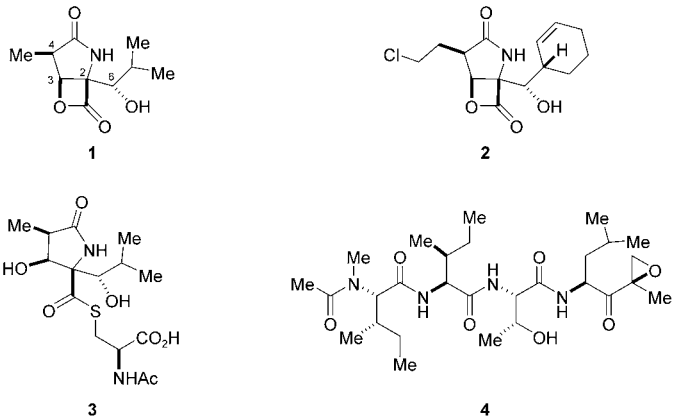

Figure 1. Examples of potent and selective proteasome inhibitors.

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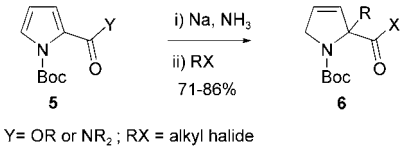
Omura et al. reported the isolation and characterisation of (+)-lactacystin (**3**)[4] in 1991 and there has been considerable interest among synthetic organic chemists and biologists ever since.[11] This is in part due to lactacystin's inhibition of the 20S proteasome and its interesting and unusual structure. (+)-Lactacystin (**3**) is now commercially available and used as an indispensable tool in neuronal research. For example, Yano et al. have used (+)-lactacystin (**3**) to investigate the aggregation of heat-denatured proteins.[12] Sawada et al. have also shown that proteasome inhibition by (+)-lactacystin (**3**) blocks 1-methyl-4-phenylpyridinium ion (MPP(+)) or rotenone-induced dopaminergic neuronal degeneration, thus implicating the 20S proteasome in neurodegenerative diseases such as Parkinson's.[13] As a consequence of its relative scarcity, (+)-lactacystin (**3**) is expensive and work towards a concise synthesis is a worthwhile endeavour.

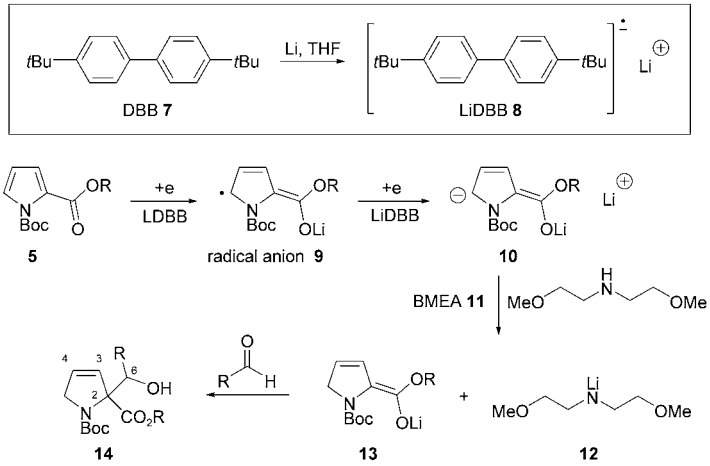
In this paper, we report the evolution of the ammonia-free reduction of electron-deficient pyrroles[14] into a strategy for the total synthesis of (±)-*clasto*-lactacystin β-lactone (**1**).[15]

Utility of pyrroles as precursors to pyrrolidine synthesis: When considering the prospects for reducing the pyrrole ring it is clear that the chemistry of pyrroles is dominated by the aromatic nucleus acting as a nucleophile in aromatic substitution reactions. Obviously, the pyrrole nucleus is extremely electron-rich and, therefore, not easily reduced. Moreover, the presence of the acidic NH (pK_a ~17) of the pyrrole presents the possibility of deprotonation by basic reducing agents. In order to develop reduction methodology that overcomes the nucleophilic reactivity of the pyrrole ring we have shown that pyrroles must first be substituted to render them *electron-deficient*. Thus, N-Boc protected pyrroles that are also substituted with acyl groups have been shown to be good substrates for dissolving metal (Birch) reduction and they give rise to a variety of useful synthetic intermediates (Scheme 1).[16]



Scheme 1. General sequence for the reductive alkylation of a pyrrole.

The use of ammonia as a solvent in the Birch reduction of pyrroles restricts the number of electrophiles that can be successfully trapped in situ; only alkyl halides and non-enolisable aldehydes can be employed. Very reactive electrophiles such as enolisable aldehydes, silyl halides, chloroformates and acid chlorides are incompatible with the nucleophilic solvent. To increase the repertoire of electrophiles that can be successfully trapped under dissolving metal conditions, an ammonia-free methodology was developed.[17] In this new procedure, di-*tert*-butylbiphenyl radical anion **8** (generated by reacting lithium with di-*tert*-butylbiphenyl **7** (DBB) in THF) provides the electrons, and bis(methoxyethyl)-amine (**11**; BMEA) acts as an acid. A general ammonia free reaction is shown in Scheme 2 with an aldehyde chosen as the electrophile.



Scheme 2. Mechanism for the partial reduction reaction.

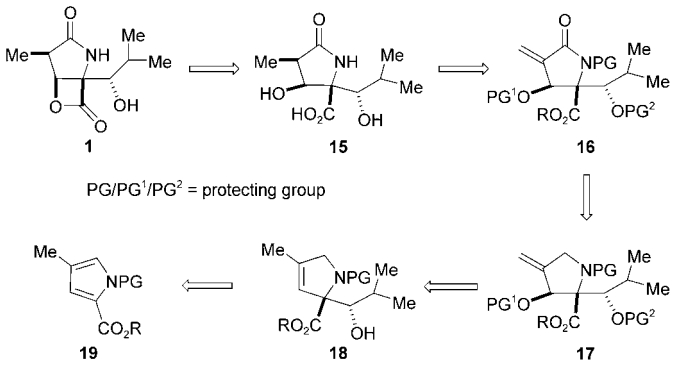
A major advantage of this ammonia-free protocol is its especial tolerance of the aforementioned set of reactive electrophiles which gives the reaction sequence much more scope for use in synthesis.

Comparison between *clasto*-lactacystin β-lactone (**1**) and generic compound **14** reveals that it contains the requisite functionalities at both C-2 and C-6 (if *i*PrCHO were the aldehyde electrophile) and also that the appropriate functional groups at C4 and C3 could be introduced easily. So, the development of methodology to access *clasto*-lactacystin β-lactone (**1**) in a short sequence from electron-deficient pyrroles became our target. The evolution of our synthetic strategy is chronicled in this paper.

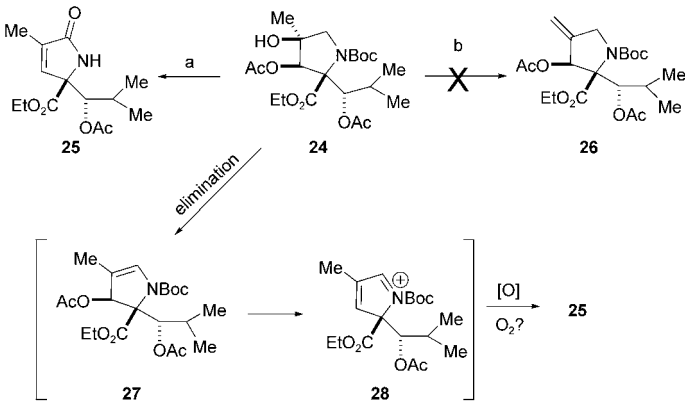
Results and Discussion

First-generation synthetic plan: We chose enone **16** as a key retrosynthetic intermediate because we envisioned lots of different ways of converting it into **15**. A diastereoselective reduction (hydrogenation) of enone **16** into advanced intermediate **15** seemed very likely as it had the necessary directing groups (e.g. the hydroxy group on C-6) that could be used to direct hydrogenation reagents plus the possibility of a bulky protecting group PG[1] sterically shielding one face of the enone **16** (Scheme 3). Moreover, compound **16** could be an ideal electrophilic intermediate for conjugate addition to make a range of analogues of lactacystin **3**.

4-Methyl *N*-Boc pyrrole **21** was obtained following standard Boc protection of commercially available pyrrole **20** (Scheme 4). Subjecting **21** to the original ammonia-free Birch conditions (Li, naphthalene, BMEA, *i*PrCHO) gave

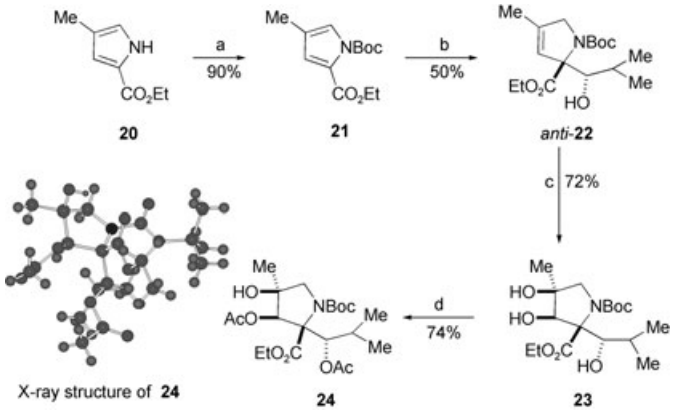


Scheme 3. First-generation synthetic plan.



Scheme 5. Attempted elimination of a tertiary alcohol: a) $POCl_3$, pyridine; b) Burgess reagent, Martin sulfurane or DAST.

the *anti*-aldol product **22** in 50% yield after column chromatography; little or no trace of the *syn*-isomer was found (at this point we made no attempt to optimise the yield of the reaction). Alkene **22** was then subjected to the Upjohn dihydroxylation conditions (Scheme 4). In line with our expectations,[18] the oxidant (OsO_4) approached alkene **22** *anti* to the face bearing the free hydroxyl and bulky isopropyl groups. Selective acetate protection of the two secondary hydroxyl groups was achieved by employing catalytic DMAP (0.03 equiv) in a mixture of acetic anhydride and pyridine. Use of stoichiometric DMAP afforded the triacetate; the structure of compound **24** was proven by X-ray crystal analysis.

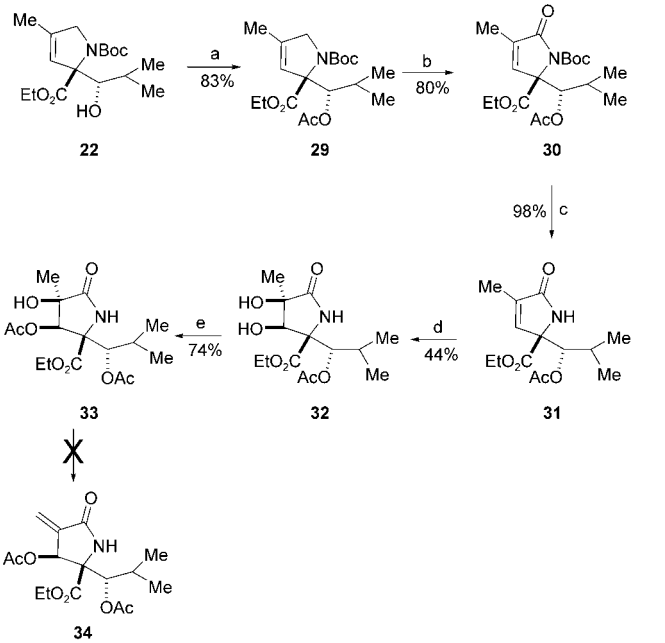


Scheme 4. Reductive aldol and oxidative manipulation reactions: a) $(Boc)_2O$, Et_3N, MeCN, DMAP, RT; b) Li, naphthalene, BMEA, THF, −78°C; iPrCHO, then NH_4Cl aq.; c) cat. OsO_4, NMO, acetone/H_2O, RT; d) Ac_2O, pyridine, cat. DMAP.

