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The 'SuperQuat' (*R*)-4-Phenyl-5,5-Dimethyl Oxazolidin-2-one as an Effective Chiral Auxiliary for Conjugate additions: Asymmetric Synthesis of (-)-Aplysillamide B.§

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Abstract: (*R*)-4-Phenyl-5,5-dimethyl-oxazolidin-2-one, readily available from D-phenylglycine, is shown to be an effective chiral auxiliary for stereoselective conjugate additions to attached α,β-unsaturated *N*-acyl moieties. Its utility is demonstrated by the asymmetric synthesis of the antifungal, antibacterial (-)-Aplysillamide B.

A plethora of chiral auxiliaries is now available to synthetic organic chemists which allows the asymmetric synthesis of a wide range of chiral compounds.[1] Particularly versatile are auxiliaries which control the stereoselectivity of reactions on attached acyl fragments. Three stages are involved in the use of such a chiral auxiliary : attachment of the acyl fragment, stereoselective reaction and finally removal of the chiral acyl fragment. In order to be considered for large scale preparations, each stage should proceed easily and efficiently. The 4-substituted oxazolidin-2-ones **1** developed by Evans have proved to be particularly effective chiral auxiliaries (Figure 1).[2]

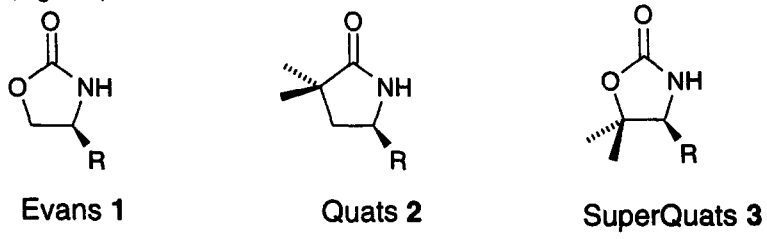

Figure 1

Although these auxiliaries often excel in ease of acylation and the degree of induced stereocontrol their recyclability is often compromised by problematic removal of the acyl fragment.[3] The position of nucleophilic attack on *N*-acyloxazolidin-2-ones is dependent upon both steric and electronic factors (Scheme 1). When the acyl fragment is of low steric bulk, attack occurs most readily at the more electron deficient exocyclic carbonyl group. However as the acyl fragment increases in bulk, particularly at the α-position unwanted endocyclic cleavage at the less hindered carbonyl of the oxazolidin-2-one becomes an increasing problem. In addition to lowering efficiency by reducing product yield this unwanted reaction can also severely complicate product purification. This problem can be ameliorated by using, for example lithium hydroperoxide or benzylthiolate as the nucleophile, which are apparently less susceptible to steric hindrance.[3] The use of these reagents on a large scale is however problematic.

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§ Dedicated to the memory of Professor Sir Derek Barton FRS

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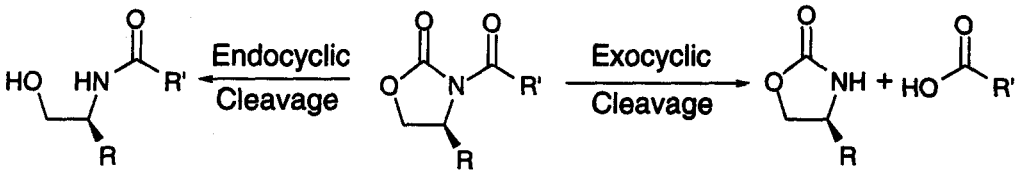
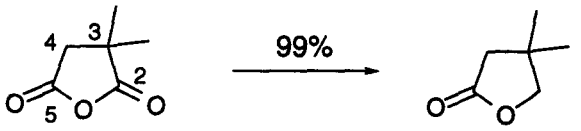


Scheme 1- Exo-*vs* Endocyclic cleavage of *N*-acyl oxazolidin-2-ones.

Herein we describe fully the evolved 'SuperQuat', 4-substituted-5,5-dimethyl-oxazolidin-2-one chiral auxiliaries **3**[4] which are equally effective in terms of stereocontrol and cleavage but are more accessible than our original 'Quats' **2**.[5, 6] We describe their facile synthesis, exocyclic cleavage properties, utility in the conjugate addition reaction and an application to the synthesis of the novel antifungal natural product Aplysillamide B.[7]

It was anticipated that the close similarity to the Evans' oxazolidin-2-ones **1** would allow easy synthesis of the species, and that the *gem*-dimethyl groups would be more effective in hindering nucleophilic attack at the endocyclic carbonyl. The rationale for this was based on the reduction of the anhydride **4** to the lactone **5**, where the carbonyl at C_5 is more effectively shielded by the *gem*-dimethyl groups compared to the carbonyl at C_2 (Scheme 2).[8-10]



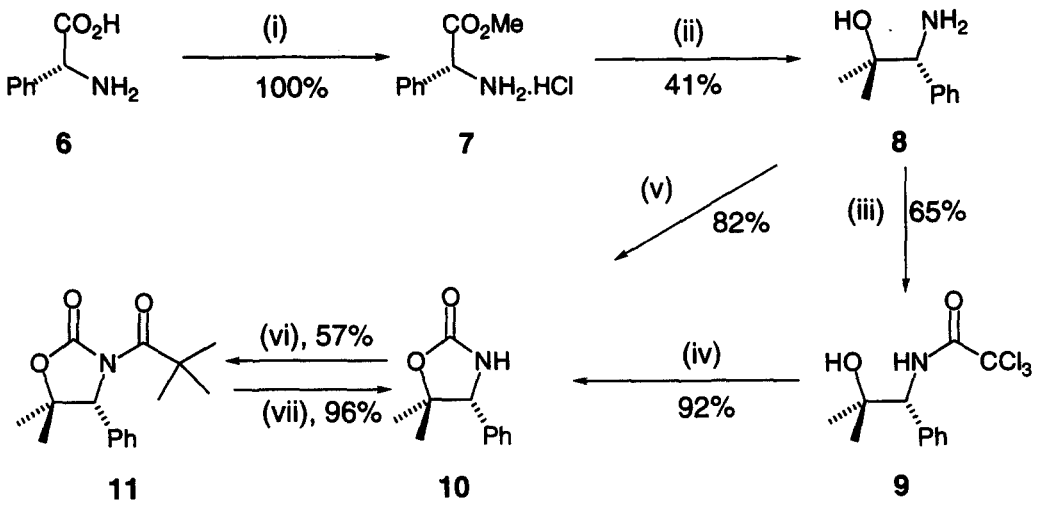
4 **5**

Scheme 2 *Reagent*: $NaBH_4$

This can be understood by considering the Burgi-Dunitz (109°) approach of an incoming nucleophile.[11] The approach to the C_2 carbonyl over the methylene group is less hindered than the approach to the C_5 carbonyl over *gem*-dimethyl groups and so the C_2 carbonyl is thus reduced. This has also been observed for other similar systems.[12] In addition, the *gem*-dimethyl groups in the 'SuperQuat' auxiliary were expected to control the conformation of the substituents at the C_4 position (Figure 1), thus enhancing the face selective shielding of the attached acyl fragments.

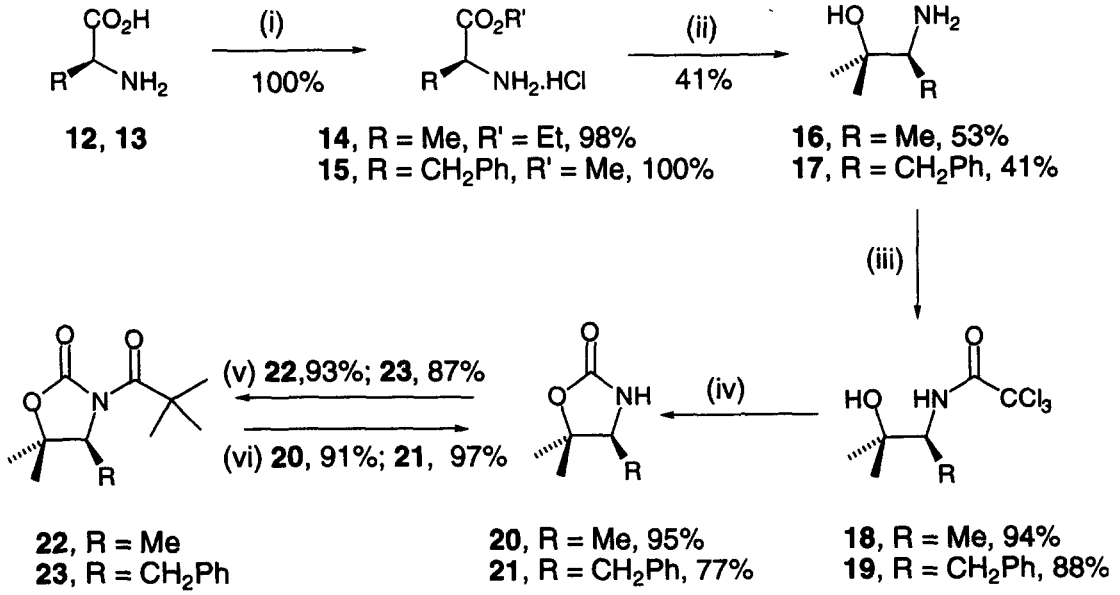
The synthesis of (*R*)-4-phenyl-5,5-dimethyl-oxazolidin-2-one **10** is illustrated in Scheme 3. The D-amino acid **6** was esterified by using thionyl chloride and methanol to give **7** in quantitative yield. Introduction of the *gem*-dimethyl substituents to give amino alcohol **8** was achieved by treatment with excess methyl magnesium iodide, which has been shown not to compromise the stereogenic centre.[13, 14] Ring closure to the oxazolidin-2-one may be effected with a variety of phosgene equivalents such as carbonyl di-imidazole or trichloroacetyl chloride eventually to afford the novel chiral auxiliary **10.** Part of this work has been previously communicated.[4]

Preparation of the bulky *N*-pivaloyl derivative of the 'SuperQuat' oxazolidinone allowed us to examine the exocyclic cleavage selectivity. The *N*-pivaloyl derivative **11** was prepared according to the Evans protocol by deprotonation of the oxazolidin-2-one with butyl lithium at -78°C and quenching with the pivaloyl chloride.[15] This gave the *N*-pivaloyl derivative **11** in an unoptimised 57% yield (Scheme 3), which when treated with LiOH in aq. THF at 0°C gave only exocyclic cleavage regenerating auxiliary **10** in 96% yield.



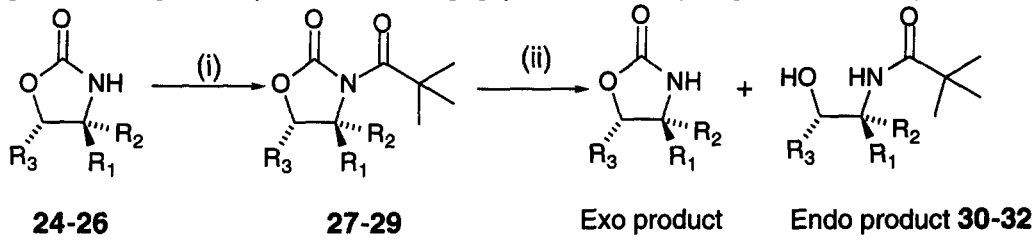
Scheme 3 *Reagents*: (i) $SOCl_2$/MeOH, reflux; (ii) excess MeMgI/Et_2O; (iii) CCl_3COCl/Pyridine/CH_2Cl_2; (iv) K_2CO_3/EtOH, reflux (v) CDI/CH_2Cl_2, reflux; (vi) ^nBuLi/THF, $C(CH_3)_3COCl$; (vii) LiOH/ THF:H_2O (3:1).

