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Asymmetric total synthesis of sperabillins B and D *via* lithium amide conjugate addition

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Received 2nd April 2004, Accepted 2nd August 2004
First published as an Advance Article on the web 24th August 2004

Diastereoselective conjugate addition of homochiral lithium (*R*)-*N*-allyl-*N*-α-methylbenzylamide to methyl (2*E*,5*E*)-hepatadienoate, followed by protecting group manipulation and subsequent iodocyclocarbamation allows a concise route to the core fragment, methyl (3*R*,5*R*,6*R*)-3,6-diamino-5-hydroxyheptanoate, of sperabillins B and D. Differentiation between the C-3 and C-6 primary amino groups of this core amino acid was readily achieved by treatment with acetone, giving the 5,6-isopropylidene and C-3-imine protected diamine, with subsequent regioselective acylation of the C-6-nitrogen facilitating the total synthesis of sperabillin D in 10.8% overall yield, and the first asymmetric synthesis of sperabillin B in 5.8% overall yield.

Introduction

Sperabillins A–D (**1**–**4** respectively) were first isolated from culture filtrates of *Pseudomonas fluorescens* YK-437,[1] and their structures elucidated unambiguously through the degradation studies of Hida *et al.*[2] The sperabillins A–D **1**–**4** are active against both Gram-positive and Gram-negative bacteria, including antibiotic resistant strains. Remarkably, their *in vivo* activities are more potent than expected from their *in vitro* results,[1,3] with the antibacterial activities of sperabillins B **2** and D **4** generally greater than those of A **1** and C **3** respectively.[1] All of these pseudopeptides consist of a core amino acid moiety, with 3-aminopropionamidine and hexa-2,4-dienoyl [in (*E*,*E*) or (2*E*,4*Z*) form] fragments attached to the *C*- and *N*-termini respectively. The core (3*R*,5*R*)-3,6-diamino-5-hydroxyhexanoic acid of sperabillins A and C is identical to that found in the potent antibiotic negamycin **5**,[4] while the (3*R*,5*R*,6*R*)-3,6-diamino-5-hydroxyheptanoic acid core of sperabillins B and D, which contains an additional C-6-methyl substituent, has been proven through total synthesis by Natsugari *et al.*[5] (Fig. 1).

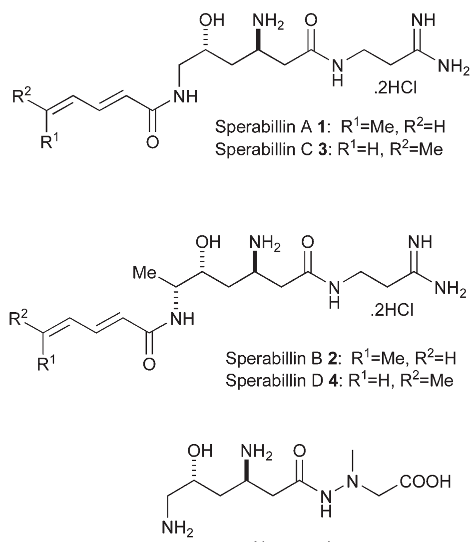
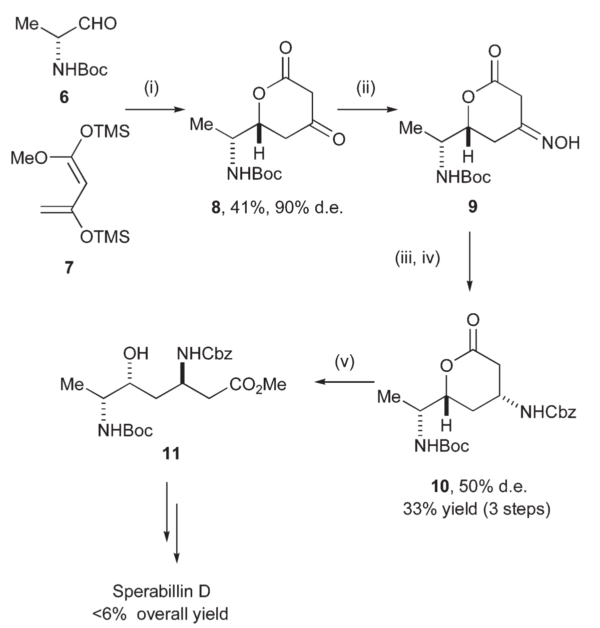


Fig. 1

A variety of methodologies have been developed previously for the preparation of negamycin in enantiomerically pure form, including syntheses from chiral pool materials[6] and the application of asymmetric synthesis,[7] that allow access to protected forms of the (3*R*,5*R*)-3,6-diamino-5-hydroxyhexanoic acid core. While the asymmetric synthesis of sperabillin C has been completed by Natsugari *et al.*,[8] the additional complication of a C-6-stereogenic centre within the amino acid motif of sperabillins B and D makes these molecules more challenging synthetic targets. Indeed, in the only reported synthesis of sperabillin D to date,[5] the C-6 stereogenic centre originated from *N*-Boc-D-alaninal **6**, with the C-5 stereocentre induced by the $SnCl_2$ catalysed cyclocondensation of diene **7** with **6**, giving lactone **8** in 90% d.e. Elaboration of lactone **8** to the oxime **9**, and subsequent reduction and *N*-protection gave the amino lactone **10** in 50% d.e. Purification to homogeneity gave **10** in 33% isolated yield over three steps. Opening of amino lactone to the corresponding methyl ester **11** and further synthetic manipulation completed the synthesis of sperabillin D in 15 steps and <6% overall yield (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) **6** and **7**, $SnCl_2$, DCM, 5–8 °C; (ii) $NH_2OH{\cdot}HCl$, pyridine, MeOH, rt; (iii) H_2, H_3PO_4–P_2O_5, 5% Pt/C; (iv) CbzCl, $NaHCO_3$ (aq), THF; (v) NaOMe, MeOH, rt.

Previous investigations from this laboratory have described the highly diastereoselective conjugate addition of homochiral lithium amides to α,β-unsaturated acceptors,[9] methodology which has been utilised extensively for the synthesis of a range of β-amino acid derivatives,[10] total syntheses,[11] kinetic resolutions[12] and asymmetric rearrangement protocols.[13] Following retrosynthetic analysis

DOI: 10.1039/b404962d

of the (3*R*,5*R*,6*R*)-3,6-diamino-5-hydroxyheptanoic acid core of sperabillins B and D, it was envisaged that conjugate addition of a differentially protected homochiral lithium amide to an (*E*,*E*)-2,5-hexadienoate acceptor could be used to install the desired (3*R*)-stereocentre. This stereogenic centre could be used to control the configuration at both C-5 and C-6 of the amino acid core *via* iodocyclocarbamation. Suitable functional group manipulation would then give access to sperabillins B and D (Fig. 2). Part of this work has been communicated previously.[14]

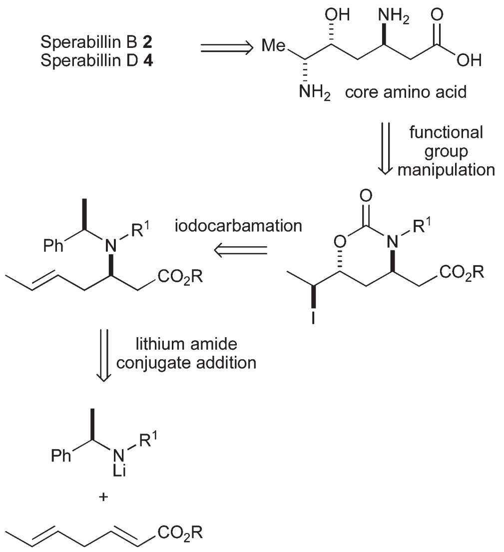


Fig. 2 Retrosynthetic route to sperabillins B and D.

Results and discussion

Synthesis of (2*E*,5*E*)-heptadienoates

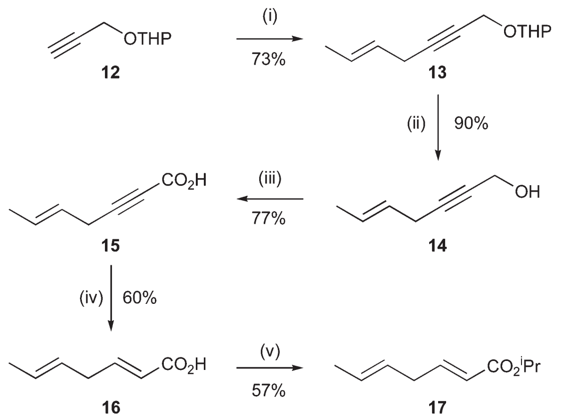
Initial studies directed toward the synthesis of an unconjugated heptadienoate focused upon the preparation of either an isopropyl or *tert*-butyl ester derivative, as it was anticipated that a sterically bulky ester protecting group would discourage 1,2-addition of the lithium amide.[15] Isopropyl (*E*,*E*)-2,5-heptadienoate **17** was therefore synthesised in 5 steps, based upon the procedures of Sharma *et al.*[16] and Binet *et al.*[17] The Grignard coupling of THP protected propargyl alcohol **12** with crotyl bromide in the presence of a Cu(I) salt gave the known ether **13** in 73% yield.[16] *O*-Deprotection using a catalytic amount of PTSA in MeOH afforded alcohol **14** in 90% yield, which was next oxidised to acid **15** with Jones' reagent in 77% yield. Subsequent *trans*-selective reduction of the alkyne was achieved using $CrSO_4$, giving (2*E*,5*E*)-2,5-heptadienoic acid **16** in 60% yield. Attempted esterification of acid **16** to the corresponding *tert*-butyl ester using isobutylene and H_2SO_4 gave a complex mixture, while esterification with DCC/DMAP was successful but also led to extensive double bond isomerisation. However, treatment of acid **16** with BF_3 etherate in isopropanol successfully led to the isolation of ester **17** in 57% yield (Scheme 2).

With isopropyl ester **17** in hand *via* this low yielding route, a direct, alternative synthesis of the corresponding unconjugated methyl ester **18** was investigated. Tkatchenko has previously reported the use of palladium catalysis for the linear codimerisation of dienes and acrylate components in the presence of a basic phosphine.[18] Optimisation of this protocol for the coupling of methyl acrylate and butadiene gave an inseparable 92 : 8 mixture of methyl (2*E*,5*E*)-2,5-heptadienoate **18** and the Diels–Alder product **19** in 83% isolated yield (Scheme 3).

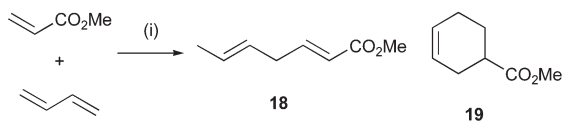
With the preparation of both isopropyl and methyl (2*E*,5*E*)-dienoates **17** and **18** in hand, elaboration to the core amino acid of sperabillins B and D was investigated.

Installation of the C(3)-stereogenic centre: lithium amide conjugate addition

In order to be able to utilise an iodocyclocarbamation strategy, differential protection of the β-amino ester resulting from conjugate



Scheme 2 *Reagents and conditions*: (i) EtMgBr, CuCl, crotyl bromide, THF; (ii) PTSA, MeOH; (iii) CrO_3, H_2SO_4; (iv) $CrSO_4$, DMF, H_2O; (v) ^iPrOH, BF_3–Et_2O.



Scheme 3 *Reagents and conditions*: (i) $Pd_2(dba)_3$, HBF_4 etherate, PBu_3, 80 °C, sealed tube.

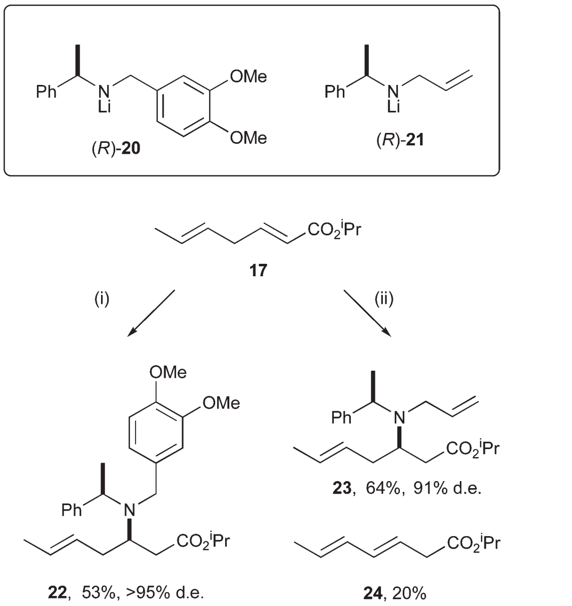
addition of a lithium amide to dienoates **17** and **18** was required. This necessitated the incorporation of an *N*-protecting group within the lithium amide that might be easily removed in the presence of the remaining unconjugated double bond. Initially, the additions of lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide **20**[19] and lithium (*R*)-*N*-allyl-*N*-α-methylbenzylamide **21**[20] to acceptor **17** were investigated, as it was predicted that selective oxidative removal of the *N*-3,4-dimethoxybenzyl-protecting group[21] or selective deprotection of the *N*-allyl-protecting group[22] within the β-amino esters resulting from conjugate addition could be readily achieved (Scheme 4). Addition of lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide **20** to isopropyl acceptor **17** afforded (3*R*,α*R*)-β-amino ester **22** in 53% yield and >95% d.e., along with products arising from the isomerisation of the acceptor **17**. Addition of lithium (*R*)-*N*-allyl-*N*-α-methylbenzylamide **21** gave (3*R*,α*R*)-β-amino ester **23** in 91% d.e. and 64% yield, contaminated with the deconjugated diene **24** after chromatography. Although **23** and **24** could be separated by Kugelrohr distillation, this material was most efficiently purified after the removal of the *N*-allyl group (*vide infra*). The configuration at C(3) within β-amino esters **22** and **23** was assigned by analogy with previous models developed to explain the stereoselectivity observed during addition of homochiral lithium amides to α,β-unsaturated acceptors.[23]

Subsequent studies showed that conjugate addition of lithium amide (*R*)-**21** to methyl ester acceptor **18** afforded (3*R*,α*R*)-β-amino ester **25** in 73% isolated yield in >96% d.e., which could be readily purified to homogeneity by chromatography (Scheme 5).[24]

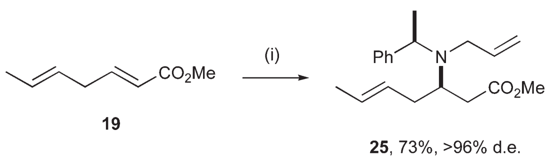
Synthesis of the core amino acid fragment: (3*R*,5*R*,6*R*)-3,6-diamino-5-hydroxyheptanoic acid

Investigations were next concerned with the conversion of *N*-allyl β-amino esters **23** and **25** into the desired core diamino hydroxy acid. The *N*-allyl protecting groups within **23** and **25** could be removed smoothly using either palladium[25] or rhodium catalysis,[26] giving amino esters **26** and **27** in 91% and >96% d.e. respectively, and in 97% yield in each case (Scheme 6).

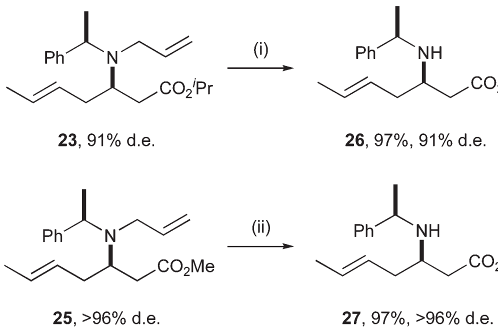
A range of potential iodocyclocarbamation substrates were next prepared for optimisation studies, with structural variation in the carbamate group, and the presence or absence of the *N*-α-methylbenzyl protecting group. The removal of the *N*-α-methylbenzyl group early in the synthetic sequence was considered advantageous, as this would circumvent any challenge of its later removal. Hydrogenolysis is usually used to remove the *N*-α-methylbenzyl protect-



Scheme 4 *Reagents and conditions*: (i) (*R*)-**20**, THF, −78 °C; (ii) (*R*)-**21**, THF, −78 °C.



Scheme 5 *Reagents and conditions*: (i) (*R*)-**21**, THF, −78 °C.

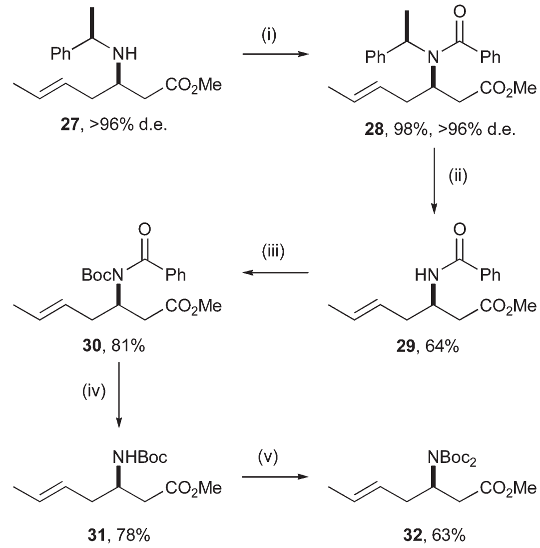


Scheme 6 *Reagents and conditions*: (i) $Pd(PPh_3)_4$, DCM, *N*,*N*-dimethylbarbituric acid, rt; (ii). $RhCl(PPh_3)_3$, $MeCN/H_2O$, Δ.

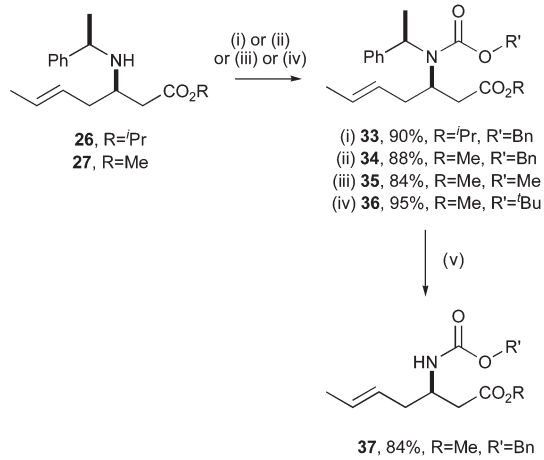
ing group, but this would simultaneously reduce the C(5)-alkene within β-amino esters **26** and **27** necessary for iodocyclocarbamation. Using a previously developed reaction sequence,[27] β-amino ester **27** was benzoylated to give **28** in 98% yield, with subsequent treatment with formic acid[28] removing the *N*-α-methylbenzyl protecting group and giving **29** in good yield. *N*-Boc protection to give **30**, and selective removal of the *N*-benzoyl group gave *N*-Boc protected amine **31**, that was further protected to give the di-*N*-Boc derivative **32** in 63% yield (Scheme 7).

As alternative substrates for iodocyclocarbamation, *N*-Cbz protection of secondary amines **26** and **27** using Cbz_2O gave the *N*-α-methylbenzyl-*N*-Cbz protected β-amino esters **33** and **34** in 90% and 88% yield respectively, with treatment of *N*-α-methylbenzyl-*N*-Cbz protected β-amino methyl ester **34** with formic acid affording *N*-Cbz amino ester **37** in 84% yield. The *N*-α-methylbenzyl-*N*-Moc and *N*-α-methylbenzyl-*N*-Boc amino derivatives **35** and **36** respectively were also prepared from β-amino ester **27** using standard procedures (Scheme 8).

With a range of homoallylic carbamates in hand, their functionalisation *via* iodocyclocarbamation was investigated. Iodocyclocarbamation has been studied by a number of groups, with the diastereoselective formation of oxazolidinones from allylic carbamates[29] and oxazinones from homoallylic carbamates[30] well



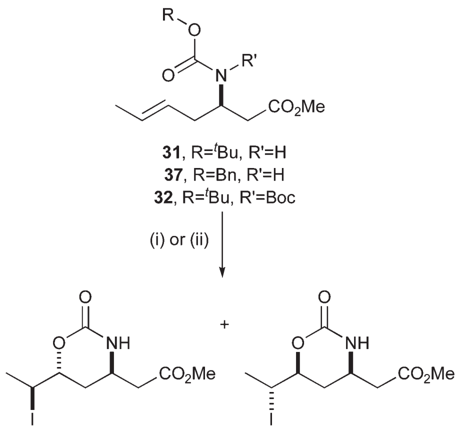
Scheme 7 *Reagents and conditions*: (i) PhCOCl, Et_3N, DMAP, DCM; (ii) HCO_2H, 60 °C; (iii) Boc_2O, Et_3N, DMAP, THF; (iv) NaOMe, MeOH; (v) Boc_2O, Et_3N, DMAP, THF.



Scheme 8 *Reagents and conditions*: (i) Cbz_2O, DCM, rt; (ii) Cbz_2O, vacuum, rt (R = Me); (iii) MeOCOCl, K_2CO_3, acetone, Δ; (iv). Boc_2O, Et_3N, DMAP, DCM, rt; (v) HCO_2H, 60 °C.

precedented in the literature. It was predicted that screening of carbamates **31**–**37** for their selectivity upon iodofunctionalisation would allow high stereocontrol to be achieved, and lead to the asymmetric synthesis of the desired amino acid core. The mono-protected derivatives *N*-Boc-**31** and *N*-Cbz-**37** were treated with TBDMSOTf and 2,6-lutidine to generate in situ the corresponding *N*-silyl derivatives,[30a] followed by iodine, giving inseparable 60 : 40 and 91 : 9 mixtures of the 3,5-*anti*-oxazin-2-one **38** and 3,5-*syn*-oxazin-2-one **39** respectively in 84% and 90% yield respectively. Treatment of the di-*N*-Boc protected substrate **32** with iodine gave an inseparable 73 : 27 mixture of the 3,5-*anti*-oxazin-2-one **38** and 3,5-*syn*-oxazin-2-one **39** in 87% isolated yield (Scheme 9). Although iodocyclocarbamation of **31**, **32** and **37** proceeded to high conversion in each case, the inseparable nature of the diastereoisomeric products **38** and **39** make this route synthetically unviable.

Attention next turned to examining the iodocyclocarbamation reactions of the *N*-α-methylbenzyl protected carbamates **33**–**36**. The presence of the *N*-α-methylbenzyl protecting group was found to generally increase the selectivity of the reaction, with the *N*-Cbz substrates **33** and **34** exhibiting the highest stereoselectivity, giving 95 : 5 and 92 : 8 mixtures of the corresponding 3,5-*anti*- and 3,5-*syn*-oxazin-2-ones (**40** : **42** and **41** : **43**) in 92% and 97% combined yield respectively (Scheme 10). The major diastereoisomeric products **40** and **41** (from iodocyclocarbamation of **33** and **34** respectively) could be isolated in >98% d.e. and in 68% and 77% yield respectively after crystallisation. The absolute (3*R*,5*R*,6*S*,α*R*)-configuration within isopropyl oxazin-2-one **40** was confirmed unambiguously

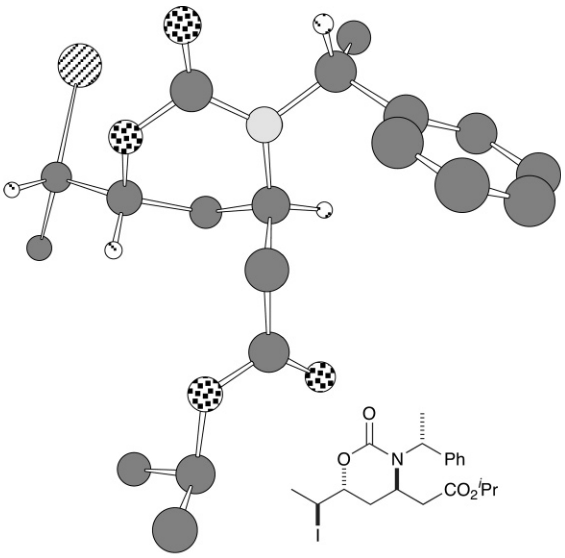


Major diastereoisomer 38
anti-3,5-oxazin-2-one

Minor diastereoisomer 39
syn-3,5-oxazin-2-one

Substrate	Conditions	Products 38:39	Yield
31	(i)	60:40	84%
37	(i)	91:9	90%
32	(ii)	73:27	87%

Scheme 9 *Reagents and conditions*: (i) TBDMSOTf, 2,6-lutidine, 0 °C, DCM then I_2, rt; (ii) I_2, 0 °C, DCM.

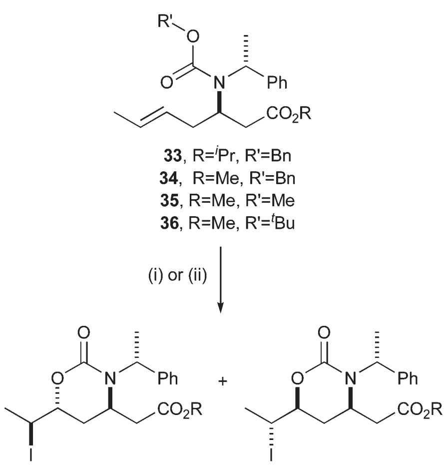


(3*R*,5*R*,6*S*,α*R*)-**40**

Fig. 3 Chem 3D representation of the X-ray crystal structure of (3*R*,5*R*,6*S*,α*R*)-**40**.

by single crystal X-ray diffraction,[31] with the configuration within **41** assigned by analogy (Fig. 3).