Next, we turned our attention to the dehydration of tertiary alcohol **24**. Could we promote the reaction and also control the regioselectivity of the alkene formation to favour the exocyclic alkene? Unfortunately, attempted dehydration of tertiary alcohol **24** returned starting material under a variety of different conditions. For example, Burgess reagent,[19] Martin sulfurane[20] and DAST[21] all failed to react with alcohol **24**. However, phosphoryl chloride did promote a reaction but that of **24** into the undesired lactam **25**. An outline mechanism for this (oxidative) transformation is shown in Scheme 5.

Our postulated mechanism for the formation of lactam **25** from alcohol **24** proceeds via endocyclic olefin **27** which would give reactive intermediate **28** after acetoxy elimination. Trapping of imminium **28** with water and a subsequent (air?) oxidation of the resulting hemiaminal would then give lactam **25**. Not only was the elimination reaction difficult to effect but when it did eventually take place it proceeded with undesired regiochemistry and gave unstable intermediates.

Therefore, we attempted to prevent this unwanted endocyclic elimination by using lactam intermediate **33** which could potentially give the desired exocyclic olefin **34** (Scheme 6).

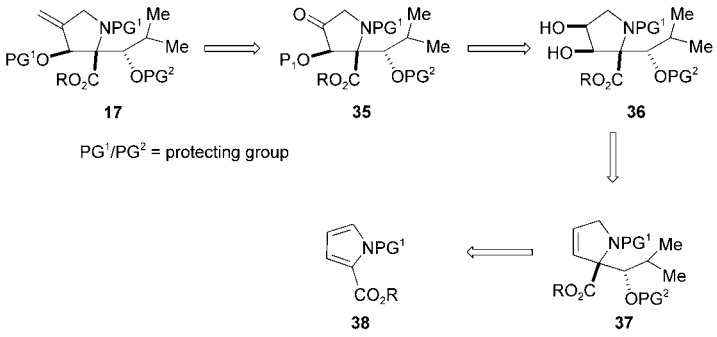


Scheme 6. Formation of a lactam ring: a) $(Ac)_2O$, pyridine, cat. DMAP, RT; b) CrO_3, pyridine, CH_2Cl_2; c) TFA, CH_2Cl_2; d) cat. OsO_4, NMO, quinuclidine, acetone/H_2O; e) Ac_2O, pyridine, CH_2Cl_2, cat. DMAP.

The synthesis of lactam **33** began with acetate protection of aldol adduct **22**, followed by chromium trioxide allylic oxidation to afford Boc-protected lactam **30** in 66% yield after two steps (Scheme 6). Unfortunately, compound **30** was resistant to dihydroxylation under a variety of conditions and it was postulated that this failure to oxidise was because of the electron withdrawing Boc-protecting group. Consequently, removal of the Boc group and subjection of compound **31** to dihydroxylation conditions (cat. OsO_4/NMO, quinuclidine in acetone/H_2O) gave diol **32** as a single diastereoisomer (stereochemistry assigned by analogy to **23**). Selective protection of the secondary alcohol with acetic anhydride in pyridine and catalytic DMAP afforded acetate **33**. Disappointingly, several attempts to dehydrate compound **33** under a variety of conditions (e.g. Burgess reagent,[19] Martin sulfurane,[20] Dast[21] and $POCl_3$) all failed.

At this point, it became clear that our initial idea of forming the exocyclic olefin *via* elimination of a tertiary alcohol was not viable partly because of the lack of reactivity of this tertiary alcohol and also the realisation that endocyclic elimination was favoured over exocyclic (Scheme 5).

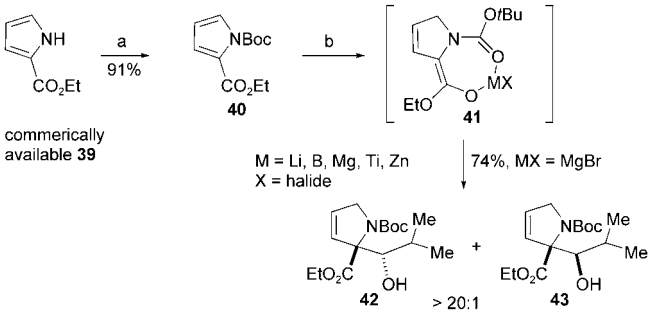
Second-generation approach: The premise of our second generation approach (Scheme 7) towards *clasto*-lactacystin β-lactone **1**, was a different disconnection from the key exocyclic alkene **17**, based on literature precedent whereby 1,1-disubstituted olefins could be obtained via a standard Wittig reaction on a ketone.[22] Thus, alkoxy ketone **35** became our next target. This route differs from the first in that it does not require a methyl group at the C-4 position of the starting pyrrole **38**.



Scheme 7. Second-generation synthetic plan.

$MgBr_2$-catalysed aldol reaction of enolate 41 with isobutyraldehyde—*anti*-aldol selectivity: The precursor to partial reduction, pyrrole **40**, was prepared in one step from commercially available **39** (Scheme 8). The aldol reaction between enolate **41**, generated under the ammonia-free conditions (M = Li) afforded both *syn*- and *anti*-aldol products, the ratio depending on the aldehyde used. Isopropylaldehyde provided a ratio of 8:1 in favour of the *anti*-aldol product **42** (see **22**, Scheme 4).

In order to increase the diastereoselectivity in this reaction, our effort focussed on transmetallation of the lithium



Scheme 8. Reductive aldol reaction on an electron deficient pyrrole: a) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2; b) Li, DBB, THF, −78°C, $(MeOCH_2CH_2)_2NH$, MX, isobutyraldehyde.

enolate **41** in situ with various metals such as boron, magnesium, titanium and zinc. Of the metals that were screened, $MgBr_2{\cdot}Et_2O$ was the most outstanding in terms of both chemical yields and diastereoselectivity. Transmetalling lithium enolate **41** with 1.1 equiv of $MgBr_2{\cdot}Et_2O$ (before quenching with isobutyraldehyde) gave products **42** and **43** with greater than 20:1 diastereoselectivity and 74% chemical yield, in favour of the *anti*-diastereoisomer **42** (Scheme 8). Models to rationalise this diastereoselectivity have been reported elsewhere.[14]

With *anti*-aldol product **42** in hand, we next investigated its dihydroxylation reaction after a standard acetate protection (Scheme 9). Alkene **44** gave diol **45** in an average yield of 65% after being subjected to catalytic OsO_4 and NMO (3 equiv) in acetone/water 4:1. This reaction was particularly slow (over 24 h) and it was assumed that the moderate yield was due to diol decomposition over the prolonged reaction time. In our experience, dihydroxylation reactions employing Poli conditions (cat. OsO_4, $Me_3NO{\cdot}2H_2O$ (3 equiv) in CH_2Cl_2)[23] were usually completed faster than the cat. OsO_4/NMO system. Consistent with our observations, subjecting **44** to the Poli conditions gave diol **45** in an excellent yield of 95% and the reaction was complete in 3 h. X-Ray crystal analysis of a derivative **46** (Figure 2) proved the ster-

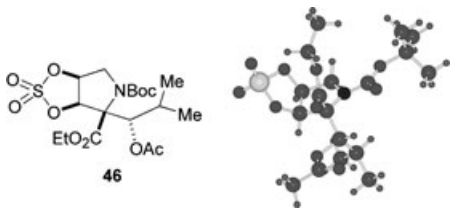
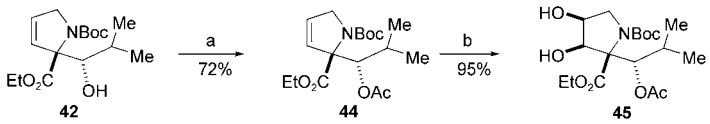


Figure 2. X-ray crystal structure of compound **46**.

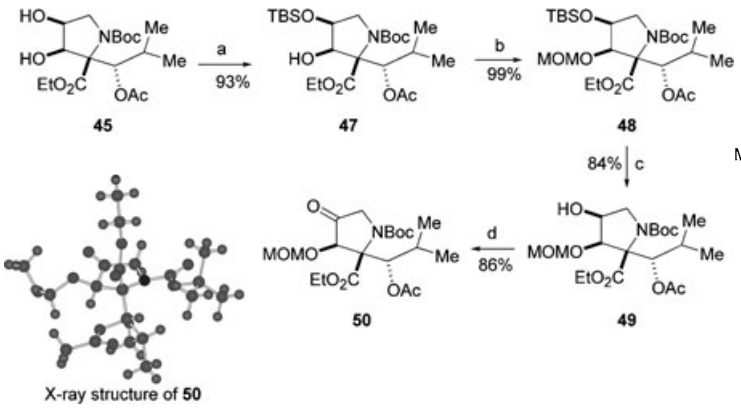
eochemistry of diol **45**. As expected, the OsO_4 reagent had approached **44** from the face *anti* to the bulky isopropyl group. This was not a surprising outcome as a similar facial selectivity had been obtained before on a similar substrate (compounds **22** and **31**, Schemes 4 and 6).

Selective silyl protection of the least hindered alcohol within diol **45** was achieved by employing TBSOTf, 2,6-luti-



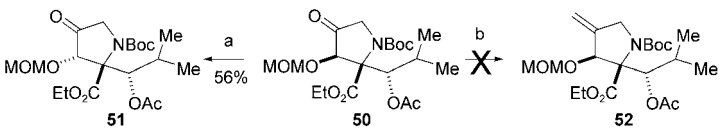
Scheme 9. Stereoselective dihydroxylation of the ring: a) Ac_2O, pyridine, DMAP; b) cat. OsO_4, $Me_3NO{\cdot}2H_2O$, CH_2Cl_2.

dine in dichloromethane at −78 °C (Scheme 10). The neopentyl alcohol functionality within compound **47** was then protected with a MOM group to give the fully protected compound **48** in an excellent yield of 99 % (Scheme 10). Cleavage of the TBS protecting group with TBAF in dry THF afforded the mono-MOM alcohol **49** in 84 % yield; the secondary alcohol was then oxidised with Dess–Martin periodinane[24] to furnish ketone **50** as a white solid in 86 % yield. The X-ray crystal structure of ketone **50** provided verification of the regio- and stereochemistry up to this stage.[25]



Scheme 10. Formation of a mono-protected cyclic ketone: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; b) MOMCl, iPr$_2$NEt, CH_2Cl_2, 50 °C; c) TBAF, THF, RT; d) Dess–Martin periodinane, CH_2Cl_2, RT.

Unfortunately, all attempts at methylenation of ketone **50** failed. Amongst other things, reaction of compound **50** with Tebbe reagent,[26] Petasis[27] or Peterson reagent[28] either returned starting material or gave degradation, as confirmed by both TLC and ^{1}H NMR analyses. Attempted Wittig olefination led to epimerisation at the stereocenter alpha to the ketone (Scheme 11) to give diastereomer **51** and none of the expected alkene **52**. The lack of (standard) reactivity of ketone **50** towards nucleophiles was further confirmed when subjecting **50** to reaction with methylmagnesium bromide only returned epimerised compound **51** (Scheme 11).



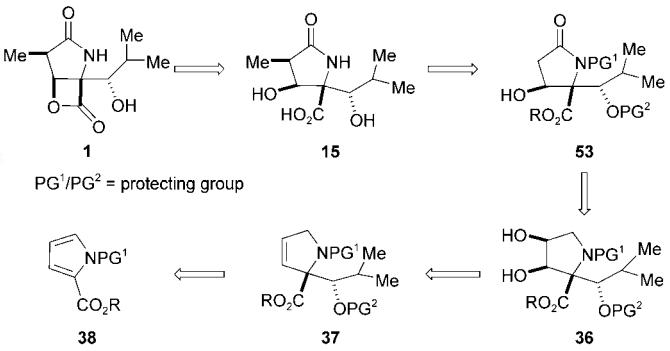
Scheme 11. Attempted olefination reactions: a) PPh_3CH_3I, nBuLi, THF, 0 °C to RT or MeMgBr, THF, 0 °C to RT; b) $Cp_2TiCH_2{\cdot}AlMe_2Cl$, THF, −40 °C to RT; or Cp_2TiMe_2, THF, RT to 70 °C; or $CeCl_3{\cdot}7H_2O$, Me_3SiCH_2Li, TMEDA, THF, −78 °C to RT.