The (*S*)-4-methyl and (*S*)-4-benzyl substituted oxazolidin-2-ones **20** and **21** 'SuperQuat' chiral auxiliaries were also prepared in a similar manner to the phenyl 'SuperQuat' **10** and subjected to *N*-acylation and cleavage with lithium hydroxide (Scheme 4). Again hydrolysis gave only exocyclic cleavage regenerating the auxiliaries in excellent yields (91%-97%).



Scheme 4 *Reagents*: (i) $SOCl_2$/MeOH, reflux or HCl/EtOH; (ii) excess MeMgI/Et_2O; (iii) CCl_3COCl/Pyridine/CH_2Cl_2; (iv) K_2CO_3/EtOH, reflux; (v) ^nBuLi/THF, $C(CH_3)_3COCl$; (vi) LiOH/ THF:H_2O (3:1).

The Evans *N*-pivaloyl species **27-29** were also synthesised and subjected to the same cleavage conditions for a comparision of the auxiliaries (Scheme 5, Table 1). In all three cases this provided a mixture of exocyclic and endocyclic products; contrary to the results obtained from the 'SuperQuats'. In some cases the products were purified by column chromatography and these endocyclic products were fully characterised.



Scheme 5 *Reagents*: (i) ^{n}BuLi/THF, $(CH_3)_3CCOCl$; (ii) LiOH/ THF:H_2O (3:1).

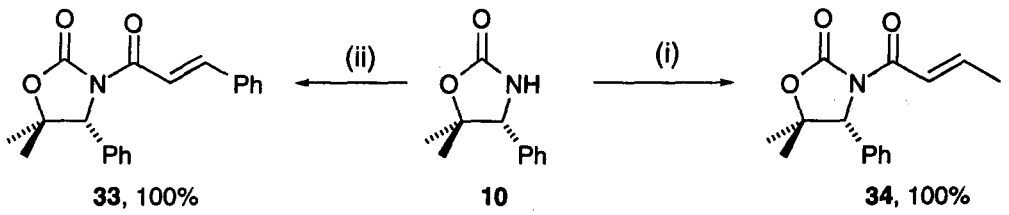
Auxiliary No	R_1	R_2	R_3	Yield of *N*-Pivaloyl	Exo:Endo (Endo Cpd No)
24	H	Me	Ph	92% (27)	94 : 6 (30)
26	CH_2Ph	H	H	54% (28)	83 : 17 (31)
27	Ph	H	H	86% (29)	62 : 38 (32)

Table 1 - Cleavage of Evans *N*-pivaloyl derivatives

Clearly the results indicate that the presence of the *gem*-dimethyl groups promotes complete exocyclic cleavage of sterically demanding *N*-acyl species.

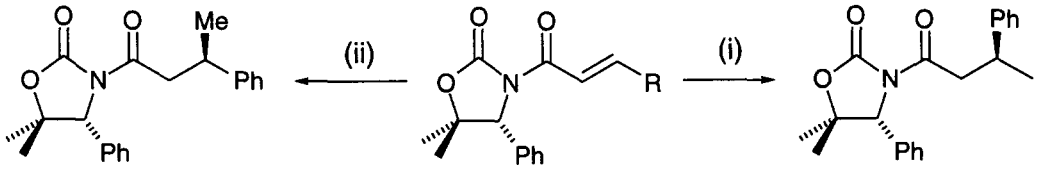
Having prepared and tested these chiral auxiliaries, a study into their utility in the asymmetric conjugate addition was investigated. The phenyl Evans oxazolidin-2-one **26** had been shown to be effective in terms of yield and diastereoselectivity in conjugate addition reactions[16] and a comparison of the benzyl and phenyl auxiliaries indicated the same was true for the 'SuperQuats' and hence auxiliary **10** was investigated fully.

The conjugate additions that were selected would result in the formation of complementary diastereoisomers and hence allow greater confidence in assessing in the measurement of diastereoselectivity. The oxazolidin-2-one **10** was *N*-acylated with crotonyl and hydrocinnamoyl chloride using the Evans protocol to provide the acceptors **33** and **34** in excellent yields (100% and 99% respectively) (Scheme 6).



Scheme 6 *Reagents*: (i) ^{n}BuLi/THF, $CH_3CH{=}CHCOCl$; (ii) ^{n}BuLi/THF, $PhCH{=}CHCOCl$

To solutions of **33** and **34** were added the complementary organocopper reagents, freshly prepared *in situ* (according to the Hruby protocol)[16, 17] *via* the addition of a Grignard reagent to a slurry of the copper bromide dimethylsulphide complex. This provided the complementary diastereoisomers **35** and **36** in 67% and 87% yield respectively (Scheme 7).

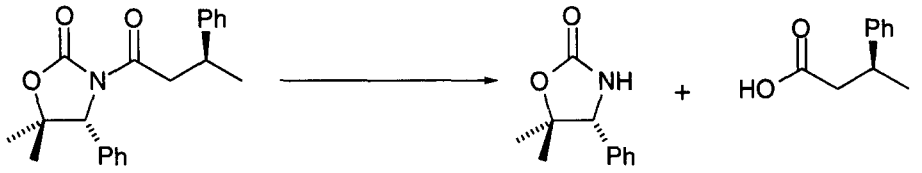


36, 87%, 92% d.e. **33**, R = Ph; **34**, R = Me **35**, 67%, 95% d.e. (recrystallised ≥99% d.e.

Scheme 7 *Reagents*: (i) CuBr/DMS/PhMgBr; (ii) CuBr/DMS/MeMgBr

The diastereoselectivity was measured by integration of the signals arising from the NC*H*Ph signals in the 500 MHz ^{1}H NMR spectrum. The diastereoselectivity was found to be 95% for the nucleophilic phenyl addition. After recrystallisation this gave (3'*S*,4*R*)-**35** with a ≥99% d.e. In the case of nucleophilic methyl addition a 92% d.e. was obtained. The diastereoselectivities in both cases are comparable to those of Hruby and co-workers for the parent Evans oxazolidin-2-ones.[16]

Cleavage of adduct **35** (with ≥99% d.e) with aqueous lithium hydroxide provided the acid (*S*)-**37** (Scheme 8). Determination of the specific rotation was used to confirm the absolute configuration of the newly formed stereogenic centre {$[\alpha]_D^{23}$ = +53.3 (*c* 0.3 in C_6H_6) [lit.,[18] for (*R*)-**37** $[\alpha]_D^{20}$ = -57.0 (*c* 9.8 in C_6H_6)}. The absolute configuration of the product **37** was in accordance with the mechanism postulated by Hruby[17] and thus confirmed the previous assumptions.



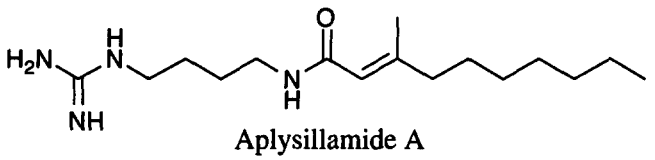
32, ≥99% d.e. **10**, 97% (*S*)-**37**, 80%, 99% e.e.

Scheme 8 *Reagents*: LiOH/ THF:H_2O (3:1)

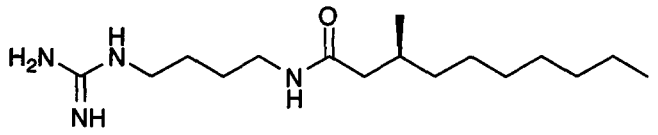
Chiral shift methodology, employing (*R*,*R*)-diphenyldiaminoethane reagent[19] (in comparison with commercially available racemic material) was used to confirm (*S*)-**37** as homochiral and that no racemisation upon cleavage had occurred of the newly formed stereogenic centre in substrate (*S*)-**37** in the conjugate adduct **35**.

Asymmetric synthesis of Aplysillamide B

Aplysillamides A and B were isolated by Kobayashi *et al* from the Okinawan marine sponge *Psammaplysilla purea*.[7] These new guanidine alkaloids show antifungal and antibacterial activity. The absolute configuration at C_3 of Aplysillamide B was established by synthesis from methyl (2*R*)-3-hydroxy-2-methylpropionate in 8 steps in 6% overall yield.[7]



Aplysillamide A

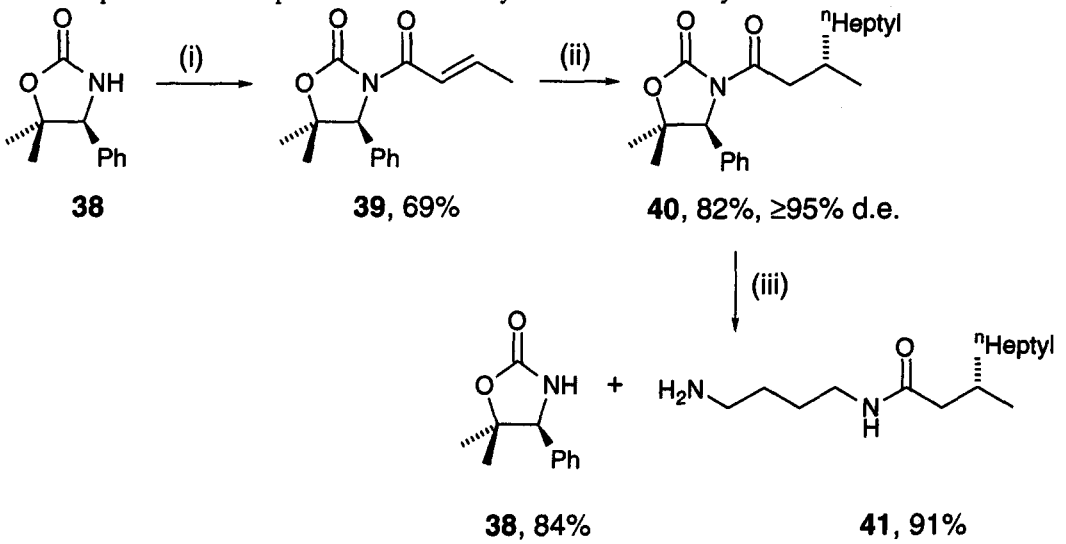


Aplysillamide B

Figure 2

Aplysillamide B was chosen to exploit the conjugate addition methodology developed above, and because the enhanced cleavage properties of the 'SuperQuat' auxiliary would allow the direct synthesis of an amide.