The stereochemical outcome of the stereoselective iodocyclocarbamation reactions of *N*-α-methylbenzyl protected carbamates **33**–**36** may be rationalised assuming a half-chair type transition state and reversible formation of an intermediate iodonium ion. In these reactions, the alkene moiety may adopt either a pseudoaxial or pseudoequatorial position, with attack of the carbonyl oxygen *anti* to the iodonium intermediate giving rise to four possible transition states **44**–**47**, that lead to the 3,5-*anti*- and 3,5-*syn*-oxazin-2-one products. Minimisation of 1,3-diaxial interactions and 1,2 strain between the *N*-α-methylbenzyl protecting group and the neighbouring C-2 alkyl substituent may then be used to predict the preferred transition states to the major and minor oxazin-2-one diastereoisomers. The major *anti*-3,5-oxazin-2-one product is presumably formed preferentially through transition state **44**, with the alkene in a pseudoequatorial orientation and the C-2 alkyl side chain adopting a pseudoaxial position to minimise 1,2 strain with the neighbouring *N*-α-methylbenzyl protecting group, favouring attack on the *Re* face of the activated alkene. The alternative transition state **46** predicting *Re* face attack to give the *anti*-3,5-oxazin-2-one positions the alkene functionality axial, and is destabilised by 1,2 strain between the *N*-α-methylbenzyl and C-2 alkyl substituents. Transition state **45** is assumed to lead to the minor *syn*-3,5-oxazin-2-one, with the alkene and C-2 alkyl side chain in pseudoequatorial positions, resulting in this transition state being destabilised by 1,2 strain between the *N*-α-methylbenzyl and the adjacent C-2 alkyl functionality. Transition state **47** is precluded from this analysis as both alkene and C-2 alkyl side chains are in axial positions (Fig. 4). This analysis may be extended directly to account for the major *anti*-3,5-oxazin-2-one diastereoisomeric product **38** formed from iodocyclocarbamation of di-*N*-Boc **32** (1,2 strain with *N*-Boc as opposed to *N*-α-methylbenzyl protecting group). The same argument can also be applied to iodocyclocarbamation of *N*-Boc **31** and *N*-Cbz **37**, as *in situ* *N*-silylation of these carbamates upon treatment with TBDMSOTf and subsequent reaction with I_2 would also be expected to lead predominantly to the *anti*-3,5-oxazin-2-one **38**.[30a] Confirmation of this was obtained by treating a 91 : 9 mixture of **38** : **39** sequentially with NaN_3 in DMF/H_2O followed by hydrogenolysis with Pd/C in MeOH which generated **57** as the major product of a 91 : 9 mixture in 43% overall yield for the two steps.



Major diastereoisomer
anti-3,5-oxazin-2-one
40, R=^{i}Pr
41, R=Me

Minor diastereoisomer
syn-3,5-oxazin-2-one
42 R=^{i}Pr
43, R=Me

Substrate	Conditions	Product ratio	Yield
33	(i)	**40**:**42** 95:5	92% (68%)
34	(i)	**41**:**43** 92:8	97% (77%)
35	(ii)	**41**:**43** 80:20	85%
36	(i)	**41**:**43** 75:25	37%

Scheme 10 *Reagents and conditions*: (i) I_2, 0 °C, DCM; (ii) I_2, KI, DCM, rt.

Transformation of the 3,5-*anti*-oxazin-2-ones **40** and **41** (>98% d.e.) into the core amino acid was next investigated. Displacement of the iodide group within **40** and **41** by nucleophilic substitution with azide resulted in an inseparable 60 : 40 mixture of the desired azide substitution products **48** and **49** and the elimination products **50** and **51** respectively, with extensive optimisation of the reaction conditions failing to produce any improvement in the product ratio. Treatment of iodide **41** with potassium phthalimide in DMF gave the elimination product **51** exclusively, allowing its isolation in 76% yield, and allowing the (*E*)-configuration within **51** to be assigned by NOE ^{1}H NMR analysis. This product configuration is consistent with the alkene arising from a stereospecific E2 *anti*-elimination of iodide **41** under the reaction conditions. Subsequent hydrogenolysis of the mixtures **48** : **50** and **49** : **51** facilitated separation of the resultant reaction components by column chromatography, affording the primary amines **52** and **53** in 53% and 52% isolated yield (Scheme 11). The absolute configuration within **52** was confirmed to be that required for the synthesis of sperabillins B and D by its transformation into the known (3*R*,5*R*,6*R*)-2,6-diamino-5-hydroxyheptanoic acid **54**. Thus, amine **52** was treated with 5 N HCl at reflux, affording the dihydrochloride salt of acid **54** in 69% yield, with spectroscopic data in good agreement with those reported in the literature, and whose specific rotation {$[\alpha]_D^{25}$ −3.1 (*c* 0.68, H_2O), lit.[2] $[\alpha]_D^{25}$ −2.7 (*c* 0.58, H_2O)} confirmed the correct enantiomeric series for the natural products had been prepared.

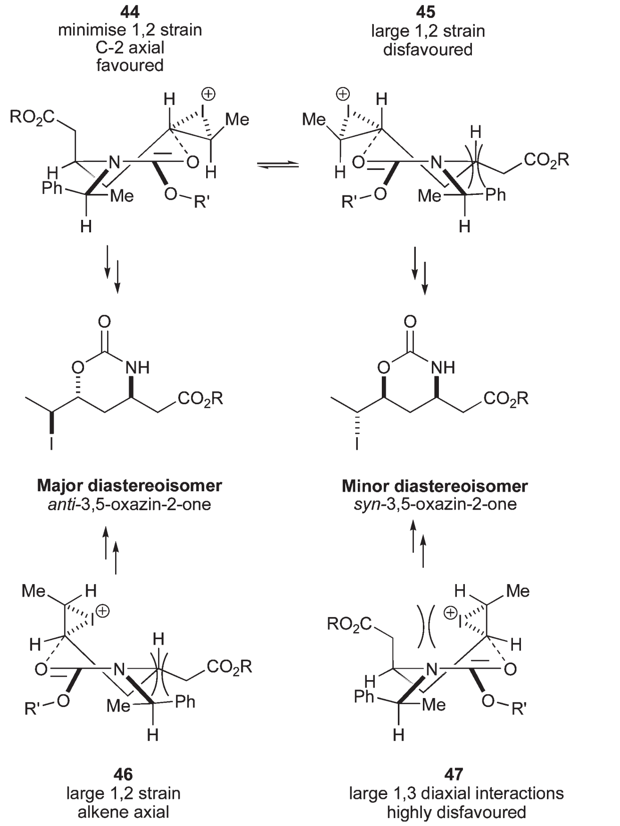
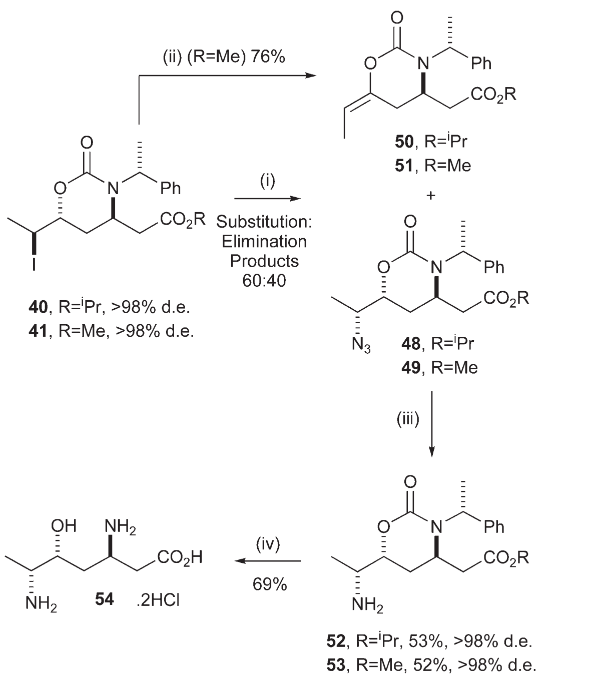


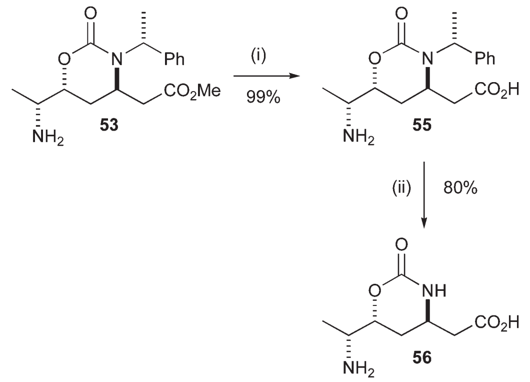
Fig. 4 Proposed transition states for iodocyclocarbamation reactions.



Scheme 11 *Reagents and conditions*: (i) NaN_3, DMF/H_2O, 120 °C; (ii) potassium phthalimide, DMF, rt; (iii) H_2 (1 atm), Pd/C, MeOH; (iv) 5 N HCl, Δ.

Attempted routes to sperabillins B and D *via* functionalised intermediates *en route* to the core fragment

Attention was next focused upon elaboration of amines **52** or **53** to the natural product targets. It seemed reasonable to remove the *N*-α-methylbenzyl protecting group at this stage and then use the oxazin-2-one ring to differentiate between the C-3 and C-6 amino functionalities during further manipulation to the sperabillins. Attempts at selectively removing the *N*-α-methylbenzyl group from **52** or **53** in one step by hydrogenolysis, dissolving metal reduction or treatment with formic acid all proved unsuccessful. However, hydrolysis of the methyl ester **53** to the corresponding carboxylic acid **55** (99% yield) and reduction with sodium in anhydrous ammonia and ethanol, afforded the desired product **56** in 80% yield (Scheme 12). Single crystal X-ray analysis of amino acid **56** allowed its relative configuration to be established unambiguously, with the absolute (3*R*,5*R*,6*R*)-configuration assigned relative to the known 3*R*-stereocentre arising from lithium amide conjugate addition (Fig. 5).



Scheme 12 *Reagents and conditions*: (i) LiOH·H_2O, THF/H_2O; (ii) Na, NH_3 (l), EtOH, THF, −78 °C, then NH_4Cl (s).

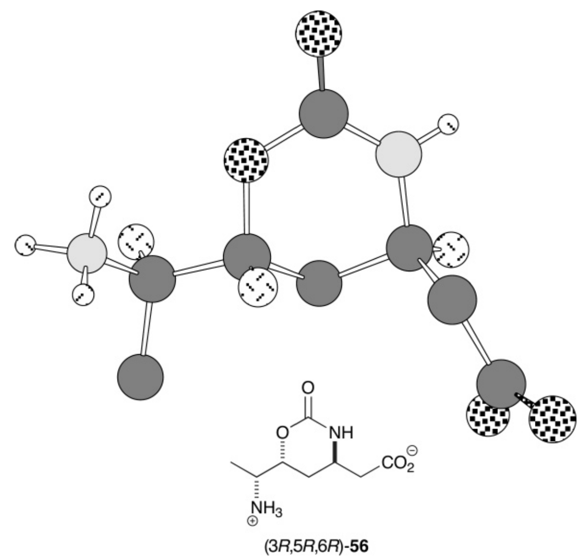
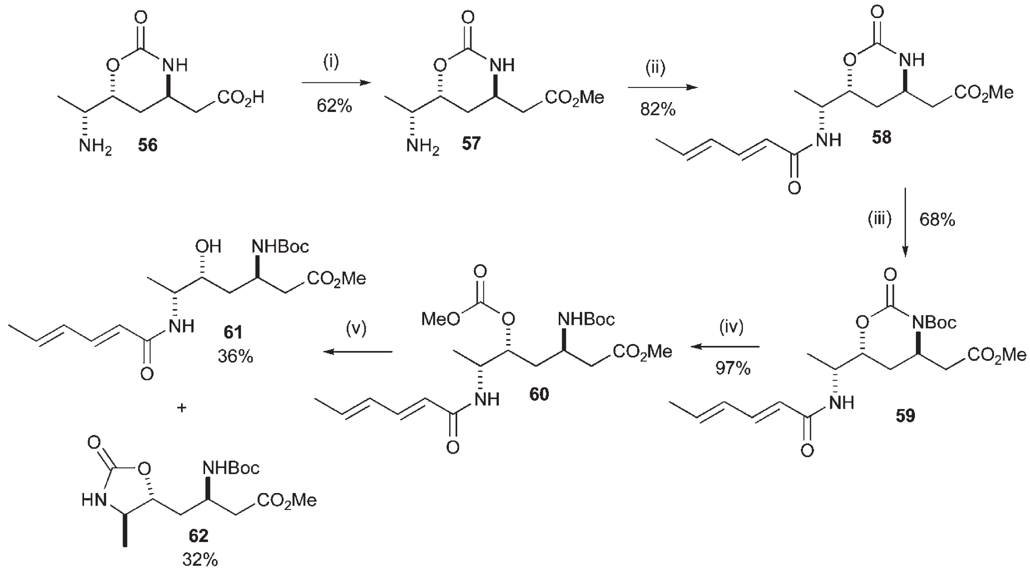


Fig. 5 Chem 3D representation of the X-ray crystal structure of (3*R*,5*R*,6*R*)-**56**.

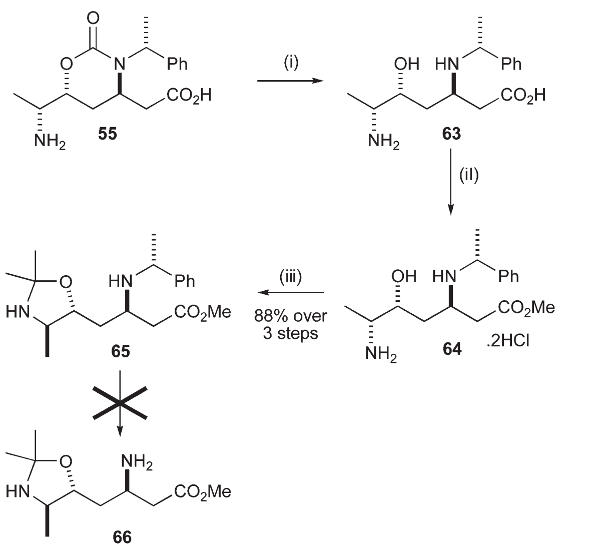
The methyl ester was next restored through treatment of acid **56** with HBF_4 etherate in methanol in the presence of sodium sulfate, giving ester **57** in 62% yield. The (*E*,*E*)-hexa-2,4-dienoyl side chain of sperabillin D was installed by acylation of **57** with sorbyl chloride, affording amide **58** in 82% yield. The oxazin-2-one was next *N*-Boc protected in 68% yield, giving a substrate **59** suitable for cyclic carbamate cleavage using catalytic caesium carbonate in methanol.[32] However, treatment of **59** with caesium carbonate led to incomplete cleavage, affording methyl carbonate **60** in 97% yield. Further treatment of **60** with stoichiometric quantities of caesium carbonate gave a separable 50 : 50 mixture of the desired alcohol **61** and the oxazolidin-2-one **62** (isolated in 36% and 32% yield respectively). Oxazolidin-2-one **62** presumably arises from competing attack on the methyl carbonate by the sorbyl amide, followed by *exo*-cyclic methanolysis (Scheme 13).

The lengthy series of steps to remove the *N*-α-methylbenzyl group, and the lack of selectivity on attempted oxazin-2-one methanolysis, illustrates this route is not synthetically viable. As an alternative strategy, it was envisaged that the inability to cleave the *N*-α-methylbenzyl group from **53** by hydrogenolysis could be circumvented by first hydrolysing the oxazin-2-one, as it is well documented that hydrogenolysis of *N*-benzyl groups from amines is much more readily achieved than from amides.[33] Consequently, the oxazin-2-one



Scheme 13 *Reagents and conditions*: (i) HBF_4 etherate, MeOH, Na_2SO_4; (ii) sorbyl chloride, Et_3N, MeCN; (iii) Boc_2O, Et_3N, DMAP, THF; (iv) 0.1 eq Cs_2CO_3, MeOH; (v) 1 eq Cs_2CO_3, MeOH.

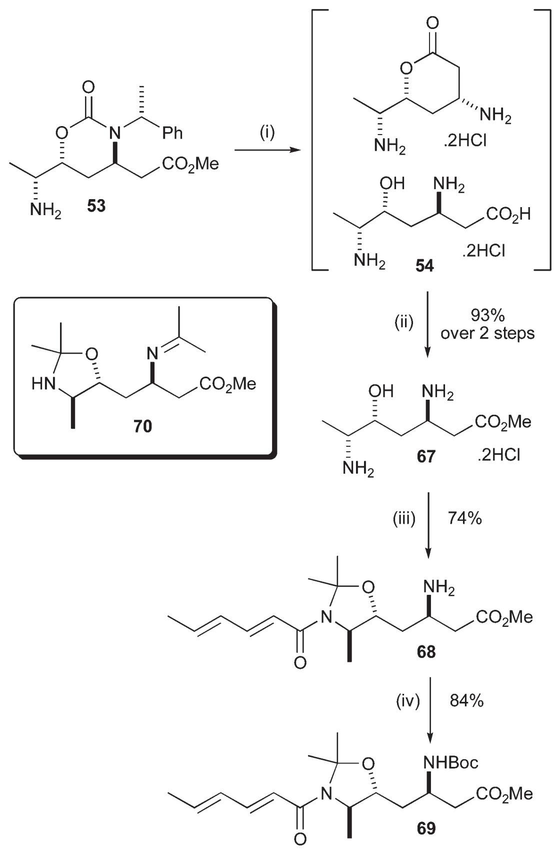
55 was hydrolysed with concentrated aqueous potassium hydroxide in ethanol to give amino acid **63**, with the methyl ester re-installed by treatment with thionyl chloride in methanol at reflux. The diamine dihydrochloride obtained in this way was protected as the isopropylidine derivative by treatment with acetone, triethylamine and magnesium sulfate, to give **65** in 88% over 3 steps. However, attempted hydrogenolysis of *N*-α-methylbenzyl protected amine **65** failed to induce any cleavage of the desired *N*-benzyl protecting group, only returning starting material (Scheme 14).



Scheme 14 *Reagents and conditions*: (i) KOH (aq), EtOH, reflux; (ii) $SOCl_2$, MeOH, reflux; (iii) acetone, Et_3N, $MgSO_4$.

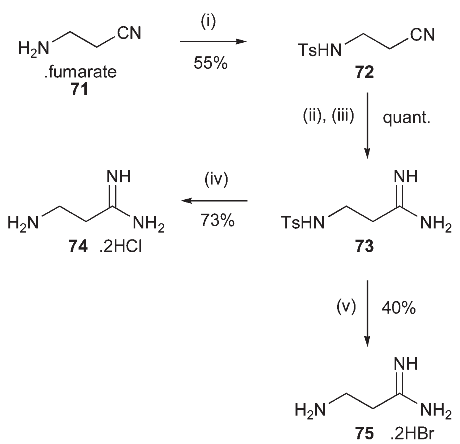
Total synthesis of sperabillins D and B *via* the core diamino acid

Having experienced difficulty in removing the *N*-α-methylbenzyl group in these latter routes, the elaboration of the core amino acid **54** in which the *N*-α-methylbenzyl group has been removed to sperabillins D and B was investigated. Generation of sperabillins B and D *via* this route necessitates differentiation between the C-3 and C-6 primary amino groups. It was envisaged that treatment of an amino ester derived from the core amino acid with acetone would generate a bis-imine that would cyclise spontaneously to form the *cis*-1,2 disubstituted 5-ring oxazolidine **70** rather than the alternative *trans*-1,3-disubstituted oxazinane, differentiating the two nitrogens by virtue of their hybridisation and allowing selective acylation of the C-6 amino group. The methyl ester **53** was thus treated with 5 N HCl at reflux, giving an unisolated 30 : 70 mixture of the diamino acid **54** and its lactone, which was immediately re-esterified with $SOCl_2$ and MeOH at reflux to give the 3,6-diamino-5-hydroxy ester **67** in 93% yield as a single diastereoisomer over 2 steps. Initial attempts at differentiating the two amino groups within **70** upon treatment of **67** with acetone were hampered by the facile hydrolysis of the imine functionality within **70**, and so a one-pot protection and acylation procedure was developed. The ester **67** was treated with acetone and Hunig's base at reflux in the presence of 3 Å molecular sieves, then cooled to 0 °C, whereupon sorbyl chloride and further Hunig's base was added. Spontaneous hydrolysis of the temporary imine protecting group upon chromatography afforded the amide **68** in 74% yield as a single regioisomer. The amine **68** was then *N*-Boc protected, affording **69** in 84% yield (Scheme 15).



Scheme 15 *Reagents and conditions*: (i) 5 N HCl (aq), reflux; (ii) $SOCl_2$, MeOH, reflux; (iii) acetone, Hunig's base, 3 Å molecular sieves, reflux then sorbyl chloride, Hunig's base, 0 °C; (iv) Boc_2O, $NaHCO_3$, MeOH.

The 3-aminopropioamidine side chain was next prepared, in a four step synthesis based upon that of Hilgetag *et al.* (Scheme 16).[34] 3-Aminopropionitrile fumarate **71** was *N*-tosylated with tosyl chloride in 55% yield, and the resulting nitrile **72** treated with HCl in ethanol, followed by a solution of ammonia in ethanol to give the amidine **73** quantitatively. **73** was detosylated either with HCl in acetic acid in a sealed tube, to afford the di-hydrochloride **74** in 73% yield, or, by a more practical but lower yielding procedure, treated with HBr in acetic acid to give the di-hydrobromide **75** in 40% yield.



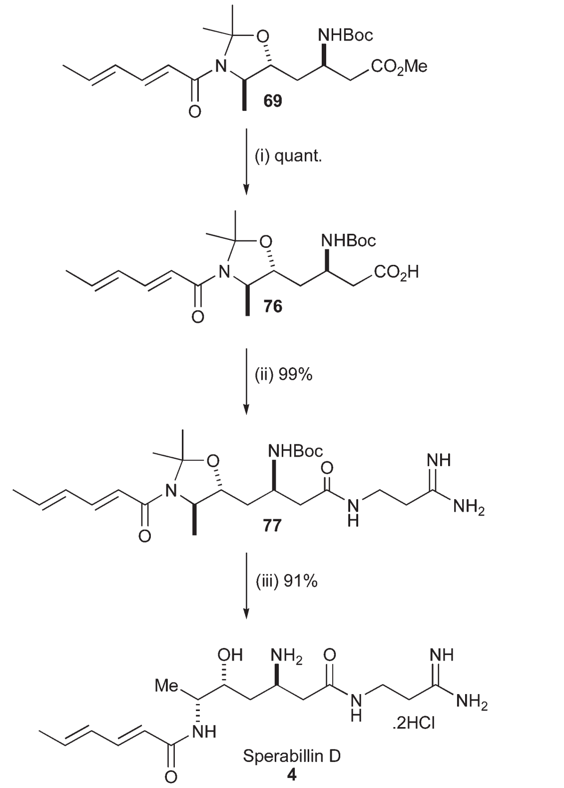
Scheme 16 *Reagents and conditions*: (i) tosyl chloride, Et_3N, DCM, 0 °C; (ii) HCl (g), EtOH, Et_2O, 5 °C; (iii) NH_3, EtOH, Et_2O; (iv) 14% HCl in acetic acid, 120 °C, sealed tube; (v) 48% HBr in acetic acid, PhOH, reflux.

N-Boc β-amino ester **69** was next hydrolysed in quantitative yield using sodium hydroxide, and the resulting acid **76** treated sequentially with HOBt and DCC in the presence of 3 Å sieves, and then amine **75**. Column chromatography of the resulting amidine salt, followed by work-up of the highly polar product with MP-carbonate scavenger resin[35] led to the isolation of pure amidine **77** in free base form in 99% yield. Attempted deprotection of **77** to the natural product with dilute hydrochloric acid led to some cleavage of the newly formed amide bond, so **77** was treated with 50% TFA in DCM, giving, after anion exchange on Amberlite IRA-402 resin (Cl^- form), sperabillin D in 91% yield (Scheme 17). Reverse phase HPLC analysis showed this material to be >94% pure, with spectroscopic data entirely consistent with the natural product: $[\alpha]_D^{25}$ +27.4 (*c* 0.22, H_2O), lit.[2] $[\alpha]_D^{25}$ +30.4 (*c* 0.50, H_2O).

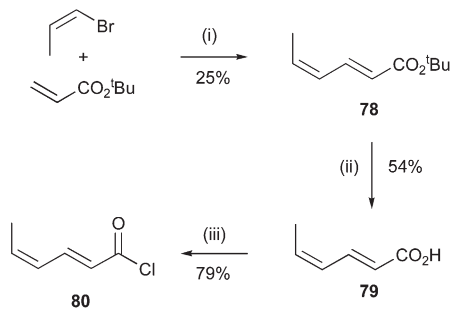
This straightforward route for the regioselective elaboration of the core fragment **67** should be applicable to the rapid generation of libraries of sperabillin analogues, differing in the groups attached to the *N*- and *C*-termini, and hence allow detailed structure activity relationship studies to be carried out. The viability of this route was validated by its application to the first total synthesis of sperabillin B, which bears the (2*E*,4*Z*)-hexadienoyl side chain. In an unoptimised three step route (Scheme 18), commercially available (*Z*)-1-bromoprop-1-ene was coupled with *tert*-butyl acrylate to afford *tert*-butyl (2*E*,4*Z*)-hexa-2,4-dienoate **78** in 25% yield and in >95 : 5 (2*E*,4*Z*) : (2*E*,4*E*) stereoselection. Cleavage of the *tert*-butyl ester was achieved with TFA in DCM, giving acid **79** in 54% yield after crystallisation. The acid **79** was then treated with oxalyl chloride and catalytic DMF to give acid chloride **80** in 79% yield.