The protecting group on the C-3 alcohol appeared irrelevant with respect to C-3 epimerisation. Swapping the MOM group in ketone **50** with a TBDMS did not have any beneficial effect in the olefination reaction, epimerisation still occurred. Therefore, this route was deemed not viable and another synthetic strategy was designed.

A third-generation synthetic strategy towards *clasto*-lactacystin β-lactone **1** would have to take into account several lessons learnt from the two previous approaches; these were:

a) The facial bias of the alkene was predictable and reagents approached the dihydropyrrolidine ring *anti* to the bulky isopropyl side chain.
b) Ketones on the pyrrolidine ring were not electrophilic, and were easily epimerised.
c) The two hydroxyl groups of diol **45** can be differentiated, with the C-4 OH being the more reactive.

With these lessons in mind, we designed a third-generation synthetic strategy (Scheme 12).

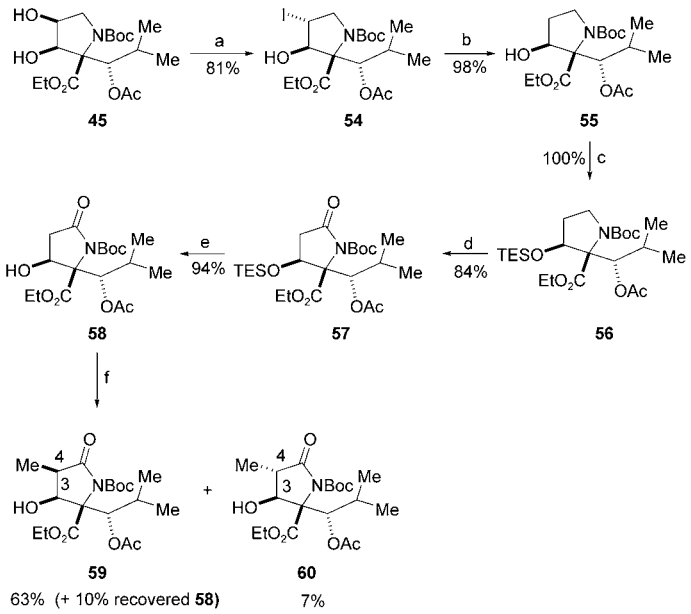


Scheme 12. Third-generation synthetic plan.

Third-generation synthetic strategy: Structure–activity relationship (SAR) requirements for proteasome inhibition by *clasto*-lactacystin β-lactone are rather stringent.[29] The only replaceable group in the molecule that retains biological activity is the C-4 methyl group.[30] Significantly, our third-generation strategy introduces the methyl group at a late stage and this holds promise for the production of analogues. Key steps of this new strategy would be; i) selective deoxygenation of the least hindered secondary alcohol within diol **36** (Scheme 12) and ii) diastereoselective methylation of lactam **53**, taking advantage of the facial bias of the pyrrolidine ring, see below.

We decided to dispense with selective protection of the C-3/4 diol. A regioselective Mitsunobu reaction of diol **45** led to iodide **54** directly whereby the least hindered alcohol had been displaced and the C-3 (neopentyl) alcohol remained intact (Scheme 13). Dehalogenation of iodide **54** following Inoue's procedure[31] led to **55** in quantitative yield. Then, standard protection of the C-3 hydroxyl functionality followed by (cat.) RuO_4 oxidation led to lactam **57**. Initially,

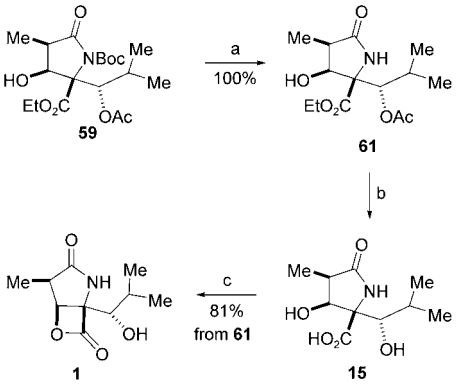
the oxidation step proved capricious, however, it was realised that desilylation of TES compound **56** in situ was responsible for the low and varied yields. Lowering the reaction temperature to 0 °C and then slowly warming to room temperature prevented this side reaction and lactam **57** was obtained in a reproducible yield of 84 %. Attempted methylation of TES compound **57** using LDA and methyl iodide led, as expected, to elimination of the silyoxy group. Therefore, we decided to deprotect **57** so that we could form the dianion prior to the methylation step. Desilylation of the TES group with HF·pyridine in THF furnished **58** in 94 % yield. The next key step in the synthesis was the diastereoselective methylation of **58**.



Scheme 13. Stereoselective enolate alkylation: a) PPh_3, DBAD, MeI, benzene; b) cat. $InCl_3$, $NaBH_4$, MeCN; c) TESCl, imidazole, DMAP, CH_2Cl_2; d) cat. $RuCl_3{\cdot}xH_2O$, *m*-$NaIO_4$, CCl_4/MeCN/H_2O; e) HF·Py, THF, pyridine; f) LDA, HMPA, MeI, THF.

Deprotonation of **58** was effected with LDA (2 equiv) followed by the addition of methyl iodide; HMPA was required in order for the lithium enolate to methylate in good yield.

Significantly, the major alkylation adduct **59** had the desired stereochemistry at C-4 and the facial selectivity exhibited by the enolate was similar to that observed for the dihydroxylation step (see **44**, Scheme 9). The structures of both **59** and **60** (the minor isomer) were proven by NOE experiments: in compound **59**, irradiation of 3-H led to an NOE enhancement of 4-H, but not of the methyl group at C-4. However, in compound **60** irradiation of the 3-H led to NOE enhancements of both 4-H and the methyl group at C-4. With the carbon skeleton intact and the stereochemistry of compound **59** correct, the end-game was accomplished by cleaving the *tert*-butoxycarbonyl group of lactam **59** with TFA in CH_2Cl_2 followed by ester hydrolysis and lactone formation with bis(2-oxo-3-oxazolidyl)phosphinic chloride (BOPCl), to give (±)-*clasto*-lactacystin β-lactone **1** in only 13 steps and in 15 % overall yield (Scheme 14). The spectroscopic data of lactone **1** (*clasto*-lactacystin β-lactone) was identical to that reported in the literature.



Scheme 14. Completion of the synthesis: a) CF_3CO_2H, CH_2Cl_2; b) NaOH (aq. 0.5 M); c) BOPCl, Et_3N, CH_2Cl_2.

Conclusion

Our synthetic studies on the Birch reduction of heteroaromatic compounds show that the methodology has broad applicability. In the last few years, we have used this methodology to synthesise important natural products such as nemorensic acid,[32] secosyrin 1[33] and 1-epi-australine.[34] In this latest work, we have successfully applied this method to the efficient (15 % overall yield) total synthesis of the biologically active *clasto*-lactacystin β-lactone **1**. Our route is noteworthy for its concise nature, high levels of stereoselectivity and late-stage introduction of the C-4 methyl group.

Experimental Section

General: All reactions were carried out under an atmosphere of argon unless otherwise stated. Solvents and reagents: THF was distilled from sodium/benzophenone under an atmosphere of argon, CH_2Cl_2 from CaH_2 under an atmosphere of argon, triethylamine and BMEA from CaH_2, and isobutyraldehyde from 4 Å molecular sieves. All distilled chemicals were stored under an atmosphere of argon. All other reagents were purified using standard procedures as required. Indium trichloride was dried in vacuo at 150 °C for 2 h prior to use. Analytical thin-layer chromatography: Performed on Merck Kieselgel 60 aluminium-backed plates and visualised with UV light (254 nm) and stained in *p*-anisaldehyde followed by gentle heating. Chromatography: Flash and gradient column chromatography was carried out by using Merck silica gel 60 (particle size 40–63 μm). Petroleum ether (PE) refers to the fraction with boiling range 40–60 °C. IR Spectroscopy: IR spectra were recorded as evaporated films from chloroform using Perkin–Elmer 881 or Perkin–Elmer Paragon 1000 Fourier transform instruments. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}) and only the structurally significant peaks are listed. NMR Spectroscopy: ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise stated, on Varian Unity Inova 300 and Varian Gemini or Bruker AV400 or 500 spectrometers. All chemical shifts are quoted in ppm relative to the internal $CDCl_3$ standard. Signal

splittings are described as; singlet (s), doublet (d), triplet (t), quartet (q), quintet (qt), sextet (st), septet (sp), multiplet (m), broad (br). Spectra were assigned with the aid of COSY experiments. Multiple peaks are present in the ^{1}H and ^{13}C NMR spectra of some compounds and due to Boc rotamers. Mass Spectrometry: Mass spectra were recorded on either Kratos MS25 or a VG Trio mass spectrometer. The modes of ionisation were ESI, APCI and CI. Exact masses were measured on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer operating at a resolution of 5000 full width half height.

4-Methyl *N*-Boc pyrrole 21: Di-*tert*-butyl dicarbonate (16.5 g, 86.3 mmol), triethylamine (30 mL, 0.26 mol) and dimethylaminopyridine (88 mg, 0.86 mmol) were added to a solution of **20** (11 g, 72 mmol) in acetonitrile (75 mL) under an atmosphere of nitrogen at 40 °C. The resulting solution was stirred for 3 h by which time analysis of the reaction by TLC indicated complete consumption of the starting material. The crude mixture was concentrated in vacuo and purification by flash column chromatography eluting with iethyl ether/PE 85:15. This furnished the product **21** as a colourless liquid (16.4 g, 90 %); ^{1}H NMR spectroscopic data was consistent with that in the literature.[34]

***anti*-Aldol adduct 22**: Lithium (32.8 mg, 4.57 mmol) and naphthalene (585 mg, 4.57 mmol) were dissolved in THF (20 mL) and sonicated for 1.5 h at RT under an atmosphere of argon. The resulting dark green solution was cooled to −78 °C and stirred for 10 min. The substrate **21** (245 mg, 0.91 mmol) and BMEDA (0.67 mL, 4.57 mmol) were premixed and titrated into the green solution until a dark red solution formed. The deep red solution was allowed to stir for a further 45 min before addition of isobutyraldehyde (0.91 mL, 9.10 mmol). The light yellow solution that formed was allowed to stir for another 50 min before finally quenching with sat. NH_4Cl. The solution was allowed to warm up to ambient temperature before concentrating to dryness. Flash chromatography on silica, eluting with acetone/PE 5:95 furnished **22** as a colourless oil (158 mg, 50 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.58 (brs, 1H; C=C-*H*), 4.43 (t, ^{3}J(H,H) = 3.0 Hz, 1H; C*H*OH), 4.36–3.61 (m, 5H; $CO_2CH_2CH_3$, C-NH_2, C-O*H*), 1.83–1.79 (m, 4H; C*H*$(CH_3)_2$, CH_3), 1.45 (s, 9H; C-(CH_3)$_3$), 1.29–1.22 (m, 3H; $CO_2CH_2CH_3$), 1.06–0.86 ppm (m, 6H; 2×CH_3); ^{13}C NMR (100 MHz $CDCl_3$): δ = 174.9, 153.7, 138.4, 121.8, 80.6, 78.6, 76.3, 61.6, 58.4, 28.9, 28.4, 28.3, 22.2, 17.2, 14.3, 14.1 ppm; IR (neat): $\tilde{\nu}$ = 3538, 2976, 2930, 2868, 1706 (C=O), 1666, 1450 cm^{-1}; MS (ESI): *m*/*z* (%): 350 (100) [M^++Na], 294 (45), 250 (44); HRMS (ESI): *m*/*z*: calcd for $C_{17}H_{29}NO_5Na$: 350.1943; found 350.1965.