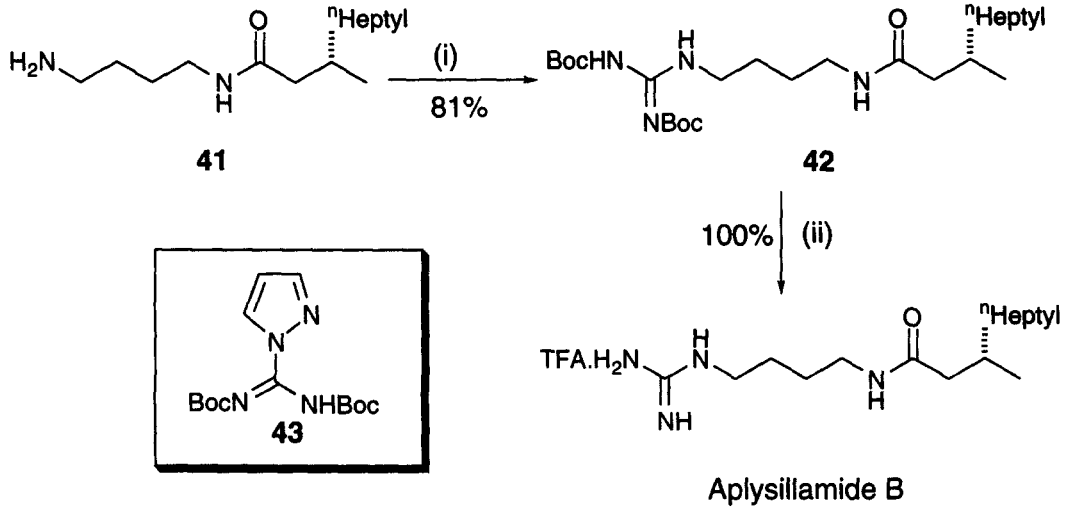
The phenyl 'SuperQuat' **38** (prepared in the same manner as its enantiomer **10**) was *N*-acylated under standard conditions to give **39** (Scheme 9). Treatment of conjugate acceptor **39** with freshly prepared ^{n}heptyl magnesium bromide and $CuBr.S(CH_3)_2$ according to the standard procedure of Hruby[16] afforded the species **40** with a tentative ≥95% d.e. assigned from the examination of the crude ^{1}H NMR. The absolute configuration of the newly created stereogenic centre was assigned as *S*, based on the model reactions above. Purification provided the compound **40** as a white crystalline solid in 82% yield.



Scheme 9 *Reagent*: (i) ^{n}BuLi/THF, $CH_3CH{=}CHCOCl$; (ii) CuBr/DMS/^{n}HeptMgBr; (iii) $NH_2(CH_2)_4NH_2$

The formation of amino amide **41** (Scheme 9) was achieved by addition of 1,4-diaminobutane as solvent and reagent and stirring for 2 hours. Purification was uncomplicated since the 1,4-diaminobutane has a relatively low boiling point and so could be removed by evaporation. The second stage of purification was achieved *via* a simple acidic extraction thus giving after neutralisation the amino amide (*S*)-**41** in 91% yield and the auxiliary **38** in 84% yield.

The final step proved to be the most difficult in the synthetic sequence. There are a multitude of methods for guanidylation of an amine.[20-22] Direct guanidylation of the substrate provided purification problems due to the amphipathic properties of the molecule i.e. polar 'head' group (guanidine) and lipophilic 'tail' (alkyl chain). Fortunately, this problem was circumvented by the use of a BOC protected guanidalating agent **43** which was prepared according to Bernatowicz and co-workers[23] and added to the amino amide. This provided the novel *bis*-BOC protected natural product (*S*)-**42** with improved physical properties, thus making purification simple (81% yield, Scheme 10).



Scheme 10 *Reagents* : (i) **43**/MeOH, DIPEA; (ii) TFA.

The final BOC deprotection step was achieved by adding trifluoroacetic acid at room temperature and stirring for thirty minutes. This gave the TFA salt of the natural product in a quantitative yield.

The natural product appears[24] only to have been isolated and synthesised as the TFA salt and so a comparison of the ^{1}H NMR, ^{13}C/DEPT NMR, mass spectral and specific rotation measurement confirmed {$[\alpha]_D^{25}$ = -2.2 (*c* 0.5 in MeOH) lit.,[7] for (*S*)-Aplysillamide B $[\alpha]_D^{21}$ = -2.4 (*c* 0.1 in MeOH)} that Aplysillamide B had been synthesised. The overall yield for the sequence is 61% for the four steps.

Conclusions

We have synthesised 4-substituted-5,5-dimethyl oxazolidin-2-one chiral auxiliaries **10**, **20**, **21**. Cleavage of an attached acyl fragment occurs with LiOH exclusively by attack of the exocyclic carbonyl. The 4-phenyl auxiliary **10** has also been used to perform highly diastereoselective conjugate addition reactions and the methodology applied to asymmetric synthesis of Aplysillamide B as its trifluoroacetate salt.

Acknowledgements.

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Experimental

All reactions described as being carried out under nitrogen were performed using standard vacuum line techniques using glassware that was flame-dried and subsequently cooled *in vacuo*.

Reactions described as being performed at -78°C were cooled by means of an acetone/dry ice bath, and those at 0°C by an ice bath. *N*-Acylations of the auxiliaries were performed according to the Evans protocol.[2] Characterisation data is quoted for the major diastereoisomer in stereoselective reactions unless otherwise stated. Melting points were recorded using either a Gallenkamp capillary apparatus or a Leica Galen III heated stage apparatus, and are uncorrected. Solvents that were required to be anhydrous were dried as follows: THF, toluene and diethyl ether were distilled under nitrogen from sodium benzophenone ketyl; dichloromethane was distilled under nitrogen from calcium hydride; methanol was distilled under nitrogen from magnesium methoxide. Petrol (the fraction of light petroleum boiling in the range 40-60°C) was redistilled before use. All other solvents were used as supplied.

Butyllithium was used as a 1.4-1.6M solution in hexanes. The molarity was estimated by titration against diphenylacetic acid. Methylmagnesium iodide was prepared as a solution in diethyl ether. Amines (diisopropylamine and triethylamine) were distilled from and stored over potassium hydroxide pellets. Acid chlorides were freshly distilled before use. All other reagents were used as supplied, without further purification (unless otherwise stated).

Flash column chromatography was performed on silica gel (Kieselgel 60). TLC was performed on Merck plates, either aluminium sheets coated with 0.2mm silica gel 60 F_{254}, or glass plates coated with 0.25mm silica gel 60 F_{254}. Plates were visualised by a variety of techniques: UV light (254 nm), iodine, or *dodeca*-molybdophosphoric acid in ethanol (followed by heating of the TLC plate).

^{1}H NMR spectra were recorded at 200MHz on Bruker AC200 or Varian Gemini 200 instruments; at 300MHz on a Bruker WH300 instrument and at 500MHz on Bruker AM500 or AMX500 instruments. ^{13}C spectra were recorded at 50.3MHz on Bruker AC200 or Varian Gemini 200 instruments and at 125.7MHz on Bruker AM500 or AMX500 instruments. The spectra obtained on the AM500 and AMX500 machines were recorded by Mrs. E. McGuinness. All spectra were referenced internally using the solvent signal. Chemical shifts (δ) are quoted in ppm downfield from tetramethylsilane. Coupling constants (J) are quoted in Hz. First order approximations are employed throughout. The multiplicities of the ^{13}C signals were determined by DEPT editing.

Mass spectra of relatively volatile, non-polar materials were obtained on a V.G. TRIO-1 GCMS instrument using chemical ionisation (CI, NH_3). Other mass spectra were obtained by Dr. R.T. Aplin or Mr. R. Proctor, chemical ionisation (CI, NH_3) and electrospray mass spectra being recorded on a V.G. BIO-Q instrument, and atmospheric pressure chemical ionisation (APCI) mass spectra being recorded on a Platform instrument.

IR spectra were obtained on a Perkin-Elmer 1750 FT spectrometer. Solution spectra were recorded in solvents were stated using 1.0 mm sodium chloride cells. Distinct and selected diagnostic peaks only are quoted.

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell, solutions being prepared in 1.0 cm^3 or 2.0 cm^3 volumetric flasks. Specific rotations are given in units of 10^{-1} deg cm^2 g^{-1}.

All yields quoted refer to isolated material. Reaction diastereoselectivities were estimated by peak integration in the ^{1}H NMR spectrum of the crude reaction products by comparision of signals from complementary

diastereoisomers were possible. Enantiomeric excesses were measured by the use of chiral shift reagents (the reagents are stated appropriately).

Preparation of D-Phenylglycine methyl ester hydrochloride 7.[25, 26] To a stirred solution of D-phenylglycine **6** (20.0 g, 132 mmol) in MeOH (100 cm^3) at -10°C was added thionyl chloride (10.6 cm^3, 146 mmol) and the solution heated at reflux for 2 h. After concentration *in vacuo* the compound was recrystallised from a MeOH-Et_2O mixture giving the ester **7** (26.6 g, 100%) as a solid; δ_H (D_2O; 200 MHz) 3.57 (3H, s, CH_3), 4.57 (obscured br s, NH_2), 5.07 (1H, s, CH), 7.27-7.30 (5H, m, ArCH).

Preparation of (*R*)-1-Amino-2-methyl-1-phenyl-2-propanol 8. D-Phenylglycine methyl ester hydrochloride **7** (5.00 g, 24.83 mmol) was added in portions, over 15 mins, to a solution of methylmagnesium iodide [prepared from methyl iodide (9.3 cm^3, 148.97 mmol) and magnesium (3.57 g, 148.97 mmol) in Et_2O (190 cm^3)] and stirred for 3 h. Saturated aqueous NH_4Cl was added dropwise with vigorous stirring. The suspension formed was filtered through celite, the organic layer was separated and dried with Na_2SO_4. Concentration *in vacuo* gave a colourless oil. The aqueous layer was made alkaline by addition of aqueous ammonia. The product was extracted with Et_2O, dried with Na_2SO_4 and concentrated *in vacuo* to give an oil. The oily residues were combined and vacuum distilled giving amino alcohol **8** (1.66 g, 41%) as a solid which was recrystallised from 40-60 petrol-ether; mp 49°C; $[\alpha]_D^{25}$ = -23.2 (*c* 1 in $CHCl_3$); (Found: C, 72.8; H, 9.05; N, 8.30. $C_{10}H_{15}NO$ requires C, 72.7; H, 9.15; N, 8.5 %); δ_H (200 MHz; $CDCl_3$) 1.04 [3H, s, $C(CH_3)_3$], 1.21 [3H, s, $C(CH_3)_3$], 2.16 (3H, apparent s, NH_2 and OH), 3.39 (1H, s, C*H*Ph), 7.27-7.34 (5H, m, ArCH); δ_C (125 MHz; $CDCl_3$) 24.69 [$C(CH_3)_2$], 27.55 [$C(CH_3)_2$], 64.54 (CH), 72.26 [$C(CH_3)_2$], 127.48 (ArCH), 128.05 (ArCH), 128.23 (ArCH), 142.82 (ArC); *m/z* (CI^+, NH_3) 166 (MH^+).

