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Total syntheses of pamamycin 607 and methyl nonactate: stereoselective cyclisation of homoallylic alcohols that had been prepared with remote stereocontrol using allylstannanes†

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The tin(IV) chloride mediated cyclisation of (*Z*)-homoallylic alcohols using phenylselenenyl chloride or phthalimide in the presence of a Lewis acid followed by reductive removal of the phenylselenenyl group was found to give 2,5-*cis*-disubstituted tetrahydrofurans with excellent stereocontrol. Using this procedure, (2*S*,4*S*,8*R*,6*Z*)-9-benzyloxy-2-*tert*-butyldiphenylsilyloxy-8-methylnon-6-en-4-ol (**11**), prepared stereoselectively *via* the tin(IV) chloride promoted reaction between the (*R*)-5-benzyloxy-4-methylpent-2-enyl(tributyl)stannane (**3**) and (*S*)-3-*tert*-butyldiphenylsilyloxybutanal (**10**), gave (2*S*,3*R*,6*S*,8*S*)-1-benzyloxy-8-*tert*-butyldiphenylsilyloxy-3,6-epoxy-2-methylnonane (**13**) after deselenation. This tetrahydrofuran was selectively deprotected, oxidized and esterified to give methyl nonactate (**2**). Having established this synthesis of 2,5-*cis*-disubstituted tetrahydrofurans, it was applied to complete a synthesis of pamamycin 607 (**1**). (2*S*,3*R*,6*S*,8*R*)-1-Benzyloxy-8-[*N*-methyl-*N*-(toluene-4-sulfonyl)amino]-3,6-epoxy-2-methylundecane (**35**) was prepared stereoselectively from (*R*)-3-[*N*-(toluene-4-sulfonyl)-*N*-methylamino]hexanal (**32**) by reaction with the stannane **3** followed by cyclisation of the resulting alkenol **33** and deselenation. Following debenzylation and oxidation, an aldol reaction of the aldehyde **37** using the lithium enolate of 2,6-dimethylphenyl propanoate (**61**) gave mainly the 2,3-*anti*-3,4-*syn*-adduct **48**. After protection of the secondary alcohol as its *tert*-butyldimethylsilyl ether **49**, reduction using DIBAL-H and oxidation, the resulting aldehyde, (2*S*,3*S*,4*R*,5*R*,8*S*,10*R*)-3-*tert*-butyldimethylsilyloxy-2,4-dimethyl-5,8-epoxy-10-[*N*-methyl-*N*-(toluene-4-sulfonyl)amino]tridecanal (**62**), was taken through to the bis-tetrahydrofuran **65** by repeating the sequence of the reactions with the stannane **3**, cyclisation and deselenation. The *N*-(toluene-4-sulfonyl) group was then replaced by an *N*-(*tert*-butoxycarbonyl) group and *O*-debenzylation and oxidation gave the carboxylic acid **70** that corresponds to the C(1)–C(18) fragment of pamamycin 607 (**1**). Similar chemistry was used to prepare the C(1′)–C(11′) fragment **89** of the pamamycin, except that in this case the configuration of the secondary alcohol introduced by the allylstannane reaction had to be inverted using a Mitsunobu reaction before the cyclisation. Esterification of the carboxylic acid of the C(1)–C(18)-fragment **70** using the alcohol **89** of the C(1′)–C(11′) fragment followed by selective deprotection, macrocyclisation, *N*-deprotection and *N*-methylation gave pamamycin 607 (**1**) that was identical to a sample of the natural product.

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Introduction

The pamamycins are macrodiolides isolated from *Streptomyces alboniger* that possess antibiotic activity against some phytopathogenic fungi and bacteria.[1,2] Their structures, *e.g.* of pamamycin 607 (**1**), are characterised by the presence of three 2,5-*cis*-disubstituted tetrahydrofuran rings similar to that in methyl nonactate (**2**).[3] The synthesis of these compounds has been of considerable interest because of their novel structures and biological activities, and several total syntheses have now been completed[4] along with additional synthetic approaches to the constituent hydroxycarboxylic acids.[5] We here report full details of the total synthesis of pamamycin 607 (**1**)[6] and a synthesis of methyl nonactate (**2**) that are based on the stereoselective cyclisation of (*Z*)-homoallylic alcohols that had been