***syn*-Diol 23**: NMO (367 mg, 3.13 mmol) and quinuclidine (87.0 mg, 0.78 mmol) were added to the substrate **22** (200 mg, 0.78 mmol) in acetone (10 mL) and H_2O (10 mL). The colourless solution was stirred for 2 min before addition of OsO_4 (10 mg, 0.04 mmol). The brown solution which formed was stirred for 28 h by which time analysis by TLC indicated complete consumption of the starting material. Silica gel was added and the solution evaporated to dryness in vacuo. Purification of the crude material by flash column chromatography eluting with methanol/diethyl ether 1:99 furnished **23** as an orange foam (203 mg, 72 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.53–4.50 (m, 1H; C*H*OH), 4.47–4.45 (m, 1H; C*H*OH), 4.43–4.25 (m, 2H; O-CH_2CH$_3$), 4.16–3.83 (m, 1H; O-*H*), 3.34 (dd, ^{3}J(H,H) = 12, ^{3}J(H,H) = 3.6 Hz, 2H; N-CH_2), 3.16, 2.74 (2× brs, 2H; 2×O-*H*), 1.85–1.70 (m, 1H; C*H*$(CH_3)_2$), 1.49–1.42 (m, 9H; C-(CH_3)$_3$), 1.42–1.35 (m, 6H; 2×CH_3), 1.10–0.96 ppm (m, 6H; 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 81.2, 80.8, 78.6, 77.9, 75.6, 75.4, 75.2, 74.8, 74.4, 62.5, 58.9, 58.3, 28.6, 28.1, 22.5, 22.0, 21.6, 18.0, 17.3, 14.0, 13.9 ppm; IR (neat): $\tilde{\nu}$ = 3940 (OH), 3451 (OH), 3244 (OH), 2974, 2933, 1704 cm^{-1} (C=O); MS (CI): *m*/*z* (%): 362 (100) [M^++H], 306 (40), 262 (20); HRMS (CI): *m*/*z*: calcd for $C_{17}H_{32}NO_7$: 362.2179; found: 362.2171.

Monoacetate 24: DMAP (5 mg, 0.04 mmol) was added to the substrate **23** (464 mg, 1.29 mmol) in pyridine (5 mL) and acetic anhydride (5 mL). The resulting solution was allowed to stir for 16 hr by which time analysis by TLC indicated complete consumption of the starting material. The crude mixture was evaporated to dryness and purification by flash column chromatography eluting with (50 % EtOAc/PE) furnished **24** as a colourless solid (423 mg, 74 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78 (d, ^{3}J(H,H) = 7.5 Hz, 1H; C*H*OAc), 5.73–5.69 (m, 1H, C*H*OAc), 5.17, 4.75 (2×brs, 1H; O*H*), 4.41–4.15 (m, 2H; $CO_2CH_2CH_3$), 4.10–3.92 (m, 1H; N-C*H*), 3.39–3.33 (m, 1H; N-C*H*), 2.10 (s, 3H; COCH_3), 1.97 (s, 3H; COCH_3), 1.94–1.79 (m, 1H; C*H*$(CH_3)_2$), 1.44 (s, 9H; C(CH_3)$_3$), 1.33–1.27 (m, 6H; 2×CH_3), 1.02–0.92 ppm (m, 6H; 2×CH_3); ^{13}C NMR (100 MHz $CDCl_3$): δ = 172.1, 172.0, 169.2, 169.0, 168.6, 168.4, 153.6, 152.4, 81.9, 81.3, 76.2, 76.0, 75.5, 74.9, 71.0, 70.9, 62.6, 62.5, 60.2, 59.4, 29.1, 28.2, 22.3, 22.0, 21.9, 21.8, 20.8, 20.7, 20.6, 18.3, 17.9, 13.9 ppm; IR (neat): $\tilde{\nu}$ = 3438, 2977, 2936, 2882, 1753, 1713, 1466, 1393, 1240, 1158, 1076, 1021 cm^{-1}; MS (CI): *m*/*z* (%): 446 (100) [M^++H], 407 (58), 390 (58), 346 (70); HRMS (CI): *m*/*z*: calcd for $C_{21}H_{36}NO_9$: 446.2390; found 446.2384.

Acetate protected aldol adduct 29: DMAP (cat.) was added to a solution of **22** (2.28 g, 6.69 mol) in acetic anhydride (10 mL) and pyridine (10 mL) at room temperature and under an inert atmosphere. The solution was left to stir overnight and then the resulting crude mixture was evaporated to dryness in vacuo. Purification by flash column chromatography eluting with (5 % acetone/PE) furnished **29** as a colourless oil (2.14 g, 83 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.72 (d, ^{3}J(H,H) = 3.6 Hz, 1H; C*H*OAc), 5.51–5.46 (m, 1H; C=C-*H*), 4.37–3.99 (m, 4H; N-CH_2, $CO_2CH_2CH_3$), 2.06, 2.05 (2×s, 3H; COCH_3), 2.03–1.88 (m, 1H; C*H*$(CH_3)_2$), 1.84, 1.82 (2×s, 3H; CH_3), 1.50–1.46 (m, 9H; C(CH_3)$_3$), 1.28–1.21 (m, 3H; $CO_2CH_2CH_3$), 0.95 (d, ^{3}J(H,H) = 6.9 Hz, 3H; CH_3), 0.80 ppm (d, ^{3}J-(H,H) = 6.9 Hz, 3H; CH_3); ^{13}C NMR (75 MHz $CDCl_3$): δ = 171.3, 170.1, 169.8, 153.5, 138.8, 122.0, 121.8, 80.9, 80.0, 61.2, 61.1, 58.4, 58.2, 29.1, 28.9, 28.3, 28.1, 21.8, 21.6, 21.1, 17.1, 15.2, 14.1, 13.9 ppm; IR (neat): $\tilde{\nu}$ = 2977(s), 2935(s), 2917(s), 1790(s), 1746(s), 1708(s), 1392(s), 1237, 1160, 1025 cm^{-1}; MS (CI): *m*/*z* (%): 370 (58) [M^++H], 331 (100), 314 (50), 270 (38); HRMS (CI): *m*/*z*: calcd for $C_{19}H_{32}NO_6$: 370.2229; found 370.2227.

***N*-Boc lactam 30**: Pyridine (86.4 mL, 737 mmol) was added to a solution of CrO_3 (10.6 g, 105 mmol) in CH_2Cl_2 (80 mL) at 0 °C under an inert atmosphere. The mixture was stirred for 10 mins at 0 °C then allowed to warm up to ambient temperature over 30 min. To the bright yellow complex was added a solution of **29** (1.94 g, 5.27 mmol) in dichloromethane (30 mL) dropwise. The resulting mixture was heated at 60 °C for 24 h. The mixture was filtered through Celite and then concentrated in vacuo. Purification of the crude material by flash chromatography eluting with (100 % Et_2O) furnished **30** as a pale green viscous oil (1.61 g, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.91 (q, ^{3}J(H,H) = 1.7 Hz, 1H; C=C-*H*), 5.95 (d, ^{3}J(H,H) = 3.15 Hz, 1H; C*H*OAc), 4.16 (m, 2H; $CO_2CH_2CH_3$), 2.20 (s, 3H; OCOCH_3), 1.89 (s, 3H; CH_3), 1.81 (m, 1H; C*H*$(CH_3)_2$), 1.60 (s, 9H; C(CH_3)$_3$), 1.24 (t, ^{3}J(H,H) = 7.1 Hz, 3H; $CO_2CH_2CH_3$), 0.95 (d, ^{3}J-(H,H) = 7.0 Hz, 3H; CH_3), 0.73 ppm (d, ^{3}J(H,H) = 7.0 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 169.7, 167.8, 139.7, 136.8, 84.1, 75.5, 71.7, 62.3, 28.6, 27.9, 21.7, 20.9, 17.2, 13.8, 10.9 ppm; IR (neat): $\tilde{\nu}$ = 2979, 2937, 2880, 1788, 1748 (br), 1717, 1393, 1370, 1329, 1235, 1156, 1025, 976, 779 cm^{-1}; MS (CI): *m*/*z* (%): 384 (30) [M^++H], 331 (60), 284 (100); HRMS (CI): *m*/*z*: calcd for $C_{19}H_{30}NO_7$: 384.2022; found 384.2021.

***N*-Deprotected lactam 31**: TFA (1.0 mL) was added to a solution of **30** (632 mg, 1.65 mmol) in CH_2Cl_2 (2 mL) at RT under an inert atmosphere. The reaction was stirred at room temperature for 30 min. The solution was then evaporated to dryness in vacuo. The crude mixture was purified by flash chromatography eluting with (20 % acetone/PE) which furnished **31** as a colourless oil (458 mg, 98 %). ^{1}H NMR (300 MHz $CDCl_3$): δ = 6.56 (brt, ^{3}J(H,H) = 1.7 Hz, 1H; C=C-*H*), 6.20 (brs, 1H; N-*H*), 5.28 (d, ^{3}J(H,H) = 5.4 Hz, 1H; C*H*OAc), 4.17 (q, ^{3}J(H,H) = 7.1 Hz, 2H; O-CH_2CH$_3$), 1.94 (s, 3H; COCH_3), 1.88 (m, 1H; C*H*$(CH_3)_2$), 1.80 (s, 3H; CH_3), 1.25 (t, ^{3}J(H,H) = 7.1 Hz, 3H; O-CH$_2$CH_3), 0.89 ppm (d, ^{3}J(H,H) = 6.7 Hz, 6H; 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 170.3, 168.5, 139.8, 135.8, 75.9, 71.0, 62.5, 29.8, 20.4, 20.2, 18.0, 13.9, 10.4 ppm; IR (neat): $\tilde{\nu}$ = 2976, 2937, 2925, 2874, 1746 (C=O), 1735 (C=O), 1704, 1654, 1475, 1372, 1232, 1193, 1028 cm^{-1}; MS (CI): *m*/*z* (%): 284 (100) [M^++H], 169 (75), 123 (10); HRMS (CI): *m*/*z*: calcd for $C_{14}H_{22}NO_5$: 284.1498; found 284.1492.

***syn*-Diol 32**: NMO (459 mg, 3.92 mmol) and quinuclidine (218 mg, 1.96 mmol) were added to compound **31** (554 mg, 1.96 mmol) in acetone and H_2O (3 mL). The colourless solution was stirred for 2 min before addition of OsO_4 (10 mg, 0.20 mmol). The brown solution that formed was stirred for 12 h and the solution evaporated to dryness in vacuo. Purification of the crude material by flash column chromatography eluting with (1 % MeOH/Et_2O) furnished **32** as a colourless solid (270 mg, 44 %).

^{1}H NMR (300 MHz, CD_3SOCD_3): δ = 8.50 (s, 1H; N*H*), 5.25 (d, ^3J(H,H) = 7.1 Hz, 1H; C*H*OH), 5.22 (d, ^3J(H,H) = 6.3 Hz, 1H; C*H*OAc), 5.13 (s, 1H; C(CH_3)O*H*), 4.12 (q, ^3J(H,H) = 7.1 Hz, 2H; $CO_2CH_2CH_3$), 3.64 (d, ^3J(H,H) = 7.1 Hz, 1H; CHO*H*), 2.07 (s, 3H; COCH_3), 1.95 (sp, ^3J(H,H) = 6.3 Hz, 1H; C*H*(CH_3)$_2$), 1.20 (m, 6H; $CO_2CH_2CH_3$, CH_3), 0.84 (d, ^3J(H,H) = 6.9 Hz, 3H; CH(CH_3)), 0.78 ppm (d, ^3J(H,H) = 6.9 Hz, 3H; CH(CH_3)); ^{13}C NMR (75 MHz, CD_3SOCD_3): δ = 176.5, 170.5, 170.4, 77.9, 75.6, 71.5, 70.6, 61.3, 29.7, 23.3, 21.1, 21.0, 19.3, 14.3 ppm; IR (neat): $\tilde{\nu}$ = 3464 (br OH), 3423 (br, OH), 2976 (s), 2936 (s), 1735 (C=O), 1709 (C=O), 1656, 1374, 1231, 1026, 824 cm^{-1}; MS (CI): *m*/*z* (%): 318 (100) [M^++H], 258 (20); HRMS (EI): *m*/*z*: calcd for $C_{14}H_{23}NO_7$: 317.1474; found 317.1470 [M^+].