Preparation of *N*-[(1*R*)-2-Hydroxy-2-methyl-1-phenylpropyl]-2,2,2-trichloroethanamide 9. To a solution of amino alcohol **8** (1.41 g, 8.56 mmol) at 0°C in pyridine (24 cm^3) was added trichloroacetyl chloride (1.1 cm^3, 9.41 mmol). After stirring for 10 mins, the reaction was left to stir overnight at room temperature. The reaction was quenched with the addition of sat. aq. NaCl solution, extracted with CH_2Cl_2 and the combined organic extracts washed with HCl (1 N), and dried over $MgSO_4$. Concentration *in vacuo* and purification by flash column chromatography using 30% EtOAc/40-60 pet. ether as eluent furnished amide **9** (1.78 g, 65%) as a solid which was recrystallised from ether/40-60 pet. ether; mp 97°C; ν_{max} ($CHCl_3$)/cm^{-1} 1716 (CO); $[\alpha]_D^{24}$ = -55.5 (*c* 1 in $CHCl_3$); (Found: C, 46.4; H, 4.3; N, 4.5. $C_{12}H_{14}Cl_3NO_2$ requires C, 46.40; H, 4.5; N, 4.5%); δ_H (200 MHz; $CDCl_3$) 1.06 [3H, s, $C(CH_3)_2$], 1.39 [3H, s, $C(CH_3)_2$], 1.94 (1H, s, OH), 4.70 (1H, d, *J* 8.3, C*H*NH), 7.29-7.39 (5H, m, ArCH), 7.79 (1H, d, *J* 8.3, NH); δ_C (125 MHz; $CDCl_3$) 27.70 [$C(CH_3)_2$], 27.86 [$C(CH_3)_2$], 63.06 (CH), 72.52 [$C(CH_3)_2$], 92.97 (CCl_3), 128.13 (ArCH), 128.35 (ArCH), 128.71 (ArCH), 137.88 (ArC), 161.51 (CO); *m/z* (CI^+, NH_3) 310 (M^+).

Preparation of (*R*)-4-Phenyl-5,5-dimethyloxazolidin-2-one 10. To a solution of amide **9** (1.655 g, 5.33 mmol) in EtOH (140 cm^3) was added potassium carbonate (0.369 g, 2.67 mmol) and the solution heated at reflux for 30 mins. After concentration *in vacuo* CH_2Cl_2 was added and the mixture was washed with sat. aq. NaCl solution. The combined organic extracts were concentrated *in vacuo* giving a crude solid which was purified by recrystallisation from EtOAc/pentane giving oxazolidin-2-one **10** (0.939 g, 92%); mp 149°C; ν_{max} ($CHCl_3$)/cm^{-1} 1753 (CO); $[\alpha]_D^{25}$ = -77.6 (*c* 0.5 in $CHCl_3$); (Found: C, 69.3; H, 7.05; N, 7.4. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%); δ_H (200 MHz; $CDCl_3$) 0.93 [3H, s, $C(CH_3)_2$], 1.61 [3H, s, $C(CH_3)_2$], 4.66 (1H, s, C*H*Ph), 6.25 (1H, s, NH), 7.25-7.44 (5H, m, ArCH); δ_C (125 MHz; $CDCl_3$) 23.53

[C(CH_3)$_2$], 28.04 [C(CH_3)$_2$], 65.93 (CH), 84.63 [C(CH_3)$_2$], 126.67 (ArCH), 128.72 (ArCH), 128.93 (ArCH), 137.16 (ArC), 159.75 (CO); *m/z* (CI^+, NH_3) 192 (MH^+).

Alternative preparation of (*R*)-4-Phenyl-5,5-dimethyloxazolidin-2-one 10. To a solution of amino alcohol **8** (1.30 g, 7.89 mmol) in CH_2Cl_2 (100 cm^3) was added carbonyl diimidazole (1.53 g, 9.47 mmol) and heated at reflux for 2 h. The reaction was quenched with HCl (1 N) and the product extracted repeatedly with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$. After concentration *in vacuo*, the residue was purified by flash column chromatography using 40% EtOAc/40-60 pet. ether as eluent which furnishing oxazolidin-2-one **10** (1.24 g, 82%) which was identical to that previously prepared.

General procedure for acylation of auxiliaries.: The substrate was dissolved and cooled to -78°C. ^{n}BuLi as a 1.3-1.6 M solution in hexane (1.01 eq.) was added dropwise and the mixture stirred at this temperature for 30 mins. The freshly distilled acid chloride (1.1 eq.) was added and the mixture left for 30 mins at this temperature and then at room temperature (followed by thin layer chromatography until complete). The reaction mixture was poured into pH 7 phosphate buffer solution and the product extracted with CH_2Cl_2 and washed with sat. aq. $NaHCO_3$ solution. The combined organic extracts were washed with sat. aq. NaCl solution and dried over $MgSO_4$. After concentration *in vacuo*, the residue was purified by recrystallisation or flash column chromatography.

General procedure for cleavage of N-acyl auxiliaries with LiOH. The substrate was dissolved in a mixture of THF/H_2O (3:1; v/v) and cooled to 0°C. Solid lithium hydroxide monohydrate (2.0-2.5 equivalents) were added and the mixture was stirred at 0°C for 1 h and warmed to room temperature (the reaction was followed by thin layer chromatography). An aqueous solution of sodium hydrogen carbonate was added and the auxiliary extracted with CH_2Cl_2. The combined organic extracts were washed with sat. aq. NaCl solution and dried over $MgSO_4$. Evaporation of solvent left the auxiliary.

Preparation of (*R*)-3-(2',2'-Dimethyl-1'oxopropyl)-4-phenyl-5,5-dimethyloxazolidin-2-one 11. The auxiliary **10** (0.155 g, 0.81 mmol) in THF (9 cm^3) at -78°C was treated with ^{n}BuLi (1.0 M, 0.819 cm^3, 0.821 mmol) and pivaloyl chloride (0.110 cm^3, 0.89 mmol) for 30 mins and at room temperature for 3 h with work-up and flash column chromatography using 20% EtOAc/40-60 pet. ether as eluent furnished the *N*-acyl derivative **11** (0.128 g, 57%) as an oil; ν_{max} ($CHCl_3$)/cm^{-1} 1687 and 1775; $[\alpha]_D^{25}$ = -60.3 (*c* 0.4 in $CHCl_3$); (Found: C, 69.9; H, 7.8; N, 4.9. $C_{16}H_{21}NO_3$ requires C, 69.80; H, 7.7; N, 5.1%); δ_H ($CDCl_3$; 300 MHz) 0.98 [3H, s, C(CH_3)$_2$], 1.39 [9H, s, C(CH_3)$_3$], 1.60 [3H, s, C(CH_3)$_2$], 5.11(1H, s, C*H*Ph), 7.14-7.37 (5H, m, ArCH); δ_C (125 MHz; $CDCl_3$) 23.66 [C(CH_3)$_2$], 26.20 [C(CH_3)$_3$], 28.68 [C(CH_3)$_2$], 41.63 [C(CH_3)$_3$], 69.03 (CH), 81.80 [C(CH_3)$_2$], 126.10 (ArCH), 128.44 (ArCH), 128.85 (ArCH), 136.80 (ArC), 153.50 (CO), 178.00 (CO); *m/z* (CI^+, NH_3) 276 (MH^+).

Cleavage of (*R*)-3-(2',2'-Dimethyl-1'oxopropyl)-4-phenyl-5,5-dimethyloxazolidin-2-one 11. The *N*-pivaloyl derivative **11** (1.08 g, 5.63 mmol) was dissolved in THF/H_2O (3:1; v/v) (18 cm^3) with lithium hydroxide monohydrate (0.345 g, 8.22 mmol). Work-up furnished the auxiliary **10** (0.717 g, 96%) which was identical to that previously prepared.

Preparation of L-Alanine ethyl ester hydrochloride 14.[27] HCl gas was bubbled into a suspension of L-alanine **12** (100 g, 1.12 mol) in dry EtOH (800 cm^3) until saturated and the solution was heated at reflux for 2 h. After concentration *in vacuo* the crude material was recrystallised from EtOH-Et_2O giving the ester **14** (168 g, 98%) as a white solid; δ_H (200 MHz; D_2O) 1.11 (3H, t, *J* 7.2, CH_2CH_3) 1.37 (3H, d, *J* 7.3, $CHCH_3$),

4.03 (1H, q, *J* 7.3, C*H*CH$_3$), 4.09 (2H, q, *J* 7.2, C*H*$_2$CH$_3$), 4.16 (obscured br s, NH$_2$); δ_C (50 MHz; D$_2$O) 13.98 (*C*H$_3$CH$_2$), 15.90 (CH*C*H$_3$), 49.65 (CH), 64.29 (CH$_2$), 171.57 (CO).

Preparation of (*S*)-3-Amino-2-methylbutan-2-ol hydrochloride 16.[28] L-Alanine ethyl ester hydrochloride **14** (3.00 g, 19.53 mmol) was added in portions, over 15 mins, to a solution of methylmagnesium iodide [prepared from methyl iodide (7.3 cm^3, 117.2 mmol) and magnesium (3.00 g, 117.2 mmol) in Et$_2$O (114 cm^3)] and heated at reflux for 30 mins. After addition of H$_2$O, the ethereal solution was decanted, and to the aqueous layer was added sodium hydroxide (15%). This mixture was filtered through celite, and the crude product was obtained by distillation in steam, and neutralisation of the distillate with HCl (1 N) followed by evaporation. The compound was purified by precipitation from hot butan-1-ol with ether, giving the amino alcohol **16** (1.45 g, 53%) as a white solid; δ_H (200 MHz; D$_2$O) 1.19 [3H, s, (C*H*$_3$)$_2$COH], 1.24 (3H, d, *J* 7.0, C*H*$_3$CH), 1.28 [3H, s, (C*H*$_3$)$_2$COH], 4.78 (obscured br s, NH$_2$); δ_C (50 MHz; D$_2$O) 13.14 (*C*H$_3$CH), 21.68 [C(*C*H$_3$)$_2$], 25.90 [C(*C*H$_3$)$_2$], 55.85 (CH), 70.67 (C).

Preparation of *N*-[(*S*)-2-Hydroxy-1,2-dimethylpropyl]-2,2,2-trichloroethanamide 18. To a solution of amino alcohol **16** (1.19 g, 8.56 mmol) at 0°C in pyridine (24 cm^3) was added trichloroacetyl chloride (1.00 cm^3, 9.41 mmol). After stirring for 10 mins, the reaction was left to stir overnight at room temperature. The reaction was quenched with the addition of sat. aq. NaCl solution, extracted with CH$_2$Cl$_2$ and the combined organic extracts washed with HCl (1 N), and dried over MgSO$_4$. Concentration *in vacuo* and purification by flash column chromatography using 30% EtOAc/40-60 pet. ether as eluent to furnished the amide **18** (1.99 g, 94%) as an oil; ν_{max} (CH$_2$Cl$_2$)/cm^{-1} 1713 (CO); $[\alpha]_D^{24}$ = +6.3 (*c* 1.2 in CHCl3); (Found: C, 33.7; H, 5.1; N, 5.7. C$_7$H$_{12}$Cl$_3$NO$_2$ requires C, 33.8; H, 4.9; N, 5.6%); δ_H (200 MHz; CDCl$_3$) 1.21 (3H, d, *J* 6.8, C*H*$_3$CH), 1.25 [3H, s, C(CH$_3$)$_2$], 1.26 [3H, s, C(CH$_3$)$_2$], 2.31 (1H, s, OH), 3.82 (1H, dq, *J* 6.8 and 8.8, C*H*CH$_3$NH), 7.10 (1H, br d, *J* 6.4, NH); δ_C (125 MHz; CDCl$_3$) 14.89 (*C*H$_3$CH), 26.68 [C(*C*H$_3$)$_2$], 27.56 [C(*C*H$_3$)$_2$], 55.19 (CH), 72.01 [*C*(CH$_3$)$_2$], 92.82 (CCl$_3$), 161.56 (CO); *m/z* (CI$^+$, NH$_3$) 248 (M$^+$).