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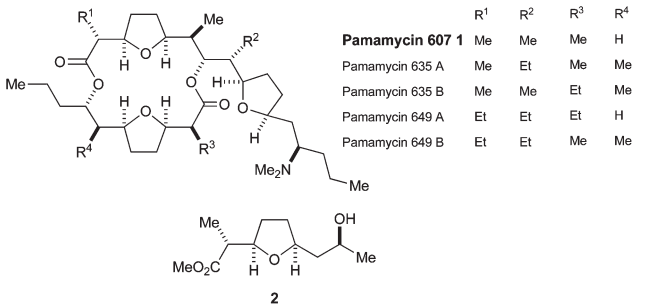
prepared with remote stereocontrol using functionalised allylstannanes.[7]



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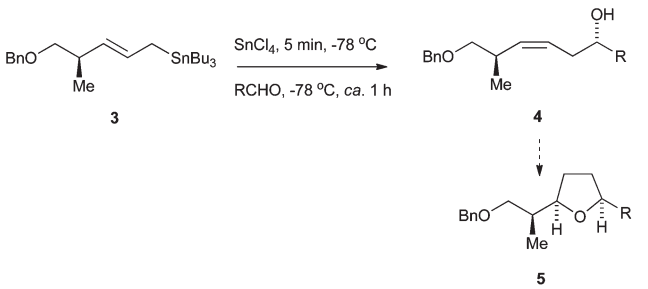
Transmetallation of the (*E*)-5-benzyloxypent-2-enylstannane **3** using tin(IV) chloride generates an allyltin trichloride that reacts with aldehydes with excellent stereoselectivity in favour of the 1,5-*anti*-(*Z*)-alk-3-enols **4**.[7] Several procedures are known for the stereoselective synthesis of 2,5-disubstituted tetrahydrofurans from homoallylic alkenols[8–10] and, as applied to the (*Z*)-alkenols **4**, were expected to provide access to the tetrahydrofurans **5** which are reminiscent of those in the pamamycins and methyl nonactate. In particular, they are characterised by the presence of a methyl-bearing stereogenic centre next to the 2,5-*cis*-disubstituted tetrahydrofuran ring.



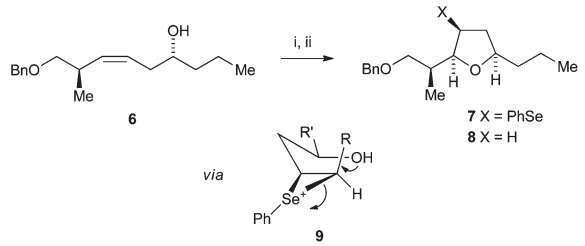
3 4 5

Results and discussion

Phenylselenenyl chloride or phthalimide induced cyclisation of (*Z*)-homoallylic alcohols; synthesis of methyl nonactate (2)

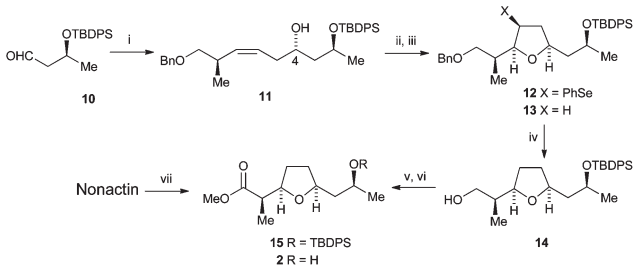
Attempts to convert (*Z*)-alkenols **4** into tetrahydrofurans using iodine in aqueous acetonitrile buffered with sodium hydrogen carbonate,[8] were complicated by competing debenzylation and gave complex mixtures of products. Initial studies using phenylselenenyl chloride[9] were also slow and inefficient. However, it was found that cyclisation could be achieved using either phenylselenenyl chloride or phthalimide in the presence of tin(IV) chloride (20 mol%). Using this procedure, the (*Z*)-non-6-en-4-ol **6**, prepared from butanal using the stannane **3**,[7] gave the tetrahydrofuran **7** that was reduced using tributyltin hydride under free-radical conditions to give the 2,5-disubstituted tetrahydrofuran **8**, see Scheme 1. Tetrahydrofuran **8** was identical to a sample prepared earlier by a longer synthesis.[11]