The strategy developed for the synthesis of sperabillin D was then applied to sperabillin B (Scheme 19). The unsaturated side chain was introduced regioselectively, giving the highly functionalised ester **81** in 71% yield, which was subsequently *N*-Boc protected to give **82** in 91% yield. Ester hydrolysis proceeding quantitatively to give **83**, with peptide coupling furnishing the fully protected sperabillin B derivative **84** in 78% yield. Deprotection afforded sperabillin B, in 60% yield after preparative HPLC, displaying spectroscopic data consistent with the natural product {$[\alpha]_D^{22}$ +48.3 (*c* 0.24, H_2O), lit.[2] $[\alpha]_D$ +56.0 (*c* 1.0, H_2O)}.

In conclusion, an efficient total synthesis of the antibiotic natural product sperabillin D has been achieved in 14 steps and in 10.8% overall yield. Additionally the first total synthesis of its isomer, sperabillin B, has also been achieved in 5.8% overall yield. The strategy used the conjugate addition of a homochiral ammonia equivalent to an α,β,δ,ε-unsaturated ester followed by an iodoyclocarbamation protocol to install the two further stereogenic centres highly stereoselectively. The core fragment of sperabillins D and B, methyl (3*R*,5*R*,6*R*)-3,6-diamino-5-hydroxyheptanoate **67**, was then taken forward to the natural products *via* a novel protection strategy.



Scheme 17 *Reagent and conditions*: (i) NaOH (aq), THF/MeOH; (ii) DCC, HOBt, THF, 3 Å molecular sieves then **75**, $NaHCO_3$ (aq); (iii) TFA, DCM then Amberlite IRA-402 (Cl^- form).

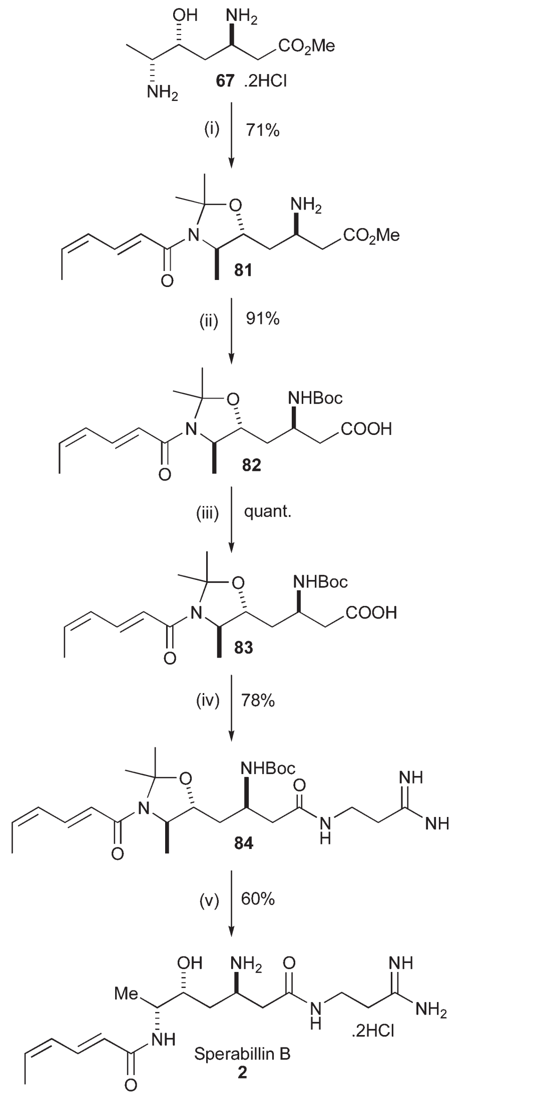


Scheme 18 *Reagents and conditions*: (i) $PdOAc_2$, K_2CO_3, PPh_3, Bu_4NHSO_4, $MeCN/H_2O$, 50 °C; (ii) TFA, DCM; (iii) $(COCl)_2$, cat. DMF, DCM.

Experimental

General experimental

Melting points were measured on a Gallenkamp capillary apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Characteristic signals are reported in cm^{-1}. NMR spectra were recorded on Bruker DPX-200 (^1H 200 MHz, ^{13}C 50 MHz), Bruker DPX-400 (^1H 400 MHz, ^{13}C 100 MHz) and Bruker DRX-500 (^1H 500 MHz, ^{13}C 125 MHz) spectrometers. Chemical shifts (*δ*) are reported in parts per million (ppm) and are referenced to the residual solvent signal. Coupling constants (*J*) are given in Hz. Low resolution mass spectra (*m*/*z*) were recorded on a VG Autospec instrument (CI, NH_3), a Platform instrument (APCI or ESI) or a Micromass GCT intrument (GC/MS,



Scheme 19 *Reagents and conditions*: (i) acetone, Hunig's base, 3 Å molecular sieves, reflux then **80**, Hunig's base, 0 °C; (ii) Boc_2O, $NaHCO_3$, MeOH; (iii) NaOH (aq), THF/MeOH; (iv) DCC, HOBt, THF, 3 Å molecular sieves then **75**, $NaHCO_3$ (aq); (v) TFA, DCM then preparative reverse-phase HPLC then Amberlite IRA-402 (Cl^- form).

CI, NH_3). Accurate mass measurements were recorded on either a VG Autospec (CI) or a Micromass LCT (ESI) mass spectrometer. Elemental analyses were performed by the Analytical Service of the Inorganic Chemistry Laboratory, University of Oxford. Column chromatography was carried out on silica gel (Merck, 70–320 mesh). TLC was carried out on aluminium backed Kieselgel 60 F_{254} plates (Merck). Plates were visualised either by UV light (254 nm), aq $KMnO_4$ or phosphomolybdic acid in ethanol. Dowex® 50WX cation exchange resin was H^+ form, Amberlite® IRA-402 anion exchange resin was Cl^- form. Both were washed with aq HCl (1 M) then H_2O prior to use. Reverse-phase HPLC was carried out on a Gilson instrument comprising of Gilson 306 pumps, Gilson 811C dynamic mixer, Gilson 806 manomeric module with automated injection by a Gilson 215 Liquid handler, configured with a Gilson 819 valve actuator. Analytical separations were performed on a Hypersil® Elite C18 column (5 µm particle size, 150 × 4.6 mm) and preparative separations on a Varian Omnisphere 5 C18 column (5 µm particle size, 150 × 10 mm). All experiments were performed under gradient elution with deionised H_2O (containing 0.1% TFA) and CH_3CN. Detection was at λ 218 and 260 nm with a Gilson 170 Diode Array Detector with equipment control and data collection managed by Gilson Unipoint LC software version 3.01. Diethyl ether is refered to as ether throughout; 40–60 petrol refers to the fraction that boils at 40–60 °C; 30–40 petrol refers to the fraction that boils at 30–40 °C. THF and ether used in reactions were distilled from sodium/benzophenone ketyl; DCM was distilled from calcium hydride. Acetone was distilled from and stored over 3 Å molecular sieves. Benzyl alcohol was dried over 3 Å molecular sieves. NH_3 was passed through BaO(s) prior to condensation. MP Carbonate resin (Argotech®) was washed twice with DCM prior to use. Cu(I)Cl was dried *in vacuo*. Jones's reagent was prepared from 67 g of CrO_3, 58 mL of conc. H_2SO_4 and 125 mL of H_2O. All other solvents and reagents were used as supplied, without further purification.

(*E*)-1-Tetrahydropyranyloxy-hept-5-en-2-yne 13. Magnesium turnings (2.4 g, 99 mmol) and THF (50 mL) were placed in a flask fitted with a reflux condenser and a small amount of EtBr added with stirring. The mixture became cloudy after *ca.* 5 min. The remainder of the EtBr (10.9 g, 100 mmol in total) was then added at such a rate that the temperature of the mixture was kept at 50–60 °C and the stirred mixture maintained at this temperature for a further 30 min. The mixture was then allowed to cool to rt and a solution of the THP ether **12** (14.0 g, 100 mmol) in THF (30 mL) was added over a period of 30 min. After stirring at 60 °C for 1 h, the mixture was allowed to cool to rt and Cu(I)Cl (1.0 g, 10 mmol) was added to give a green-yellow suspension, which was stirred at rt for 15 min. A solution of crotyl bromide (13.5 g, 100 mmol) in THF (30 mL) was added dropwise to the suspension over a period of 20 min and stirring was continued for a further 1 h. The reaction was quenched by addition of aq sat NH_4Cl (5 mL) and the mixture poured into brine (200 mL), extracted with ether (3 × 100 mL) and dried ($MgSO_4$). Filtration and removal of the solvent *in vacuo*, followed by purification by dry flash chromatography on silica gel (10% ether in 40–60 petrol) to afford the title compound **13** as a colourless oil[16] (14.2 g, 73%); δ_H (200 MHz, $CDCl_3$) 1.65 (3H, dd, J = 9.5, 1.6, CH_3CH=CH), 1.51–2.91 (6H, m, $CHOCH_2CH_2CH_2CH_2$), 2.93 (2H, m, CH=CHCH_2), 3.51 (1H, m, OC*H*HCH_2), 3.84 (1H, m, OC*H*HCH_2), 4.27 (2H, m, C≡CCH_2O), 4.82 (1H, m, OC*H*O), 5.34–5.78 (2H, m, CH_3C*H*=C*H*).

(*E*)-Hept-5-en-2-yn-1-ol 14. To a solution of the THP ether **13** (13.4 g, 69 mmol) in methanol (100 mL) was added a catalytic amount of PTSA (500 mg), and the mixture was stirred at 50–60 °C. After 2 h, TLC analysis of the mixture indicated complete consumption of the starting material. $NaHCO_3$ (2.0 g) was added and the majority of the solvent removed *in vacuo*. The residue was partitioned between H_2O (150 mL) and ether (3 × 70 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification *via* dry flash chromatography on silica gel (20% ether in 40–60 petrol) afforded the alcohol **14** as a colourless oil[16] (6.88 g, 90%); δ_H (200 MHz, $CDCl_3$) 1.70 (3H, dd, J = 6.4, 1.5, CH_3CH=CH), 1.82 (1H, m, OH), 2.93 (2H, m, CH=CHCH_2), 4.27 (2H, m, CH_2OH), 5.35–5.78 (2H, m, CH_3C*H*=C*H*).

(*E*)-Hept-5-en-2-ynoic acid 15. A solution of the alcohol **14** (9.16 g, 83.3 mmol) in acetone (250 mL) was cooled to 0 °C and Jones' reagent (47 mL, 2.67 M) added drop-wise. The temperature of the mixture was maintained below 20 °C during the addition. The resulting dark red solution was stirred at rt for 2.5 h. The mixture was poured into H_2O (1 L), extracted with ether (4 × 500 mL) and dried ($MgSO_4$). Filtration and removal of the solvent *in vacuo* gave the acid **15** as a pale orange oil[17] (7.98 g, 77%); δ_H (200 MHz, $CDCl_3$) 1.71 (3H, dd, J = 6.4, 1.5, CH_3CH=CH), 3.07 (2H, m, CH=CHCH_2), 5.40, 5.73 (2 × 1H, m, CH_3C*H*=C*H*), 8.33 (1H, br s, CO_2*H*).

(*E*,*E*)-Hepta-2,5-dienoic acid 16. To an aq solution of Cr(II)SO_4 (*ca.* 0.7 M, 225 mL, *ca.* 150 mmol) was added a degassed solution of acid **15** (5.0 g, 40.3 mmol) in DMF (200 mL) and the resulting dark green solution was stirred under N_2 at rt for 3 days. KOH(s) was added to the mixture until it became basic and the resulting slurry was filtered through Celite®, eluting with further H_2O (100 mL). The combined filtrate and washings were acidified by addition of aq HCl (1 M), extracted with ether (4 × 100 mL) and the combined extracts dried ($MgSO_4$). Filtration and removal of the solvent *in vacuo* afforded the acid **16** as a pale yellow oil (3.24 g, 64%); δ_H (200 MHz, $CDCl_3$) 1.58 (3H, d, *J* = 6.4, CH_3CH=CH), 2.93 (2H, m, CH_2CH=CH), 5.33–5.62 (2H, m, CH_3*CH*=*CH*), 5.82 (1H, d, *J* = 15.5, CH=C*H*CO), 7.06 (1H, dt, *J* = 15.5, 6.4, C*H*=CHCO).

(*E*,*E*)-Isopropyl hepta-2,5-dienoate 17. To a solution of the acid **16** (11.8 g, 93.7 mmol) in dry ^iPrOH (200 mL) was added $BF_3{\cdot}Et_2O$ (13.8 mL, 112.4 mmol) and the mixture heated to reflux under N_2 for 22 h. The solution was poured into H_2O (200 mL) and extracted with ether (3 × 70 mL). The combined extracts were washed with aq sat $NaHCO_3$ (150 mL) and dried ($MgSO_4$). Filtration and distillation under reduced pressure (bp 67–70 °C, 2 mmHg) afforded the title compound **17** as a colourless oil (11.6 g, 57%); $C_{10}H_{16}O_2$ requires C, 71.4, H, 9.6%; found C, 71.7, H, 9.4%; ν_{max} (film) 1715 (C=O), 1655 (C=C); δ_H (200 MHz, $CDCl_3$) 1.26 (6H, d, *J* = 6.3, $(CH_3)_2$CH), 1.69 (3H, d, *J* = 4.8, CH_3CH=CH), 2.87 (2H, m, CHCH_2CH), 5.06 (1H, septet, *J* = 6.3, $(CH_3)_2$C*H*), 5.46 (2H, m, CH_3C*H*=C*H*), 5.80 (1H, d, *J* = 15.7, CH=C*H*CO), 6.95 (1H, dt, *J* = 15.6, 6.5, C*H*=CHCO); δ_C (50 MHz, $CDCl_3$) 17.6 (*C*H$_3$CH=CH), 21.6 (($CH_3)_2$CH), 34.8 (CH*C*H$_2$CH), 67.2 (($CH_3)_2$*C*H), 122.1 (CH=*C*HCO), 126.8 (CH_3*C*H=CH), 128.0 (CH_3CH=*C*H), 147.2 (*C*H=CHCO), 166.2 (*C*=O); *m*/*z* (CI) 186 (MNH_4^+, 42%), 169 (MH^+, 100).

(*E*,*E*)-Methyl hepta-2,5-dienoate 18. Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (1.61 g, 1.55 mmol), methyl acrylate (66.92 g, 777 mmol), tri-*n*-butyl phosphine (0.77 mL, 3.10 mmol) and tetrafluoroboric acid (6.15 M in ether, 0.85 mL, 6.20 mmol) were placed in a thick walled glass vessel under N_2. The mixture was cooled to −78 °C and buta-1,3-diene (70 mL, 777 mmol) condensed into the vessel. The vessel was tightly sealed with a wire secured, rubber bung and the mixture stirred at 80 °C for 5 h. After cooling to −78 °C, the vessel was opened and the mixture was allowed to warm to rt, allowing the evaporation of any remaining buta-1,3-diene. The mixture was filtered through Celite® and the remaining volatile material removed *in vacuo*. The residue was purified by passage through a short plug of silica gel (50% ether in 40–60 petrol) to afford a colourless oil containing a mixture of **18** and **19** (90.3 g, 83%, **18** : **19** 92 : 8).

***Data for 18*[17].** δ_H (200 MHz, $CDCl_3$) 1.67 (3H, d, *J* = 4.8, CH_3CH=CH), 2.86 (2H, m, CH_2), 3.71 (2H, s, OCH_3), 5.32–5.60 (2H, m, CH_3C*H*=C*H*), 5.81 (1H, d, *J* = 15.7, CH=C*H*CO), 6.96 (1H, dt, *J* = 15.7, 6.5, C*H*=CHCO).

(3*R*,5*E*,α*R*)-Isopropyl 3-(*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamino)hept-5-enoate 22. To a solution of (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamine (2.1 g, 7.75 mmol) in THF (15 mL) was added *n*-BuLi (1.6 M in hexanes, 4.5 mL, 7.2 mmol) at −78 °C and the resulting pink solution was stirred for 15 min. A pre-cooled (−78 °C) solution of ester **17** (500 mg, 4.76 mmol) in THF (5 mL) was added and the resulting mixture stirred for 1.5 h. The reaction was quenched by addition of aq sat NH_4Cl (2 mL) and the mixture allowed to warm to rt. The reaction mixture was poured into brine (50 mL), extracted with ether (3 × 30 mL) and the combined extracts dried ($MgSO_4$). Filtration and removal of the solvent *in vacuo* was followed by purification by column chromatography on silica gel. Elution (40–60 petrol) gave an oil containing the isomerised ester **24** (88 mg, 18 wt.% of the starting ester **17**) and further elution (20% ether in 40–60 petrol) afforded the Michael adduct **22** as a colourless oil (690 mg, 53%, >95% de).

Data for 22. $C_{27}H_{37}NO_4$ requires C, 73.8, H, 8.4%; found C, 73.8, H, 8.4%; $[\alpha]_D^{25}$ +1.86 (*c* = 1.0, $CHCl_3$); ν_{max} (film) 1725 (C=O); δ_H (200 MHz, $CDCl_3$) 1.17 (3H, d, *J* = 3.5, CH_3CHCH$_3$), 1.19 (3H, d, *J* = 3.5, CH_3CHC*H*$_3$), 1.37 (3H, d, *J* = 7.0, PhCHC*H*$_3$), 1.69 (3H, d, *J* = 4.0, CH_3CH=CH), 2.03 (2H, m, CH=CHC*H*$_2$), 1.94–2.35 (2H, m, CHC*H*$_2$CO), 3.45 (1H, m, C*H*CH$_2$CO), 3.52, 3.73 (2H, AB system, J_{AB} = 14.8, NC*H*$_2$), 3.90 (1H, m, PhC*H*CH$_3$), 3.90 (3H, s, C*H*$_3$O), 3.92 (3H, s, C*H*$_3$O), 4.91 (1H, septet, *J* = 6.3, $(CH_3)_2$C*H*), 5.48 (2H, m, CH_3C*H*=C*H*), 6.81–7.33 (8H, m, Ph, $(CH_3O)_2C_6H_3$); δ_C (50 MHz, $CDCl_3$) 17.9 (*C*H$_3$CH=CH), 19.2 (PhCH*C*H$_3$), 21.6 (CH(*C*H$_3$)$_2$), 36.3, 37.1 (CH=CH*C*H$_2$, CH*C*H$_2$CO), 49.5 (($CH_3O)_2C_6H_3$*C*H$_2$), 54.7 (*C*HCH$_2$CO), 55.5, 55.8 (2 × *C*H$_3$O), 57.5 (Ph*C*HCH$_3$), 67.8 (CO$_2$*C*H(CH$_3$)$_2$), 110.7, 111.4, 120.1, 126.5, 126.8, 127.9, 128.0, 129.5 (aromatic *C*H, CH_3*C*H=*C*H), 134.1, 143.2 (2 × *ipso*-*C*), 148.7, 148.9 (2 × *C*OCH$_3$), 172.2 (*C*=O); *m*/*z* (CI) 440 (MH^+, 92%), 384 (24), 151 (100).

Data for 24. δ_H (200 MHz, $CDCl_3$) 1.22 (6H, d, *J* = 5.3, CH(C*H*$_3$)$_2$), 2.77 (3H, d, *J* = 7.9, C*H*$_3$CH=CH), 3.04 (1H, m, CHC*H*HCO), 3.17 (1H, m, CHCH*H*CO), 5.01 (1H, m, C*H*(CH$_3$)$_2$), 5.25–6.48 (4H, m, CH_3C*H*=CHC*H*=C*H*).

(3*R*,5*E*,α*R*)-Isopropyl 3-(*N*-allyl-*N*-α-methybenzylamino)-hept-5-enoate 23. To a solution of (*R*)-*N*-allyl-*N*-α-methylbenzylamine (7.19 g, 44.7 mmol) in THF (50 mL) was added *n*-BuLi (1.3 M in hexanes, 34.4 mL, 44.7 mmol) at −78 °C and the resulting solution stirred for 15 min. A pre-cooled (−78 °C) solution of the ester **17** (5.0 g, 29.8 mmol) in THF was added and the resulting mixture stirred for 30 min. The reaction was quenched by addition of aq sat NH_4Cl (5 mL) and the mixture poured into brine (150 mL), extracted with ether (3 × 70 mL) and the combined extracts dried ($MgSO_4$). Filtration, removal of the solvent *in vacuo* and column chromatography on silica gel (20% ether in 40–60 petrol) afforded a mixture of the Michael adduct **23** and isomerized ester **24** (6.88 g, 83 : 17 **23** : **24**, 64% yield of **23** in 91% de). A small amount of **23** was isolated for full characterisation by removing the ester **24** by Kugelrohr distillation followed by column chromatography of the residue on silica gel (DCM) to afford **23** as a colourless oil; $C_{21}H_{31}NO_2$ requires C, 76.6, H, 9.5%; found C, 76.3, H, 9.8%; $[\alpha]_D^{25}$ −12.0 (*c* = 1.9, $CHCl_3$); ν_{max} (film) 1730 (C=O); δ_H (200 MHz, $CDCl_3$) 1.18 (3H, d, *J* = 3.9, C*H*$_3$CHCH$_3$), 1.21 (3H, d, *J* = 3.9, CH$_3$CHC*H*$_3$), 1.38 (3H, d, *J* = 6.9, PhCHC*H*$_3$), 1.66 (3H, d, *J* = 4.1, C*H*$_3$CH=CH), 1.97 (1H, m, CH=CHC*H*H), 2.19 (2H, d, *J* = 7.1, CHC*H*$_2$CO), 2.23 (1H, m, CH=CHCH*H*), 3.12, 3.21 (2H, ABX system AB part, J_{AX} 5.9, J_{BX} 6.4, J_{AB} 15.4, CH$_2$=CHC*H*$_2$N), 3.41 (1H, quintet, *J* = 6.5, C*H*CH$_2$CO), 3.96 (1H, q, *J* = 6.9, PhC*H*CH$_3$), 4.95 (1H, m, C*H*(CH$_3$)$_2$), 4.97–5.20 (2H, m, C*H*$_2$=CH), 5.41 (2H, m, CH$_3$C*H*=C*H*), 5.83 (1H, m, CH$_2$=C*H*CH$_2$N), 7.18–7.34 (5H, m, Ph); δ_C (50 MHz, $CDCl_3$) 17.9 (*C*H$_3$CH=CH), 20.1 (PhCH*C*H$_3$), 21.7 (CH(*C*H$_3$)$_2$), 37.6, 35.7 (CH=CH*C*H$_2$, *C*H$_2$CO), 48.9 (N*C*H$_2$CH=CH$_2$), 55.6 (*C*HCH$_2$CO), 58.1 (Ph*C*HCH$_3$), 67.3 (*C*H(CH$_3$)$_2$), 115.5 (NCH$_2$CH=*C*H$_2$), 126.9, 127.1 (aromatic *C*H, CH$_3$*C*H=CH), 127.8, 128.2 (aromatic *C*H), 129.2 (CH$_3$CH=*C*H), 139.3 (NCH$_2$*C*H=CH$_2$), 145.0 (*ipso*-*C*), 172.6 (*C*=O); *m*/*z* (CI) 330 (MH^+, 100%), 169 (37).

(3*R*,5*E*,α*R*)-Methyl 3-(*N*-allyl-*N*-α-methybenzylamino)hept-5-enoate 25. A stirred solution of (*R*)-*N*-allyl-*N*-α-methylbenzylamine (28.6 g, 184 mmol) in THF (350 mL), under Ar, was cooled to −78 °C and BuLi (1.45 M in hexanes, 117 mL, 169 mmol) was added drop-wise. After stirring for 1 h, a solution of ester **18** (19.8 g, containing 1.6 g of **19**, 141 mmol) in THF (50 mL) was added *via* cannula and the mixture was stirred at −78 °C for a further 1 h. Aq sat NH_4Cl (20 mL) was added and the solution allowed to warm to rt, before aq citric acid (10%, 100 mL) was added. The organic material was extracted into ether (3 × 100 mL), the combined extracts washed with brine (150 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification *via* column chromatography on silica gel (7% ether in 40–60 petrol) afforded the title compound **25** as a pale yellow oil (31.1 g, 73%, >96% de); $[\alpha]_D^{22}$ −6.0 (*c* = 1.2, $CHCl_3$); ν_{max} (film) 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* = 6.9, PhCHC*H*$_3$), 1.66 (3H, d, *J* = 5.7, C*H*$_3$CH=CH), 1.97 (1H, m, CHC*H*HCH), 2.21–2.30 (3H, m, C*H*HCHC*H*$_2$), 3.13–3.24 (2H, m, NC*H*$_2$), 3.40 (1H, quintet, *J* = 6.9, CH$_2$C*H*CH$_2$), 3.56 (3H, s, OC*H*$_3$), 3.98 (1H, q, *J* = 6.9, PhC*H*CH$_3$), 5.04 (1H, dd, *J* = 10.1, 1.6, CH=C*H*H) 5.14 (1H, dd, *J* = 15.6, 1.6 CH=CH*H*), 5.35–5.47 (2H, m, C*H*=C*H*), 5.84 (1H, m, C*H*=CH$_2$), 7.19–7.32 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 17.9 (*C*H$_3$CH=CH), 19.4 (*C*H$_3$CHPh), 35.8 (CH*C*H$_2$CH), 37.4 (*C*H$_2$C=O), 48.9 (N*C*H$_2$), 51.3 (O*C*H$_3$), 55.5 (N*C*HCH$_2$), 57.8 (Ph*C*HCH$_3$), 115.7 (CH=*C*H$_2$), 126.8, 127.2, 127.8, 128.2, 129.0 (aromatic *C*H, *C*H=*C*H), 139.2 (*C*H=CH$_2$), 145.1 (*ipso-C*), 173.5 (*C*=O); *m*/*z* (APCI) 302 (MH^+, 30%), 198 (95), 105 (100); HRMS (ESI) $C_{19}H_{27}NO_2^+$ requires 302.2120; found 302.2119.