Preparation of (*S*)- 4,5,5-Trimethyloxazolidin-2-one 20. To a solution of amide **18** (1.96 g, 7.92 mmol) in EtOH (140 cm^3) was added potassium carbonate (0.547 g, 3.96 mmol) and the solution heated at reflux for 30 mins. After concentration *in vacuo* CH$_2$Cl$_2$ was added and the mixture was washed with sat. aq. NaCl solution. The combined organic extracts were concentrated *in vacuo* to give a crude crystalline solid which was purified by recrystallisation from toluene/60-80 pet. ether to give oxazolidin-2-one **20** (0.968 g, 95%) as a solid; mp 60°C; ν_{max} (CDCl$_3$)/cm^{-1} 1758 (CO); $[\alpha]_D^{24}$ = +1.2 (*c* 2 in CHCl$_3$); (Found: C, 56.1; H, 8.85; N, 10.8. C$_6$H$_{11}$NO$_2$ requires C, 55.80; H, 8.6; N, 10.8%); δ_H (500 MHz; CDCl$_3$) 1.12 (3H, d, *J* 6.6, CHC*H*$_3$), 1.27 [3H, s, C(CH$_3$)$_2$], 1.39 [3H, s, C(CH$_3$)$_2$], 3.59 (1H, q, *J* 6.6, C*H*CH$_3$), 7.27 (1H, s, NH); δ_C (125 MHz; CDCl$_3$) 16.07 (CH*C*H$_3$), 21.46 [C(*C*H$_3$)$_2$], 27.14 [C(*C*H$_3$)$_2$], 57.12 (CH), 83.50 [*C*(CH$_3$)$_2$], 159.00 (CO); *m/z* (CI$^+$, NH$_3$) 130 (MH$^+$).

Preparation of L-Phenylalanine methyl ester hydrochloride 15.[29] To a stirred solution of L-phenylalanine **13** (40.0 g, 242 mmol) in MeOH (193 cm^3) at -10°C was added thionyl chloride (19.5 cm^3, 266 mmol) and the solution heated at reflux for 2 h. After concentration *in vacuo* the crude material was recrystallised from a MeOH-Et$_2$O mixture giving the ester **15** (52.2 g, 100%) as a solid; δ_H (D$_2$O; 200 MHz) 2.95-3.18 (2H, m, C*H*$_2$CH), 3.62 (3H, s, CH$_3$), 4.21 (1H, dd, *J* 6.1 and 7.4, CH$_2$C*H*), 4.59 (obscured br s, NH$_2$), 7.06-7.27 (5H, m, ArCH).

Preparation of (*S*)-3-Amino-2-methyl-4-phenyl-butan-2-ol 17.[30] L-Phenylalanine methyl ester hydrochloride **15** (8.00 g, 37.09 mmol) was added in portions, over 15 mins, to a solution of methylmagnesium iodide [prepared from methyl iodide (13.8 cm^3, 222.6 mmol) and magnesium (5.34 g, 222.6 mmol) in Et_2O (304 cm^3)] and heated at reflux for 6 h. A saturated solution of NH_4Cl (19.8 g) in H_2O (70 cm^3) was added dropwise with vigorous stirring. The insoluble product was filtered off through celite, and the organic layer was separated and dried with Na_2SO_4. Concentration *in vacuo* gave a colourless oil. The aqueous layer was made alkaline by addition of aqueous ammonia. The product was extracted with Et_2O, dried with Na_2SO_4 and concentrated *in vacuo*. The oily residues were combined and vacuum distilled (bp 160°C/0.1 mm) giving the amino alcohol **17** (2.69 g, 41%) as an oil; δ_H (200 MHz, $CDCl_3$) 1.21 [3H, s, $C(CH_3)_2$], 1.31 [3H, s, $C(CH_3)_2$], 1.91 (1H, s, OH), 2.16 (2H, s, NH_2), 2.26 (1H, dd, *J* 11.2 and *J* 13.3, CH_2Ph), 2.80 (1H, dd, *J* 2.7 and *J* 11.2, CH_2Ph), 3.02 (1H, dd, *J* 2.7 and *J* 13.3, $CHCH_2$), 7.18-7.37 (5H, m, ArCH).

Preparation of *N*-[(*S*)-1-Benzyl-2-hydroxy-2-methylpropyl]-2,2,2-trichloroethanamide 19. To a solution of amino alcohol **17** (2.57 g, 14.37 mmol) at 0°C in pyridine (50 cm^3) was added trichloroacetyl chloride (1.9 cm^3, 17.25 mmol). After stirring for 10 mins, the reaction was left to stir overnight at room temperature. The reaction was quenched with the addition of sat. aq. NaCl solution, extracted with CH_2Cl_2 and the combined organic extracts washed with HCl (1 N), and dried over $MgSO_4$. Concentration *in vacuo* and purification by flash column chromatography using 30% EtOAc/40-60 pet. ether as eluent gave the amide **19** (4.09 g, 88%) as a solid; mp 88°C; ν_{max} ($CDCl_3$)/cm^{-1} 1713; $[\alpha]_D^{24}$ = -26.8 (*c* 0.8 in $CHCl_3$); (Found: C, 48.3; H, 4.6; N, 4.1. $C_{13}H_{16}Cl_3NO_2$ requires C, 48.2; H, 5.0; N, 4.3%) δ_H (300 MHz; $CDCl_3$) 1.32 [3H, s, $C(CH_3)_2$], 1.40 [3H, s, $C(CH_3)_2$], 1.91 (1H, s, OH), 2.75 (1H, dd, *J* 10.9 and 14.2, CH_2Ph), 3.20 (1H, dd, *J* 4.0 and 14.2, CH_2Ph), 4.04-4.13 (1H, m, $CHCH_2$), 6.80 (1H, br d, *J* 9.3, NH) 7.17-7.30 (5H, m , ArCH); δ_C (125 MHz; $CDCl_3$) 27.18 [$C(CH_3)_2$], 27.74 [$C(CH_3)_2$], 35.43 (CH_2), 60.25 (CH), 72.92 [$C(CH_3)_2$], 93.00 (CCl_3), 126.89 (ArCH), 128.78 (ArCH), 129.33 (ArCH), 137.66 (ArC), 162.07 (CO); *m/z* (CI^+, NH_3) 324 (M^+).

Preparation of (*S*)-4-Benzyl-5,5-dimethyloxazolidin-2-one 21. To a solution of amide **19** (4.09 g, 12.63 mmol) in EtOH (280 cm^3) was added potassium carbonate (0.872 g, 6.32 mmol) and the solution heated at reflux for 30 mins. After concentration *in vacuo* CH_2Cl_2 was added and the mixture was washed with sat. aq. NaCl solution. The combined organic extracts were concentrated *in vacuo* to give a crude solid which was purified by recrystallisation in Et_2O/40-60 pet. ether giving oxazolidin-2-one **21** (2.00 g, 77%) as a solid; mp 59°C; ν_{max} ($CHCl_3$)/cm^{-1} 1753 (CO); $[\alpha]_D^{25}$ = -103.5 (*c* 0.6 in $CHCl_3$); (Found: C, 70.5; H, 7.1; N, 6.5. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%); δ_H (200 MHz; $CDCl_3$) 1.45 [6H, s, $C(CH_3)_2$], 2.64-2.88 (2H, m, CH_2Ph), 3.72 (1H, dd, *J* 4.5 and 10.9, $CHCH_2$), 5.45 (1H, s, NH), 7.18-7.38 (5H, m, ArCH); δ_C (125 MHz; $CDCl_3$) 21.82 [$C(CH_3)_2$], 27.42 [$C(CH_3)_2$], 36.99 (CH_2), 63.08 (CH), 83.28 [$C(CH_3)_2$], 127.32 (ArCH), 129.08 (ArCH), 129.22 (ArCH), 137.19 (ArC), 158.47 (CO); *m/z* (CI^+, NH_3) 206 (MH^+).

Preparation of (*S*)-3-(2',2'-Dimethyl-1'-oxopropyl)-4,5,5-trimethyloxazolidin-2-one 22. The auxiliary **20** (0.180 g, 1.40 mmol) in THF (3 cm^3) at -78°C was treated with ^nBuLi (1.4 M, 1 cm^3, 1.41 mmol) and pivaloyl chloride (0.190 cm^3, 1.55 mmol) for 30 mins and at room temperature for 1 h with work-up and recrystallisation at *ca* -10°C from 60-80 pet. ether furnished the *N*-acyl derivative **22** (0.276 g, 93%) as a solid; ν_{max} (CH_2Cl_2)/cm^{-1} 1683 (CCO) and 1775 (OCO); $[\alpha]_D^{24}$ = +51.3 (*c* 1 in $CHCl_3$); (Found: C, 62.25; H, 9.1; N, 6.45. $C_{11}H_{19}NO_3$ requires C, 61.95; H, 9.0; N, 6.6%); δ_H ($CDCl_3$; 300 MHz) 1.20 (3H, d, *J* 6.5, CH_3CH),

1.31 [9H, s, $C(CH_3)_3$], 1.33 [3H, s, $C(CH_3)_2$], 1.37 [3H, s, $C(CH_3)_2$], 4.11(1H, q, *J* 6.5, $CHCH_3$); δ_C (50 MHz; $CDCl_3$) 14.33 (CH_3CH), 21.41 [$C(CH_3)_2$], 26.31 [$C(CH_3)_3$], 27.22 [$C(CH_3)_2$], 41.60 [$C(CH_3)_3$], 60.92 (CH), 81.01 [$C(CH_3)_2$], 151.75 (CO), 179.08 (CO); *m/z* (CI^+, NH_3) 214 (MH^+).

Preparation of (*S*)-3-(2',2'-Dimethyl-1'oxopropyl)-4-benzyl-5,5-dimethyloxazolidin-2-one 23. The auxiliary **21** (0.085 g, 0.415 mmol) in THF (2 cm^3) at -78°C was treated with ^nBuLi (1.6 M, 0.262 cm^3, 0.419 mmol) and pivaloyl chloride (0.056 cm^3, 0.456 mmol) for 30 mins and at room temperature for 2 h with work-up and flash column chromatography using 30% EtOAc/40-60 pet. ether furnished the *N*-acyl species **23** (0.104 g, 87%) as an oil; ν_{max} ($CDCl_3$)/cm^{-1} 1687 (CCO) and 1742 (OCO); (Found: C, 70.4; H, 7.9; N, 4.9. $C_{17}H_{23}NO_3$ requires C, 70.5; H, 8.0; N, 4.8%); δ_H ($CDCl_3$; 300 MHz) 1.30 [3H, s, $C(CH_3)_2$], 1.34 [9H, s, $C(CH_3)_3$], 1.35 [3H, s, $C(CH_3)_2$], 2.86 (1H, dd, *J* 9.3 and 14.2, CH_2Ph), 3.05 (1H, dd, *J* 4.2 and 14.2, CH_2Ph), 4.53 (1H, dd, *J* 4.2 and 9.3, $CHCH_2$), 7.18-7.28 (5H, m, ArCH); δ_C (125 MHz; $CDCl_3$) 22.10 [$C(CH_3)_2$], 26.29 [$C(CH_3)_3$], 28.07 [$C(CH_3)_2$], 35.24 (CH_2), 41.68 [$C(CH_3)_3$], 65.47 (CH), 81.80 [$C(CH_3)_2$], 126.94 (ArCH), 128.76 (ArCH), 129.38 (ArCH), 137.19 (ArC), 152.03 (CO), 179.49 (CO); *m/z* (CI^+, NH_3) 290 (MH^+).