This cyclisation of alkenol **6** into the tetrahydrofuran **7** is consistent with reversible alkene phenylselenation followed by



6 7 X = PhSe 8 X = H 9

Scheme 1 Direct cyclisation of homoallylic alcohols. Reagents and conditions: (i) PhSeCl or PhSePhth, DCM, $SnCl_4$ (20 mol%), r.t., 5 h (typically 50%); (ii) Bu_3SnH, benzene, reflux, 2 h (85%).



10 11 12 X = PhSe 13 X = H 14 15 R = TBDPS 2 R = H

Scheme 2 Synthesis of (–)-methyl nonactate (**2**). Reagents and conditions: (i) **3**, $SnCl_4$, –78 °C, 5 min, add **10**, –78 °C, 45 min (82%, 4,8-*anti* : 4,8-*syn* > 96 : 4); (ii) PhSePhth, DCM, $SnCl_4$ (20 mol%), r.t., 20 h (62%); (iii) Bu_3SnH, benzene, reflux, 2 h (85%); (iv) 10% Pd/C, H_2, EtOH, AcOH, r.t., 52 h (73%); (v) (a) PDC, DMF, r.t., 24 h (82%), (b) Me_3SiCHN_2, hexane, benzene, MeOH, r.t., 30 min (78%); (vi) TBAF, THF, r.t., 7 h (78%); (vii) MeOH, cH_2SO_4, reflux, 48 h (66%).

cyclisation with participation of the envelope conformation **9** in which the R′ group is in the less hindered pseudo equatorial position.[12] However, this mechanism was not investigated and it was not confirmed whether kinetic or thermodynamic factors were controlling the stereoselectivity of product formation under these conditions.

This procedure was applied to complete a synthesis of (–)-methyl nonactate (**2**), see Scheme 2. The tin(IV) chloride mediated reaction between the stannane **3** and (*S*)-3-*tert*-butyldiphenylsilyloxybutanal (**10**)[13] gave the (*Z*)-4,8-*anti*-product **11** with useful stereoselectivity (4,8-*anti* : 4,8-*syn* > 96 : 4). This on treatment with phenylselenenyl phthalimide and 20 mol% tin(IV) chloride cyclised to give the tetrahydrofuran **12**. Deselenation was achieved using tributyltin hydride, tetrahydrofuran **13** being isolated essentially as a single stereoisomer (>95 : 5) after chromatography. Hydrogenolysis gave the primary alcohol **14** that was oxidised to the corresponding carboxylic acid using pyridinium dichromate. Esterification using trimethylsilyl diazomethane then gave the ester **15** and desilylation with tetrabutylammonium fluoride gave (–)-methyl nonactate (**2**).[3] The structure of (–)-methyl nonactate was confirmed by comparison with a racemic sample prepared from nonactin using a known procedure, see Scheme 2.[14]

Synthesis of the C(1)–C(18) component of pamamycin 607

This synthesis of (–)-methyl nonactate (**2**) shows how the phenylselenenyl induced cyclisation of homoallylic alcohols

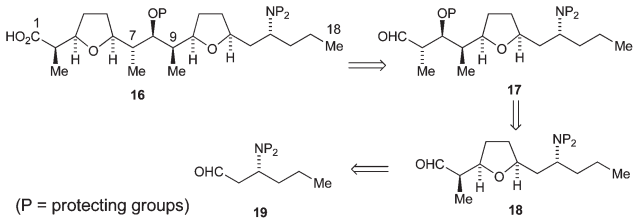


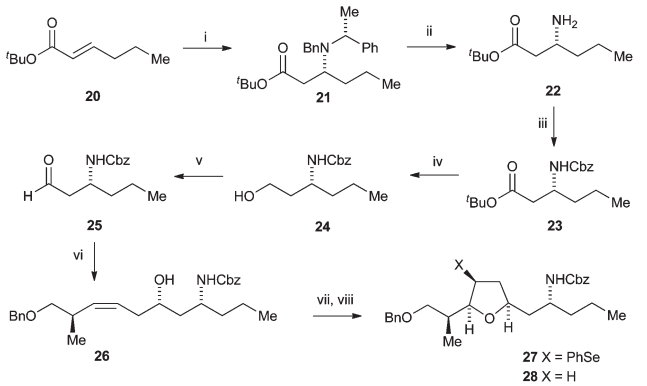
Fig. 1 Strategy for synthesis of the C(1)–C(18) fragment of pamamycin 607.