Monoacetate 33: Acetic anhydride (84.4 μL, 0.89 mmol) and DMAP (cat.) was added to the substrate **32** (177 mg, 0.55 mmol) in pyridine (1 mL) and CH_2Cl_2 (2 mL). The resulting solution was allowed to stir for 12 h and the crude mixture was then evaporated to dryness. Purification by flash column chromatography eluting with (2% MeOH/CH_2Cl_2) furnished **33** as a colourless oil (423 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.8 (s, 1H; N-*H*), 5.43 (d, ^3J(H,H) = 6.2 Hz, 1H; C*H*OAc), 5.2 (s, 1H; C*H*OAc), 4.34 (m, 2H; $CO_2CH_2CH_3$), 3.2 (br s, 1H; O*H*), 2.19 (s, 3H; COCH_3), 2.14 (s, 3H; COCH_3), 1.94 (sp, ^3J(H,H) = 6.2 Hz, 1H; C*H*(CH_3)$_2$), 1.51 (s, 3H; CH_3), 1.38 (t, ^3J(H,H) = 7.1 Hz, 3H; $CO_2CH_2CH_3$), 1.01 (d, ^3J(H,H) = 6.9 Hz, 3H; CH_3), 0.96 ppm (d, ^3J(H,H) = 6.9 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 169.9, 169.0, 75.8, 74.9, 72.3, 69.0, 62.8, 30.3, 22.8, 20.7, 20.4, 18.5, 14.0 ppm; IR (neat): $\tilde{\nu}$ = 3404 (br), 2977 (s), 2938 (s), 1729 (br), 1714 (s), 1373 (s), 1225 cm^{-1}; MS (CI): *m*/*z* (%): 377 (65), 360 (100) [M^++H]; HRMS (EI): *m*/*z*: calcd for $C_{16}H_{25}NO_8$: 359.1678; found 359.1682.

***N*-Boc ethyl ester pyrrole 40**: DMAP (cat.), distilled triethylamine (4.2 mL, 30 mmol) and di-*tert*-butyl dicarbonate (3.1 g, 14 mmol) were added to a stirred solution of ethyl ester pyrrole **39** (1.4 g, 10 mmol) in distilled MeCN (10 mL). The mixture was then heated at 50°C for 48 h. The reaction mixture was poured into water (30 mL) and extracted with Et_2O (3×30 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 10% acetone/PE) to afford the *N*-Boc ethyl ester pyrrole **40** (2.2 g, 91%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (dd, ^3J(H,H) = 3.6, ^3J(H,H) = 2.0 Hz, 1H; ArH), 6.83 (dd, ^3J(H,H) = 3.6, ^3J(H,H) = 1.6 Hz, 1H; ArH), 6.17 (t, ^3J(H,H) = 3.6 Hz, 1H; ArH), 4.31 (q, ^3J(H,H) = 7.2 Hz, 2H; OCH_2Me), 1.59 (s, 9H; CMe_3), 1.36 ppm (t, ^3J(H,H) = 7.2 Hz, 3H; OCH_2Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.9, 148.4, 126.5, 125.6, 120.6, 110.0, 84.7, 60.8, 27.6, 14.3 ppm; IR (neat): $\tilde{\nu}$ = 2982–2875 (CH), 1752 (C=O), 1725 cm^{-1} (C=O); HRMS (ESI): *m*/*z*: calcd for $C_{14}H_{20}N_2O_4Na$: 303.1320; found 303.1320 [M^++CH_3CN+Na].

***anti*-Aldol adduct 42**: Small strips of lithium ribbon (119 mg, 17.0 mmol), antibumping granules and di-*tert*-butylbiphenyl (4.5 g, 16.9 mmol) were placed in a Schlenk tube which was then evacuated and purged with argon several times. The mixture was ground with a magnetic stirrer until all the lithium became a dark powder. Freshly distilled THF (50 mL) was then added and the mixture was cooled down to −78°C before a mixture of *N*-Boc ethyl ester pyrrole **40** (1.1 g, 4.4 mmol) and bis-methoxyethylamine (0.8 mL, 5.3 mmol) in freshly distilled THF (25 mL) was added dropwise to the turquoise solution. The mixture was then stirred at −78°C for a further 15 min after which freshly prepared $MgBr_2$ (1.0 g, 5.4 mmol) in THF (20 mL) was added and the mixture was stirred for a further 30 min. Distilled isobutyraldehyde (0.7 mL, 7.0 mmol) was then added and after 30 min the reaction mixture was quenched with saturated NH_4Cl (10 mL). Stirring was continued at −78°C for a further 30 min and then warmed to ambient temperature. The reaction mixture was poured into aqueous HCl (1.0 M, 50 mL) and extracted with Et_2O (3×60 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by gradient column chromatography (eluting with neat PE to recover the DBB and then 5% acetone/PE) to afford the *anti*-aldol **42** (1.07 g, 74%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.98, 5.93, 5.91(dt, s, dt, ^3J(H,H) = 8.4, ^3J(H,H) = 2.0, $^3J'$(H,H) = 8.4, $^3J'$(H,H) = 2.4 Hz, 2H; CH=CH), 4.41, 4.38 (dd, dt, ^3J(H,H) = 5.6, ^3J(H,H) = 2.8, J'(H,H) = 18.0, J'(H,H) = 2.0 Hz, 1H; C*H*OH), 4.34–4.00 (m, 4H; OCH_2Me, NCH_2), 3.89, 3.62 (2×dd, ^3J(H,H) = 3.2, ^3J(H,H) = 0.8 Hz, 1H; OH), 1.90–1.70 (m, 1H; C*H*Me$_2$), 1.44, 1.41 (2×s, 9H; CMe$_3$), 1.24, 1.21 ppm (2×t, ^3J(H,H) = 7.6, $^3J'$(H,H) = 7.2 Hz, 3H; OCH_2Me), 0.97, 0.95 (2×d, ^3J(H,H) = 6.8 Hz, 3H; CH*Me*), 0.87, 0.84 ppm (2×d, ^3J(H,H) = 6.8 Hz, 3H; CH*Me*); ^{13}C NMR (125 MHz $CDCl_3$): δ = 174.8, 174.6, 154.3, 153.5, 129.0, 128.6, 128.5, 81.2, 80.6, 78.8, 78.4, 76.7, 76.0, 62.1, 61.9, 56.0, 55.9, 29.4, 29.0, 28.7, 22.6, 22.3, 17.7, 17.1, 14.5, 14.4 ppm; IR (neat): $\tilde{\nu}$ = 3543 (br OH), 2974–2872 (CH), 1705 cm^{-1} (br C=O); MS (ESI): *m*/*z* (%): 214 (100) [M^+−Boc], 336 (36) [M^++Na]; HRMS (ESI): *m*/*z*: calcd for $C_{16}H_{27}NO_5Na$: 336.1787; found 336.1787 [M^++Na].

Acetate 44: DMAP (cat.), acetic anhydride (15 mL) and distilled pyridine (15 mL) were added to the *anti*-aldol product **42** (4.33 g, 13.8 mmol) and the mixture was stirred for 48 h. The reaction mixture was poured into water (50 mL) and aqueous $CuSO_4$ (20 mL), and then extracted with Et_2O (3×50 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 5% acetone/PE) to afford the acetate protected *anti*-aldol product **44** (3.4 g, 72%) as a very pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.12–5.98 (m, 1H; C*H*=CH), 5.91–5.85 (m, 1H; CH=C*H*), 5.84, 5.77 (2×d, ^3J(H,H) = 3.6, $^3J'$(H,H) = 3.3 Hz, 1H; C*H*OAc), 4.51–4.35 (m, 1H; NC*H*), 4.30–4.20 (m, 1H NC*H*), 4.14 (q, ^3J(H,H) = 7.1 Hz, 2H; OCH_2Me), 2.14 (s, 3H; CO*Me*), 2.08–1.92 (m, 1H; C*H*Me$_2$), 1.50 (s, 9H; CMe_3), 1.26 (t, ^3J(H,H) = 7.1 Hz, 3H; OCH_2Me), 0.98 (d, ^3J(H,H) = 6.9 Hz, 3H; CH*Me*), 0.83 ppm (d, ^3J(H,H) = 6.9 Hz, 3H; CH*Me*); ^{13}C NMR (75 MHz; $CDCl_3$): δ = 170.9, 170.1, 153.2, 129.1, 129.0, 128.3, 128.1, 81.1, 80.2, 61.4, 61.3, 55.5, 55.4, 30.9, 29.1, 29.0, 28.9, 28.4, 28.3, 28.2, 28.1, 21.9, 21.7, 21.1, 17.2, 16.9, 13.9 ppm; IR (neat): $\tilde{\nu}$ = 2975 (CH), 1744 (C=O), 1707 cm^{-1} (C=O); HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{30}NO_6$: 356.2073; found 356.2077 [M^++H].

***syn*-Diol 45**: Trimethylamine *N*-oxide (3 mmol) and osmium tetroxide (cat.) was added to the acetate protected *anti*-aldol product **44** (1 g, 3 mmol) in CH_2Cl_2 (50 mL), and the reaction mixture was stirred for 4 h. Saturated Na_2SO_3 (20 mL) was then added to the reaction mixture and stirred for a further 0.5 h and then evaporated to dryness. The reaction mixture was then extracted with CH_2Cl_2 (3×100 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 100% Et_2O) to afford the diol **45** (1.08 g, 95%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82, 5.75 (2×d, ^3J(H,H) = 4.8, $^3J'$(H,H) = 4.4 Hz, 1H; C*H*OAc), 4.72, 4.64 (2×t, ^3J(H,H) = 5.2 Hz, 1H; C*H*OH$_B$), 4.41, 4.06 (2×d, ^3J(H,H) = 11.6, $^3J'$(H,H) = 12.4 Hz, 1H; OH$_A$), 4.34–3.92 (m, 4H; OCH_2Me, C*H*OH$_A$, NC*H*), 3.52, 3.48 (2×dd, ^2J(H,H) = 8.4, ^3J(H,H) = 4.0 Hz, 1H; NC*H*), 2.97, 2.89 (2×d, ^3J(H,H) = 7.6, $^3J'$(H,H) = 6.8 Hz, 1H; OH$_B$), 2.12, 2.10 (s, 3H; CO*Me*), 1.90–1.75 (m, 1H; C*H*Me$_2$), 1.44, 1.43 (2×s, 9H; CMe_3), 1.28 (t, ^3J(H,H) = 7.2 Hz, 3H; OCH_2Me), 0.99 (d, ^3J(H,H) = 6.8 Hz, 3H; CH*Me*), 0.89 ppm (d, ^3J(H,H) = 7.2 Hz, 3H; CH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 169.8, 153.0, 81.8, 81.1, 75.9, 75.8, 75.0, 72.9, 72.7, 71.0, 70.4, 62.6, 62.5, 54.8, 54.1, 30.9, 29.1, 28.2, 22.2, 21.9, 21.0, 20.9, 18.4, 18.0, 13.8 ppm; IR (neat): $\tilde{\nu}$ = 3424 (br OH), 2976–2874 (CH), 1746 (C=O), 1710 cm^{-1} (C=O); MS (ESI): *m*/*z* (%): 412 (100) [M^++Na], 390 (28) [M^++H]; HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{31}NO_8Na$: 412.1947; found 412.1944 [M^++Na].

Cyclic sulfate 46: Triethylamine (1.1 mL, 7.9 mmol) was added to a stirred solution of the diol **45** (381 mg, 0.980 mmol) in distilled CH_2Cl_2 (2 mL) at 0°C, followed by the dropwise addition of thionylchloride (110 μL, 1.51 mmol) over 0.5 h. After 1 h the reaction mixture was warmed to room temperature and stirred for 24 h. The reaction mixture was then poured into water (30 mL), extracted with Et_2O (3×40 mL) and the combined organic extract was washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to afford the cyclic sulfite (355 mg, 84%) as a brown solid, which was taken straight through to the next step without purification.