(3*R*,5*E*,α*R*)-Isopropyl 3-(*N*-α-methylbenzylamino)hepten-5-oate 26. Tetrakis(triphenylphosphine)palladium (400 mg, 0.35 mmol) and *N*,*N*′-dimethylbarbituric acid (10.0 g, 64.0 mmol) were placed in a schlenk tube under N_2. A degassed solution of the Michael adduct **23** (7.0 g, containing 1.4 g of ester **24**) in DCM (100 mL) was added to the mixture. The resulting solution was stirred at 30–35 °C for 2 h. The solvent was removed *in vacuo* and the residue dissolved in ether (200 mL), washed with aq Na_2CO_3 (100 mL) and dried ($MgSO_4$). Filtration, removal of the solvent *in vacuo* and purification by column chromatography on silica gel (50% ether in 40–60 petrol) afforded the title compound **26** as a pale yellow oil (4.82 g, 97%, 91% de); $C_{18}H_{27}NO_2$ requires C, 74.7, H 9.4, N, 4.8%; found C, 74.9, H, 9.6, N, 4.8%; $[\alpha]_D^{25}$ +7.3 (*c* = 1.0, $CHCl_3$); ν_{max}(film) 1730 (s, C=O); δ_H (200 MHz, $CDCl_3$) 1.24 (6H, d, *J* = 6.2, $CH(CH_3)_2$), 1.57 (1H, br s, NH), 1.33 (3H, d, *J* = 6.5, $PhCHCH_3$), 1.65 (3H, dd, *J* = 6.0, *J* = 0.9, CH_3CH=CH), 2.08 (2H, t, *J* = 6.7, CH=$CHCH_2$), 2.37 (2H, d, *J* = 6.0, $CHCH_2CO$), 2.84 (1H, quintet, *J* = 6.2, $CHCH_2CO$), 3.86 (1H, q, *J* = 6.6, $PhCHCH_3$), 5.02 (1H, septet, *J* = 6.2, $CH(CH_3)_2$), 5.17–5.53 (2H, m, CH_3CH=*CH*), 7.23–7.32 (5H, m, Ph); δ_C (50 MHz, $CDCl_3$) 17.9 (CH_3CH=CH), 21.8 ($CO_2CH(CH_3)_2$), 24.4 ($PhCHCH_3$), 38.1, 39.0 (CH_2CHCH_2CO), 52.0 ($CHCH_2CO$), 55.2 ($PhCHCH_3$), 67.5 ($CO_2CH(CH_3)_2$), 126.8, 127.0, 127.7, 128.4, 128.5 (aromatic *C*H, CH_3CH=CH), 146.2 (*ipso-C*), 172.3 (*C*=O); *m*/*z* (CI) 290 (MH^+, 100%).

(3*R*,5*E*,α*R*)-Methyl 3-(*N*-α-methybenzylamino)hept-5-enoate 27. To a stirred solution of Michael adduct **25** (18.9 g, 62.8 mmol) in MeCN/H_2O (4 : 1, 500 mL), under Ar, was added Wilkinson's catalyst (2.90 g, 3.14 mmol) and the mixture heated at reflux for 2 h, with propanal being removed by azeotropic distillation. After being allowed to cool to rt, the solvent was removed *in vacuo*, and the residue passed through a column of deactivated neutral alumina (ether). Purification by column chromatography on silica gel (50% ether in 40–60 petrol) afforded the title compound **27** as a pale yellow oil (15.9 g, 97%, >96% de); $[\alpha]_D^{22}$ +8.2 (*c* = 1.1, $CHCl_3$); ν_{max} (film) 2963 (C–H), 1737 (C=O), 1603 (C=C); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* = 6.6, $PhCHCH_3$), 1.56 (1H, br, N*H*), 1.65 (3H, dd, *J* = 6.4, 1.2, CH_3CH=CH), 2.06–2.11 (2H, m, CH=$CHCH_2$), 2.41 (2H, d, *J* = 6.1, CH_2C=O), 2.84 (1H, m, CH_2CHCH_2), 3.67 (3H, s, OCH_3), 3.84 (1H, q, *J* = 6.6, $PhCHCH_3$), 5.25 (1H, m, CH_3CH=*CH*), 5.46 (1H, m, CH_3CH=CH), 7.22–7.34 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 18.0 (CH_3CH=CH), 24.5 (CH_3CHPh), 38.2 ($CHCH_2CH$), 38.7 (CH_2C=O), 51.4 (OCH_3), 51.8 (CH_2CHCH_2), 55.2 ($PhCHCH_3$), 126.6, 126.7, 126.9, 127.4, 128.4 (aromatic *C*H, *C*H=*C*H), 145.9 (*ipso-C*), 172.9 (*C*=O); *m*/*z* (APCI) 262 (MH^+, 40%), 158 (100), 105 (98); HRMS (ESI) $C_{16}H_{23}NO_2^+$ requires 262.1807; found 262.1812.

(3*R*,5*E*,α*R*)-Methyl 3-(*N*-benzoyl-*N*-α-methylbenzylamino)-hept-5-enoate 28. To a solution of **27** (3.06 g, 12.0 mmol) in DCM (50 mL) was added DMAP (147 mg, 1.20 mmol), Et_3N (8.16 mL, 18 mmol) and benzoyl chloride (8.20 mL, 70.0 mmol). The mixture was stirred at rt for 17 h and then the volatile material removed *in vacuo*. The residue was partitioned between aq sat $NaHCO_3$ (50 mL) and EtOAc (3 × 70 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (25% ether in 40–60 petrol) to afford the title compound **28** as a colourless oil (4.29 g, 98%, >96% de); $[\alpha]_D^{24}$ +46.2 (*c* = 1.0, $CHCl_3$); ν_{max} (film) 1734 (C=O ester), 1632 (C=O amide); δ_H (500 MHz, $CDCl_3$) 1.58 (3H, br s, $PhCHCH_3$), 1.73 (3H, d, *J* = 5.9, CH_3CH=CH), 1.83 (1H, m, CHC*H*HCH), 2.42 (1H, m, CHCH*H*CH), 2.89–3.04 (2H, m, CH_2CO_2), 3.47 (3H, s, OCH_3), 3.60 (1H, m, CH_2CHCH_2), 5.00 (1H, br m, $PhCHCH_3$), 5.49–5.60 (2H, m, CH_3CH=*CH*), 7.24–8.18 (10H, m, Ph); δ_C (50 MHz, $CDCl_3$) 16.4, 17.9 ($PhCHCH_3$, CH_3CH=CH), 34.8, 38.0 (CH_2CHCH_2), 51.3 (OCH_3), 51.7, 57.3 (CH_2CHCH_2, $PhCHCH_3$), 126.4, 127.6, 128.5, 128.8, 129.0, 129.7, 130.2, 133.2 (aromatic *C*H, *C*H=*C*H), 138.2, 139.8 (2 × *ipso-C*), 171.6, 172.8 (2 × *C*=O); HRMS (ESI) $C_{23}H_{28}NO_3^+$ requires 366.2069; found 366.2079.

(3*R*,5*E*)-Methyl 3-(*N*-benzoylamino)hept-5-enoate 29. A solution of **28** (3.03 g, 8.30 mmol) in formic acid (40 mL) was heated to 60 °C for 14 h. The volatile material was removed *in vacuo* and the residue purified by column chromatography on silica gel (50% ether in 40–60 petrol) to afford the title compound **29** as a white solid (1.39 g, 64%, >96% de); $C_{15}H_{19}NO_3$ requires C, 69.0, H, 7.3, N, 5.4%; found C, 68.6, H, 7.6, N, 5.3%; $[\alpha]_D^{24}$ +22.8 (*c* = 1.5, $CHCl_3$); ν_{max} (KBr disc) 3317 (N–H), 1733 (C=O ester), 1634 (C=O amide); δ_H (500 MHz, $CDCl_3$) 1.67 (3H, d, *J* = 6.4, CH_3CH=CH), 2.37 (2H, m, $CHCH_2CH$), 2.67 (2H, m, CH_2CO_2), 3.71 (3H, s, OCH_3), 4.47 (1H, m, CH_2CHCH_2), 5.43 (1H, m, CH_3CH=*CH*), 5.56 (1H, dq, *J* = 6.4, 15.2, CH_3CH=CH), 6.88 (1H, d, N*H*), 7.42–7.51 (3H, m, Ph), 7.77 (2H, m, Ph); δ_C (50 MHz, $CDCl_3$) 18.0 (CH_3CH=CH), 37.0, 37.2 (CH_2CHCH_2), 46.3 (CH_2CHCH_2), 51.7 (OCH_3), 126.9, 128.4, 128.5, 129.1, 131.4 (aromatic *C*H, *C*H=*C*H), 134.6 (*ipso-C*), 166.7 (*C*=O amide), 172.6 (*C*=O ester); *m*/*z* (CI, NH_3) 262 (MH^+, 100%).

(3*R*,5*E*)-Methyl 3-(*N*-*tert*-butoxycarbonyl-*N*-benzoylamino)-hept-5-enoate 30. To a solution of **29** (1.29 g, 4.94 mmol) in THF (10 mL) was added Boc_2O (10.0 g, 46 mmol), Et_3N (0.76 mL, 5.45 mmol) and DMAP (120 mg, 0.98 mmol) and the mixture stirred at rt for 24 h. The volatile material was removed *in vacuo* and the residue purified by column chromatography on silica gel (17% ether in 40–60 petrol) to afford the title compound **30** as a colourless oil (1.44 g, 81%, >96% de); $[\alpha]_D^{26}$ −20.9 (*c* = 0.2, $CHCl_3$); ν_{max} (film) 1734 (C=O ester), 1602 (C=O amide), 1583 (C=O carbamate); δ_H (500 MHz, $CDCl_3$) 1.08 (9H, s, $C(CH_3)_3$), 1.61 (3H, d, *J* = 6.0, CH_3CH=CH), 2.44 (1H, m, CHC*H*HCH), 2.65 (1H, m, CHCH*H*CH), 2.70, 3.12 (2H, ABX system, AB part, J_{AX} = 5.4, J_{BX} = 9.4, J_{AB} = 15.8, CH_2CO_2), 3.62 (3H, s, OCH_3), 4.87 (1H, m, CH_2CHCH_2), 5.40–5.51 (2H, m, C*H*=C*H*), 7.34–7.53 (5H, m, Ph); δ_C (50 MHz, $CDCl_3$) 17.1 (CH_3CH=CH), 27.0 ($C(CH_3)_3$), 35.7, 37.3 (CH_2CHCH_2), 51.4 (OCH_3), 53.6 (CH_2CHCH_2), 82.6 ($C(CH_3)_3$), 127.1, 127.8, 128.1, 128.9, 131.1 (aromatic *C*H, *C*H=*C*H), 138.5 (*ipso-C*), 153.5 (*C*=O carbamate), 172.1, 173.6 (*C*=O amide, *C*=O ester); HRMS (ESI) $C_{20}H_{28}NO_5^+$ requires 362.1967; found 362.1981.

(3*R*,5*E*)-Methyl 3-(*N*-*tert*-butoxycarbonylamino)hept-5-enoate 31. To a solution of **30** (1.07 g, 3.00 mmol) in MeOH (20 mL) was added NaOMe (0.208 g, 3.85 mmol) and the resulting mixture stirred for 60 h at rt. Citric acid (2.22 g, 12.0 mmol) was added and then the volatile material was removed *in vacuo*. The residue was taken up in H_2O (30 mL) and the organic material extracted with ether (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification *via* column chromatography on silica gel (25% ether in 40–60 petrol) gave the title compound **31** as a white solid (0.60 g, 78%, >96% de); $C_{13}H_{23}NO_4$ requires C, 60.7, H, 8.95, N, 5.45%; found C, 61.1, H, 9.3, N, 5.4%; $[\alpha]_D^{23}$ −1.0 (*c* = 1.4, $CHCl_3$); ν_{max} (KBr disc) 3323 (N–H), 1746 (C=O ester), 1531 (C=O carbamate); δ_H (500 MHz, $CDCl_3$) 1.56 (9H, s, $C(CH_3)_3$), 1.67 (3H, d, *J* = 6.4, CH_3CH=CH), 2.23 (2H, m, $CHCH_2CH$), 2.52 (2H, d, *J* = 5.7, CH_2CO_2), 3.69 (3H, s, OCH_3), 3.94 (1H, m, CH_2CHCH_2), 4.89 (1H, br s, N*H*), 5.39 (1H, m, CH_3CH=*CH*), 5.52 (1H, dq, *J* = 15.2, 6.4, CH_3CH=CH); δ_C (50 MHz, $CDCl_3$) 17.8 (CH_3CH=CH), 28.2 ($C(CH_3)_3$), 37.5, 38.1 (CH_2CHCH_2), 47.3 (CH_2CHCH_2), 51.5 (OCH_3), 79.1 ($C(CH_3)_3$), 126.5, 129.0 (*C*H=*C*H), 155.4 (*C*=O carbamate), 172.3 (*C*=O ester); *m*/*z* (CI, NH_3) 258 (MH^+, 5%), 158 ((M–Boc)H_2^+, 100%).

(3*R*,5*E*)-Methyl 3-(*N*,*N*-di-*tert*-butoxycarbonylamino)hept-5-enoate 32. To a solution of **31** (32 mg, 0.125 mmol) in THF (1 mL) was added Boc_2O (300 mg, 1.37 mmol), Et_3N (0.019 mL, 0.14 mmol) and DMAP (5 mg, 0.04 mmol) and the resulting mixture stirred for 22 h. The volatile material was removed *in vacuo* and the residue purified by column chromatography on silica gel (17% ether in 40–60 petrol) to afford the title compound **32** as a colourless oil (28 mg, 63%, >96% de); $[\alpha]_D^{26}$ −10.2 (*c* = 0.4, $CHCl_3$); ν_{max}(film) 1738 (C=O ester), 1704 (C=O carbamate); δ_H (500 MHz, $CDCl_3$) 1.50 (18H, s, 2 × C(CH_3)$_3$), 1.64 (3H, d, *J* = 6.4, CH_3CH=CH), 2.32 (1H, m, CHC*H*HCH, 2.51 (1H, m, CHCH*H*CH), 2.62, 2.90 (2H, ABX system, AB part, J_{AX} 6.1, J_{BX} 8.5, J_{AB} 15.7, CH_2CO_2), 3.66 (3H, s, OCH_3), 4.62 (1H, m, CH_2C*H*CH_2), 5.37 (1H, m, CH_3CH=C*H*), 5.49 (1H, dq, *J* = 15.1, 6.4, CH_3C*H*=CH); δ_C (50 MHz, $CDCl_3$) 17.9 (CH_3CH=CH), 27.9 (2 × C(CH_3)$_3$), 36.1, 37.6 (CH_2CHCH_2), 51.6 (OCH_3), 54.3 (CH_2CHCH_2), 82.8 (2 × *C*(CH_3)$_3$), 126.9, 128.3 (*C*H=*C*H), 152.5, 154.2 (2 × *C*=O carbamate), 171.9 (*C*=O ester); HRMS (ESI) $C_{19}H_{31}NO_6^+$ requires 358.2229; found 358.2229.

Dibenzyl dicarbonate. NaH (60% dispersion in mineral oil, 10.64 g, 0.293 mol) was placed in a three necked flask, equipped with a mechanical stirrer, under N_2 and washed with pentane (2 × 10 mL). THF (400 mL) was added and the stirred suspension cooled to 0 °C. Benzyl alcohol (28.9 g, 0.266 mol) was added as a solution in THF (50 mL) *via* cannula. The mixture was stirred at 0 °C for 1 h, allowed to warm to rt over 1 h and then heated to reflux for 2 h. After cooling again to 0 °C, CO_2 (g, dried by passage through aq H_2SO_4 (10 M)) was bubbled through the solution for 30 min, transforming the reaction mixture into a thick slurry. Benzyl chloroformate (45.5 g, 0.266 mol) was added as a solution in THF (100 mL) *via* cannula and the reaction mixture stirred at rt for 18 h. The resulting solution was filtered through Celite® and the solvent removed *in vacuo* to afford the title compound as a colourless, viscous oil, with spectroscopic properties consistent with commercially available samples (59.9 g, 79%); δ_H (200 MHz, $CDCl_3$) 5.34 (4H, s, 2 × CH_2), 7.42–7.48 (10H, m, Ph).

The oil solidified on standing in a freezer (−25 °C) for 24 h, and was stored at this temperature. Dibenzyl dicarbonate prepared in this way also contains dibenzyl carbonate as an impurity.

(3*R*,5*E*,α*R*)-Isopropyl 3-(*N*-benzyloxycarbonyl-*N*-α-methybenzylamino)hept-5-enoate 33. Amino ester **26** (3.6 g, 12.5 mmol) and dibenzyl dicarbonate (17.8 g, *ca* 62.5 mmol, containing dibenzyl carbonate as an impurity) were mixed in a flask and DCM (2 mL) added until the mixture became homogeneous. The mixture was allowed to stand at rt for 4 days, during which time CO_2 evolved slowly indicating the progress of the reaction. The reaction mixture was diluted with DCM (100 mL) and filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography on silica gel (10% ether in 40–60 petrol) to afford an inseparable mixture of the *N*-Cbz derivative **33** and dibenzyl carbonate (5.76 g, 7 : 3 **33** : dibenzyl carbonate, 90% yield for **33**). The mixture was used for the next step without further purification.

Data for 33. δ_H (200 MHz, $CDCl_3$) 1.10 (3H, d, *J* = 6.2, CH_3CHCH$_3$), 1.11 (3H, d, *J* = 6.2, CH_3CHC*H*$_3$), 1.55 (3H, d, *J* = 7.2, PhCHC*H*$_3$), 1.64 (3H, d, *J* = 5.1, CH_3CH=CH), 1.92 (1H, m, CH=CHC*H*H), 2.35 (1H, m, CH=CHCH*H*), 2.53 (2H, br s, CHC*H*$_2$CO), 3.67 (1H, m, C*H*CH_2CO), 4.80 (1H, septet, *J* = 6.3, CO_2C*H*(CH_3)$_2$), 5.06–5.65 (2H, m, CH_3C*H*=C*H*), 5.20 (2H, s, PhC*H*$_2$), 5.35 (1H, m, PhC*H*CH_3), 7.25–7.43 (10H, m, Ph).

(3*R*,5*E*,α*R*)-Methyl 3-(*N*-benzyloxycarbonyl-*N*-α-methybenzylamino)hept-5-enoate 34. To secondary amine **27** (27.9 g, 107 mmol) was added dibenzyl dicarbonate (61.2 g, *ca.* 214 mmol, containing dibenzyl carbonate as an impurity) and the mixture stirred under high vacuum for 4 days. Purification by column chromatography on silica gel (20% ether in 40–60 petrol) afforded an inseparable mixture of the title compound **34** and dibenzyl carbonate as a colourless oil (32.6 g, 8 : 2 **34** : dibenzyl carbonate, 88% yield of **34**), which was used without further purification.

Data for 34. ν_{max} (film) 2951 (C–H), 1737 (C=O ester), 1692 (C=O carbamate); δ_H (200 MHz, $CDCl_3$) 1.59 (3H, d, *J* = 7.2, PhCHC*H*$_3$), 1.67 (3H, d, *J* = 4.8, CH_3CH=CH), 1.90–2.80 (4H, br m, CH_2CHCH_2), 3.50 (3H, s, OCH_3), 3.69 (1H, m, CH_2C*H*CH_2), 5.27 (2H, s, C*H*$_2$Ph), 5.19–5.51 (3H, m, C*H*=C*H*, CH_3C*H*Ph), 7.30–7.45 (10H, m, Ph); *m*/*z* (APCI) 418 (MNa$^+$, 32%), 292 (35), 242 (100), 105 (65).

(3*R*,5*E*,α*R*)-Methyl 3-(*N*-methoxycarbonyl-*N*-α-methylbenzylamino)hept-5-enoate 35. To a solution of **27** (201 mg, 0.77 mmol) in acetone (3 mL) was added K_2CO_3 (640 mg, 4.63 mmol) and methyl chloroformate (294 mg, 3.11 mmol) and the resulting mixture heated to reflux for 24 h. The volatile material was then removed *in vacuo* and the residue taken up in H_2O (15 mL). The organic material was extracted with DCM (3 × 15 mL), the combined extracts dried ($MgSO_4$), filtered and the solvent removed *in vacuo.* Purification *via* column chromatography on silica gel (33% ether in 40–60 petrol) afforded the title compound **35** as an oil (207 mg, 84%); $[\alpha]_D^{26}$ +35.1 (*c* = 1.5, $CHCl_3$); ν_{max} (film) 2954 (C–H), 1738 (C=O ester), 1700 (C=O carbamate); δ_H (200 MHz, $CDCl_3$) 1.54 (3H, d, *J* = 7.2, PhCHC*H*$_3$), 1.64 (3H, d, *J* = 6.6, CH_3CH=CH), 2.00 (1H, br m, C*H*HCO_2), 2.72 (3H, m, CH*H*CO_2, CHC*H*$_2$CH), 3.48 (3H, s, $CH_2CO_2CH_3$), 3.61 (1H, m, CH_2C*H*CH_2), 3.75 (3H, s, NCO_2CH_3), 5.25–5.54 (3H, m, CH_3C*H*=C*H*, PhC*H*CH_3), 7.25–7.35 (5H, m, Ph); δ_C (50 MHz, $CDCl_3$) 17.4, 17.7 (*C*H$_3$CH=CH, PhCH*C*H$_3$), 36.8, 38.5 (*C*H$_2$CH*C*H$_2$), 51.2, 54.1 (CH_2CO_2*C*H$_3$, NCO_2*C*H$_3$), 127.6, 127.7, 128.0, 128.2, 128.5 (aromatic *C*H, *C*H=*C*H), 141.0 (*ipso*-C), 156.2 (*C*=O carbamate), 172.2 (*C*=O ester); HRMS (ESI) $C_{18}H_{25}NO_4^+$ requires 320.1859; found 320.1861.

(3*R*,5*E*,α*R*)-Methyl 3-(*N*-*tert*-butoxycarbonyl-*N*-α-methylbenzylamino)hept-5-enoate 36. To a solution of **27** (308 mg, 1.18 mmol) in DCM (2 mL) was added Et_3N (0.33 mL, 2.36 mmol), DMAP (14 mg, 0.118 mmol) and Boc_2O (1.55 g, 7.10 mmol). The resulting mixture was stirred at rt for 17 h and then the volatile material removed *in vacuo.* Purification *via* column chromatography on silica gel (20% ether in 40–60 petrol) afforded the title compound **36** as an oil (404 mg, 95%); $[\alpha]_D^{26}$ +43.6 (*c* = 1.5, $CHCl_3$); ν_{max} (film) 1732 (C=O); δ_H (500 MHz, $CDCl_3$) 1.57 (9H, s, C(CH_3)$_3$), 1.60 (3H, d, *J* = 6.8, PhC*H*CH_3), 1.67 (3H, d, *J* = 6.5, CH_3CH=CH), 2.06 (1H, br d, *J* = 16.1, C*H*$_2CO_2$), 2.43 (1H, m, CHCH*H*CH), 2.66 (1H, m, CHC*H*HCH), 2.80 (1H, dd, *J* = 16.1, 8.8, C*H*$_2CO_2$), 3.48 (3H, s, OCH_3), 3.60 (1H, m, CH_2C*H*CH_2), 5.25 (1H, q, *J* = 6.8, PhC*H*CH_3), 5.37 (1H, m, CH_3CH=C*H*), 5.56 (1H, dq, *J* = 15.1, 6.5, CH_3C*H*=CH), 7.30–7.39 (5H, m, Ph); δ_C (125 MHz, $CDCl_3$) 17.1 (*C*H$_3$CH=CH), 17.4 (PhCH*C*H$_3$), 27.3 (C(*C*H$_3$)$_3$), 35.1, 37.4 (*C*H$_2$CH*C*H$_2$), 51.3 (O*C*H$_3$), 52.9, 56.5 (Ph*C*HCH$_3$, CH_2*C*HCH_2), 84.7 (*C*(CH_3)$_3$), 127.2, 127.7, 128.1, 128.7, 128.9 (aromatic *C*H, *C*H=*C*H), 140.0 (*ipso*-*C*), 172.0 (*C*=O ester); HRMS (ESI) $C_{21}H_{31}NO_4^+$ requires 326.2331; found 326.2331.