prepared using allylstannanes with (*Z*)-1,5-*anti*-stereocontrol can be used to synthesize 2,5-*cis*-disubstituted tetrahydrofurans reminiscent of those in pamamycin 607 (**1**). Pamamycin 607 is a macrodiolide and it was decided to prepare the two constituent hydroxy-acids separately leaving the esterification and macrocyclisation steps to the end of the synthesis. A linear synthesis was envisaged for the more complex C(1)–C(18) hydroxy-acid starting at the C(18) end, see Fig. 1. Retrosynthetically, the C(1)–C(18)-acid **16** was to be prepared from the aldehyde **17** by reaction with allylstannane **3** followed by phenylselenenyl induced cyclisation to form the second 2,5-*cis*-disubstituted tetrahydrofuran ring. The aldehyde **17** should be accessible by a Felkin–Anh controlled *anti*-selective aldol reaction of the aldehyde **18** that in turn should be available from the protected 3-aminohexanal **19** by reaction with allylstannane **3**, phenylselenenyl induced cyclisation and deselenation.

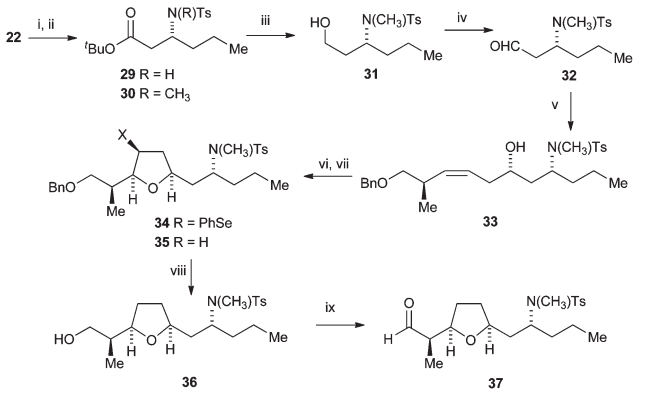
The diastereoselective conjugate addition of chiral lithium amides to α,β-unsaturated esters developed by Davies was used to prepare the protected (*R*)-3-aminohexanal **25**.[15] The conjugate addition of lithiated (*R*)-*N*-benzyl-α-methylbenzylamine to *tert*-butyl (*E*)-hex-2-enoate (**20**)[16] gave the adduct **21** with excellent stereoselectivity and transfer hydrogenolysis gave the amino-ester **22** that was protected as its *N*-benzyloxycarbonyl derivative **23**. Reduction to the alcohol **24** and oxidation led to aldehyde **25** and the tin(IV) promoted reaction of this with stannane **3** gave the (*Z*)-2,6-*anti*-alkenol **26** with good stereoselectivity. Cyclisation of the alkenol using phenylselenenyl chloride in the presence of tin(IV) chloride gave the tetrahydrofuran **27**, but only in a modest 25%, yield. Nevertheless, deselenation using tributyltin hydride gave the 2,5-*cis*-disubstituted tetrahydrofuran **28**, see Scheme 3.

Configurations were assigned to the products **26–28** on the basis of precedent and were consistent with spectroscopic data. However, the key cyclisation step was accompanied by the formation of several side-products that were not tetrahydrofurans and it appeared that the cbz-protected amine had interfered with the cyclisation. It was therefore necessary to study other amine derivatives to see if alternative protecting groups could be found that were more compatible with the tetrahydrofuran formation.