To the crude cyclic sulfite (355 mg, 0.820 mmol) were added MeCN (2 mL), CCl_4 (2 mL) and water (3 mL). The reaction mixture was then cooled down to 0°C, followed by the additon of ruthenium trichloride hydrate (cat.) and sodium *m*-periodate (279 mg, 1.30 mmol), and the mixture was stirred for 1.5 h at room temperature. The dark brown reaction mixture was then extracted with Et_2O (3×40 mL) and the combined or-

ganic extract was washed with brine (10 mL) and saturated $NaHCO_3$ (10 mL), dried (Na_2SO_4), filtered through a pad of charcoal and Celite and concentrated in vacuo to afford the cyclic sulfate **46** (345 mg, 93%) as a white solid. M.p. 133–138°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92, 5.82 (2×d, ^3J(H,H) = $^3J'$(H,H) = 3.6 Hz, 1H; C*H*OAc), 5.76, 5.69 (2×d, ^3J(H,H) = 6.8, $^3J'$(H,H) = 7.2 Hz, 1H; C*H*OSO$_2$), 5.43–5.34 (m, 1H; NCH$_2$C*H*OSO$_2$), 4.35–4.01 (m, 4H; OC*H*$_2$Me, NC*H*$_2$), 2.14, 2.13 (2×s, 3H; CO*Me*), 1.93–1.82 (m, 1H; C*H*Me$_2$), 1.47, 1.46 (2×s, 9H; C*Me*$_3$), 1.30, 1.26 (2×t, ^3J(H,H) = $^3J'$(H,H) = 7.2 Hz, 3H; OCH$_2$*Me*), 0.99 (d, ^3J-(H,H) = 7.6 Hz, 3H; CH*Me*), 0.82 ppm (d, ^3J(H,H) = 6.8 Hz, 3H; CH*Me*); ^{13}C NMR (125 MHz $CDCl_3$): δ = 170.1, 167.9, 152.9, 85.4, 84.5, 83.5, 79.7, 79.1, 75.2, 73.9, 63.3, 63.0, 53.1, 52.9, 29.7, 29.5, 28.6, 28.5, 21.6, 21.5, 17.9, 17.6, 14.2 ppm; IR (neat): $\tilde{\nu}$ = 2977–2886 (CH), 1755 (C=O), 1694 cm^{-1} (C=O); MS (ESI): *m*/*z* (%): 474 (100) [*M*$^+$+Na]; HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{29}NO_{10}SNa$: 474.1414; found 474.1410 [*M*$^+$+Na].

Monoprotected diol 47: Distilled 2,6-lutidine (0.76 mL, 6.50 mmol) was added to the diol **45** (1.02 g, 2.62 mmol) in distilled CH_2Cl_2 (20 mL) and the mixture was stirred at −78°C for 0.5 h followed by dropwise addition of *tert*-butyldimethylsilyl triflate (0.90 mL, 3.9 mmol). The reaction mixture was then stirred at −78°C for 1.5 h and then allowed to warm to room temperature for 20 h. The mixture was poured into dilute HCl (0.1 M, 30 mL) and extracted with CH_2Cl_2 (3×40 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 10% acetone/PE) to afford the mono-TBDMS protected diol **47** (1.2 g, 93%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81, 5.77 (2×d, ^3J(H,H) = $^3J'$-(H,H) = 4.0 Hz, 1H; C*H*OAc), 4.67, 4.49 (2×t, ^3J(H,H) = 6.6, $^3J'$(H,H) = 6.2 Hz, 1H; C*H*OH), 4.36–4.26 (m, 1H; C*H*OTBS), 4.18–4.04 (m, 2H; OC*H*$_2$Me), 3.78–3.53 (m, 2H; NC*H*$_2$), 3.33, 3.27 (2×d, ^3J(H,H) = $^3J'$-(H,H) = 6.8 Hz, 1H; O*H*), 2.14, 2.13 (2×s, 3H; CO*Me*), 1.94–1.83 (m, 1H; C*H*Me$_2$), 1.45 (s, 9H; C*Me*$_3$), 1.26 (t, ^3J(H,H) = 7.2 Hz, 3H; OCH$_2$*Me*), 0.97 (d, ^3J(H,H) = 6.8 Hz, 3H; CH*Me*), 0.92, 0.91 (2×s, 9H; OSiMe$_2$C*Me*$_3$), 0.86 (d, ^3J(H,H) = 7.2 Hz, 3H; CH*Me*), 0.14, 0.12 ppm (2×s, 6H; OSi*Me*$_2$CMe$_3$); ^{13}C NMR (125 MHz $CDCl_3$): δ = 170.3, 169.7, 153.5, 81.3, 76.2, 75.4, 74.7, 74.4, 73.6, 69.6, 68.8, 61.1, 61.0, 54.2, 54.0, 29.1, 28.8, 28.2, 28.1, 25.5, 22.0, 21.9, 21.1, 18.0, 17.6, 14.0, −4.8, −5.1, −5.2 ppm; IR (neat): $\tilde{\nu}$ = 3503 (br OH), 2963–2800 (CH), 1747 (C=O), 1706 cm^{-1} (C=O); MS (ESI): *m*/*z* (%): 526 (40) [*M*$^+$+Na]; HRMS (CI): *m*/*z*: calcd for $C_{24}H_{46}NO_8Si$: 504.2993; found 504.2993 [*M*$^+$+H].

Diprotected diol 48: Diisopropylethylamine (5.0 mL, 28 mmol) was added to the mono-TBDMS protected diol **47** (709 mg, 1.41 mmol) in distilled CH_2Cl_2 (10 mL) and the mixture was stirred for 45 min. Chloromethyl methoxy ether (1.61 mL, 21.2 mmol) was then added dropwise and the mixture was heated at 50°C for 21 h. The dark orange reaction mixture was then quenched with saturated NH_4Cl (5 mL) and the mixture was stirred for a further 0.5 h, then poured into water (30 mL) and extracted with Et_2O (3×40 mL). The combined organic extract was washed with brine (20 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 10% acetone/PE) to afford the bis-protected diol **48** (764 mg, 99%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80, 5.74 (2×d, ^3J(H,H) = 4.0, $^3J'$(H,H) = 3.6 Hz, 1H; C*H*OAc), 4.81, 4.78 (2×d, ^3J(H,H) = 7.2, $^3J'$(H,H) = 6.8 Hz, 1H; OC*H*OMe), 4.64–4.60 (m, 1H; OC*H*OMe), 4.60, 4.50 (2×d, ^3J(H,H) = 6.8, $^3J'$(H,H) = 5.2 Hz, 1H; C*H*OMOM), 4.28–3.98 (m, 3H; OC*H*$_2$Me, C*H*OTBDMS), 3.77, 3.62 (2×dd, ^3J(H,H) = 9.6, ^3J(H,H) = 6.8, $^3J'$(H,H) = 10.0, $^3J'$(H,H) = 7.2 Hz, 1H; NC*H*), 3.48, 3.45 (2×t, ^3J(H,H) = $^3J'$(H,H) = 9.6 Hz, 1H; NC*H*), 3.35 (s, 3H; OCH$_2$O*Me*), 2.14, 2.13 (2×s, 3H; CO*Me*), 1.99–1.84 (m, 1H; C*H*Me$_2$), 1.45 (s, 9H; C*Me*$_3$), 1.26, 1.23 (2×t, ^3J(H,H) = 7.2, $^3J'$-(H,H) = 6.8 Hz, 3H; OCH$_2$*Me*), 1.00, 0.98 (2×d, ^3J(H,H) = $^3J'$(H,H) = 6.8 Hz, 3H; CH*Me*), 0.91, 0.90 (2×s, 9H; OSiMe$_2$C*Me*$_3$), 0.88, 0.84 (2×d, ^3J(H,H) = $^3J'$(H,H) = 6.8 Hz, 3H; CH*Me*), 0.12, 0.11, 0.10 ppm (3×s, 6H; OSi*Me*$_2$CMe$_3$); ^{13}C NMR (125 MHz $CDCl_3$): δ = 170.3, 169.9, 169.5, 169.1, 153.7, 96.7, 81.3, 80.2, 77.7, 77.5, 75.5, 74.7, 74.5, 74.1, 70.4, 70.0, 61.0, 60.9, 56.0, 52.0, 51.6, 28.8, 28.4, 28.1, 26.1, 25.7, 22.3, 22.1, 21.0, 18.1, 18.0, 17.9, 13.8, −4.8, −5.0 ppm; IR (neat): $\tilde{\nu}$ = 2961–2858 (CH), 1748 (C=O), 1709 cm^{-1} (C=O); MS (ESI): *m*/*z* (%): 570 (47) [*M*$^+$+Na]; HRMS (CI): *m*/*z*: calcd for $C_{26}H_{50}NO_9Si$: 548.3255; found 548.3255 [*M*$^+$+H].

MOM protected diol 49: TBAF (2.40 mL, 2.40 mmol) was added dropwise to the bis-protected diol **48** (662 mg, 1.21 mmol) in distilled THF (10 mL), and the mixture was stirred for 1 h. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and stirred for a further 10 min and then poured into water (30 mL) and extracted with Et_2O (3×40 mL). The combined organic extract was washed with brine (20 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash column chromatography eluting with 20% EtOAc/PE to afford the mono-MOM protected diol **49** (443 mg, 84%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80, 5.76 (2×d, ^3J(H,H) = $^3J'$(H,H) = 4.8 Hz, 1H; C*H*OAc), 4.83, 4.82 (2×d, ^3J(H,H) = 6.8, $^3J'$-(H,H) = 6.4 Hz, 1H; OC*H*OMe), 4.71, 4.70 (2×d, ^3J(H,H) = $^3J'$(H,H) = 6.4 Hz, 1H, OC*H*OMe), 4.61, 4.27 (2×d, ^3J(H,H) = 11.2, ^3J(H,H) = 11.6 Hz, 1H; O*H*), 4.51, 4.42 (2×d, ^3J(H,H) = 4.4, $^3J'$(H,H) = 4.8 Hz, 1H; C*H*OMOM), 4.36–4.11 (m, 3H; OC*H*$_2$Me, C*H*OH), 4.09, 3.94 (2×d, ^3J-(H,H) = 12.8, $^3J'$(H,H) = 12.4 Hz, 1H; NC*H*), 3.48 (s, 3H; OCH$_2$O*Me*), 3.43, 3.41 (2×dd, ^3J(H,H) = 12.8, ^3J(H,H) = 3.6, $^3J'$(H,H) = 12.4, $^3J'$-(H,H) = 3.6 Hz, 1H; NC*H*), 2.07, 2.05 (2×s, 3H; CO*Me*), 1.91–1.78 (m, 1H; C*H*Me$_2$), 1.45, 1.44 (2×s, 9H; C*Me*$_3$), 1.28, 1.26 (2×t, ^3J(H,H) = $^3J'$-(H,H) = 7.2 Hz, 3H; OCH$_2$*Me*), 1.00, 0.99 (2×d, ^3J(H,H) = $^3J'$(H,H) = 6.8 Hz, 3H; CH*Me*), 0.89, 0.88 ppm (2×d, ^3J(H,H) = 6.8, $^3J'$(H,H) = 6.4 Hz, 3H; CH*Me*); ^{13}C NMR (100 MHz $CDCl_3$): δ = 171.9, 169.5, 169.4, 153.8, 152.9, 96.5, 96.4, 81.7, 81.0, 80.6, 79.7, 76.0, 71.4, 71.2, 70.4, 69.9, 62.2, 62.1, 56.1, 55.7, 55.0, 30.9, 29.6, 28.9, 28.2, 28.1, 22.4, 22.2, 21.0, 20.9, 18.5, 18.2, 13.8 ppm; IR (neat): $\tilde{\nu}$ = 3435 (br OH), 2973–2800 (CH), 1746 (C=O), 1710 cm^{-1} (C=O); MS (ESI): *m*/*z* (%): 456 (100) [*M*$^+$+Na], 334 (53); HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{36}NO_9$: 434.2390; found 434.2386 [*M*$^+$+H].