(3*R*,5*E*)-Methyl 3-(*N*-benzyloxycarbonylamino)hept-5-enoate 37. A solution of **34** (4.80 g, 13 mmol) in formic acid (50 mL) was heated to 60 °C for 4 h. The volatile material was removed *in vacuo* and the residue purified by column chromatography on silica gel (33% ether in 40–60 petrol) to afford the title compound **37** as a colourless oil (3.18 g, 84%); $[\alpha]_D^{23}$ +2.2 (*c* = 1.0, $CHCl_3$); ν_{max} (film) 3338 (N–H), 1733 (C=O ester), 1531 (C=O carbamate); δ_H (500 MHz, $CDCl_3$) 1.65 (3H, d, *J* = 6.4, CH_3CH=CH), 2.26 (2H, m, CHC*H*$_2$CH), 2.55 (2H, d, *J* = 5.2, C*H*$_2CO_2$), 3.67 (3H, s, OCH_3), 4.02 (1H, m, CH_2C*H*CH_2), 5.10 (2H, s, C*H*$_2$Ph), 5.20 (1H, br d, *J* = 7.4 N*H*), 5.37 (1H, m, CH_3CH=C*H*), 5.51 (1H, dq, *J* = 15.2, 6.4, CH_3C*H*=CH), 7.30–7.38 (5H, m, Ph); δ_C (50 MHz, $CDCl_3$) 17.9 (*C*H$_3$CH=CH), 37.4, 37.9 (*C*H$_2$CH*C*H$_2$), 47.9 (CH_2*C*HCH_2), 51.6 (O*C*H$_3$), 66.6 (*C*H$_2$Ph), 126.3, 128.4, 128.5, 129.1, 129.4 (aromatic *C*H, *C*H=*C*H), 136.8 (*ipso*-*C*), 156.0 (*C*=O carbamate), 172.3 (*C*=O ester); HRMS (ESI) $C_{16}H_{21}NO_4^+$ requires 292.1553; found 292.1549.

(4*R*,6*R*,1′*S*)- and (4*R*,6*S*,1′*R*)-4-(methoxycarbonylmethyl)-6-(1′-iodoethyl)-1,3-oxazin-2-one (4*R*,6*R*,1′*S*)-*anti*-38 and (4*R*,6*S*,1′*R*)-*syn*-39. ***From N-Boc amine 31.*** To a solution of **31** (100 mg, 0.389 mmol) in DCM (10 mL) at 0 °C, TBDMSOTf (154 mg, 0.583 mmol) and 2,6-lutidine (83 mg, 0.775 mmol) were added. After stirring for 1 h at 0 °C, I_2 (395 mg, 1.56 mmol) was added and the resulting mixture stirred for a further 2 h at 0 °C. The reaction mixture was diluted with DCM (30 ml), washed with aq $Na_2S_2O_3$ (1 M, 10 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification *via* column chromatography on silica gel (9% MeOH in DCM) afforded an inseparable mixture of the title compounds *anti*-**38** and *syn*-**39** (111 mg, 87%, ratio 60 : 40 *anti*-**38** : *syn*-**39**).

From N,N-di-Boc amine 32. To a solution of **32** (20 mg, 0.056 mmol) in DCM (5 mL) at 0 °C, I_2 (57 mg, 0.225 mmol) was added and the resulting mixture stirred for 2 h at 0 °C. The reaction mixture was diluted with DCM (20 ml) and washed with aq $Na_2S_2O_3$ (1 M, 10 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification *via* column chromatography on silica gel (9% MeOH in DCM) afforded an inseparable mixture of the title compounds *anti*-**38** and *syn*-**39** (15 mg, 84%, 73 : 27 *anti*-**38** : *syn*-**39**).

From carboxybenzyl amine 37. To a solution of **37** (2.09 g, 7.17 mmol) in DCM (30 mL) at 0 °C, TBDMSOTf (5.69 g, 22.0 mmol) and 2,6-lutidine (3.07 g, 29.0 mmol) were added. After stirring for 1 h at 0 °C, I_2 (10.9 g, 43.0 mmol) was added and the resulting mixture stirred for a further 2 h at 0 °C. The reaction mixture was diluted with DCM (100 ml), washed with aq $Na_2S_2O_3$ (1 M, 50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification *via* column chromatography on silica gel (9% MeOH in DCM) afforded an inseparable mixture of the title compounds *anti*-**38** and *syn*-**39** (2.11 g, 90%, 91 : 9 *anti*-**38** : *syn*-**39**); ν_{max}(film) 1731 (C=O ester), 1682 (C=O carbamate); *anti*-**38** δ_H (500 MHz, $CDCl_3$) 2.01 (3H, d, *J* = 6.8, C*H*$_3$CHI), 2.17 (2H, m, CHC*H*$_2$CH), 2.53 (1H, dd, *J* = 16.7, 4.9, C*H*HCO$_2$), 2.64 (1H, dd, *J* = 16.7, 9.1, CH*H*CO$_2$), 3.72 (3H, s, OC*H*$_3$), 3.96 (1H, m, C*H*N), 4.12 (1H, m, C*H*O), 4.20 (1H, quintet, *J* = 6.8, C*H*I), 6.31 (1H, br s, N*H*); δ_C (50 MHz, $CDCl_3$) 23.8 (*C*H$_3$CHI), 26.4 (*C*HI), 29.9 (CH*C*H$_2$CH), 40.4 (*C*H$_2$CO$_2$), 44.6 (*C*HN), 50.2 (O*C*H$_3$), 52.1 (*C*HO), 153.6 (*C*=O carbamate), 171.3 (*C*=O ester); *syn*-**39** selected δ_H (500 MHz, $CDCl_3$) 1.95 (3H, d, *J* = 7.0, C*H*$_3$CHI), 2.68 (1H, dd, *J* = 16.7, 9.1, C*H*$_2$CO$_2$), 3.71 (3H, s, OC*H*$_3$), 4.05 (1H, m, C*H*O), 4.27 (1H, m, C*H*I), 6.41 (1H, br s *N*H); HRMS (ESI) $C_9H_{14}INO_4^+$ 328.0041; found 328.0046.

(4*R*,6*R*,1′*S*,α*R*)- and (4*R*,6*S*,1′*R*,α*R*)-3-(α-methylbenzyl)-4-(isopropoxycarbonylmethyl)-6-(1′-iodoethyl)-1,3-oxazin-2-one (4*R*,6*R*,1′*S*,α*R*)-*anti*-40 and (4*R*,6*S*,1′*R*,α*R*)-*syn*-42. A solution of **33** (13.7 g, containing dibenzyl carbonate, 76% **33**, 24.8 mmol) in DCM (150 mL) was cooled to 0 °C and I_2 (25.1 g, 98.9 mmol) was added. The resulting mixture was stirred at 0 °C for 3 h, then washed with aq $Na_2S_2O_3$ (1 M, 100 mL) and dried ($MgSO_4$). After filtration and removal of the solvent *in vacuo*, purification of the residue by column chromatography on silica gel (20% EtOAc in DCM) gave a mixture of the two diastereomers *anti*-**40** and *syn*-**42** (10.41 g, 92%, 95 : 5 *anti*-**40** : *syn*-**42**). Recrystallisation from EtOAc/hexane afforded oxazin-2-one *anti*-**40** as a single diastereomer as colourless needles (7.0 g). Additional **40** was obtained from the mother liquor by removal of the solvent and chromatographic purification of the residue followed by recrystallization (combined yield 7.67 g, 68%, >98% de); $C_{19}H_{26}INO_4$ requires C, 49.7, H, 5.7, N, 3.05%; found C, 49.9, H, 5.95, N, 3.3%; mp 104–106 °C; $[\alpha]_D^{25}$ +30.9 (*c* = 1.0, $CHCl_3$); ν_{max} (film) 1730 (C=O ester), 1685 (C=O carbamate); δ_H (500 MHz, $CDCl_3$) 1.16 (3H, d, *J* = 6.3, C*H*$_3$CHCH$_3$), 1.18 (3H, d, *J* = 6.3, CH$_3$CHC*H*$_3$), 1.62 (3H, d, *J* = 7.1, PhCHC*H*$_3$), 1.68 (1H, ddd, *J* = 15.6, 3.3, 1.3, CHC*H*HCH), 1.82 (1H, dddd, *J* = 13.9, 12.2, 4.4, 1.3, CHCH*H*CH), 1.98 (3H, d, *J* = 6.9, C*H*$_3$CHI), 2.21 (1H, dd, *J* = 15.7, 11.2, C*H*HCO), 2.38 (1H, ddd, *J* = 15.6, 3.3, 1.3, CH*H*$_2$CO), 3.93 (1H, dddd, *J* = 10.5, 4.8, 3.8, 2.3, C*H*CH$_2$CO), 4.08 (1H, ddd, *J* = 11.6, 7.3, 4.0, CHIC*H*CH$_2$), 4.29 (1H, m, CHI), 4.90 (1H, septet, *J* = 6.3, CO$_2$C*H*(CH$_3$)$_2$), 5.62 (1H, q, *J* = 7.1, PhC*H*CH$_3$), 7.29–7.44 (5H, m, Ph); δ_C (50 MHz, $CDCl_3$) 16.0 (*C*H$_3$CHI), 21.6, 21.7 (*C*H$_3$CH*C*H$_3$), 23.9 (PhCH*C*H$_3$), 29.3 (*C*HI), 32.0 (CH*C*H$_2$CH), 38.3 (CH*C*H$_2$CO), 46.6 (*C*HCH$_2$CO), 54.6 (CHI*C*HCH$_2$), 68.3 (*C*H(CH$_3$)$_2$), 77.7 (Ph*C*HCH$_3$), 127.9, 128.1, 128.6 (aromatic *C*H), 139.3 (*ipso*-*C*), 152.1 (*C*=O carbamate), 169.6 (*C*=O ester); *m*/*z* (CI) 460 (MH$^+$, 94%), 290 (100).

X-Ray crystal structure determination for 40. Data were collected using an Enraf-Nonius CAD4 diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at room temperature. The structure was solved by direct methods (SHELXS86), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[36]

X-Ray crystal structure data for 40 [$C_{19}H_{26}INO_4$]. M = 459.3, orthorhombic, space group *P* 21 21 21, *a* = 8.2499(9) Å, *b* = 13.392(3) Å, *c* = 18.480(2) Å, *V* = 2041.8 Å^3, *Z* = 4, μ = 126.5 cm^{-1}, colourless crystals, crystal dimensions = 0.2 × 0.25 × 0.5 mm. A total of 2441 unique reflections were measured for $0 < \theta < 72$ and 1639 reflections were used in the refinement. The final parameters were wR_2 = 0.040 and R_1 = 0.036 [$I > 3\sigma(I)$], Flack enantiopole −0.011(12).

CCDC reference number 234778. See http://www.rsc.org/suppdata/ob/b4/b404962d/ for crystallographic data in .cif or other electronic format.

(4*R*,6*R*,1′*S*,α*R*)- and (4*R*,6*S*,1′*R*,α*R*)-3-(α-methylbenzyl)-4-(methoxycarbonylmethyl)-6-(1′-iodoethyl)-1,3-oxazin-2-one (4*R*,6*R*,1′*S*,α*R*)-*anti*-41 and (4*R*,6*S*,1′*R*,α*R*)-*syn*-43. *From N-benzyloxycarbonyl-N-α-methylbenzylamine 34.* To a solution of **34** (2.09 g, 5.29 mmol) in DCM (50 mL) under N_2 at 0 °C, I_2 (5.37 g, 21.2 mmol) was added and the resulting mixture was stirred at 0 °C for 3 h. The mixture was then added to aq NaS_2O_3 (1 M, 40 mL) and extracted with DCM (3 × 80 mL). The combined organic material was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a mixture of two diastereoisomers (97%, 92 : 8 *anti*-**41** : *syn*-**43**). Purification *via* column chromatography on silica gel (25% EtOAc in 40–60 petrol) and recrystallisation from EtOAc/hexane afforded the title compound *anti*-**41** as white needles (1.66 g, 77%, >98% de).

From N-methoxycarbonyl-N-α-methylbenzylamine 35. To a solution of **35** (104 mg, 0.312 mmol) in DCM (10 mL) at 0 °C, I_2 (238 mg, 0.938 mmol) and KI (78 mg, 0.470 mmol) were added and the resulting mixture was stirred at 0 °C for 1 h, then at rt for 76 h. The mixture was then washed with aq $Na_2S_2O_3$ (1 M, 10 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification *via* column chromatography on silica gel (25% EtOAc in 40–60 petrol) afforded a mixture of the title compounds *anti*-**41** and *syn*-**43** (114 mg, 85%, 80 : 20 *anti*-**41** : *syn*-**43**).

From N-tert-butoxycarbonyl-N-α-methylbenzylamine 36. To a solution of **36** (136 mg, 0.377 mmol) in DCM (5 mL) at 0 °C, I_2 (382 mg, 1.51 mmol) was added and the resulting mixture was stirred at 0 °C for 4 h. The mixture was then washed with aq $Na_2S_2O_3$ (1 M, 50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification *via* column chromatography on silica gel (25% EtOAc in 40–60 petrol) afforded a mixture of the title compounds *anti*-**41** and *syn*-**43** (60 mg, 37%, 75 : 25 *anti*-**41** : *syn*-**43**).

Data for anti-41. $C_{17}H_{22}INO_4$ requires C, 47.35, H, 5.1, N, 3.25%; found C, 47.3, H, 5.0, N, 3.2%; mp 106 °C; $[\alpha]_D^{24}$ +36.2 (*c* = 0.7, $CHCl_3$); ν_{max} (KBr disc) 1734 (C=O ester), 1680 (C=O carbamate); δ_H (400 MHz, $CDCl_3$) 1.62 (3H, d, *J* = 7.1, PhCHC*H*$_3$), 1.71 (1H, m, CH*H*C=O), 1.83 (1H, m, CHCH*H*CH), 1.97 (3H, d, *J* = 7.0, C*H*$_3$CHI), 2.25 (1H, dd, *J* = 16.1, 10.9, CH*H*C=O), 2.36 (1H, ddd, *J* = 13.9, 3.9, 2.3, CHC*H*HCH), 3.58 (3H, s, OC*H*$_3$), 3.94 (1H, m, CH$_2$C*H*CH$_2$), 4.07 (1H, m, C*H*O), 4.23 (1H, m, C*H*I), 5.68 (1H, q, *J* = 7.1, PhC*H*CH$_3$), 7.24–7.43 (5H, m, Ph); δ_C (50 MHz) 16.4 (PhCH*C*H$_3$), 24.4 (*C*H$_3$CHI), 29.8 (*C*HI), 32.6 (CH*C*H$_2$CH), 38.2 (*C*H$_2$C=O), 46.9 (CH$_2$*C*HCH$_2$), 52.3 (O*C*H$_3$), 55.1 (Ph*C*HCH$_3$), 78.0 (*C*HO), 128.4, 128.6, 129.2 (aromatic *C*H), 139.9 (*ipso*-*C*), 152.6 (*C*=O carbamate), 171.1 (*C*=O ester); *m*/*z* (APCI) 454 (MNa$^+$, 20%), 432 (MH$^+$, 38), 328 (20), 284 (50), 200 (48), 158 (25), 105 (100).

(4*R*,6*R*,1′*R*,α*R*)-3-(α-Methylbenzyl)-4-(isopropoxycarbonylmethyl)-6-(1′-azidoethyl)-1,3-oxazin-2-one 48. To a solution of **40** (4.03 g, 8.78 mmol) in DMF–H_2O (25 : 1, 52 mL) was added sodium azide (2.90 g, 44.6 mmol) and the mixture stirred at 100–110 °C for 4.5 h. The reaction mixture was diluted with H_2O (150 mL) and extracted with ether (3 × 70 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*, affording a very viscous oil (3.06 g, 1.5 : 1 **48** : **50**, 59% yield of **48**), which was used without further purification.

Data for 48. Selected δ_H (200 MHz, $CDCl_3$) 3.55 (1H, dq, *J* = 7.5, 5.9, CH_3CHN_3), 3.92 (1H, m, CHCH$_2$CO), 4.29 (1H, dt, *J* = 10.7, 5.3, CHCHO), 4.87 (1H, m, C*H*(CH_3)$_2$), 5.62 (1H, q, *J* = 6.4, PhC*H*CH_3).

Data for 50. Selected δ_H (200 MHz, $CDCl_3$) 1.50 (3H, d, *J* = 7.9, CH_3CH=C), 2.80 (1H, d, *J* = 14.9, CHHCHCH$_2$), 3.92 (1H, m, CHCH$_2$CO), 4.87 (1H, m, C*H*(CH_3)$_2$), 5.31 (1H, q, *J* = 6.9, CH_3C*H*=C), 5.67 (1H, q, *J* = 6.4, PhC*H*CH_3).

(4*R*,6*R*,1′*R*,α*R*)-3-(α-Methylbenzyl)-4-(isopropoxycarbonylmethyl)-6-(1′-aminoethyl)-1,3-oxazin-2-one 52. To a solution of a mixture of **48** and **50** (5.75 g, 1.5 : 1 **48** : **50**, 9.68 mmol **48**) in MeOH (100 mL) was added Pd on C (600 mg) and the mixture stirred under H_2 (1 atm) at rt for 23 h. The catalyst was removed by filtration through Celite®. Removal of the solvent *in vacuo* followed by purification by column chromatography on silica gel (17% MeOH in DCM) afforded the desired amine **52** as a white solid (3.04 g, 90%); $C_{19}H_{28}N_2O_4$ requires C, 66.1, H, 7.3, N, 8.1%; found C, 66.0, H, 7.35, N 8.1%; mp 63–65 °C; $[\alpha]_D^{25}$ +33.6 (*c* = 0.7, $CHCl_3$); ν_{max} (film) 3340 (N–H), 1730 (C=O ester), 1670 (C=O carbamate); δ_H (200 MHz, $CDCl_3$) 1.08 (3H, d, *J* = 6.6, CH_3CHNH$_2$), 1.14 (3H, d, *J* = 6.2, CH_3CHCH$_3$), 1.15 (3H, d, *J* = 6.2, CH$_3$CHCH_3), 1.53 (2H, s, NH_2), 1.60 (3H, d, *J* = 7.3, PhCHCH_3), 1.63–1.97 (3H, m, CHCH_2CH, CHC*H*HCO), 2.19 (1H, dd, *J* = 10.9, 5.1, CHCH*H*CO), 2.97 (1H, quintet, *J* = 5.1, CH$_3$C*H*NH$_2$), 3.92–4.11 (2H, m, C*H*CH$_2$C*H*), 4.88 (1H, septet, *J* = 6.3, C*H*(CH_3)$_2$), 5.62 (1H, q, *J* = 7.1, PhC*H*CH$_3$), 7.27–7.44 (5H, m, Ph); *m*/*z* (CI) 349 (MH$^+$, 100%).

(4*R*,6*R*,1′*R*,α*R*)-3-(α-Methylbenzyl)-4-(methoxycarbonylmethyl)-6-(1′-azidoethyl)-1,3-oxazin-2-one 49. To a solution of oxazin-2one *anti*-**41** (3.27 g, 7.53 mmol) in DMF/H_2O (25 : 1, 62.5 mL), NaN_3 (2.45 g, 37.7 mmol) was added and the mixture heated to 110 °C for 5 h. The reaction mixture was allowed to cool, H_2O (400 mL) added and the organic material extracted with ether (3 × 250 mL). The combined organic extracts were washed with brine (300 mL), filtered, and the solvent removed *in vacuo* to afford a mixture of the title compound **49** and the elimination product **51** as a white solid (2.84 g, 3 : 2 **49** : **51**), which was used without further purification.

Data for 49. Selected δ_H (200 MHz, $CDCl_3$) 1.39 (3H, d, *J* = 6.8, CH_3CHN$_3$), 1.62 (3H, d, *J* = 7.1, PhCHCH_3), 3.56 (3H, s, OCH_3), 4.29 (1H, dt, *J* = 12.0, 4.1, C*H*O), 5.67 (1H, q, *J* = 7.1, PhC*H*).

(4*R*,6*E*,α*R*)-Methyl 3-(α-methylbenzyl)-4-(methoxycarbonylmethyl)-6-ethylene-1,3-oxazin-2-one 51. To a stirred solution of iodide **41** (180 mg, 0.418 mmol) in DMF (2 mL) under Ar, was added potassium phthalimide (155 mg, 0.836 mmol) and the resulting mixture stirred for 48 h. Aq sat NH_4Cl (5 mL) was added, then H_2O (20 mL), and the organic material extracted with ether (3 × 25 mL). The organic extracts were combined, washed with brine (50 mL), aq NaOH (1 M, 50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by column chromatography (25% EtOAc in 30–40 petrol) afforded the title compound **51** as colourless needles (96 mg, 76%); $C_{17}H_{21}NO_4$ requires C, 67.3; H, 7.0; N, 4.6%; found C, 67.2; H, 6.95; N, 4.6%; mp 91 °C; $[\alpha]_D^{26}$ +56.3 (*c* = 0.90, $CHCl_3$); ν_{max} (KBr disc) 2952 (C–H), 1732 (C=O ester), 1714 (C=O carbamate), 1676 (C=C); δ_H (400 MHz, $CDCl_3$) 1.49 (1H, m, C*H*HC=O), 1.50 (3H, dd, *J* = 7.2, 1.8, CH_3CH=C), 1.60 (3H, d, *J* = 7.0, PhCHCH_3), 2.17 (1H, dd, *J* = 16.4, 10.9, CH*H*C=O), 2.31 (1H, m, CCH*H*CH), 2.81 (1H, dd, *J* = 14.8, 2.0, CC*H*HCH), 3.53 (3H, s, OCH_3), 3.91 (1H, m, CH$_2$C*H*CH$_2$), 5.31 (1H, dq, *J* = 7.2, 2.1, C*H*=C), 5.69 (1H, q, *J* = 7.1, CH$_3$C*H*Ph), 7.27–7.43 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 10.4 (CH_3CH=C), 15.9 (CH_3CHN), 27.0 (CCH_2CH), 36.9 (CH_2C=O), 45.9 (CH$_2$CHCH$_2$), 51.6 (OCH_3), 54.6 (CH$_3$CHN), 104.7 (CH=C), 128.0, 128.3, 128.7 (aromatic CH), 139.0 (*ipso*-C), 144.1 (C=CH), 151.0 (C=O carbamate), 170.9 (C=O ester); *m*/*z* (APCI$^+$) 304 (MH$^+$, 35%), 303 (50), 200 (65), 199 (100).

(4*R*,6*R*,1′*R*,α*R*)-3-(α-Methylbenzyl)-4-(methoxycarbonylmethyl)-6-(1′-aminoethyl)-1,3-oxazin-2-one 53. To a solution of azide **49** (2.84 g, 3 : 2 **49** : **51**, from 7.53 mmol oxazin-2-one *anti*-**41**) in degassed MeOH (60 mL) was added 10% Pd on C (100 mg), and the resulting mixture was stirred under 1 atm of H_2 for 28 h. The reaction mixture was filtered through Celite®, eluting with further MeOH (100 mL) and the solvent removed *in vacuo*. Purification *via* column chromatography on silica gel (9% MeOH in DCM then 17% MeOH in DCM) afforded the title compound **53** as a white solid (1.24 g, 52% over 2 steps); mp 91–92 °C; $[\alpha]_D^{22}$ +32.1 (*c* = 0.9, $CHCl_3$); ν_{max} (KBr disc) 3348 (N–H), 1732 (C=O ester), 1661 (C=O carbamate); δ_H (400 MHz, $CDCl_3$) 1.06 (3H, d, *J* = 6.3, CH_3CHNH$_2$), 1.57 (3H, d, *J* = 7.1, PhCHCH_3), 1.66 (1H, dd, *J* = 16.4, 2.6, C*H*HC=O), 1.76–1.89 (2H, m, CHCH_2CH), 1.95 (2H, br, NH_2), 2.22 (1H, dd, *J* = 16.4, 10.8, CH*H*C=O), 2.94 (1H, br, C*H*NH$_2$), 3.51 (3H, s, OCH_3), 3.94 (1H, m, CH$_2$C*H*CH$_2$), 4.03 (1H, m, C*H*O), 5.60 (1H, q, *J* = 7.1, CH$_3$C*H*Ph), 7.24–7.39 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 15.9 (CH_3CHNH$_2$), 19.1 (CH_3CHPh), 29.0 (CHCH_2CH), 37.5 (CH_2C=O), 46.5, 50.7 (CH$_3$CHNH$_2$, CH$_2$CHCH$_2$), 51.7 (OCH_3), 54.7 (PhCHCH$_3$), 78.9 (CHO), 127.8, 128.0, 128.6 (aromatic CH), 139.5 (*ipso*-C), 152.9 (C=O carbamate), 170.7 (C=O ester); *m*/*z* (APCI) 641 (M_2H^+, 100%), 343 (MNa$^+$, 15), 321 (MH$^+$, 52); HRMS (ESI) $C_{17}H_{24}N_2O_4^+$ requires 321.1814; found 321.1802.