N-Tosylation of the amino-ester **22** gave the sulfonamide **29** that was methylated on nitrogen to introduce the first of the two *N*-methyl groups present in the pamamycins. The resulting *N*-methylsulfonamide **30** was then converted into the aldehyde **32**, by reduction to alcohol **31** followed by oxidation, and the

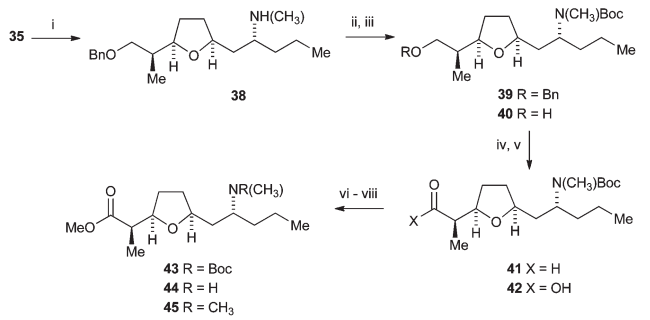


Scheme 3 Synthesis of an amidoalkyl substituted tetrahydrofuran. Reagents and conditions: (i) (*R*)-BnNCH(CH$_3$)Ph, ^{n}BuLi, −78 °C, THF, −78 °C, 30 min, add **20**, −78 °C, 2 h (89%); (ii) Pd(OH)$_2$/C, MeOH, ammonium formate, r.t., 15 min, add **21**, r.t., 1 h (91%); (iii) K_2CO_3, $BnCO_2Cl$, Et_2O, H_2O, 0 °C – r.t., 3 h (88%); (iv) $LiAlH_4$, Et_2O, 0 °C – r.t., 2 h (80%); (v) $(COCl)_2$, DMSO, DCM, −78 °C, 5 min, add alcohol **24**, −78 °C, 20 min, add Et_3N, warm to r.t. (99%); (vi) **3**, $SnCl_4$, −78 °C, 5 min, add **25**, −78 °C, 50 min (64%); (vii) PhSeCl, $SnCl_4$, DCM, r.t., 15 h (25%); (viii) Bu_3SnH, AIBN (cat.), toluene, reflux, 1 h (64%).



Scheme 4 Synthesis of the C(8)–C(18) fragment of pamamycins. Reagents and conditions: (i) TsCl, Et_3N, DCM, 0 °C – r.t., 24 h (95%); (ii) NaH, MeI, THF, r.t., 15 h (99%); (iii) $LiAlH_4$, Et_2O, 0 °C, 1.5 h (96%); (iv) $(COCl)_2$, DMSO, DCM, −78 °C, 5 min, add alcohol **31**, −78 °C, 20 min, Et_3N, r.t., 1.5 h (99%); (v) **3**, $SnCl_4$, DCM, −78 °C, 5 min, add **32**, −78 °C, 50 min (64%); (vi) PhSeCl, $SnCl_4$, DCM, r.t., 20 h (42%); (vii) Bu_3SnH, AIBN (cat.), benzene, reflux, 1.25 h (94%); (viii) 10% Pd/C, EtOH, AcOH, H_2, r.t., 16 h (91%); (ix), $(COCl)_2$, DMSO, DCM, −78 °C, 5 min, add alcohol **36**, −78 °C, 20 min, Et_3N, r.t., 1.5 h (90%).

tin(IV) halide promoted reaction of aldehyde **32** with the stannane **3** gave the required homoallylic alcohol **33** with excellent stereoselectivity. Although the cyclisation of the alcohol **33** induced by reaction with phenylselenenyl chloride–tin(IV) chloride still gave some non-tetrahydrofuran containing side-products, the yield of the tetrahydrofuran **34** was 42% after chromatography and this was deemed acceptable at this stage of the project. Reduction using tributyltin hydride gave the 2,5-*cis*-disubstituted tetrahydrofuran **35**. This was hydrogenolysed to give the alcohol **36** that was oxidised to complete a synthesis of the aldehyde **37**, see Scheme 4. Aldehyde **37** corresponds to the aldehyde **18** in the proposed strategy for a synthesis of pamamycin 607 (see Fig. 1).