MOM protected ketone 50: Dess–Martin periodinane (188 mg, 0.440 mmol) was added to the mono-MOM protected diol **49** (90 mg, 0.21 mmol) in distilled CH_2Cl_2 (4 mL) and the mixture was stirred for 1.5 h. Et_2O (10 mL) was then added to the resulting cloudy white solution followed by a 1:1 mixture of saturated $NaHCO_3$ (2 mL) and saturated $Na_2S_2O_3$ (2 mL) and stirred for a further 1 h. The reaction mixture was then poured into water (15 mL), extracted with Et_2O (3×20 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 20% EtOAc/PE) to afford the ketone **50** (77.2 mg, 86%) as a white solid. M.p. 80–88°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10, 6.04 (brs, d, ^3J(H,H) = 2.8 Hz, 1H; C*H*OAc), 4.90 (d, ^3J(H,H) = 6.4 Hz, 1H; OC*H*OMe), 4.69 (d, ^3J(H,H) = 6.4 Hz, 1H; OC*H*OMe), 4.72–4.62 (m, 1H; C*H*OMOM), 4.28–4.04 (m, 3H; OC*H*$_2$Me, NC*H*), 3.90 (d, ^2J(H,H) = 19.2 Hz, 1H; NC*H*), 3.53 (s, 3H; OCH$_2$O*Me*), 2.17–1.95 (m, 1H; C*H*Me$_2$), 2.10 (s, 3H; CO*Me*), 1.48 (s, 9H; C*Me*$_3$), 1.22 (t, ^3J(H,H) = 7.2 Hz, 3H; OCH$_2$*Me*), 1.01 (d, ^3J(H,H) = 6.8, 3H; CH*Me*), 0.90 ppm (d, ^3J(H,H) = 7.2 Hz, 3H, CH*Me*); ^{13}C NMR (125 MHz $CDCl_3$): δ = 205.3, 169.3, 168.8, 96.6, 82.6, 78.9, 74.8, 71.1, 61.5, 56.4, 52.8, 29.3, 28.0, 21.4, 20.9, 17.6, 13.9 ppm; IR (neat): $\tilde{\nu}$ = 2980–2922 (CH), 1778 (C=O), 1759 (C=O), 1711 cm^{-1} (C=O); MS (ESI): *m*/*z* (%): 454 (48) [*M*$^+$+Na]; HRMS (CI): *m*/*z*: calcd for $C_{20}H_{34}NO_9$: 432.2240; found 432.2234 [*M*$^+$+H].

Epimerised MOM protected ketone 51: *n*BuLi (1.6 M solution in hexane, 0.34 mL, 0.54 mmol) was added slowly at 0°C to methyl triphenylphosphonium iodide (228 mg, 0.560 mmol) in distilled THF (2 mL), and the reaction mixture was stirred for 1 h. Ketone **50** (117 mg, 0.270 mmol) in distilled THF (5 mL) was then added dropwise to the orange solution, which was stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and stirred for a further 15 min, then poured into water (20 mL) followed by extraction with Et_2O (3×30 mL). The combined organic extract was washed with brine (15 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 10% EtOAc/PE) to afford the ketone **51** (62.6 mg, 56%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.41 (s, 1H; C*H*OAc), 4.70, 4.69 (2×d, ^3J(H,H) = 6.4, $^3J'$(H,H) = 6.8 Hz, 1H; OC*H*OMe), 4.64 (s, 1H; C*H*OMOM), 4.58 (d, ^3J(H,H) = 6.8 Hz, 1H; OC*H*OMe), 4.46–4.02 (m, 3H; OC*H*$_2$Me, NC*H*), 3.76, 3.74 (2×d, ^2J(H,H) = 17.6, $^2J'$(H,H) = 18.8 Hz, 1H; NC*H*), 3.36 (s, 3H; OCH$_2$O*Me*), 2.75, 2.69–2.57 (sp, m, ^3J-(H,H) = 6.8 Hz, 1H; C*H*Me$_2$), 1.91, 1.90 (2×s, 3H; CO*Me*), 1.47, 1.46 (2×s, 9H; C*Me*$_3$), 1.36, 1.32 (2×t, ^3J(H,H) = $^3J'$(H,H) = 7.6 Hz, 3H;

OCH_2Me), 1.04, 1.03 (2×d, ^3J(H,H) = $^3J'$(H,H) = 7.2 Hz, 3H; CHMe), 0.78, 0.75 ppm (2×d, ^3J(H,H) = 6.8, $^3J'$(H,H) = 6.4 Hz, 3H; CHMe); ^{13}C NMR (100 MHz $CDCl_3$): δ = 204.5, 203.7, 169.5, 169.1, 153.0, 152.7, 97.4, 97.2, 82.5, 81.6, 70.5, 69.9, 62.0, 56.5, 56.3, 51.4, 50.9, 28.4, 28.3, 28.1, 23.0, 20.4, 17.0, 16.8, 14.0, 13.9 ppm; IR (neat): $\tilde{\nu}$ = 2978–2810 (CH), 1782 (C=O), 1754 (C=O), 1707 cm^{-1} (C=O); MS (ESI): m/z (%): 454 (100) [M^++Na], 449 (58) [M^++NH_4]; HRMS (ESI): m/z: calcd for $C_{20}H_{34}NO_9$: 432.2234; found 432.2235 [M^++H].

Iodohydrin 54: Triphenylphosphine (4.19 g, 16.0 mmol) and di-*tert*-butylazodicarboxylate (3.67 g, 15.9 mmol) were added to the diol **45** (1.0 g, 2.6 mmol) in distilled benzene (14 mL), and the reaction mixture was stirred for 20 min. Methyliodide (1.91 mL, 30.7 mmol) was then added dropwise and the mixture was heated at reflux at 80 °C for 34 h. The reaction mixture was then poured into water (100 mL), extracted with dichloromethane (3×100 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 5% acetone/PE) to afford the iodide **54** (1.04 g, 81%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.26 (br s, 1H; OH), 5.81, 5.73 (2×d, ^3J(H,H) = 4.8, $^3J'$(H,H) = 4.4 Hz, 1H; CHOAc), 4.79, 4.73 (2× dd, ^3J(H,H) = 9.8 Hz, ^3J(H,H) = 3.4, $^3J'$(H,H) = 9.6, $^3J'$(H,H) = 3.2 Hz, 1H; CHOH), 4.44–4.06 (m, 4H; OCH_2Me, CHI, NCH), 3.61–3.46 (m, 1H; NCH), 2.12, 2.11 (2×s, 3H; COMe), 1.98–1.82 (m, 1H; CHMe$_2$), 1.44, 1.42 (2×s, 9H; CMe$_3$), 1.26, 1.22 (2×t, ^3J(H,H) = 7.2 Hz, 3H; OCH_2Me), 1.00, 0.99 (2×d, ^3J(H,H) = 6.8, $^3J'$(H,H) = 7.2 Hz, 3H; CHMe), 0.92, 0.91 ppm (2×d, ^3J(H,H) = 6.8 Hz, 3H; CHMe); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 169.8, 169.0, 155.6, 152.4, 83.2, 82.4, 81.9, 81.3, 81.2, 71.0, 61.6, 61.5, 54.1, 29.0, 28.1, 28.0, 27.8, 27.7, 22.0, 21.7, 20.9, 19.0, 18.6, 18.0, 17.7, 14.0, 13.9 ppm; IR (neat): $\tilde{\nu}$ = 3337 (br OH), 2979–2885 (CH), 1741 (C=O), 1708 cm^{-1} (C=O); HRMS (ESI): m/z: calcd for $C_{18}H_{34}N_2IO_7$: 517.1400; found 517.1411 [M^++NH_4].

Mono-alcohol 55: A mixture of freshly dried indium trichloride (312 mg, 1.4 mmol) and sodium borohydride (102 mg, 2.8 mmol) in distilled MeCN (6 mL) was stirred at −78 °C for 10 min. The heterogeneous solution was then warmed to ambient temperature and the iodide **54** (897 mg, 1.8 mmol) in distilled MeCN (14 mL) was added dropwise and stirred for 2 h. The reaction mixture was then poured into water (40 mL) and extracted with Et_2O (3×50 mL). The combined organic extract was washed with brine (20 mL), dried organic extract was washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to afford the alcohol **55** (658 mg, 98%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87, 5.79 (2×d, ^3J(H,H) = 4.4, $^3J'$(H,H) = 4.0 Hz, 1H; CHOAc), 4.85, 4.78 (dd, t, ^3J(H,H) = 10.0, J = 7.6, J' = 8.8 Hz, 1H; CHOH), 4.29–4.07 (m, 2H; OCH_2Me), 4.03–3.92, 3.90–3.81 (2×m, 1H; NCH), 3.34–3.22 (m, 1H; NCH), 2.22–2.09 (m, 2H; NCH$_2$CH_2), 2.13, 2.12 (2×s, 3H; COMe), 2.00–1.80 (m, 1H; CHMe$_2$), 1.45, 1.43 (2×s, 9H; CMe$_3$), 1.27, 1.23 (2×t, ^3J(H,H) = 7.2 Hz, 3H; OCH_2Me), 1.00, 0.99 (2×d, ^3J(H,H) = 7.2, $^3J'$(H,H) = 6.8 Hz, 3H; CHMe), 0.91, 0.90 ppm (2×d, ^3J(H,H) = 6.8, $^3J'$(H,H) = 7.2 Hz, 3H; CHMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 170.5, 169.2, 169.0, 81.1, 80.3, 77.8, 75.6, 74.7, 72.1, 71.9, 61.2, 61.0, 45.4, 44.9, 30.8, 30.2, 29.7, 29.5, 29.2, 28.9, 28.1, 28.0, 27.8, 22.0, 21.7, 20.9, 18.2, 17.9, 14.0 ppm; IR (neat): $\tilde{\nu}$ = 3490 (br OH), 2977–2884 (CH), 1743 (C=O), 1703 cm^{-1} (C=O); HRMS (ESI): m/z: calcd for $C_{18}H_{31}NO_7Na$: 396.1998; found, 396.2004 [M^++Na].

TES protected alcohol 56: DMAP (226 mg, 1.85 mmol), imidazole (1.26 g, 18.5 mmol) and triethylsilylchloride (1.86 mL, 11.1 mmol) were added to a stirred solution of the alcohol **55** (1.38 g, 3.70 mmol) in distilled CH_2Cl_2 (25 mL). The reaction mixture was stirred for 24 h and then poured into water (50 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic extract was washed with brine (50 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 5% acetone/PE) to afford the TES protected alcohol **56** (1.8 g, 100%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84, 5.81 (2×d, ^3J(H,H) = 4.4 Hz, 1H; CHOAc), 4.85, 4.75 (2×t, ^3J(H,H) = 7.8, $^3J'$(H,H) = 7.4 Hz, 1H; CHOTES), 4.20–4.00 (m, 2H; OCH_2Me), 4.00–3.91, 3.86–3.79 (2× m, 1H; NCH), 3.33–3.22, 3.14–3.05 (2×m, 1H; NCH), 2.13–2.04 (m, 2H; NCH$_2$CH_2), 2.09 (s, 3H; COMe), 1.98–1.84 (m, 1H; CHMe$_2$), 1.44, 1.43 (2×s, 9H; CMe_3), 1.24, 1.21 (2×t, ^3J(H,H) = 7.2 Hz, 3H; OCH_2Me), 0.97 (d, ^3J(H,H) = 6.8 Hz, 3H; CHMe), 0.96 (t, ^3J(H,H) = 8.0 Hz, 9H; OSi-(CH$_2$$Me$)$_3$), 0.88 (d, ^3J(H,H) = 6.4 Hz, 3H; CHMe), 0.60, 0.59 ppm (2×q, ^3J(H,H) = 8.0 Hz, 6H; OSi(CH_2Me)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 170.0, 153.9, 153.3, 80.9, 79.9, 76.1, 75.8, 75.4, 73.5, 72.8, 60.6, 60.4, 46.0, 45.4, 33.0, 32.3, 29.0, 28.9, 28.2, 28.1, 27.8, 22.3, 22.1, 21.0, 18.1, 17.9, 14.0, 6.6, 6.3, 4.9, 4.8 ppm; IR (neat): $\tilde{\nu}$ = 2963–2878 (CH), 1749 (C=O), 1707 cm^{-1} (C=O); MS (ESI): m/z (%): 510 (100) [M^++Na], 488 (69) [M^++H], 388 (81); HRMS (ESI): m/z: calcd for $C_{24}H_{46}NO_7Si$: 488.3044; found 488.3048 [M^++H].