Cleavage of (*S*)-3-(2',2'-Dimethyl-1'oxopropyl)-4,5,5-trimethyloxazolidin-2-one 22. The *N*-pivaloyl derivative **22** (0.170 g, 0.80 mmol) was dissolved in THF/H_2O (3:1; v/v) (4 cm^3) with lithium hydroxide monohydrate (0.084 g, 2.0 mmol). Work-up furnished the auxiliary **20** (0.094 g, 91%) which was identical to that previously prepared.

Cleavage of (*S*)-3-(2',2'-Dimethyl-1'oxopropyl)-4-benzyl-5,5-dimethyloxazolidin-2-one 23. The *N*-pivaloyl derivative **23** (3.00 g, 10.38 mmol) was dissolved in THF/H_2O (3:1; v/v) (52 cm^3) with lithium hydroxide monohydrate (0.915 g, 21.80 mmol). Work-up furnished the auxiliary **21** (2.07 g, 97%) which was identical to that previously prepared.

Preparation of (4*R*, 5*S*)-3-(2',2'-Dimethyl-1'oxopropyl)-4-methyl-5-phenyl-oxazolidin-2-one 27. The auxiliary **24** (3.00 g, 16.95 mmol) in THF (80 cm^3) at -78°C was treated with ^nBuLi (1.48 M, 11.6 cm^3, 17.19 mmol) and pivaloyl chloride (2.23 cm^3, 18.64 mmol) for 30 mins and at room temperature for 2 h with work-up and flash column chromatography using 15% EtOAc/40-60 pet. ether furnished the *N*-acyl species **27** (4.058 g, 92%) as a solid; mp 74°C; ν_{max} ($CHCl_3$)/cm^{-1} 1685 (CCO) and 1780 (OCO); $[\alpha]_D^{25}$= +33.2 (*c* 0.6 in $CHCl_3$); δ_H ($CDCl_3$; 200 MHz) 0.78 (3H, d, *J* 6.5, CH_3CH), 1.31 [9H, s, $C(CH_3)_3$], 4.67-4.74 (1H, m, $CHCH_3$), 5.59 (1H, d, *J* 7.1, CHPh), 7.19-7.32 (5H, m, ArCH); δ_C (125 MHz; $CDCl_3$) 14.18 ($CHCH_3$), 26.23 [$C(CH_3)_3$], 41.44 [$C(CH_3)_3$], 56.78 (CHN), 78.69 (CHO), 125.59 (ArCH), 128.49 (ArCH), 133.67 (ArC), 151.83 (CO), 177.97 (CO); (Found: MH^+ 262.1452. $C_{15}H_{20}NO_3$ requires MH^+ 262.1443).

Preparation of (*S*)-3-(2',2'-Dimethyl-1'-oxopropyl)-4-benzyl-oxazolidin-2-one 28. The auxiliary **25** (1.00 g, 5.65 mmol) in THF (20 cm^3) at -78°C was treated with ^nBuLi (1.48M, 3.86 cm^3, 5.71 mmol) and pivaloyl chloride (0.765 cm^3, 6.22 mmol) for 30 mins and at room temperature for 2 h with work-up and flash column chromatography using 15% EtOAc/40-60 pet. ether furnished the *N*-acyl species **28** (0.794 g, 54 %) as a solid; mp. 86°C; $[\alpha]_D^{21}$= +43.4 (*c* 1 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1}: 1682 (CCO) and 1790 (OCO); (Found: C, 68.8; H, 7.4; N, 5.2. $C_{15}H_{19}NO_3$ requires C, 68.9; H, 7.3; N, 5.4%); δ_H (200 MHz, $CDCl_3$) 1.40 [9H, s, $C(CH_3)_3$], 2.76 (1H, dd, *J* 9.6 and *J* 13.2, CH_2Ph), 3.23 (1H, dd, *J* 3.2 and *J* 13.2, CH_2Ph), 4.09-4.24 (2H, m, OCH_2), 4.64-4.76 (1H, m, CH), 7.20-7.38 (5H, m, Ph); δ_C (125 MHz, $CDCl_3$) 26.34 [$C(CH_3)_3$], 37.82 (CH_2),

41.68 [$C(CH_3)_3$], 57.40 (CH), 66.15 (OCH_2), 127.26 (ArCH), 128.87 (ArCH), 129.47 (ArCH), 135.56 (ArC), 152.31 (CO), 178.46 (CO); *m/z* (CI^+, NH_3) 262 (MH^+).

Preparation of (*S*)-3-(2',2'-Dimethyl-1'oxopropyl)-4-phenyl-oxazolidin-2-one 29. The auxiliary **26** (0.500 g, 3.07 mmol) in THF (10 cm^3) at -78°C was treated with ^nBuLi (1.48 M, 2.09 cm^3, 3.10 mmol) and pivaloyl chloride (0.416 cm^3, 3.37 mmol) for 30 mins and at room temperature for 2 h with work-up and flash column chromatography using 15% EtOAc/40-60 pet. ether furnished the *N*-acyl species **29** (0.654 g, 86%) as a solid; mp 82-83°C; ν_{max} ($CHCl_3$)/cm^{-1} 1693 (CCO) and 1790 (OCO); $[\alpha]_D^{25}$= +84.9 (*c* 1 in $CHCl_3$); (Found: C, 67.7; H, 7.3; N, 5.6. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.9; N, 5.7%); δ_H ($CDCl_3$; 200 MHz) 1.34 [9H, s, $C(CH_3)_3$], 4.15 (1H, dd, *J* 4.7 and *J* 8.7, CH_2CHPh), 4.64 (1H, apparent t, *J* 8.7, CH_2CHPh), 5.46 (1H, dd, *J* 4.7 and *J* 8.7, CH_2CHPh), 7.24-7.41 (5H, m, ArCH); δ_C (50 MHz; $CDCl_3$) 26.21 [$C(CH_3)_3$], 41.61 [$C(CH_3)_2$], 59.67 (CH_2), 69.84 (CH), 125.57 (ArCH), 128.45 (ArCH), 129.10 (ArCH), 139.42 (ArC), 152.77 (CO), 178.13 (CO); *m/z* (CI^+, NH_3) 248 (MH^+).

Cleavage of (4*R*, 5*S*)-3-(2',2'-Dimethyl-1'oxopropyl)-4-methyl-5-phenyl-oxazolidin-2-one 27. The *N*-pivaloyl derivative **27** (0.822 g, 3.15 mmol) was dissolved in THF/H_2O (3:1; v/v) (16 cm^3) with lithium hydroxide monohydrate (0.277 g, 6.6 mmol). Work-up and purification by flash column chromatography using 30% EtOAc/40-60 pet. ether furnished the auxiliary **24** (0.377 g, 61%) and endocyclic cleaved product **30** (0.030 g) [auxiliary:endocyclic cleaved product (94 : 6) by ^1H NMR of crude reaction mixture]; data for endocyclic cleaved product (2*S*', 1*R*')-*N*-(2'-hydroxy-1'-methyl-2'-phenylethyl)-2,2-dimethylpropanamide; mp 60°C; ν_{max} ($CDCl_3$)/cm^{-1} 1641 (CO); $[\alpha]_D^{25}$= +87.5 (*c* 0.2, $CHCl_3$); δ_H ($CDCl_3$; 200 MHz) 1.02 (3H, d, *J* 7.0, CH_3CH), 1.18, [9H, s, $C(CH_3)_3$], 4.20-4.36 (2H, m, $CHCH_3$ and OH), 4.80 (1H, d, *J* 2.8, $CHCHCH_3$), 5.69 (1H, br d, *J* 6.1, NH), 7.23-7.29 (5H, m, ArCH): δ_C (125 MHz; $CDCl_3$) 15.11 ($CHCH_3$), 27.47 [$C(CH_3)_3$], 38.59 [$C(CH_3)_3$], (50.87 ($CHCH_3$), 76.97 ($CHCHCH_3$), 125.89 (ArCH), 126.43 (ArCH), 127.47 (ArCH), 128.02 (ArCH), 128.46 (ArCH), 140.64 (ArC), 179.51 (CO); (Found: MH^+ 236.1645. $C_{14}H_{22}NO_2$ requires MH^+ 236.1651).

Cleavage of (*S*)-3-(2',2'-Dimethyl-1'oxopropyl)-4-benzyl-oxazolidin-2-one 28. The *N*-pivaloyl derivative **28** (3.00 g, 11.49 mmol) was dissolved in THF/H_2O (3:1; v/v) (52 cm^3) with lithium hydroxide monohydrate (1.01 g, 24.12 mmol). Work-up gave an inseparable mixture of auxiliary **25** and endocyclic cleaved product **31** (83 : 17 by ^1H NMR of crude reaction mixture) selected data for endocyclic cleaved product *N*-[(1*S*)-1-benzyl-2-hydroxyethyl)-2,2-dimethylpropanamide; δ_H ($CDCl_3$; 200 MHz) 1.10 [9H, s, $(CH_3)_3C$], 2.77-2.99 (2H, obscured m, CH_2Ph), 4.02-4.16 (2H, obscured m, CH_2CH), 4.34-4.44 (1H, m, CH_2CH), 6.15 (1H, br d, NH), 7.14-7.37 (5H, m, ArCH).

Cleavage of (*S*)-3-(2',2'-Dimethyl-1'oxopropyl)-4-phenyl-oxazolidin-2-one 29. The *N*-pivaloyl derivative **29** (0.953 g, 3.86 mmol) was dissolved in THF/H_2O (3:1; v/v) (20 cm^3) with lithium hydroxide monohydrate (0.340 g, 8.10 mmol). Work-up and purification by flash column chromatography using 30% EtOAc/40-60 pet. ether furnished the auxiliary **26** (0.345 g, 55%) and endocyclic cleaved product **32** (0.253 g). [auxiliary:endocyclic cleaved product (62 : 38) by ^1H NMR of crude reaction mixture]; data for endocyclic cleaved product *N*-[(1*S*)-2-hydroxy-1-phenylethyl)-2,2-dimethylpropanamide; mp 147-148°C; ν_{max} ($CDCl_3$)/cm^{-1} 1652 (CO); $[\alpha]_D^{21}$= +62.3 (*c* 1 in $CHCl_3$); δ_H ($CDCl_3$; 200 MHz) 1.25 [9H, s, $C(CH_3)_2$], 2.87 (1H, t, *J* 6.0, OH), 3.89 (2H, m, CH_2CH), 5.01-5.07 (1H, m, CH_2CH), 6.34 (1H, s, NH), 7.28-7.43 (5H, m, ArCH); δ_C (125 MHz; $CDCl_3$) 27.41 [$C(CH_3)_3$], 38.69 [$C(CH_3)_3$], 55.59 (CH), 66.51 (CH_2), 126.63 (ArCH),

127.86 (ArCH), 128.96 (ArCH), 139.51 (ArC), 179.44 (CO); (Found: MH^+ 222.1501. $C_{13}H_{20}NO_2$ requires MH^+ 222.1494).