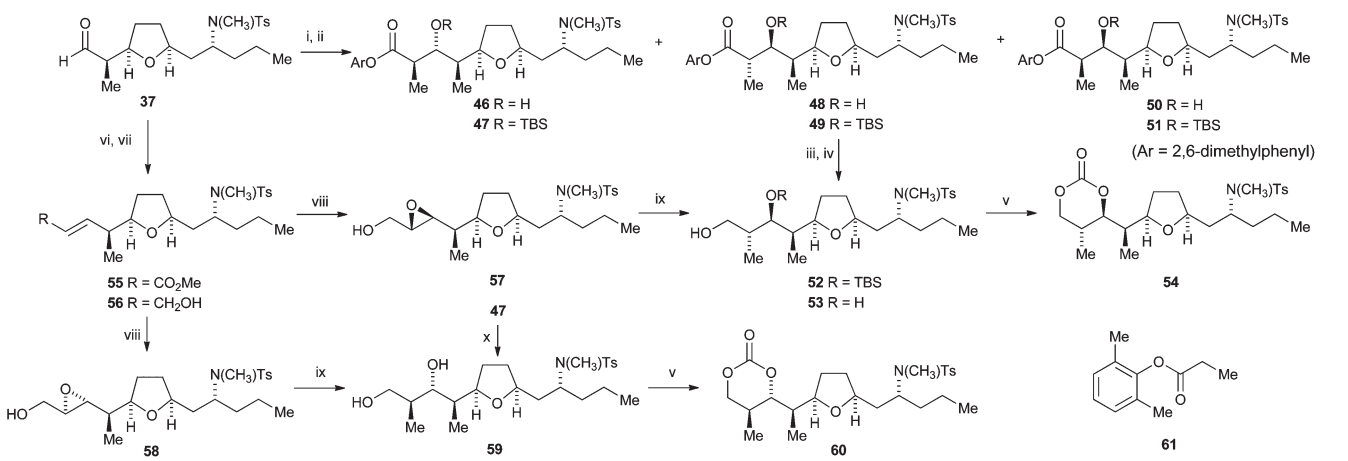
Scheme 5 Correlation of the tetrahydrofuran **35** with the known ester **45**. Reagents and conditions: (i) Na, naphthalene, DME, sonicated, r.t., 12 min, added to **35** in DME, −60 °C, 1 h (85%); (ii) $(^tBuOCO)_2O$, Et_3N, THF, r.t., 16 h (90%); (iii) 10% Pd/C, EtOH, H_2, r.t., 16 h (89%); (iv) Dess–Martin periodinane, DCM, r.t., 40 min (*ca.* 100%); (v) $NaClO_2$, ^tBuOH, H_2O, 2-methylbut-2-ene, NaH_2PO_4, r.t., 2 h; (vi) Me_3SiCHN_2, benzene, MeOH, r.t., 1.5 h (75% from the aldehyde); (vii) cHCl, EtOAc, r.t., 15 h (48%); (viii) formalin, MeCN, $NaBH_3CN$, r.t., 1 h (52%).

Although the structure of the tetrahydrofuran **35** was consistent with the earlier work and with its spectroscopic data, it was decided to confirm its structure by correlation with a known compound. Thus sodium naphthalenide was used to reduce the tosylamide **35** to the amine **38** and this was acylated to prepare its *N*-Boc derivative **39**. Hydrogenolysis gave the alcohol **40** and oxidation *via* the aldehyde **41** provided the ester **43** after reaction of the intermediate acid **42** with trimethylsilyl diazomethane. Following removal of the Boc-group under acidic conditions,[17] reductive methylation of the resulting secondary amine **44** using formalin and sodium cyanoborohydride[18] gave the dimethylamino-ester **45**, see Scheme 5. This had spectroscopic data in good agreement with those reported in the literature.[5k]