TBS protected lactam 57: MeCN (17 mL), CCl_4 (17 mL) and water (26 mL) were added to the TES protected alcohol **56** (450 mg, 0.16 mmol), followed by the additon of sodium *m*-periodate (150 mg, 0.70 mmol) and ruthenium trichloride hydrate (33 mg, 0.16 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and then warmed to room temperature and stirred for 4 h. The reaction mixture was filtered through a pad of Celite and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 5% acetone/PE) to afford the lactam **57** (389 mg, 84%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.94 (d, ^3J(H,H) = 3.6 Hz, 1H; CHOAc), 4.85 (dd, ^3J(H,H) = 8.8, ^3J(H,H) = 6.8 Hz, 1H; CHOTES), 4.19–4.08 (m, 2H; OCH_2Me), 2.91, 2.87 (2×d, ^3J(H,H) = 8.8 Hz, 1H; NCOCH), 2.70, 2.65 (2×d, ^3J(H,H) = 6.4 Hz, 1H; NCOCH), 2.13 (s, 3H; COMe), 1.81, 1.80 (2×sp, ^3J(H,H) = 6.8 Hz, 1H; CHMe$_2$), 1.50 (s, 9H; CMe_3), 1.24 (t, ^3J(H,H) = 7.2 Hz, 3H; OCH_2Me), 0.98–0.92 (m, 12H; CHMe, OSi-(CH$_2$$Me$)$_3$), 0.84 (d, ^3J(H,H) = 6.8 Hz, 3H; CHMe), 0.60 ppm (q, ^3J-(H,H) = 8.0 Hz, 6H; OSi(CH_2Me)$_3$); ^{13}C NMR (125 MHz; $CDCl_3$): δ = 172.1, 169.7, 168.3, 148.4, 84.4, 74.6, 74.2, 65.5, 61.2, 61.0, 40.9, 29.2, 27.7, 27.6, 25.0, 21.4, 21.0, 17.1, 13.9, 7.0, 6.6, 6.5, 6.3, 6.1, 4.7 ppm; IR (neat): $\tilde{\nu}$ = 2961–2879 (CH), 1798 (C=O), 1757 (C=O), 1725 cm^{-1} (C=O); MS (ESI): m/z (%): 524 (100) [M^++Na], 424 (79); HRMS (ESI): m/z: cald for $C_{24}H_{43}NO_8SiNa$: 524.2656; found 524.2649 [M^++Na].

Hydroxyl substituted lactam 58: Distilled pyridine (20 mL) and HF•pyridine solution (20 mL) were added to the lactam **57** (850 mg, 1.70 mmol) in distilled THF (100 mL) and the mixture was stirred for 15 min at 0 °C before warming to room temperature. After 2 h $NaHCO_3$ was added to the reaction mixture until pH 7. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (3×150 mL). The combined organic extract was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 10% acetone/PE) to afford the β-hydroxyketone **58** (617 mg, 94%) as a clear oil. ^{1}H NMR(400 MHz, $CDCl_3$): δ = 5.92 (d, ^3J-(H,H) = 3.2 Hz, 1H; CHOAc), 4.90 (t, ^3J(H,H) = 9.0 Hz, 1H; CHOH), 4.23 (q, ^3J(H,H) = 7.2 Hz, 2H; OCH_2Me), 2.92, 2.88 (2×d, ^3J(H,H) = 9.6, $^3J'$(H,H) = 8.8 Hz, 1H; NCOCH), 2.79, 2.75 (2×d, ^3J(H,H) = 8.8, $^3J'$-(H,H) = 9.2 Hz, 1H; NCOCH), 2.16 (s, 3H; COMe), 2.14, 1.52 (2×br s, 1H; OH), 1.86, 1.85 (2×sp, ^3J(H,H) = 6.8 Hz, 1H; CHMe$_2$), 1.51 (s, 9H; CMe_3), 1.27 (t, ^3J(H,H) = 7.2 Hz, 3H; OCH_2Me), 0.98 (d, ^3J(H,H) = 6.8 Hz, 3H; CHMe), 0.89 ppm (d, ^3J(H,H) = 6.8 Hz, 3H; CHMe); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4, 168.9, 148.6, 84.6, 75.6, 73.6, 65.7, 61.8, 37.9, 29.6, 29.0, 27.7, 21.3, 20.9, 17.2, 13.9 ppm; IR (neat): $\tilde{\nu}$ = 3489 (br OH), 2977–2855 (CH), 1790 (C=O), 1754 cm^{-1} (C=O); MS (ESI): m/z (%): 310 (100); HRMS (ESI): m/z: calcd for $C_{18}H_{29}NO_8Na$:410.1791; found 410.1795 [M^++Na].

Methylated lactam 59: *n*BuLi (1.6 M in hexane, 1.56 mL, 2.5 mmol) was added to a solution of distilled diisopropylamine (325 μL, 2.6 mmol) in distilled THF (0.5 mL) at −78 °C and stirred for 15 min. Methyl iodide (600 μL, 9.5 mmol) was then added followed by the dropwise addition of a stirred solution of the alcohol **58** (400 mg, 1.03 mmol) and HMPA (3 mL) in distilled THF (10 mL). The reaction mixture was stirred at −78 °C for 6 h and then quenched with saturated NH_4Cl (3 mL) and stirred for a further 10 min. The reaction mixture was then poured into water (20 mL), extracted with Et_2O (3×50 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 5–10% acetone/PE) to afford the lactam **59** (261 mg, 63%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (d, ^3J(H,H) = 3.6 Hz, 1H; CHOAc), 4.90 (d, ^3J(H,H) = 9.6 Hz, 1H; CHOH), 4.21 (q, ^3J(H,H) = 7.2 Hz, 2H; OCH_2Me), 2.91 (dq, ^3J-(H,H) = 9.6, ^3J(H,H) = 7.6 Hz, 1H; NCOCHMe), 2.16 (s, 3H; COMe),

1.96 (br s, 1H; OH), 1.85–1.82 (m, 1H; C*H*Me$_2$), 1.52 (s, 9H; CMe$_3$), 1.33 (d, ^3J(H,H) = 7.6 Hz, 3H; NCOCH*Me*), 1.27 (t, ^3J(H,H) = 7.2 Hz, 3H; OCH$_2$*Me*), 0.98 (d, ^3J(H,H) = 6.8 Hz, 3H; CH*Me*), 0.86 ppm (d, J = 6.8 Hz, 3H; CH*Me*); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 176.0, 169.6, 169.4, 84.6, 75.5, 74.3, 66.8, 61.9, 40.7, 29.2, 27.8, 21.5, 21.1, 17.2, 13.9, 10.5, 6.7 ppm; IR (neat): $\tilde{\nu}$ = 3491 (br OH), 2977–2882 (CH), 1786 (C=O), 1752 cm^{-1} (C=O); MS (ESI): m/z (%): 424 (100) [M^++Na], 302 (84), 324 (72); HRMS (ESI): m/z: calcd for $C_{19}H_{31}NO_8Na$: 424.1947; found 424.1935 [M^++Na].

Free acid 61: Trifluoroacetic acid (2 mL) was added dropwise to the lactam **59** (250 mg, 0.62 mmol) in distilled CH_2Cl_2 (4.0 mL) at 0 °C, and the mixture was stirred for 10 min and then warmed to room temperature. After 1 h the reaction mixture was evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 25 % acetone/PE) to afford the amine **61** (190 mg, 100 %) as a white solid. M.p. 135–142 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.01 (br s, 1H; N*H*), 5.56 (d, ^3J(H,H) = 6.0 Hz, 1H; C*H*OAc), 4.40–4.29 (m, 2H, OC*H*$_2$Me), 4.26 (d, ^3J(H,H) = 6.0 Hz, 1H; C*H*OH), 2.63 (appqt, ^3J(H,H) = 6.8 Hz, 1H; NCOC*H*Me), 2.10 (s, 3H; CO*Me*), 1.94 (sp, ^3J(H,H) = 6.7 Hz, 1H; C*H*Me$_2$), 1.37 (t, ^3J(H,H) = 7.2, 3H; OCH$_2$*Me*), 1.17 (d, ^3J(H,H) = 8.0 Hz, 3H, NCOCH*Me*), 0.93 ppm (t, ^3J(H,H) = 7.0 Hz, 6H; CH*Me*$_2$); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 179.3, 171.2, 170.0, 78.2, 76.3, 74.7, 62.5, 61.0, 40.8, 30.2, 20.8, 19.6, 18.0, 13.9, 7.8 ppm; IR (neat): $\tilde{\nu}$ = 3321 (br OH), 2980–2884 (CH), 1730 (C=O), 1698 cm^{-1} (C=O); MS (ESI): m/z (%): 324 (100) [M^++Na], 302 (46) [M^++H]; HRMS (ESI): m/z: calcd for $C_{14}H_{24}NO_6$: 302.1604; found 302.1607 [M^++H].

(±)-Lactacystin β-lactone 1: a) Cold (0 °C) aqueous NaOH (0.5 M, 10 mL) was added to lactam **61** (120 mg, 0.40 mmol) and left in the fridge for 6.5 d at 4 °C. Aqueous HCl (1.0 M) was then added dropwise to the reaction mixture until a pH of 1 was obtained, and the mixture was concentrated in vacuo. Hot THF (100 mL) was added to the residue and the insoluble inorganic salt was filtered. The filtrate was concentrated in vacuo to afford crude dihydroxyacid **15** (95 mg) as a white solid that was used in the next step without purification.

b) A suspension of crude dihydroxyacid **15** (20 mg) in CH_2Cl_2 (2 mL) was treated with Et_3N (36 μL, 0.26 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 33 mg, 0.13 mmol) at ambient temperature. After 1 h of stirring at room temperature, water (2 mL) was added to the reaction mixture and extracted with EtOAc (3×5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The solid residue was recrystallised from EtOAc/hexane to give lactacystin β-lactone **1** (14.6 mg, 81 % over two steps). Both ^{1}H and ^{13}C NMR matched those reported in the literature. M.p. 182–183 °C (lit:[36] 185 °C); ^{1}H NMR (500 MHz, [D$_5$]pyridine): δ = 10.37 (s, 1H; NH), 7.76 (br s, 1H; OH), 5.65 (d, ^3J(H,H) = 6.1 Hz, 1H; CHOCO), 4.35–4.31 (m, 1H; OC*H*CH), 3.02 (dq, J_1 = 6.1, J_2 = 7.3 Hz, 1H, C*H*Me), 2.14–2.05 (m, 1H; C*H*(Me)$_2$), 1.45 (d, ^3J(H,H) = 7.6 Hz, 3H; CH*Me*), 1.11 (d, ^3J(H,H) = 6.7 Hz, 3H; CH(*Me*)$_2$), 0.99 ppm (d, ^3J(H,H) = 6.7 Hz, 3H; CH(*Me*)$_2$); ^{13}C NMR (125 MHz, [D$_5$]pyridine): δ = 177.3, 172.4, 80.5, 77.0, 70.6, 38.9, 29.8, 20.4, 16.5, 8.8 ppm; HRMS (Cl, NH$_3$): m/z: calcd for $C_{10}H_{19}N_2O_4$: 231.1344; found, 231.1349 [M^++NH$_4$].

Literature NMR data, see ref. [36].

^{1}H NMR (500 MHz, [D$_5$]pyridine): δ = 10.50 (s, 1H; NH), 7.85 (d, ^3J(H,H) = 6.8 Hz, 1H; OH), 5.68 (d, ^3J(H,H) = 6.1 Hz, 1H; CHOCO), 4.33 (dd, ^3J(H,H) = 3.6, ^3J(H,H) = 6.7 Hz, 1H; OC*H*CH), 3.03 (dq, ^3J(H,H) = 6.1, ^3J(H,H) = 7.4 Hz, 1H; C*H*Me), 2.09 (m, 1H; C*H*(Me)$_2$), 1.45 (d, ^3J(H,H) = 7.5 Hz, 3H; CH*Me*), 1.10 (d, ^3J(H,H) = 6.8 Hz, 3H; CH(*Me*)$_2$), 0.98 (d, ^3J(H,H) = 6.8 Hz, 3H; CH(*Me*)$_2$); ^{13}C NMR (125 MHz, [D$_5$]pyridine): δ = 177.4, 172.4, 80.5, 77.0, 70.6, 38.9, 29.8, 20.4, 16.5, 8.8 ppm.

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