Preparation of (4*R*)-3-[2'(E)-Butenoyl]-4-phenyl-5,5-dimethyloxazolidin-2-one 34. The auxiliary **10** (0.416 g, 2.19 mmol) in THF (10 cm^3) at -78°C was treated with ^nBuLi (1.3 M, 1.70 cm^3, 2.20 mmol) and crotonyl chloride (0.230 cm^3, 2.40 mmol) for 30 mins and at room temperature for 2 h. Standard work-up and flash column chromatography using 20% EtOAc/40-60 pet. ether as eluent furnished the *N*-acyl derivative **34** (0.564 g, 100%) as a solid; mp 104°C; ν_{max} ($CDCl_3$)/cm^{-1} 1687 (CCO) and 1769 (OCO); $[\alpha]_D^{24}$= -82.6 (*c* 1 in $CHCl_3$); (Found: C, 69.60 ; H, 6.6 ; N, 5.35. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.40%); δ_H ($CDCl_3$; 200 MHz) 0.99 [3H, s, $C(CH_3)_2$], 1.60 [3H, s, $C(CH_3)_2$], 1.93 (3H, d, *J*5.4, CH_3CHCH), 5.13 (1H, s, C*H*Ph), 7.02-7.40 (7H, m, ArCH and CH_3CH=C*H* and CH_3CH=CH); δ_C (125 MHz; $CDCl_3$) 18.39 (CH_3CH=CH), 23.60 [$C(CH_3)_2$], 28.81 [$C(CH_3)_2$], 67.09 (*C*HPh), 82.87 [$C(CH_3)_2$], 122.14 (CH_3CH=*C*H), 126.08 (ArCH), 126.19 (ArCH), 128.71 (ArCH), 129.08 (ArCH), 136.61 (ArC), 147.31 (CH_3CH=CH), 153.50 (CO), 165.07 (CO); *m/z* (CI^+, NH_3) 260 (M^++1).

Preparation of (4*R*)-3-[3'-Phenyl-2'(E)-propenoyl]-4-phenyl-5,5-dimethyloxazolidin-2-one 33. The auxiliary **10** (0.300 g, 1.57 mmol) in THF (10 cm^3) at -78°C was treated with BuLi (1.5 M, 1.10 cm^3, 1.59 mmol) and cinnamoyl chloride (0.230 cm^3, 1.73 mmol) for 10 mins and at room temperature for 2 h. Standard work-up and flash column chromatography using 20% EtOAc/40-60 pet. ether as eluent furnished the *N*-acyl derivative **33** (0.503 g, 99%) as a solid; recrystallised EtOAc/40-60 pet. ether; mp 149°C; ν_{max} ($CDCl_3$)/cm^{-1} 1682 (CCO) and 1771 (OCO); $[\alpha]_D^{26}$= +26.0 (*c* 1 in $CHCl_3$); (Found: C, 74.8; H, 5.9; N, 4.3. $C_{20}H_{19}NO_3$ requires C, 74.75; H, 6.0; N, 4.4%); δ_H ($CDCl_3$; 200 MHz) 1.04 [3H, s, $C(CH_3)_2$], 1.65 [3H, s, $C(CH_3)_2$], 5.24 (1H, s, C*H*Ph), 7.20-7.64 (10H, m, ArCH), 7.80 (1H, d, *J*15.8, C*H*=CHPh), 8.07 (1H, d, *J* 15.8, CH=C*H*Ph); δ_C (125 MHz; $CDCl_3$) 23.78 [$C(CH_3)_2$], 28.99 [$C(CH_3)_2$], 67.24 (*C*HPh), 82.47 [$C(CH_3)_2$], 117.17 (CH=*C*HPh), 126.37 (ArCH), 128.48 (ArCH), 128.90 (ArCH), 130.70 (ArCH), 134.54 (ArC), 136.38 (ArC), 146.53 (*C*H=CHPh), 153.33 (CO), 165.04 (CO); *m/z* (CI^+, NH_3) 322 (MH^+).

Preparation of (3'*S*,4*R*)-3-(1'-Oxobutyl-3'-phenyl)-4-phenyl-5,5-dimethyloxazolidin-2-one 35. To copper bromide dimethylsulfide complex (0.227 g, 1.12 mmol) and $(CH_3)_2S$ (2 cm^3) at -40°C in THF (4 cm^3) was added phenylmagnesium bromide (1M as a solution in THF, 2.25 cm^3, 2.24 mmol). The reaction was left to stir for 10 mins, warmed to -15°C and the *N*-acyl derivative **34** (0.193 g, 0.75 mmol) dissolved in THF (3 cm^3) added. After 15 mins the reaction was quenched with saturated aqueous NH_4Cl (3 cm^3) and the solvents evaporated. H_2O/EtOAc (1:3; v/v) were added and the resulting suspension filtered through glass wool. The aqueous layer was separated and the organic was washed with 10% aqueous NH_4OH (twice), H_2O, and sat. aq. NaCl solution and then dried over $MgSO_4$. After concentration *in vacuo* the diastereoisomeric excess was found to be 95% by integration of the signals due to NC*H*Ph on a 500 MHz NMR spectrum. Purification with flash column chromatography using 20% EtOAc/40-60 pet. ether as eluent gave the Michael adduct **35** (0.168 g, 67%) as a solid; this was recrystallised as a single diastereoisomer from EtOAc/pentane; mp 114°C; ν_{max} (CH_2Cl_2)/cm^{-1} 1704 (CCO) and 1775 (OCO); $[\alpha]_D^{28}$= -28.8 (*c* 1 in $CHCl_3$); (Found: C, 74.9; H, 6.8; N, 4.1. $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.9; N, 4.15%); δ_H ($CDCl_3$; 200 MHz) 0.96 [3H, s, $C(CH_3)_2$], 1.30 (3H, d, *J* 6.8, $CHCH_3$), 1.60 [3H, s, $C(CH_3)_2$], 3.14 (1H, dd, *J* 7.7 and 15.1, CH_2CHPh), 3.24-3.43 (1H, m, CH_2CHPh), 3.54 (1H, d, *J* 8.4 and 15.1, CH_2CHPh), 5.06 (1H, s, NC*H*Ph), 6.94-7.31 (10H, m, ArCH); δ_C (125 MHz; $CDCl_3$) 21.88 ($CHCH_3$), 23.71 [$C(CH_3)_2$], 28.94 [$C(CH_3)_2$], 36.06 ($CHCH_3$), 43.22 (CH_2), 66.98

(NCHPh), 82.17 [C(CH$_3$)$_2$], 126.05 (ArCH), 126.30 (ArCH), 126.90 (ArCH), 128.34 (ArCH), 128.44 (ArCH), 128.75 (ArCH), 136.01 (ArC), 145.56 (ArC), 153.10 (CO), 171.78 (CO); *m/z* (CI$^+$, NH$_3$) 338 (MH$^+$).

Preparation of (3'*R*,4*R*)-3-(1'-Oxobutyl-3'-phenyl)-4-phenyl-5,5-dimethyloxazolidin-2-one 36. To copper bromide dimethylsulfide complex (0.176 g, 0.86 mmol) and (CH$_3$)$_2$S (2 cm^3) at -40°C in THF (4 cm^3) was added methylmagnesium bromide (3M as a solution in THF, 0.580 cm^3, 1.73 mmol). The reaction was left to stir for 10 mins, warmed to -15°C and *N*-acyl derivative **33** (0.185 g, 0.58 mmol) dissolved in THF (3 cm^3) added. After 1 h the reaction was quenched with saturated aqueous NH$_4$Cl (3 cm^3) and the solvents evaporated. H$_2$O/EtOAc (1:3; v/v) were added and the resulting suspension filtered through glass wool. The aqueous layer was separated and the organic was washed with 10% aqueous NH$_4$OH (twice), H$_2$O, and sat. aq. NaCl solution and then dried over MgSO$_4$. After concentration *in vacuo* the diastereoisomeric excess was found to be 92% by integration of the signals due to NC*H*Ph on a 500 Mhz NMR. Purification with flash column chromatography using 20% EtOAc/40-60 pet. ether as eluent gave the Michael adduct **36** (0.169 g, 87%) as a solid; mp 112°C; ν_{max} (CH$_2$Cl$_2$)/cm^{-1} 1704 (CCO) and 1774 (OCO); (Found: C, 74.7; H, 6.7; N, 4.1. C$_{21}$H$_{23}$NO$_3$ requires C, 74.75; H, 6.9; N, 4.15%); δ_H (CDCl$_3$; 200 MHz) 0.98 [3H, s, C(CH$_3$)$_2$], 1.32 (3H, d, *J* 6.9, CHC*H*$_3$), 1.43 [3H, s, C(CH$_3$)$_2$], 3.18 (1H, dd, *J* 6.1 and 15.6, C*H*$_2$CHPh), 3.33-3.43 (1H, m, CH$_2$C*H*Ph), 3.60 (1H, d, *J* 8.1 and 15.6, C*H*$_2$CHPh), 4.98 (1H, s, NC*H*Ph), 7.12-7.39 (10H, m, ArCH); δ_C (125 MHz; CDCl$_3$) 22.45 (CH*C*H$_3$), 23.61 [C(*C*H$_3$)$_2$], 28.66 [C(*C*H$_3$)$_2$], 36.30 (*C*HCH$_3$), 43.13 (CH$_2$), 66.93 (N*C*HPh), 82.36 [*C*(CH$_3$)$_2$], 126.41 (ArCH), 127.05 (ArCH), 128.51 (ArCH), 128.58 (ArCH), 128.44 (ArCH), 136.34 (ArC), 145.68 (ArC), 153.27 (CO), 171.72 (CO); *m/z* (CI$^+$, NH$_3$) 339 (MH$^+$).

Cleavage of (3'*S*,4*R*)-3-(1'-Oxobutyl-3'-phenyl)-4-phenyl-5,5-dimethyloxazolidin-2-one 35. The *N*-acyl derivative **35** (0.110 g, 0.40 mmol) (with 99% d.e) dissolved in THF/H$_2$O (3:1; v/v) (4 cm^3) with lithium hydroxide monohydrate (0.034 g, 0.81 mmol) furnished the auxiliary **10** (0.074 g, 97%) and the acid **37** (0.052 g, 80%). The enantiomeric excess of the acid **37** was ≥99% (elucidated by the use of a chiral shift reagent (*R,R*)-diphenyldiaminoethane. $[\alpha]_D^{23}$ = +53.3 (*c* 0.3 in C$_6$H$_6$) [lit.,[18] for (*R*)-**37** $[\alpha]_D^{20}$ = -57.0 (*c* 9.8 in C$_6$H$_6$)]; δ_H (200 MHz; CDCl$_3$) 1.32 (3H, d, *J* 7.0, C*H*$_3$CH), 2.52-2.75 (2H, m, CH$_2$CO), 3.22-3.33 (1H, m, CHPh), 7.18-7.35 (5H, m, ArCH).