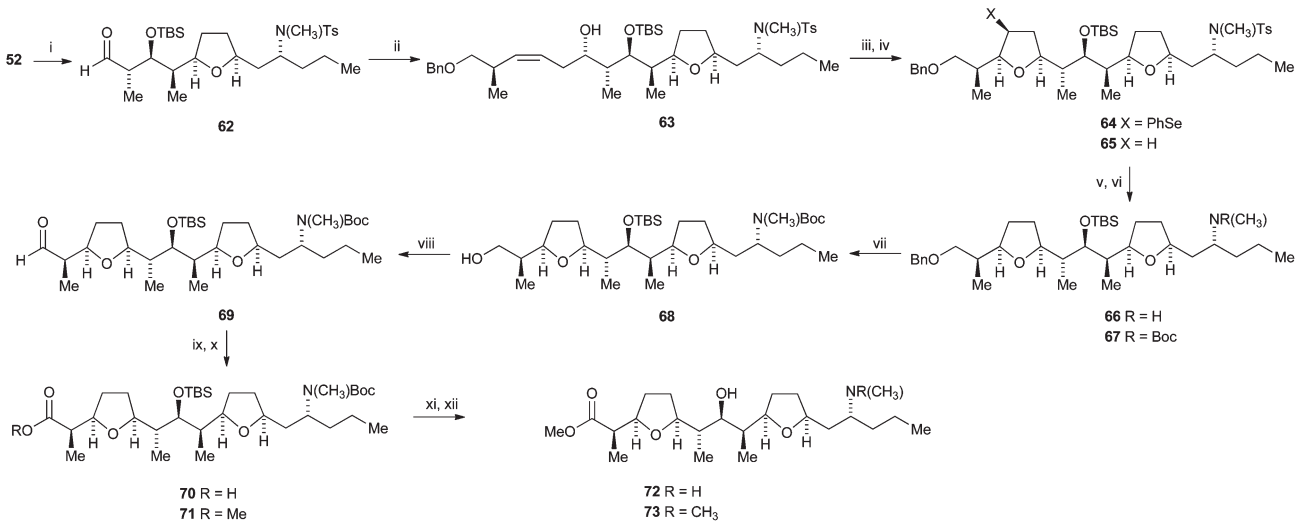
The next stage in the synthesis was to carry out a Felkin–Anh controlled *anti*-aldol condensation of aldehyde **37** to prepare a compound with the correct configurations at C(2) and C(3) for incorporation into a pamamycin, *cf.* **17** in Fig. 1. To minimise the use of chiral reagents, it was decided to employ the lithium enolate derived from 2,6-dimethylphenyl propanoate (**61**).[19]

In the event, the reaction of the lithium enolate of the aryl ester **61** with aldehyde **37** gave three products in a ratio of 19 : 72 : 9 that were identified as the *anti*,*anti*-, the *anti*,*syn*- and the *syn*,*syn*-products **46**, **48** and **50**, respectively. The most polar product was the *syn*,*syn*-isomer **50** that could be separated from a mixture of the less polar products **46** and **48**. The two 2,3-*anti*-products **46** and **48** could not be separated but after silylation of the mixture, the *tert*-butyldimethyl silyl ethers **47** and **49** could be separated. The *syn*,*syn*-isomer **50** was also converted into its *tert*-butyldimethyl silyl ether **51** for comparison, see Scheme 6.

To confirm the structure of the major silyl ether **49**, it was reduced to the alcohol **52**. This was desilylated to give the diol **53** and treatment of this with carbonyl di-imidazole gave the cyclic carbonate **54**. Authentic samples of the cyclic carbonate **54** and its *anti*,*anti*-diastereoisomer **60**, were prepared from the starting aldehyde **37** *via* the ester **55** synthesized by an (*E*)-selective Wittig reaction using methoxycarbonylmethylene triphenylphosphorane. Reduction of ester **55** gave the allylic alcohol **56** and epoxidation of this alcohol under Sharpless conditions gave epoxide **57** using (+)-diethyl tartrate and epoxide **58** using (−)-diethyl tartrate, with excellent stereoselectivities in both cases, the configurations of these epoxides being assigned by the Sharpless mnemonic.[20] Ring-opening the epoxide **57** using a methyl cuprate gave the diol **53** and hence the carbonate **54** that had been prepared from the