(3*R*,5*R*,6*R*)-3,6-Diamino-5-hydroxyheptanoic acid dihydrochloride 54. A solution of the amine **52** (382 mg, 0.59 mmol) in HCl (5 M, 3 mL) was heated to reflux for 72 h. The volatile material was removed *in vacuo* and the crude product passed through a column of Amberlite XAD-II resin, chloride form (H_2O). Lyophilization afforded the dihydrochloride **54** as a pale yellow powder (101 mg, 69%); $[\alpha]_D^{25}$ −3.1 (*c* = 0.68, H_2O) {lit.[2] $[\alpha]_D$ −2.7 (*c* = 0.58, H_2O)}; δ_H (200 MHz, D_2O) 1.28 (3H, d, *J* = 6.7, CH_3), 1.88 (1H, ddd, *J* = 15.1, 9.7, 4.2, CHC*H*HCH), 2.06 (1H, ddd, *J* = 15.1, 7.9, 2.8, CHCH*H*CH), 2.86 (2H, m, CH_2CO_2), 3.32 (1H, quintet, *J* = 6.9, CH$_3$C*H*NH$_2$), 3.86 (2H, m, C*H*OH, CH$_2$C*H*CH$_2$); δ_C (50 MHz, D_2O) 15.5 (CH_3) 35.4, 37.3 (CHCH_2CH, CH_2CO_2), 46.4 (CH$_2$CHCH$_2$), 52.7 (CH$_3$CHNH$_2$), 69.5 (CHOH), 174.5 (C=O); *m*/*z* (ESI) 199 (MNa$^+$, 26%), 177 (MH$^+$, 100), 159 (27).

(4*R*,6*R*,1′*R*,α*R*)-3-(*N*-α-Methylbenzyl)-4-(carboxymethyl)-6-(1′-aminoethyl)-1,3-oxazin-2-one 55. To a stirred solution of ester **53** (1.84 g, 5.75 mmol) in THF/H_2O (3 : 1, 200 mL), LiOH (0.725 g, 17.3 mmol) was added. The solution was stirred at rt for 3 h and the volatile material removed *in vacuo*. The crude product was passed through a column of Dowex® 50WX ion-exchange resin (H_2O then aq NH_3 (1 M)). The ninhydrin positive fractions were combined and the solvent removed *in vacuo* to afford a white solid, which was dissolved in warm MeOH (250 mL). The solvent was removed *in vacuo* to afford the title compound **55** as a white powder (1.74 g, 99%); mp 222 °C; $[\alpha]_D^{24}$ +20.9 (*c* = 0.9, H_2O); Calculated for $C_{16}H_{22}N_2O{\cdot}xH_2O$, *x* = 1.3: C 58.3, H 7.5, N 8.50%. Found: C 58.3, H 7.55, N 8.5%; ν_{max} (KBr disc) 3418 (br, N–H), 1658 (s, C=O acid), 1544 (s, C=O carbamate); δ_H (500 MHz, D_2O) 1.23 (3H, d, *J* = 6.8, CH_3CHNH$_2$), 1.58 (3H, d, *J* = 7.1, PhCHCH_3), 1.87–2.23 (4H, m, CH_2CHCH_2), 3.41 (1H, m, NH$_2$C*H*), 4.01 (1H, m, CH$_2$C*H*CH$_2$), 4.46 (1H, m, C*H*O), 5.05 (1H, q, *J* = 7.1, PhC*H*CH$_3$), 7.26–7.34 (5H, m, Ph); δ_C (125 MHz, D_2O) 14.3, 16.4 (CH_3CHPh, CH_3CHNH$_2$), 28.2 (CHCH_2CH), 41.2 (CH_2C=O), 51.1, 51.3 (CH_3*C*HN, CH_2*C*HCH_2), 57.4 (Ph*C*HCH_3), 75.4 (*C*HO), 127.4, 128.3, 129.1 (aromatic *C*H), 140.0 (*ipso-C*), 153.9 (*C*=O carbamate), 178.4 (*C*=O acid); *m*/*z* (APCI) 305 ((M − H)$^-$, 100%), 261 (50), 212 (14), 164 (22), 114 (14).

(4*R*,6*R*,1′*R*,α*R*)-4-(Carboxymethyl)-6-(1′-aminoethyl)-1,3-oxazin-2-one 56. To a flask containing NH_3(l) (70 mL, condensed at −78 °C), purged with Ar, was added EtOH (2.0 mL), followed by Na (0.420 g, 18.3 mmol) in small pieces. The resulting blue solution was stirred at −78 °C for 5 min before amino acid **55** (500 mg, 1.64 mmol) was added in one portion. The reaction mixture was stirred at −78 °C for a further 1 h, then NH_4Cl (1.80 g) was added. The mixture was allowed to warm to rt over 18 h, during which time the NH_3 evaporated. MeOH (500 mL) was added, the solution filtered and the solvent removed *in vacuo*. The crude material was passed through a column of Dowex® 50WX ion-exchange resin (H_2O then aq NH_3 (1 M)). The ninhydrin positive fractions were combined and the solvent removed *in vacuo* to afford a white solid, which was dissolved in warm MeOH (250 mL). The solvent was removed *in vacuo* to afford the title compound **56** as a white powder (263 mg, 80%); $C_8H_{14}N_2O_4.H_2O$ requires C, 43.6, H, 7.3, N, 12.7%; found C, 43.5, H, 7.4, N, 12.6%; mp 222–224 °C; $[\alpha]_D^{23}$ −95.0 (*c* = 1.1, H_2O); ν_{max} (KBr disc) 3371 (br, N–H), 3232 (br, NH_3^+), 1680 (s, C=O), 1533 (m, CO_2^-); δ_H (400 MHz, D_2O) 1.24 (3H, d, *J* = 6.8, C*H*$_3$), 1.87–1.94 (2H, m, CHC*H*$_2$CH), 2.29, 2.41 (2H, ABX system, AB part, J_{AB} 15.1, J_{AX} 7.5, J_{BX} 7.1, C*H*$_2$C=O), 3.46 (1H, m, C*H*NH_2), 3.81 (1H, m, CH_2C*H*CH_2), 4.37 (1H, m, C*H*O); δ_C (125 MHz, D_2O) 14.4 (*C*H_3), 26.7 (CH*C*H_2CH), 43.7 (*C*H_2CO), 46.1, 50.5 (2 × *C*HN), 75.6 (*C*HO), 155.5 (*C*=O carbamate), 178.9 (*C*=O acid); *m*/*z* (APCI) 201 ((M − H)$^-$, 100%), 157 (84).

X-Ray crystal structure determination for 56. Data were collected using an Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at room temperature. The structure was solved by direct methods (SHELXS86), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[36]

X-Ray crystal structure data for 56 [$C_8H_{16}N_2O_5$]. *M* = 220.23, orthorhombic, space group *P* 21 21 21, *a* = 5.804(1) Å, *b* = 11.033(1) Å, *c* = 15.991(1) Å, *V* = 1023.99225(4) Å^3, *Z* = 4, μ = 0.119 cm^{-1}, colourless block, crystal dimensions = 0.2 × 0.3 × 0.4 mm. A total of 1196 unique reflections were measured for $0 < \theta < 26$ and 1159 reflections were used in the refinement. The final parameters were $wR_2 = 0.039$ and $R_1 = 0.031$ [$I > 3\sigma(I)$].

CCDC reference number 234756. See http://www.rsc.org/suppdata/ob/b4/b404962d/ for crystallographic data in .cif or other electronic format.

(4*R*,6*R*,1′*R*,α*R*)-4-(Methoxycarbonylmethyl)-6-(1′-aminoethyl)-1,3-oxazin-2-one 57. To a stirred solution of amino-acid **56** (530 mg, 2.62 mmol) in MeOH (30 mL), under Ar, was added Na_2SO_4 (350 mg, 2.46 mmol) and HBF_4 (54% in ether, 0.71 mL, 5.24 mmol) drop-wise *via* syringe. The mixture was stirred for 18 h then the pH adjusted to 7 by addition of Et_3N. The resulting mixture was filtered and the volatile material removed *in vacuo*. Purification *via* column chromatography on silica gel (5% MeOH in DCM then 20% MeOH in DCM) and concentration of the more polar fraction afforded the title compound **57** as a colourless oil (352 mg, 62%); $[\alpha]_D^{22}$ −81.8 (*c* = 0.9, MeOH); ν_{max} (film) 3364 (N–H,), 1694 (C=O); δ_H (400 MHz, CD_3OD) 1.18 (3H, d, *J* = 6.5, C*H*$_3$CH), 1.92–2.03 (2H, m, CHC*H*$_2$CH), 2.61–2.74 (2H, m, C*H*$_2$C=O), 3.07 (1H, br, C*H*NH_2), 3.73 (3H, s, OC*H*$_3$), 3.97 (1H, m, CH_2C*H*CH_2), 4.17 (1H, m, C*H*O); δ_C (100 MHz, CD_3OD) 18.4 (*C*H_3CH), 28.5 (CH*C*H_2CH), 41.6 (*C*H_2C=O), 46.9, 51.2 (*C*HNH_2, *C*HNH), 52.3 (O*C*H_3), 80.0 (*C*HO), 156.6 (*C*=O carbamate), 173.2 (*C*=O ester); *m*/*z* (APCI) 217 (MH$^+$, 80%), 156 (100), 124 (26); HRMS (ESI) $C_9H_{16}N_2O_4^+$ requires 217.1195; found 217.1188.

(*E*,*E*)-Hexa-2,4-dienoyl chloride (sorbyl chloride). To a stirred solution of (*E*,*E*)-hexa-2,4-dienoic acid (1.0 g, 8.93 mmol) in DCM (15 mL), oxalyl chloride (1.17 mL, 13.4 mmol) was added drop-wise, followed by 2 drops of DMF. The flask was fitted with a drying tube and stirred for 2.5 h. The solvent was removed *in vacuo* and the crude material purified *via* Kugelrohr distillation (bp 40 °C, 1 mmHg) to afford the title compound as a colourless oil (1.02 g, 88%); ν_{max} (film) 1753 (C=O), 1637 (C=C), 1591 (C=C); δ_H (200 MHz, $CDCl_3$) 2.00 (3H, d, *J* = 6.1, C*H*$_3$), 6.06 (1H, d, *J* = 14.9, C*H*CO), 6.26–6.57 (2H, m, CH_3C*H*=C*H*), 7.50 (1H, dd, *J* = 14.9, 9.9, C*H*=CHCO).

(4*R*,6*R*,1′*R*,2″*E*,4″*E*)-4-(Methoxycarbonylmethyl)-6-(*N*-[hexa-2″,4″-dienoyl]-1′-aminoethyl)-1,3-oxazin-2-one 58. A stirred solution of oxazin-2-one **57** (403 mg, 0.574 mmol) in MeCN (10 mL) under Ar was cooled to 0 °C and Et_3N (473 mg, 4.68 mmol) added. After 20 min sorbyl chloride (366 mg, 2.81 mmol), as a solution in DCM (3 mL), was added drop-wise and the reaction mixture stirred at 0 °C for 3 h, then the volatile material was removed *in vacuo*. Purification *via* column chromatography on silica gel (10% MeOH in EtOAc) afforded the title compound **58** as a cream foam (475 mg, 82%); mp 65–70 °C; $[\alpha]_D^{22}$ −12.9 (*c* = 0.8, MeOH); ν_{max} (KBr disc) 3284 (N–H), 1714 (C=O); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* = 7.0, C*H*$_3$CHN), 1.74 (1H, m, CHC*H*HCH), 1.82 (3H, d, *J* = 7.1 C*H*$_3$CH=CH), 1.97 (1H, m, CHCH*H*CH), 2.46, 2.67 (2H, ABX system, AB part, J_{AB} 16.6, J_{AX} 9.2, J_{BX} 5.2, C*H*$_2$C=O), 3.67 (3H, s, OC*H*$_3$), 3.91 (1H, m, CH_2C*H*CH_2), 4.27 (1H, m, C*H*O), 4.34 (1H, m, CH_3C*H*N), 5.80 (1H, d, *J* = 15.0, CH=C*H*C=O), 6.02–6.17 (2H, m, CH_3C*H*=C*H*), 6.24 (1H, d, *J* = 3.5, N*H* carbamate), 6.40 (1H, d, *J* = 9.3, N*H* amide), 7.15 (1H, dd, *J* = 15.0, 10.4, C*H*=CHCO); δ_C (100 MHz, $CDCl_3$) 17.8, 18.5 (*C*H_3CHN, *C*H_3CH=CH), 27.9 (CH*C*H_2CH), 40.8 (*C*H_2C=O), 45.1, 46.5 (2 × *C*HN), 52.0 (O*C*H_3), 76.2 (*C*HO), 121.2 (CH=*C*HC=O), 129.6 (CH_3CH=*C*H), 141.7 (CH_3*C*H=CH), 143.1 (*C*H=CHC=O), 154.0 (*C*=O carbamate), 166.4 (*C*=O amide), 171.2 (*C*=O ester); *m*/*z* (APCI) 333 (MNa$^+$, 20%), 311 (MH$^+$, 100), 267 (15), 156 (40); HRMS (ESI) $C_{15}H_{23}N_2O_5^+$ requires 311.1607; found 311.1618.

(4*R*,6*R*,1′*R*,2″*E*,4″*E*)-3-(*tert*-Butoxycarbonyl)-4-(methoxycarbonylmethyl)-6-(*N*-[hexa-2″,4″-dienoyl]-1′-aminoethyl)-1,3-oxazin-2-one 59. To a stirred solution of oxazin-2-one **58** (156 mg, 0.503 mmol) in THF (50 mL) under Ar was added Boc_2O (121 mg, 0.554 mmol), Et_3N (56 mg, 0.554 mmol) and DMAP (15 mg, 0.125 mmol) and the mixture stirred for 3 h. Removal of the volatile material *in vacuo* and purification *via* column chromatography on silica gel (EtOAc) afforded the title compound **59** as a viscous colourless oil (140 mg, 68%); $[\alpha]_D^{26}$ +16.0 (*c* = 0.6, $CHCl_3$); ν_{max} (film) 3316 (N–H), 2980 (C–H), 1788 (C=O), 1737 (C=O carbamate, C=O Boc), 1661 (C=O amide), 1634 (C=C), 1615 (C=C), 1538 (amide II); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* = 7.0, C*H*$_3$CHNH), 1.53 (9H, s, C(C*H*$_3$)$_3$), 1.85 (3H, d, *J* = 5.8, C*H*$_3$CH=CH), 1.97–2.18 (2H, m, CHC*H*$_2$CH), 2.59, 2.81 (2H, ABX system, AB part, J_{AB} 15.4, J_{AX} 10.4, J_{BX} 3.4, C*H*$_2$C=O), 3.71 (3H, s, OC*H*$_3$), 4.34 (1H, m, CH_3C*H*N), 4.45 (1H, m, C*H*O), 4.67 (1H, m, CH_2C*H*CH_2), 5.73 (1H, d, *J* = 9.3, N*H*), 5.75 (1H, d, *J* = 15.0, CH=C*H*C=O), 6.08–6.17 (2H, m, CH_3C*H*=C*H*), 7.19 (1H, dd, *J* = 15.0, 10.1, C*H*=CHC=O); δ_C (100 MHz, $CDCl_3$) 18.0 (*C*H_3CHNH), 18.6 (*C*H_3CH=CH), 27.8 (C(*C*H_3)$_3$), 28.1 (CH*C*H_2CH), 37.9 (*C*H_2C=O), 46.4, 49.7 (2 × *C*HN), 52.1 (O*C*H_3), 77.5 (*C*HO), 84.4 (*C*(CH_3)$_3$), 120.8 (CH=*C*HC=O), 129.5 (CH_3CH=*C*H), 138.6 (CH_3*C*H=CH), 142.2 (*C*H=CHC=O), 148.9, 151.1 (*C*=O, carbamate, *C*=O Boc), 166.2 (*C*=O amide), 170.0 (*C*=O ester); *m*/*z* (APCI) 367 ((M − CO_2)H_2^+, 35%), 311 ((M − Boc)H_2^+, 100), 267 (52); HRMS (ESI) $C_{20}H_{30}N_2O_7^+$ requires 367.2233; found 367.2230.

(3*R*,5*R*,6*R*,2′*E*,4′*E*)-Methyl 3-(*N*-*tert*-butoxycarbonylamino)-5-(methoxycarbonyloxy)-6-(*N*-hexa-2′,4′-dienoyl)heptanoate 60. To a stirred solution of *N*-Boc oxazin-2-one **59** (62 mg, 0.15 mmol) in MeOH (30 mL) was added Cs_2CO_3 (5 mg, 0.015 mmol). The mixture was stirred until TLC analysis revealed complete consumption of the starting material (24 h). Aq sat citric acid (2 mL) was added and the MeOH removed *in vacuo*. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were combined, washed with aq sat $NaHCO_3$ (30 mL) then brine (30 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the crude title compound **60** as a white solid (65 mg, 97%), which was used immediately without further purification; δ_H (200 MHz, $CDCl_3$) 1.22 (3H, d, *J* = 6.8, C*H*$_3$CHN), 1.40–1.95 (2H, m, CHC*H*$_2$CH), 1.47 (9H, s, C(C*H*$_3$)$_3$), 1.88 (3H, d, *J* = 5.4, C*H*$_3$CH=CH), 2.53–2.58 (2H, m, C*H*$_2$C=O), 3.72 (3H, s, OC*H*$_3$ ester), 3.82 (3H, s, OC*H*$_3$ carbonate), 4.10 (1H, m, CH$_3$C*H*N), 4.36 (1H, m, CH$_2$C*H*CH$_2$), 4.94 (1H, m, C*H*O), 5.38 (1H, br s, N*H*), 5.78 (1H, d, *J* = 15.2, CH=C*H*C=O), 5.89 (1H, br s, N*H*), 6.12–6.19 (2H, m, CH$_3$C*H*=C*H*), 7.26 (1H, m, C*H*=CHC=O); δ_C (50 MHz, $CDCl_3$) 18.6, 19.0 (*C*H$_3$CHN, *C*H$_3$CH=CH), 28.8 (C(*C*H$_3$)$_3$), 36.6, 39.9 (CH*C*H$_2$CH, *C*H$_2$CO$_2$), 44.6, 48.3 (CH$_3$*C*HN, CH$_2$*C*HCH$_2$), 52.1, 55.5 (CH$_2$CO$_2$*C*H$_3$, OCO$_2$*C*H$_3$), 79.8 (*C*HO), 121.6 (CH=*C*HC=O), 130.1, 138.6 (CH$_3$*C*H=*C*H), 142.2 (*C*H=CHC=O), 155.6, 156.0 (*C*=O carbamate, *C*=O carbonate), 166.5 (*C*=O amide), 172.3 (*C*=O ester).

(3*R*,5*R*,6*R*,2′*E*,4′*E*)-Methyl 3-(*N-tert*-butoxycarbonyl)amino-5-hydroxy-6-(*N*-hexa-2′,4′-dienoyl)heptanoate 61 and (4*R*,5*R*,2′*R*)-4-methyl-5-(2′-[*N-tert*-butoxycarbonyl]amino-1′-methoxycarbonylpropyl)oxazolidin-2-one 62. To a stirred solution of crude carbonate **60** from the previous reaction (65 mg, 0.15 mmol) in MeOH (30 mL), was added Cs_2CO_3 (0.15 mmol, 49 mg). The mixture was stirred for 18 h, aq sat citric acid (4 mL) added and the MeOH removed *in vacuo*. The residues were diluted with H_2O (10 mL) and the organic material extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with aq sat $NaHCO_3$ (30 mL) then brine (30 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. ^{1}H NMR spectroscopic analysis revealed a 1 : 1 mixture of alcohol **61** and oxazolidin-2-one **62**. Purification *via* column chromatography on silica gel (60% EtOAc in hexane) gave alcohol **61** as a colourless foam (21 mg, 36%); $[\alpha]_D^{24}$ +1.8 (*c* = 0.4, $CHCl_3$); ν_{max} (KBr disc) 3459 (O–H), 3341 (N–H), 3322 (N–H), 1736 (C=O ester), 1657, 1651 (C=O amide, C=O carbamate), 1630 (C=C), 1614 (C=C), 1530 (amide II); δ_H (500 MHz, $CDCl_3$) 1.24 (3H, d, *J* = 6.7, C*H*$_3$CHN), 1.45 (9H, s, C(C*H*$_3$)$_3$), 1.48–1.59 (2H, m, CHC*H*$_2$CH), 1.84 (3H, d, *J* = 6.3, C*H*$_3$CH=CH), 2.46, 2.63 (2H, ABX system, AB part, J_{AB} 16.3, J_{AX} 5.3, J_{BX} 4.9, C*H*$_2$C=O), 3.55 (1H, br m, C*H*OH), 3.69 (3H, s, OC*H*$_3$), 4.04–4.13 (2H, m, CH$_3$C*H*N, CH$_2$C*H*CH$_2$), 4.35 (1H, br s, O*H*), 5.55 (1H, d, *J* = 9.4, N*H*Boc), 5.76 (1H, d, *J* = 15.0, CH=C*H*C=O), 5.90 (1H, d, *J* = 9.0, CH$_3$CHN*H*), 6.06–6.18 (2H, m, CH$_3$C*H*=C*H*), 7.17 (1H, dd, *J* = 15.0, 10.5, C*H*=CHC=O); δ_C (125 MHz, $CDCl_3$) 18.4 (*C*H$_3$CH=CH), 19.1 (*C*H$_3$CHNH), 28.1 (C(*C*H$_3$)$_3$), 38.7 (*C*H$_2$C=O), 40.1 (CH*C*H$_2$CH), 44.2 (CH$_2$*C*HCH$_2$), 48.3 (CH$_3$*C*HN), 51.7 (O*C*H$_3$), 70.1 (*C*HO), 80.1 (*C*(CH$_3$)$_3$), 121.6 (CH=*C*HC=O), 129.6 (CH$_3$CH=*C*H), 137.5 (CH$_3$*C*H=CH), 141.0 (*C*H=CHC=O), 157.1 (*C*=O carbamate), 166.0 (*C*=O amide), 172.1 (*C*=O ester); *m*/*z* (APCI) 385 (MH$^+$, 34%), 297 (16), 285 (100), 267 (36), 253 (14); HRMS (ESI) $C_{19}H_{33}N_2O_6^+$ requires 385.2339; found 385.2330.

In a repetition of the above reaction, further elution (EtOAc) afforded oxazolidin-2-one **62** as cream needles (11 mg, 32% from **59**); mp 163–165 °C; $[\alpha]_D^{25}$ +59.5 (*c* 0.19, $CHCl_3$); ν_{max} (KBr disc) 3394 (N–H oxazolidin-2-one), 3270 (N–H Boc), 2971 (C–H), 1753 (C=O ester), 1720 (C=O, oxazolidin-2-one), 1691 (C=O oxazolidin-2-one, C=O Boc), 1520 (amide II); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* = 6.2, C*H*$_3$CHN), 1.44 (9H, s, C(C*H*$_3$)$_3$), 1.90 (1H, m, CHC*H*HCH), 2.11 (1H, m, CHCH*H*CH), 2.61–2.70 (2H, m, C*H*$_2$C=O), 3.58 (1H, m, CH$_3$C*H*N), 3.70 (3H, s, OC*H*$_3$), 4.03 (1H, m, C*H*NHBoc), 4.21 (1H, m, C*H*O), 5.23 (1H, br s, *H*NBoc), 5.32 (1H, s, CH$_3$CHN*H*); δ_C (100 MHz, $CDCl_3$) 20.0 (*C*H$_3$CH), 28.2 (C(*C*H$_3$)$_3$), 38.0 (*C*H$_2$C=O), 38.2 (CH*C*H$_2$CH), 45.1 (*C*HNBoc), 51.7 (O*C*H$_3$), 53.6 (CH$_3$*C*HNH), 79.4 (*C*(CH$_3$)$_3$), 81.4 (*C*HO), 155.0 (*C*=O Boc), 158.2 (*C*=O oxazolidin-2-one) 171.9 (*C*=O ester); *m*/*z* (APCI) 217 ((M − Boc)H$_2^+$, 100%); HRMS (ESI) $C_{14}H_{25}N_2O_6^+$ requires 317.1713; found 317.1703.

(3*R*,5*R*,6*R*,α*R*)-3-(*N*-α-Methylbenzylamino)-5-hydroxy-6-aminoheptanoic acid 63. To a stirred solution of acid **55** (92 mg, 0.301 mmol) in ethanol (5 mL) was added aq KOH (8 M, 5 mL) and the mixture heated to 80 °C for 72 h. The mixture was allowed to cool to rt and a small sample removed and dried *in vacuo* for ^{1}H NMR spectroscopic analysis, which revealed complete conversion to the title compound **63**; δ_H (200 MHz, D_2O) 0.69 (3H, d, *J* = 6.6, C*H*$_3$CHNH$_2$), 1.16 (3H, d, *J* = 6.6, C*H*$_3$CHPh), 1.26–1.32 (2H, m, CHC*H*$_2$CH), 1.99 (1H, m, C*H*HC=O), 2.21–2.38 (2H, m, CH*H*C=O, CH$_3$C*H*NH$_2$), 2.71 (1H, m, CH$_2$C*H*CH$_2$), 3.16 (1H, m, C*H*O), 3.73 (1H, q, *J* = 6.6, PhC*H*CH$_3$), 7.12–7.30 (5H, m, Ph); *m*/*z* (APCI) 279 ((M − H)$^-$, 100%), 158 (85). The reaction mixture was cooled to 0 °C and aq HCl (10 M, 4 mL) was added drop-wise. The solvent was removed *in vacuo* to give a white solid containing the title compound **63** and KCl, which was used without further purification.