Preparation of (4*S*)-3-[2(E)-Butenoyl]-4-phenyl-5,5-dimethyloxazolidin-2-one 39. The auxiliary **38** (5.0 g, 26.2 mmol) in THF (150 cm^3) at -78°C was treated with ^{n}BuLi (1.44 M, 19.1 cm^3, 27.5 mmol) and crotonyl chloride (2.76 cm^3, 29.9 mmol) for 30 mins and at room temperature for 2 h. Standard work-up and flash column chromatography using 20% EtOAc/40-60 pet. ether as eluent furnished the *N*-acyl derivative **39** (4.59 g, 69%) as a solid with ^{1}H NMR spectrum identical to the previously prepared **34**; $[\alpha]_D^{23}$ = +84.2 (*c* 1.1 in CHCl3).

Preparation of (3'*S*,4*S*)-3-(3'-Methyl-1'-Oxodecyl)-4-phenyl-5,5-dimethyloxazolidin-2-one 40. To copper bromide dimethylsulfide complex (5.40 g, 26.59 mmol) and (CH$_3$)$_2$S (25 cm^3) at -40°C in THF (4 cm^3) was added ^{n}heptylMgBr (0.54M as a solution in THF, 98.2 cm^3, 53.18 mmol). The reaction was left to stir for 10 mins, warmed to -15°C and *N*-acyl oxazolidinone **39** (4.591 g, 17.73 mmol) dissolved in THF (20 cm^3) added. After 30 mins the reaction was quenched with saturated aqueous NH$_4$Cl (100 cm^3) and the solvents evaporated. H$_2$O/EtOAc (1:3; v/v) were added. The aqueous layer was separated and the organic was washed with 10% aqueous NH$_4$OH (twice), H$_2$O, and sat. aq. NaCl solution and then dried over MgSO$_4$. After

concentration *in vacuo* and purification with flash column chromatography using 20% EtOAc/40-60 pet. ether as eluent gave the Michael adduct **40** (5.219 g, 82%) as a solid; mp 33°C; ν_{max} ($CDCl_3$)/cm^{-1} 1703 (CCO) and 1774 (OCO); $[\alpha]_D^{23}$ = +37.7 (*c* 1.1 in CH_2Cl_2); (Found: C, 73.3; H, 9.6; N, 3.8. $C_{22}H_{33}NO_3$ requires C, 73.50; H, 9.25; N, 3.90 %); δ_H (200 MHz; $CDCl_3$) 0.88 (6H, m, CH_3CH and CH_3), 0.99 [3H, s, $(CH_3)_2C$], 1.25 [12H, app. s, $(CH_2)_6$], 1.59 [3H, s, $(CH_3)_2C$], 2.02 (1H, m, $CHCH_3$), 2.75 (1H, dd, *J* 8.3 and 15.9, $COCH_2CH$), 3.25 (1H, dd, *J* 5.6 and 15.9, $COCH_2CH$), 5.09 (1H, s, CHPh), 7.12-7.40 (5H, m, ArCH); δ_C (50 MHz; $CDCl_3$) 14.11 (CH_3CH_2), 19.57 ($CHCH_3$), 22.65 (CH_3CH_2), 23.65 [$C(CH_3)_2$], 26.86 ($CH_3CH_2CH_2$), 28.97 ($CHCH_3$), 29.27 [$CH_3(CH_2)_2CH_2$], 29.73 [$CH_3(CH_2)_3CH_2$ and $C(CH_3)_2$], 31.84 [$CH_3(CH_2)_4CH_2$], 36.85 [$CH_3(CH_2)_5CH_2$], 42.63 ($COCHCH_2$), 66.92 ($NCHCH_3$), 82.14 [$C(CH_3)_2$], 126.32 (ArCH), 128.5 (ArCH), 128.8 (ArCH), 136.49 (ArC), 153.18 (CO), 172.65 (CO); (Found: MH^+, 360.2546. $C_{22}H_{34}NO_3$ requires MH^+ 360.2539).

Preparation of (3*S*)-*N*-(4-Aminobutyl)-3-methyldecanamide 41. To the Michael adduct **40** (2.00 g, 5.56 mmol) was added 1,4 diaminobutane (12.82 cm^3, 127.78 mmol) and reaction mixture left to stir for 24 h. After concentration *in vacuo* Et_2O saturated with HCl was added and the solid filtered off and basified with a saturated solution potassium carbonate and amine extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated *in vacuo* to give amide **41** (1.294, 91%) as a solid; mp 60-62°C; ν_{max} (Nujol)/cm^{-1} 1636 (CO); $[\alpha]_D^{23}$ = -3.3 (*c* 0.6 in $CHCl_3$); δ_H (200 MHz; $CDCl_3$) 0.84-0.93 (6H, m, CH_3CH and CH_3CH_2), 1.27 [12H, m, $(CH_2)_6$], 1.43-1.63 (6H, m, NH_2 and $NH_2CH_2CH_2CH_2CH_2NH$), 1.84-2.19 (3H, m, $COCH_2CHCH_3$), 2.70-2.76 (2H, m, $NH_2CH_2CH_2CH_2CH_2NH$), 3.22-3.31 (2H, m, $NH_2CH_2CH_2CH_2CH_2NH$), 5.90 (1H, s, NH); δ_C (50 MHz; $CDCl_3$) 13.98 (CH_2CH_3), 19.53 ($CHCH_3$), 22.55 (CH_3CH_2), 26.87 ($CH_3CH_2CH_2$), 27.02 [$CH_3(CH_2)_2CH_2$], 29.23 [$CH_3(CH_2)_3CH_2$], 29.68 [$CH_3(CH_2)_4CH_2$], 30.70 [$CH_3(CH_2)_5CH_2$ and CH), 31.78 ($NH_2CH_2CH_2CH_2CH_2NH$), 36.81 ($NH_2CH_2CH_2CH_2CH_2NH$), 39.17 ($COCHCH_2$), 41.65 ($NH_2CH_2CH_2CH_2CH_2NH$), 44.70 ($NH_2CH_2CH_2CH_2CH_2NH$), 172.98 (CO); (Found: MH^+, 257.2597 $C_{15}H_{33}N_2O$ requires MH^+ 257.2593); The residue was evaporated giving the auxiliary **38** (0.887g, 84%) which was identical to that previously prepared.

Preparation of (3*S*)-*N*,*N*'-bis-*tert*Butoxycarbonyl-(4-guanadinobutyl)-3-methyldecanamide 42. To a solution of amide **41** (0.211 g, 0.831 mmol) in MeOH (2 cm^3) was added N, N'-bis-*tert*butoxycarbonyl-1H-pyrazole-1-carboxamide **43** (0.259 g, 0.831 mmol), and DIEA (0.142 cm^3, 0.831 mmol). The reaction was stirred for 2 h at room temperature. Work up, concentration *in vacuo* and purification by column chromatography using 50% EtOAc/40-60 pet. ether as eluent furnished guanadino amide **42** (0.335g, 81%) as an oil; ν_{max} ($CDCl_3$)/cm^{-1} 1719 (CO); $[\alpha]_D^{23}$ = +0.6 (*c* 0.33 in CH_2Cl_2); (Found: C, 62.3; H, 10.0; N, 11.0. $C_{26}H_{50}N_4O_5$ requires C, 62.6; H, 10.1; N, 11.2%); δ_H (200 MHz; $CDCl_3$) 0.73-0.81 (6H, m, CH_3CH and CH_3CH_2), 1.15 [12H, m, $(CH_2)_6$], 1.39 [18H, s, $(CH_3)_3CO$ and $(CH_3)_3CO$] 1.46 (4H, m, $CH_2CH_2CH_2NHCO$ and $CH_2CH_2CH_2NHCO$), 1.82-2.11 (3H, m, $COCH_2CHCH_3$ and $COCH_2CHCH_3$), 3.18-3.32 (4H, m, $NH_2CH_2CH_2$ and CH_2CH_2NHCO), 6.38 (1H, t, *J* 5.7, NHCO) 8.27 (1H, t, *J* 4.9, NHCNHBoc), 11.41 (1H, s, NHBoc); δ_C (50 MHz; $CDCl_3$) 13.93 (CH_3CH_2), 19.48 ($CHCH_3$), 22.50 (CH_3CH_2), 26.29 ($CH_3CH_2CH_2$), 26.53 [$CH_3(CH_2)_2CH_2$], 26.83 [$CH_3(CH_2)_3CH_2$], 27.89 [$NHCO_2C(CH_3)_3$], 28.14 [$NCO_2C(CH_3)_3$], 29.17 [$CH_3(CH_2)_4CH_2$], 29.64 [$CH_3(CH_2)_5CH_2$], 30.58 (CH), 31.71 (CH_2CH_2NHCO), 36.77 ($NH_2CH_2CH_2$), 38.78 ($COCH_2CH$), 40.17 ($N{=}CNHCH_2CH_2$), 44.48 (CH_2NHCO), 79.30 [$C(CH_3)_3$], 83.18 [$C(CH_3)_3$], 153.49 (C=N), 156.50 (CO), 163.76 (CO), 173.11 (CO); *m/z* (CI^+, NH_3) 499 (MH^+).

Preparation of Aplysillamide B.[7] To guanadino amide **42** (0.100 g, 0.202 mmol) in CH_2Cl_2 was added trifluoroacetic acid (2 cm^3) at room temperature and the reaction was stirred for 30 min. Concentration *in vacuo* gave (-)-Aplysillamide B (0.060 g, 100%) as an oil; δ_H (200 MHz; d_6-DMSO) 0.74-0.84 (6H, m, CH_3 and CH_3), 1.07-1.48 [16H, m, $(CH_3)_6$ and $(CH_2)_2CH_2NH$], 1.78-1.86 (2H, m, CH_2CHCH_3 and CH_2CHCH_3), 1.94-2.02 (1H, m, CH_2CHCH_3), 3.00-3.07 (4H, m, $NHCH_2CH_2CH_2CH_2NHCO$), 7.17-7.34 (3H, br, C=NH and NH_2), 7.77-7.84 (2H, m, CONH and CH_2NH); δ_C (125 MHz; d_6-DMSO) 14.26 (CH_3), 19.78 (CH_3), 22.44 (CH_2), 26.28 (CH_2), 26.68 (CH_2), 26.74 (CH_2 and CH_2), 29.03 (CH_2), 29.57 (CH_2), 30.44 (CH), 31.62 (CH_2), 36.60 (CH_2), 40.83 (CH_2), 43.49 (CH_2), 157.00 (CO), 172.30 (C=N); {$[\alpha]_D^{25}$ = -2.2 (*c* 0.5 in MeOH) lit.,[7] for (*S*)-Aplysillamide B $[\alpha]_D^{21}$ = -2.4 (*c* 0.1 in MeOH)}; Electrospray 299 (MH^+).

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