(3*R*,5*R*,6*R*,α*R*)-Methyl 3-(*N*-α-methylbenzylamino)-5-hydroxy-6-aminoheptanoate dihydrochloride 64. To the mixture of acid **63** and KCl from the previous step (from 0.301 mmol acid **55**), was added MeOH (15 mL). The stirred suspension was cooled to 0 °C and $SOCl_2$ (0.5 mL) added drop-wise. The mixture was heated to reflux for 72 h, allowed to cool to rt and the solvent removed *in vacuo* to give a cream solid containing the title compound **64** and KCl, which was used without further purification; δ_H (200 MHz, CD_3OD) 1.21 (3H, d, *J* = 6.6, C*H*$_3$CHNH$_2$), 1.79 (3H, d, *J* = 6.8, C*H*$_3$CHPh), 1.91–1.97 (2H, m, CHC*H*$_2$CH), 2.97–3.03 (3H, m, C*H*$_2$C=O, CH$_3$C*H*NH$_2$), 3.61–3.73 (2H, m, C*H*O, CH$_2$C*H*CH$_2$), 3.78 (3H, s, OC*H*$_3$), 4.71 (1H, q, *J* = 6.8, PhC*H*CH$_3$), 7.49–7.69 (5H, m, Ph); *m*/*z* (APCI) 295 (MH$^+$, 20%), 191 (12), 159 (45), 141 (23), 105 (100).

(3*R*,5*R*,6*R*,α*R*)-Methyl 3-(*N*-α-methylbenzylamino)-5,6-(isopropylidene-5-oxy-6-amino)heptanoate 65. To the crude ester **64** (from 0.301 mmol acid **55**) from the previous step was added acetone (2 mL) and Et_3N (0.06 mL, 0.6 mmol) and the mixture stirred for 1 h, after which time it was diluted with DCM (4 mL) and $MgSO_4$ added (200 mg). The suspension was stirred for 18 h, filtered and the volatile material removed *in vacuo*. The remaining material was triturated with ether, the solid filtered off and the solvent removed from the filtrate *in vacuo* to give **65** as a yellow oil (88 mg, 88% over 3 steps); $[\alpha]_D^{22}$ +28.2 (*c* = 0.4, $CHCl_3$); ν_{max} (film) 3334 (N–H), 2928 (C–H), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* = 6.3, C*H*$_3$CHNHC(CH$_3$)$_2$), 1.23 (3H, s, C*H*$_3$CCH$_3$), 1.31 (3H, d, *J* = 6.5, C*H*$_3$CHPh), 1.34 (3H, s, CH$_3$CC*H*$_3$), 1.47 (1H, m, CHC*H*HCH), 1.60 (1H, m, CHCH*H*CH), 1.87–2.03 (2H, br m, 2 × N*H*), 2.42, 2.66 (2H, ABX system, AB part, J_{AB} 15.2, J_{AX} 5.6, J_{BX} 5.5, C*H*$_2$C=O), 2.75 (1H, m, CH$_3$C*H*NCMe$_2$), 3.01 (1H, m, CH$_2$C*H*CH$_2$), 3.40 (1H, m, C*H*O), 3.67 (3H, s, OC*H*$_3$), 3.90 (1H, q, *J* = 6.5, PhC*H*), 7.19–7.34 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 16.6 (*C*H$_3$CHNHCMe$_2$), 25.0 (*C*H$_3$CHPh), 28.6 (*C*H$_3$CCH$_3$), 28.4 (CH$_3$C*C*H$_3$), 38.3 (CH*C*H$_2$CH), 39.1 (*C*H$_2$C=O), 50.4 (CH$_2$*C*HCH$_2$), 51.3 (O*C*H$_3$), 55.1 (Ph*C*HCH$_3$), 59.0 (CH$_3$*C*HNHCMe$_2$), 81.4 (*C*HO), 93.9 (*C*(CH$_3$)$_2$), 126.7, 128.3 (aromatic *C*H), 145.8 (*ipso*-*C*), 172.9 (*C*=O); *m*/*z* (ESI) 335 (MH$^+$, 100%); HRMS (ESI) $C_{19}H_{31}N_2O_3^+$ requires 335.2335; found 335.2341.

(3*R*,5*R*,6*R*)-3,6-Diamino-5-hydroxyheptanoic acid dihydrochloride 54. Oxazin-2-one **53** (1.52 g, 4.75 mmol) was dissolved in aq HCl (5 M, 50 mL) and the mixture heated to reflux for 24 h. The mixture was allowed to cool to rt then diluted with H_2O (200 mL), washed with DCM (4 × 200 mL) and the aqueous layer concentrated *in vacuo* to afford a mixture of the title compound **54** and its lactone as their dihydrochloride salts as a hydroscopic colourless solid (1.11 g, 30 : 70 **54** : lactone), which was used without further purification. The amino acid **54** displayed spectroscopic properties consistent with previous samples.

Data for 54. δ_H (200 MHz, D_2O) 1.29 (3H, d, *J* = 6.8, C*H*$_3$), 1.73 (1H, m, CHC*H*HCH), 2.44 (1H, m, CHCH*H*CH), 2.63, 3.09 (2H, ABX system, AB part J_{AB} 17.8, J_{AX} 9.6, J_{BX} 6.7, C*H*$_2$CO$_2$H), 3.52, 3.82, 4.47 (3 × 1H, m, C*H*C*H*CH$_2$C*H*).

(3*R*,5*R*,6*R*)-Methyl 3,6-diamino-5-hydroxyheptanoate dihydrochloride 67. To a stirred solution of a mixture of amino acid **54** and its lactone (from 4.27 mmol ester **53**) in MeOH (50 mL) at 0 °C was added thionyl chloride (2.54 g, 1.56 mL, 21.4 mmol) drop-wise. The mixture was heated at reflux for 18 h, allowed to cool, and the volatile material removed *in vacuo* to afford the title compound **67** as a colourless foam (1.07 g, 93% over 2 steps); $[\alpha]_D^{21}$ +2.6 (*c* = 0.7, MeOH); ν_{max} (KBr disc) 3418 (O–H), 3014 (N–H, C–H), 1727 (C=O); δ_H (400 MHz, CD_3OD) 1.34 (3H, d, *J* = 6.6, CHC*H*$_3$), 1.88 (1H, m, CHC*H*HCH), 2.03 (1H, m, CHCH*H*CH), 2.85, 2.93 (2H, ABX system, AB part J_{AB} 17.5, J_{AX} 7.2, J_{BX} 5.5, C*H*$_2$C=O), 3.27 (1H, m, CH$_3$C*H*NH$_2$), 3.77 (1H, s, OC*H*$_3$), 3.82–3.88 (2H, m, C*H*OH, CH$_2$C*H*CH$_2$); δ_C (100 MHz, CD_3OD) 16.3 (*C*H$_3$CH), 37.0 (CH*C*H$_2$CH), 38.1 (*C*H$_2$C=O), 47.5 (CH$_2$*C*HCH$_2$), 53.2 (O*C*H$_3$), 53.7 (CH$_3$*C*H), 70.3 (*C*HOH), 172.7 (*C*=O); *m/z* (APCI) 191 (MH$^+$, 100%), 174 (28), 159 (20), 124 (13); HRMS (ESI) $C_8H_{19}N_2O_3^+$ requires 191.1396; found 191.1393.

(3*R*,5*R*,6*R*,2′*E*,4′*E*)-Methyl 3-amino-5,6-(isopropylidene-5-oxy-6-[hex-2′,4′-dienoylamino])heptanoate 68. To a stirred solution of ester **67** (200 mg, 0.760 mmol) in acetone (15 mL) under Ar was added DIPEA (0.265 mL, 1.52 mmol) and powdered 3 Å molecular sieves (800 mg). The mixture was refluxed for 2 h, cooled to 0 °C, and further DIPEA (0.15 mL, 0.836 mmol) added, followed by addition of sorbyl chloride (109 mg, 0.836 mmol) drop-wise as a solution in acetone (5 mL). The mixture was stirred at 0 °C for 1 h and then at rt for 18 h. The mixture was filtered, H_2O (10 mL) added and the acetone removed *in vacuo*. Aq sat $NaHCO_3$ (20 mL) was added and the organic material extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and the volatile material removed *in vacuo*. Purification *via* column chromatography on silica gel (EtOAc then 8% MeOH in EtOAc) and concentration of the more polar fraction afforded the title compound **68** as an orange oil (183 mg, 74%); $[\alpha]_D^{20}$ +84.6 (*c* = 0.8, $CHCl_3$); ν_{max} (film) 3436 (N–H), 2981 (C–H), 1732 (C=O ester), 1652 (C=O amide), 1627 (C=C), 1599 (C=C); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* = 6.2, C*H*$_3$CHN), 1.48–1.73 (2H, m, CHC*H*$_2$CH), 1.58 (3H, s, C*H*$_3$CCH$_3$), 1.65 (3H, s, CH$_3$CC*H*$_3$), 1.82 (3H, d, *J* = 6.4, C*H*$_3$CH=CH), 2.17 (2H, br s, N*H*$_2$), 2.37, 2.54 (2H, ABX system, AB part, J_{AB} 15.9, J_{AX} 8.3, J_{BX} 4.3, C*H*$_2$C=O), 3.45 (1H, m, CH$_2$C*H*CH$_2$), 3.67 (3H, s, OC*H*$_3$), 3.73 (1H, m, CH$_3$C*H*N), 4.02 (1H, m, C*H*O), 5.96 (1H, d, *J* = 14.8, CH=C*H*C=O), 6.05–6.22 (2H, m, CH$_3$C*H*=C*H*), 7.23 (1H, dd, *J* = 14.7, 10.7, C*H*=CHC=O); δ_C (100 MHz, $CDCl_3$) 18.6 (*C*H$_3$CH=CH), 21.4 (*C*H$_3$CHN), 27.2 (*C*H$_3$CCH$_3$), 28.5 (CH$_3$C*C*H$_3$), 41.1 (CH*C*H$_2$CH), 42.5 (*C*H$_2$C=O), 45.5 (CH$_2$*C*HCH$_2$), 51.6 (O*C*H$_3$), 58.0 (CH$_3$*C*HN), 79.2 (*C*HO), 96.0 (*C*(CH$_3$)$_2$), 120.5 (CH=*C*HC=O), 129.8 (CH$_3$CH=*C*H), 138.3 (CH$_3$*C*H=CH), 142.4 (*C*H=CHC=O), 163.6 (*C*=O amide), 172.5 (*C*=O ester); *m/z* (APCI) 325 (MH$^+$, 100%), 307 (15); HRMS (ESI) $C_{17}H_{29}N_2O_4^+$ requires 325.2127; found 325.2133.

(3*R*,5*R*,6*R*,2′*E*,4′*E*)-Methyl 3-(*tert*-butoxycarbonylamino)-5,6-(isopropylidene-5-oxy-6-[hexa-2′,4′-dienoylamino])-heptanoate 69. To a stirred solution of amine **68** (159 mg, 0.49 mmol) in MeOH (15 mL) under N_2 was added $NaHCO_3$ (124 mg, 1.47 mmol) then Boc_2O (161 mg, 0.74 mmol). The mixture was stirred at rt for 72 h, filtered and the volatile material removed *in vacuo*. The resulting oil was triturated with ether (20 mL), filtered and the filtrate was concentrated *in vacuo*. Purification *via* column chromatography on silica gel (40% EtOAc in pentane) afforded the title compound **69** as a colourless oil (175 mg, 84%); $[\alpha]_D^{27}$ +73.3 (*c* = 0.9, $CHCl_3$); ν_{max} (film) 3342 (N–H), 2978 (C–H), 1738 (C=O ester), 1713 (C=O carbamate) 1651 (C=O amide), 1626 (C=C), 1599 (C=C), 1519 (amide II); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* = 6.2, C*H*$_3$CHN), 1.44 (9H, s, C(C*H*$_3$)$_3$), 1.61 (3H, s, C*H*$_3$CCH$_3$), 1.67 (3H, s, CH$_3$CC*H*$_3$), 1.85 (3H, d, *J* = 6.4, C*H*$_3$CH=CH), 1.83 (1H, m, CHC*H*HCH), 1.97 (1H, m, CHCH*H*CH), 2.59–2.69 (2H, m, C*H*$_2$C=O), 3.69 (3H, s, OC*H*$_3$), 3.76 (1H, m, CH$_3$C*H*N), 3.93 (1H, m, C*H*O), 4.12 (1H, m, CH$_2$C*H*CH$_2$), 5.28 (1H, br d, *J* = 7.2, N*H*), 5.97 (1H, d, *J* = 14.8, CH=C*H*C=O), 6.08–6.25 (2H, m, CH$_3$C*H*=C*H*), 7.26 (1H, dd, *J* = 14.7, 10.7, C*H*=CHC=O); δ_C (100 MHz, $CDCl_3$) 18.6 (*C*H$_3$CH=CH), 21.4 (*C*H$_3$CHN), 26.0 (*C*H$_3$CCH$_3$), 27.1 (CH$_3$C*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$), 37.9 (CH*C*H$_2$CH), 38.7 (*C*H$_2$C=O), 45.5 (CH$_2$*C*HCH$_2$), 51.6 (O*C*H$_3$), 57.7 (CH$_3$*C*HN), 77.2 (*C*(CH$_3$)$_3$), 79.3 (*C*HO), 96.0 (*C*(CH$_3$)$_2$), 120.5 (CH=*C*HC=O), 129.8 (CH$_3$CH=*C*H), 138.1 (CH$_3$*C*H=CH), 142.3 (*C*H=CHC=O), 155.1 (*C*=O carbamate), 163.5 (*C*=O amide), 172.0 (*C*=O ester); *m/z* (APCI) 425 (MH$^+$, 19%), 369 (12), 325 (17), 311 (100), 285 (30); HRMS (ESI) $C_{22}H_{36}N_2O_6Na^+$ requires 447.2471; found 447.2479.

(3*R*,5*R*,6*R*,2′*E*,4′*E*)-3-(*N*-*tert*-Butoxycarbonylamino)-5,6-(isopropylidene-5-oxy-6-[hexa-2′,4′-dienoylamino])heptanoic acid 76. To a stirred solution of ester **69** (175 mg, 0.413 mmol) in MeOH/THF (2 : 1, 15 mL) at 0 °C was added aq NaOH (1 M, 1.65 mL, 1.65 mmol). The mixture was stirred at 0 °C for 1 h then at rt for 18 h. The volatile material was removed *in vacuo*, the residue dissolved in H_2O (50 mL) and washed with ether (50 mL). The aqueous layer was acidified to pH 3 with aq $KHSO_4$ (0.5 M) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the title compound **76** as a colourless oil (170 mg, quant) which was used without further purification; $[\alpha]_D^{23}$ +50.8 (*c* = 1.0, $CHCl_3$); ν_{max} (film) 3332 (O–H, N–H), 2980 (C–H), 1714 (C=O carbamate, C=O acid) 1652 (C=O amide), 1625 (C=C), 1595 (C=C), 1514 (amide II); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* = 6.1, C*H*$_3$CHN), 1.42 (9H, s, C(C*H*$_3$)$_3$), 1.57 (3H, s, C*H*$_3$CCH$_3$), 1.65 (3H, s, CH$_3$CC*H*$_3$), 1.83 (3H, d, *J* = 6.2, C*H*$_3$CH=CH), 1.73–2.11 (2H, m, CHC*H*$_2$CH), 2.53–2.73 (2H, m, C*H*$_2$C=O), 3.76 (1H, m, CH$_3$C*H*N), 3.91 (1H, m, C*H*O), 4.09 (1H, m, CH$_2$C*H*CH$_2$), 5.37 (1H, br d, *J* = 7.3, N*H*), 5.96 (1H, d, *J* = 14.8, CH=C*H*C=O), 6.06–6.23 (2H, m, CH$_3$C*H*=C*H*), 7.25 (1H, dd, *J* = 14.7, 10.5, C*H*=CHC=O); δ_C (100 MHz, $CDCl_3$) 18.6 (*C*H$_3$CH=CH), 21.3 (*C*H$_3$CHN), 26.1 (*C*H$_3$CCH$_3$), 27.2 (CH$_3$C*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$), 37.8 (CH*C*H$_2$CH), 38.6 (*C*H$_2$C=O), 45.3 (CH$_2$*C*HCH$_2$), 57.9 (CH$_3$*C*HN), 79.5, 79.6 (*C*HO, *C*(CH$_3$)$_3$), 96.2 (*C*(CH$_3$)$_2$), 120.3 (CH=*C*HC=O) 129.9, (CH$_3$CH=*C*H), 138.6 (CH$_3$*C*H=CH), 142.8 (*C*H=CHC=O), 155.3 (*C*=O carbamate), 164.0 (*C*=O amide), 175.3 (*C*=O acid); *m/z* (APCI) 411 (MH$^+$, 10%), 355 (18), 311 (40), 297 (100), 293 (15), 271 (23), 253 (22), 141 (23); HRMS (ESI) $C_{21}H_{34}N_2O_6Na^+$ requires 433.2320; found 433.2315.

3-(*p*-Toluenesulfonylamino)propionitrile 72. To a solution of 3-aminopropionitrile fumarate (12.0 g, 94 mmol) in DCM (150 mL), triethylamine (14.0 g, 137 mmol) was added and the mixture was cooled to 0 °C. *p*-Toluenesulfonyl chloride (13.5 g, 70.8 mmol) was added in several portions over a period of 20 min and the resulting slurry was stirred for a further 10 min. The reaction mixture was then poured into H_2O (40 mL), extracted with DCM (3 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Recrystallization from EtOH/H_2O (1 : 1) afforded the title compound **72** as colourless crystals (6.06 g, 55%); mp 83–83.5 °C {lit.[34] mp 86 °C}; ν_{max} (film) 3275 (N–H), 2252 (C≡N), 1329 (SO_2), 1161 (SO_2); δ_H (200 MHz, $CDCl_3$) 2.44 (3H, s, C*H*$_3$), 2.60 (2H, t, *J* = 6.6, C*H*$_2$CN), 3.22 (2H, q, *J* = 6.6, C*H*$_2$NH), 5.63 (1H, br t, *J* = 6.6, N*H*), 7.34, 7.66 (4H, AA′ BB′ system, *J* = 8.2, CH$_3$C$_6$*H*$_4$); δ_C (50 MHz, $CDCl_3$) 19.2 (*C*H$_2$CN), 21.4 (*C*H$_3$), 38.9 (*C*H$_2$NH), 117.8 (*C*≡N), 127.2, 130.2 (aromatic *C*H), 136.6 (*ipso*-*C*SO$_2$), 144.4 (*ipso*-*C*CH$_3$); *m/z* (APCI) 225 (MH$^+$, 15%), 155 (Ts$^+$, 100), 102 (35).

Ethyl 3-(*p*-toluenesulfonylamino)propionimidate hydrochloride. A solution of 3-(*p*-toluenesulfonylamino)propionitrile **72** (3.17 g, 13.0 mmol) in a mixture of ether (20 mL) and ethanol (15 mL) was cooled to 0 °C and HCl (g) bubbled through it until the solution saturated. The mixture was placed in a refrigerator (5 °C) for 18 h. The white precipitate formed was collected by suction filtration and washed with ether. Further precipitate from the filtrate was likewise collected and the combined solid dried *in vacuo* to afford the title compound as a hygroscopic white powder which was used immediately (4.00 g, quant); ν_{max} (KBr disc) 3223 (N–H), 3076 (N–H), 2941 (C–H), 1632 (C=N), 1331 (SO_2), 1162 (SO_2); δ_H (200 MHz, d_6 DMSO) 1.30 (3H, t, *J* = 7.0, CH_2CH_3), 2.37 (3H, s, ArCH_3), 2.74 (2H, t, *J* = 6.3, $NHCH_2CH_2$), 3.02 (2H, q, *J* = 6.3, $NHCH_2CH_2$), 4.33 (2H, q, *J* = 7.0, OCH_2), 7.40, 7.66 (4H, AA′ BB′ system, *J* = 8.2, Ar), 8.01 (1H, t, *J* = 6.1, N*H*); *m*/*z* (APCI) 271 (MH^+, 100%), 226 (20), 225 (14), 184 (50).

3-(*p*-Toluenesulfonylamino)propionamidine 73. NH_3 (g) was condensed at −78 °C (2 mL), EtOH (5 mL) added and the mixture was added to a solution of ethyl 3-(*p*-toluenesulfonylamino)propionimidate hydrochloride (4.00 g, 13.0 mmol) in EtOH (15 mL). After standing at rt for 72 h, ether (80 mL) was added and the white solid formed was collected by suction filtration and dried *in vacuo* to afford the title compound **73** as a white powder (3.60 g, quant); mp 145 °C, lit.[34] mp 150 °C; ν_{max} (KBr disc) 3117 (N–H), 1682 (C=N), 1160 (SO_2), 1091 (SO_2); δ_H (200 MHz, D_2O) 2.20 (3H, s, CH_3), 2.41 (2H, t, *J* = 6.3, $NHCH_2CH_2$), 3.03 (2H, t, *J* = 6.3, $NHCH_2$), 7.23, 7.52 (4H, AA′ BB′ system, *J* = 8.0, Ar); *m*/*z* (APCI) 242 (MH^+, 100%).

3-Aminopropionamidine dihydrochloride 74. A solution of HCl in AcOH (14% wt.) was prepared by bubbling HCl (g) through AcOH with cooling (ice-bath). Amidine **73** (3.19 g, 11.5 mmol) was dissolved in this HCl–AcOH solution (20 ml), the mixture placed in a Fischer–Porter bottle, sealed, and heated to 120 °C for 4 h (maximum pressure 6.5 atm). The bottle was then cooled with an ice-bath and opened carefully. Removal of the volatile material *in vacuo* gave a very viscous yellow oil which was crystallised from EtOH to afford the title compound **74** as colourless crystals (1.34 g, 73%); mp 180–181 °C {lit.[34] 167 °C}; ν_{max} (KBr disc) 3320 (N–H), 3100 (N–H), 1695 (C=N); δ_H (200 MHz, D_2O) 2.83 (2H, m, CH_2N), 3.30 (2H, m, CH_2C=N).

3-Aminopropionamidine dihydrobromide 75. Phenol (1.02 g, 10.8 mmol) was dissolved in 48% HBr in AcOH (10 mL) and 3-(*p*-toluenesulfonylamino)propionamidine **73** (1.0 g, 3.60 mmol) added. The flask was fitted with a condenser and drying tube and the mixture refluxed for 2 h and then allowed to cool to rt. The mixture was diluted with H_2O (60 mL), washed with EtOAc (3 × 50 mL) and the aqueous layer concentrated *in vacuo*. The resulting solid was recrystallised from EtOH/ether, affording the title compound **75** as white needles (360 mg, 40%): mp 161 °C {lit.[34] mp 162 °C}; ν_{max} (KBr disc) 3335 (N–H), 3096 (N–H), 1695 (C=N); δ_H (400 MHz, D_2O) 2.83 (2H, t, *J* = 7.8, CH_2C=N), 3.30 (2H, t, *J* = 7.8, CH_2N); δ_C (100 MHz, D_2O) 30.5 (CH_2C=N), 36.6 (CH_2N).

(3*R*,5*R*,6*R*,2″*E*,4″*E*)-3′-Amidinopropionyl 3-(*N*-*tert*-butoxycarbonylamino)-5,6-(isopropylidene-5-oxy-6-[hexa-2″,4″-dienoylamino])heptanamide 77. To a stirred solution of acid **76** (24 mg, 0.059 mmol) in THF (2 mL) and 3 Å molecular sieves (100 mg) under Ar, was added DCC (16 mg, 0.080 mmol) and HOBT (10 mg, 0.071 mmol) and the mixture stirred for 3 h. The resulting suspension was filtered, the precipitate washed with further THF (2 × 10 mL) and to the combined filtrate and washings was added 3-aminopropionamidine dihydrobromide **75** (15 mg, 0.059 mmol) and $NaHCO_3$ (10 mg, 0.12 mmol), both dissolved in one portion of H_2O (2 mL). The resulting mixture was stirred for 48 h and the solvent removed *in vacuo*. Purification *via* column chromatography on silica gel (3% MeOH in DCM then 20% MeOH in DCM) and concentration of the more polar fraction afforded the title compound **77** as a *ca.* 5 : 1 mixture of its hydrobromide and HOBT salts. This mixture was dissolved in DCM/MeOH (10 : 1, 10 mL), MP carbonate resin (Argotech®, 120 mg, 2.55 mmol g^{-1}, 0.31 mmol) added and the mixture stirred for 2 h. After removal of the resin by filtration, and washing with DCM (2 × 10 mL), the solvent was removed from the combined filtrate and washings *in vacuo* to afford the title compound **77** as a pale yellow oil (28 mg, 99%); $[\alpha]_D^{24}$ +47.7 (*c* = 0.59, $CHCl_3$); ν_{max} (film) 3298 (N–H), 2934 (C–H), 1691, 1654 (C=O, C=N), 1626 (C=C), 1597 (C=C), 1527 (amide II); δ_H (500 MHz, $CDCl_3$) 1.25 (2H, br s, CH_2C=N), 1.32 (3H, d, *J* = 5.9, CH_3CHN), 1.43 (9H, s, $C(CH_3)_3$), 1.58 (3H, s, CH_3CCH_3), 1.66 (3H, s, CH_3CCH_3), 1.73–1.99 (2H, m, $CHCH_2CH$), 1.84 (3H, d, *J* = 6.5, CH_3CH=CH), 2.44–2.48 (2H, m, CH_2C=O), 3.46–3.52 (2H, m, CH_2N), 3.75 (1H, m, CH_3CHN), 3.92 (1H, m, C*H*O), 4.04 (1H, m, CH_2CHCH_2), 5.96 (1H, d, *J* = 14.8, CH=C*H*C=O), 6.08–6.23 (2H, m, CH_3CH=C*H*), 7.23 (1H, dd, *J* = 14.8, 10.9, C*H*=CHC=O); δ_C (125 MHz, $CDCl_3$) 18.5 (CH_3CH=CH), 21.2 (CH_3CHN), 25.9 (CH_3CCH_3), 27.1 (CH_3CCH_3), 28.3 ($C(CH_3)_3$), 29.6 (CH_2C=N), 36.1 (CH_2N), 37.9 ($CHCH_2CH$), 40.7 (CH_2C=O), 46.3 (CH_2CHCH_2), 57.8 (CH_3CHN), 79.3 ($C(CH_3)_3$), 79.5 (*C*HO), 95.9 ($C(CH_3)_2$), 120.5 (CH=*C*HC=O), 129.8 (CH_3CH=*C*H), 138.2 (CH_3CH=CH), 142.3 (*C*H=CHC=O), 155.5 (*C*=O carbamate), 163.6 (CH=CH*C*=O), 166.0 (*C*=N), 171.0 (CH_2C=O); *m*/*z* (APCI) 480 (MH^+, 100%), 380 (10); HRMS (ESI) $C_{24}H_{42}N_5O_5^+$ requires 480.3186; found 480.3195.

Sperabillin D hydrochloride 4. To a stirred solution of amidine **77** (28 mg) in DCM (1 mL), under Ar, was added TFA (1 mL) dropwise. The resulting mixture was stirred for 30 min and the volatile material removed *in vacuo*. The crude material was passed through a column of Amberlite IRA-402 (H_2O) and the volatile material removed *in vacuo* to afford Sperabillin D hydrochloride **4** as a pale yellow foam (22 mg, 91%, 94% purity by HPLC): $[\alpha]_D^{25}$ +27.4 (*c* = 0.22, H_2O) {lit.[2] $[\alpha]_D^{25}$ +30.4 (*c* = 0.50, H_2O)}; ν_{max} (KBr disc) 3387 (N–H, O–H) 1686, 1654 (C=O, C=N), 1627 (C=C), 1612 (C=C), 1550 (amide II); δ_H (500 MHz, D_2O) 0.96 (3H, d, *J* = 7.1, CH_3CHN), 1.47–1.62 (2H, m, $CHCH_2CH$), 1.61 (3H, d, *J* = 6.0, CH_3CH=CH), 2.43 (2H, t, *J* = 6.9, CH_2C=N), 2.49 (2H, d, *J* = 6.6, CH_2C=O), 3.27–3.37 (2H, m, NCH_2), 3.60–3.65 (2H, m, C*H*OH, CH_2CHCH_2), 3.77 (1H, dq, *J* = 6.9, 3.5, CH_3CHN), 5.75 (1H, d, *J* = 15.3, CH=C*H*C=O), 5.99–6.10 (2H, m, CH_3CH=C*H*), 6.90 (1H, dd, *J* = 15.1, 9.9, C*H*=CHC=O); δ_C (125 MHz, D_2O) 18.4 (CH_3CHN), 20.3 (CH_3CH=CH), 34.9 (CH_2C=N), 37.0 ($CHCH_2CH$), 38.8 (CH_2N), 39.5 (CH_2C=O), 48.8 ($CHNH_2$), 51.8 (*C*HNH), 72.0 (*C*HOH), 122.6 (CH=*C*HC=O), 131.6 (CH_3CH=*C*H), 142.7 (CH_3CH=CH), 144.9 (*C*H=CHC=O), 171.1, 171.3 (*C*=N, CH=CH*C*=O), 174.2 (CH_2C=O); *m*/*z* (APCI$^+$) 340 (MH^+, 36%), 325 (15), 250 (27), 220 (100), 165 (18); HRMS (ESI) $C_{16}H_{30}N_5O_3^+$ requires 340.2349; found 340.2350.

(2*E*,4*Z*)-*tert*-Butyl hexa-2,4-dienoate 78. To a stirred solution of *tert*-butyl acrylate (16.9 g, 18.9 mL, 132 mmol), *cis*-bromopropene (8.0 g, 5.6 mL, 66 mmol), K_2CO_3 (22.8 g, 165 mmol), triphenylphosphine (1.73 g, 6.6 mmol) and Bu_4NHSO_4 (22.4 g, 66 mmol) in MeCN/H_2O (10 : 1, 100 mL) under Ar was added palladium acetate (739 mg, 3.3 mmol). The mixture was heated to 50 °C for 48 h, then allowed to cool to rt and filtered through Celite®, eluting with ether (250 mL). The resulting organic solution was washed with H_2O (150 mL) then brine (150 mL), dried ($MgSO_4$), filtered and the volatile material removed *in vacuo*. 400 MHz ^{1}H NMR spectroscopic analysis revealed that reaction had occurred in 95 : 5 dr. Purification *via* repeated column chromatography on silica gel (0.5% ether in 30–40 petrol) afforded the title compound **78** as a colourless oil (2.70 g, 24%, 97 : 3 dr); ν_{max} (film) 2979 (C–H), 1709 (C=O), 1636 (C=C), 1607 (C=C); δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, $C(CH_3)_3$), 1.87, (3H, dd, *J* = 7.2, 1.7, CH_3CH=CH), 5.81 (1H, d, *J* = 15.3, CH=C*H*C=O), 5.89 (1H, m, CH_3CH=CH), 6.13 (1H, m, CH_3CH=CH), 7.56 (1H, ddd, *J* = 15.3, 11.6, 1.0, C*H*=CHC=O); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3CH=CH), 28.1 ($C(CH_3)_3$), 80.2 ($C(CH_3)_3$), 122.9 (CH=*C*HC=O), 127.4 (CH_3CH=*C*H), 135.0 (CH_3CH=CH), 138.1 (*C*H=CHC=O), 166.7 (*C*=O); *m*/*z* (GC/MS CI$^+$) 186 (MNH_4^+, 25%), 169 (MH^+, 80), 130 (100), 113 (32); HRMS (ESI) $C_{10}H_{17}O_2^+$ requires 169.1229; found 169.1225.

(2*E*,4*Z*)-Hexa-2,4-dienoic acid 79. To a stirred solution of (2*E*,4*Z*)-*tert*-butyl hex-2,4-dienoate **79** (2.52 mg, 15.0 mmol, 97 : 3 dr) in DCM (25 mL) at 0 °C was added TFA (25 mL) drop-wise. The mixture was stirred for 30 min at rt and the volatile material removed *in vacuo*. Purification *via* column chromatography on silica gel (75% ether in 30–40 petrol) and recrystallisation twice (pentane at −78 °C) afforded the title compound **79** as a yellow powder (911 mg, 54%, 94 : 6 dr); mp 33–34 °C {lit.[37] mp 35–38 °C}; ν_{max} (film) 3500–2500 (O–H), 3027 (C–H), 1689 (C=O), 1631 (C=C), 1607 (C=C); δ_H (400 MHz, $CDCl_3$) 1.92 (3H, dd, *J* = 7.2, 1.6, C*H*$_3$), 5.89 (1H, d, *J* = 15.2, CH=C*H*C=O), 6.01 (1H, m, CH_3C*H*=CH), 6.20 (1H, m, CH_3CH=C*H*), 7.74 (1H, ddd, *J* = 15.2, 11.7, 0.8, C*H*=CHC=O); *m*/*z* (GC/MS CI$^+$) 128 (MNH_4^+, 70%), 111 (MH^+, 71).

(2*E*,4*Z*)-Hexa-2,4-dienoyl chloride 80. To a stirred solution of (2*E*,4*Z*)-hex-2,4-dienoic acid **79** (500 mg, 4.46 mmol, 94 : 6 dr) in DCM (10 mL) was added oxalyl chloride (0.58 mL, 6.70 mmol) drop-wise, followed by 2 drops of DMF. The flask was fitted with a drying tube and stirred for 2 h after which time the solvent was removed *in vacuo* and the crude material purified *via* Kugelrohr distillation (bp 55 °C, 1 mmHg) to afford the title compound **80** as a colourless oil (460 mg, 79%, 96 : 4 dr); δ_H (200 MHz, $CDCl_3$) 2.00 (3H, d, *J* = 6.1, C*H*$_3$), 6.06 (1H, d, *J* = 14.9, CH=C*H*C=O), 6.26–6.57 (2H, m, CH_3C*H*=C*H*), 7.50 (1H, dd, *J* = 14.9, 9.9, C*H*=CHC=O).

(3*R*,5*R*,6*R*,2′*E*,4′*Z*)-Methyl 3-amino-5,6-(isopropylidene-5-oxy-6-[hexa-2′,4′-dienoylamino])heptanoate 81. To a stirred solution of ester **67** (223 mg, 0.848 mmol) in acetone (15 mL) under Ar was added DIPEA (0.29 mL, 1.70 mmol) and powdered 3 Å molecular sieves (800 mg). The mixture was refluxed for 2 h, cooled to 0 °C, further DIPEA (0.16 mL, 0.933 mmol) added, then (2*E*,4*Z*)-hexa-2,4-dienoyl chloride (122 mg, 0.933 mmol), as a solution in acetone (5 mL), was added drop-wise. The mixture was stirred at 0 °C for 1 h then at rt for 18 h. The mixture was filtered, H_2O (10 mL) added and the acetone removed *in vacuo*. Aq sat $NaHCO_3$ (20 mL) was added and the organic material extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and the volatile material removed *in vacuo*. Purification *via* column chromatography on silica gel (EtOAc then 8% MeOH in EtOAc) and concentration of the more polar fraction afforded the title compound **81** as a yellow oil (194 mg, 71%, 4′*Z* : 4′*E* > 95 : 5); $[\alpha]_D^{22}$ +95.0 (*c* = 1.0, $CHCl_3$); ν_{max} (film) 3379, 3298 (N–H), 2981 (C–H), 1735 (C=O ester), 1650 (C=O amide), 1614 (C=C), 1598 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* = 6.5, C*H*$_3$CHN), 1.55–1.84 (2H, m, obscured CHC*H*$_2$CH), 1.61 (3H, s, C*H*$_3$CCH$_3$), 1.67 (3H, s, CH_3CC*H*$_3$), 1.76 (2H, br s, N*H*$_2$), 1.87 (3H, dd, *J* = 7.2, 1.1, C*H*$_3$CH=CH), 2.36, 2.54 (2H, ABX system, AB part, J_{AB} 15.9, J_{AX} 8.4, J_{BX} 4.3, C*H*$_2$C=O), 3.46 (1H, m, CH_2C*H*CH_2), 3.69 (3H, s, OC*H*$_3$), 3.80 (1H, m, CH_3C*H*N), 4.03 (1H, m, C*H*O), 5.88 (1H, m, CH_3C*H*=CH), 6.07 (1H, d, *J* = 14.7, CH=C*H*C=O), 6.16 (1H, appt t, *J* = 10.6, CH_3CH=C*H*), 7.66 (1H, dd, *J* = 14.7, 12.1, C*H*=CHC=O); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*H$_3$CH=CH), 21.4 (*C*H$_3$CHN), 26.2 (*C*H$_3$CCH$_3$), 27.3 (CH_3C*C*H$_3$), 41.4 (CH*C*H$_2$CH), 42.8 (*C*H$_2$C=O), 45.4 (CH_2*C*HCH_2), 51.6 (O*C*H$_3$), 58.0 (CH_3*C*HN), 79.3 (*C*HO), 96.0 (*C*(CH_3)$_2$), 122.5 (CH=*C*HC=O), 127.5 (CH_3CH=*C*H), 134.8 (CH_3*C*H=CH), 136.8 (*C*H=CHC=O), 163.6 (*C*=O amide), 175.3 (*C*=O ester); *m*/*z* (ESI$^+$) 325 (MH^+, 100%); HRMS (ESI) $C_{17}H_{29}N_2O_4^+$ requires 325.2127; found 325.2132.

(3*R*,5*R*,6*R*,2′*E*,4′*Z*)-Methyl 3-(*N*-*tert*-butoxycarbonylamino)-5,6-(isopropylidene-5-oxy-6-[*N*′-hexa-2′,4′-dienoylamino])heptanoate 82. To a stirred solution of amine **81** (147 mg, 0.454 mmol) in MeOH (15 mL) under N_2 was added $NaHCO_3$ (114 mg, 1.36 mmol) then Boc_2O (148 mg, 0.681 mmol). The mixture was stirred at rt for 18 h, filtered and the volatile material removed *in vacuo*. The resulting oil was triturated with ether (20 mL), filtered and the filtrate concentrated *in vacuo*. Purification *via* column chromatography on silica gel (50% EtOAc in pentane) afforded the title compound **82** as a pale yellow foaming oil (175 mg, 91%, 4′*Z* : 4′*E* > 95 : 5); $[\alpha]_D^{22}$ +82.9 (*c* = 0.7, $CHCl_3$); ν_{max} (KBr disc) 3432 (N–H), 2980 (C–H), 1741 (C=O ester), 1713 (C=O carbamate) 1649 (C=O amide), 1614 (C=C), 1598 (C=C), 1523 (amide II); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* = 6.2, C*H*$_3$CHN), 1.41 (9H, s, C(C*H*$_3$)$_3$), 1.58 (C*H*$_3$CCH$_3$), 1.65 (3H, s, CH_3CC*H*$_3$), 1.73–1.94 (2H, m, CHC*H*$_2$CH), 1.85 (3H, dd, *J* = 7.2, 1.5, C*H*$_3$CH=CH), 2.56–2.69 (2H, m, C*H*$_2$C=O), 3.66 (3H, s, OC*H*$_3$), 3.72 (1H, m, CH_3C*H*N), 3.91 (1H, m, C*H*O), 4.08 (1H, m, CH_2C*H*CH_2), 5.26 (1H, br d, *J* = 5.5, N*H*), 5.86 (1H, dq, *J* = 10.6, 7.2, CH_3CH=C*H*), 6.04 (1H, d, *J* = 14.7, CH=C*H*C=O), 6.14 (1H, m, CH_3C*H*=CH), 7.63 (1H, dd, *J* = 14.4, 11.8, C*H*=CHC=O); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*H$_3$CH=CH), 21.5 (*C*H$_3$CHN), 26.1 (*C*H$_3$CCH$_3$), 27.1 (CH_3C*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$), 37.9 (CH*C*H$_2$CH), 38.7 (*C*H$_2$C=O), 45.5 (CH_2*C*HCH_2), 51.6 (O*C*H$_3$), 57.8 (CH_3*C*HN), 79.4 (*C*HO), 96.1 (*C*(CH_3)$_2$), 122.5 (CH=*C*HC=O), 127.5 (CH_3CH=*C*H), 134.8 (CH_3*C*H=CH), 136.7 (*C*H=CHC=O), 155.1 (*C*=O carbamate), 163.5 (*C*=O amide), 172.0 (*C*=O ester); *m*/*z* (ESI) 871 (M_2Na^+, 62%), 447 (MNa^+, 100), 425 (40); HRMS (ESI) $C_{22}H_{37}N_2O_6^+$ requires 425.2652; found 425.2648.

(3*R*,5*R*,6*R*,2′*E*,4′*Z*)-3-(*N*-*tert*-Butoxycarbonylamino)-5,6-(isopropylidene-5-oxy-6-[*N*-hexa-2′,4′-dienoylamino])heptanoic acid 83. To a stirred solution of ester **82** (54 mg, 0.127 mmol) in MeOH/THF (2 : 1, 4.5 mL) at 0 °C was added aq NaOH (1 M, 0.51 mL, 0.509 mmol). The mixture was stirred at 0 °C for 0.5 h then at rt for 4.5 h. The volatile material was removed *in vacuo*, the residue dissolved in H_2O (50 mL) and washed with ether (50 mL). The aqueous layer was acidified to pH 3 with aq $KHSO_4$ (0.5 M) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the title compound **83** as a colourless oil (53 mg, quant, 4′*Z* : 4′*E* > 95 : 5) which was used without further purification; $[\alpha]_D^{22}$ +64.6 (*c* = 1.2, $CHCl_3$); ν_{max} (KBr disc) 3430 (O–H, N–H), 2979 (C–H), 1716 (C=O carbamate, C=O acid) 1646 (C=O amide), 1612 (C=C), 1595 (C=C), 1517 (amide II); δ_H (500 MHz, $CDCl_3$) 1.31 (3H, d, *J* = 6.0, C*H*$_3$CHN), 1.40 (9H, s, C(C*H*$_3$)$_3$), 1.57 (3H, s, C*H*$_3$CCH$_3$), 1.65 (3H, s, CH_3CC*H*$_3$), 1.73–1.99 (2H, m, CHC*H*$_2$CH), 1.85 (3H, dd, *J* = 7.4, 1.1, C*H*$_3$CH=CH), 2.50–2.72 (2H, m, C*H*$_2$C=O), 3.76 (1H, m, CH_3C*H*N), 3.91 (1H, m, C*H*O), 4.09 (1H, m, CH_2C*H*CH_2), 5.37 (1H, br d, *J* = 6.7, N*H*), 5.87 (1H, m, CH_3C*H*=CH), 6.03 (1H, d, *J* = 14.5, CH=C*H*C=O), 6.14 (1H, appt t, *J* = 10.7, CH_3CH=C*H*), 7.64 (1H, appt t, *J* = 13.2, C*H*=CHC=O), 10.79 (1H, br s, O*H*); δ_C (125 MHz, $CDCl_3$) 14.4 (*C*H$_3$CH=CH), 21.8 (*C*H$_3$CHN), 26.5 (*C*H$_3$CCH$_3$), 27.5 (CH_3C*C*H$_3$), 28.8 (C(*C*H$_3$)$_3$), 38.3 (CH*C*H$_2$CH), 39.1 (*C*H$_2$C=O), 45.8 (CH_2*C*HCH_2), 58.3 (CH_3*C*HN), 80.0 (*C*HO), 96.7 (*C*(CH_3)$_2$), 122.8 (CH=*C*HC=O) 127.9, (CH_3CH=*C*H), 135.6 (CH_3*C*H=CH), 137.7 (*C*H=CHC=O), 155.7 (*C*=O carbamate), 164.4 (*C*=O amide), 176.5 (*C*=O acid); *m*/*z* (ESI) 409 ((M − H)$^-$, 80%), 335 (100), 252 (40), 186 (40). HRMS (ESI) $C_{21}H_{33}N_2O_6^-$ requires 409.2339; found 409.2341.

(3*R*,5*R*,6*R*,2″*E*,4″*Z*)-3′-Amidinopropionyl 3-(*N*-*tert*-butoxycarbonylamino)-5,6-(isopropylidene-5-oxy-6-[*N*-hexa-2″,4″-dienoylamino])heptanamide 84. To a stirred solution of acid **83** (35 mg, 0.085 mmol) and 3 Å molecular sieves (100 mg) in THF (2 mL) under Ar was added DCC (24 mg, 0.115 mmol) and HOBT (14 mg, 0.102 mmol). The resulting mixture was stirred for 2 h and then the suspension was filtered, the precipitate washed with further THF (2 × 10 mL) and to the combined filtrate and washings were added 3-aminopropionamidine dihydrobromide **75** (21 mg, 0.085 mmol) and $NaHCO_3$ (14 mg, 0.17 mmol), both dissolved in one portion of H_2O (2 mL). The resulting mixture was stirred for 48 h and the solvent removed *in vacuo*. Purification *via* column chromatography on silica gel (3% MeOH in DCM then 20% MeOH in DCM) and concentration of the more polar fraction afforded the title compound **84** as a *ca.* 5 : 1 mixture of its hydrobromide and HOBT salts. This mixture was dissolved in DCM/MeOH (10 : 1, 10 mL), MP carbonate resin (Argotech®, 234 mg, 2.55 mmol g^{-1}, 0.60 mmol) added and the mixture stirred for 2 h. After removal of the resin by filtration, and washing with DCM (2 × 10 mL), the solvent was removed from the combined filtrate and washings *in vacuo* to afford the title compound **84** as a pale yellow oil (32 mg, 78%, 4″*Z*:4″*E* > 95:5); $[\alpha]_D^{22}$ +41.5 (*c* = 0.3, $CHCl_3$); ν_{max} (film) 3291 (N–H), 2979 (C–H), 1694, 1683, 1651, 1645 (C=O carbamate, C=O amide, C=N), 1614 (C=C), 1595 (C=C), 1532 (amide II); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* = 6.8, CH_3CHN), 1.42 (9H, s, C(CH_3)$_3$), 1.58 (3H, s, CH_3CCH$_3$), 1.66 (3H, s, CH_3CCH_3), 1.71–1.92 (2H, m, CHCH_2CH), 1.86 (3H, d, *J* = 7.2, CH_3CH=CH), 2.38–2.47 (4H, m, CH_2C=O, CH_2C=N), 3.48 (2H, m, CH_2N), 3.75 (1H, m, CH_3*CH*N), 3.92 (1H, m, *CH*O), 4.03 (1H, m, CH_2*CH*CH_2), 4.75 (4H, br s, N*H*), 5.75 (1H, br s, N*H*), 5.88 (1H, dq, *J* = 10.6, 7.1, CH_3*CH*=CH), 6.05 (1H, d, *J* = 14.7, CH=*CH*C=O), 6.15 (1H, m, CH_3CH=*CH*), 7.63 (1H, dd, *J* = 14.2, 11.8, *CH*=CHC=O); δ_C (125 MHz, $CDCl_3$) 13.8 (*C*H$_3$CH=CH), 21.3 (*C*H$_3$CHN), 25.9 (*C*H$_3$CCH$_3$), 27.0 (CH$_3$*C*CH$_3$), 28.3 (C(*C*H$_3$)$_3$), 36.2 (*C*H$_2$C=N), 37.4 (*C*H$_2$N), 38.0 (CH*C*H$_2$CH), 40.7 (*C*H$_2$C=O), 46.3 (CH$_2$*C*HCH$_2$), 57.8 (CH$_3$*C*HN), 79.3 (*C*HO), 96.0 (*C*(CH$_3$)$_2$), 122.5 (CH=*C*HC=O), 127.4 (CH$_3$CH=*C*H), 134.8 (CH$_3$*C*H=CH), 136.7 (*C*H=CHC=O), 155.5 (*C*=O carbamate), 163.7 (CH=CH*C*=O), 166.0 (*C*=NH), 171.0 (CH$_2$*C*=O); *m*/*z* (ESI) 480 (MH^+, 100%); HRMS (ESI) $C_{24}H_{42}N_5O_5^+$ requires 480.3186; found 480.3189.

Sperabillin B hydrochloride 2. To a stirred solution of amidine **84** (29 mg, 0.0605 mmol) in DCM (3 mL) under Ar, was added TFA (1 mL) drop-wise. The resulting mixture was stirred for 30 min and the solvent removed *in vacuo*. The resulting crude product was 4″*Z*:4″*E* > 95:5 by ^{1}H NMR spectroscopic analysis. Purification by preparative HPLC and concentration *in vacuo* of the fractions absorbing at λ = 260 nm followed by passage of the residue through Amberlite IRA-402 (H_2O), and removal of the volatile material *in vacuo* afforded sperabillin B hydrochloride **2** as a colourless foam (15 mg, 60%, 4″*Z*:4″*E* 93:7); $[\alpha]_D^{22}$ +48.3 (*c* = 0.24, H_2O) {lit.[2] $[\alpha]_D$ +56.0 (*c* = 1.0, H_2O)}; ν_{max} (KBr disc) 3269, 3068 (N–H, O–H), 1692, 1654 (C=O amide, C=N), 1618 (C=C), 1609 (C=C), 1546 (amide II); δ_H (500 MHz, D_2O) 1.10 (3H, d, *J* = 6.6, CH_3CHN), 1.61–1.74 (2H, m, CHCH_2CH), 1.77 (3H, d, *J* = 7.2, CH_3CH=CH), 2.53–2.60 (2H, m, CH_2C=N), 2.62 (2H, d, *J* = 6.7, CH_2C=O) 3.41–3.49 (2H, m, CH_2N) 3.72–3.78 (2H, m, CH$_2$*CH*CH$_2$, *CH*O), 3.92 (1H, qd, *J* = 6.7, 3.8, CH$_3$*CH*NH), 5.91 (1H, dq, *J* = 10.7, 7.4, CH$_3$*CH*=CH), 5.97 (1H, d, *J* = 15.2, CH=*CH*C=O), 6.12 (1H, appt t, *J* = 11.2, CH$_3$CH=*CH*), 7.45 (1H, dd, *J* = 15.2, 11.7, *CH*=CHC=O); δ_C (125 MHz, D_2O) 13.6 (*C*H$_3$CH=CH), 16.4 (*C*H$_3$CHN), 35.0 (*C*H$_2$C=N), 36.6 (*C*H$_2$N, CH*C*H$_2$CH), 37.5 (*C*H$_2$C=O), 46.7 (CH$_2$*C*HCH$_2$), 49.8 (CH$_3$*C*HN), 70.0 (*C*HO), 122.8 (CH=*C*HC=O), 127.1 (CH$_3$CH=*C*H), 136.9, 137.0 (CH$_3$*C*H=CH, *C*H=CHC=O), 169.2, 172.2 (*C*=NH, CH$_2$*C*=O, CH=CH*C*=O); *m*/*z* (ESI) 340 (MH^+, 100%), 253 (30), 246 (60), 242 (60), 239 (40), 212 (37), 191 (40); HRMS (ESI) $C_{16}H_{30}N_5O_3^+$ requires 340.2349; found 340.2349.

Acknowledgements

The authors wish to thank the EPSRC (A. J. P. M.) and Rhône-Poulenc Rôrer (R. J. K.) for funding and New College, Oxford, for a Junior Research Fellowship (A. D. S.).

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