Scheme 6 The anti-aldol condensation and confirmation of the structures of the products. Reagents and conditions: (i) $^iPr_2NH$, ^nBuLi, THF, 0 °C, 15 min, cool to −78 °C, add **61**, −78 °C, 1 h, add **37**, −78 °C, 1 h (**46** + **48**, 63%, **46** : **48** = 20 : 80; **50**, 7%); (ii) 2,6-lutidine, TBSOTf, DCM, r.t., 15 h (**47**, 17%; **49**, 66%, from **46** + **48**; **51**, 70% from **50**); (iii) DIBAL-H, DCM, −78 °C, 30 min, warm to r.t., 1 h (80%); (iv) TBAF, THF, r.t., 2 h (89%); (v) $CO(imid)_2$, benzene, reflux, 15 h (**54**, 87%; **60**, 67%); (vi) Ph_3PCHCO_2Me, DCM, r.t., 48 h (81%); (vii) DIBAL-H, DCM, hexane, −78 °C, 30 min, warmed to r.t., 90 min (74%); (viii) (+)-DET (for **57**), (−)-DET (for **58**), DCM, $Ti(OiPr)_4$, −23 °C, ^tBuOOH, toluene, −23 °C, 2 h (**57**, 70%, **57** : **58** = 95 : 5; **58**, 80%, **58** : **57** = 98 : 2); (ix) CuI, Et_2O, MeLi, −10 °C, 30 min, add epoxide, −10 °C, 5 h (**53**, 57%; **59**, 72%); (x) (a) DIBAL-H, DCM, −78 °C, 30 min, warm to r.t., 1.5 h (38%) (b) TBAF, THF, r.t., 2 h (70%).



Scheme 7 Completion of the C(10)–C(18) fragment. Reagents and conditions: (i) $(COCl)_2$, DMSO, DCM, −78 °C, 5 min, add **52**, −78 °C, 20 min, Et_3N, r.t., 1.5 h (95%); (ii) **3**, $SnCl_4$, DCM, −78 °C, 5 min, add **62**, −78 °C, 50 min (83%); (iii) $ZnCl_2$, PhSePhth, r.t., 2 h (54%); (iv) Bu_3SnH, AIBN (cat.), benzene, reflux, 1.25 h (*ca.* 85%); (v) Na, naphthalene, DME, sonicated, r.t., 12 min, added to **65** in DME, −60 °C, 1 h (83%); (vi) $(^tBuOCO)_2O$, Et_3N, THF, r.t., 16 h (95%); (vii) 10% Pd/C, EtOH, H_2, r.t., 16 h (82%); (viii) Dess–Martin periodinane, DCM, r.t., 40 min (*ca.* 100%); (ix) $NaClO_2$, ^tBuOH, H_2O, 2-methylbut-2-ene, NaH_2PO_4, r.t., 2 h (90%); (x) Me_3SiCHN_2, benzene, MeOH, r.t. (73% from **69**); (xi) *c*HCl, EtOH, r.t., 16 h (50%); (xii) formalin, $NaCNBH_3$, MeCN, r.t., 1 h, AcOH, r.t., 16 h (48%).

major aldol product **48**. The diastereoisomeric epoxide **58** gave the diol **59** on treatment with the methyl cuprate and hence the carbonate **60**. The diol **59** was also prepared from the minor aldol product **46** by reduction of the corresponding silyl ether **47** and desilylation. The diols **53** and **59**, and the carbonates **54** and **60**, had distinctly different ^1H and ^{13}C NMR spectra that were consistent with the assigned structures, *e.g.* with H(2) and H(3) showing diaxial coupling in both cases, see Scheme 6.

This correlation confirmed the configuration assigned to the major aldol product **48** as the required 2,3-*anti*-3,4-*syn*-diastereoisomer formed by an *anti*-selective aldol reaction under Felkin–Anh[21] control. The structure of the minor 2,3-*anti*-3,4-*anti*-isomer **46** followed from its correlation with the diol **59**. The second minor product had to be a 2,3-*syn*-isomer and its 3,4-*syn*-configuration was assigned on the basis of Felkin–Anh control. It was now necessary to develop the chemistry of the alcohol **52** prepared from the major aldol product **48** to complete a synthesis of the C(1)–C(18) component of pamamycin 607, see Scheme 7.

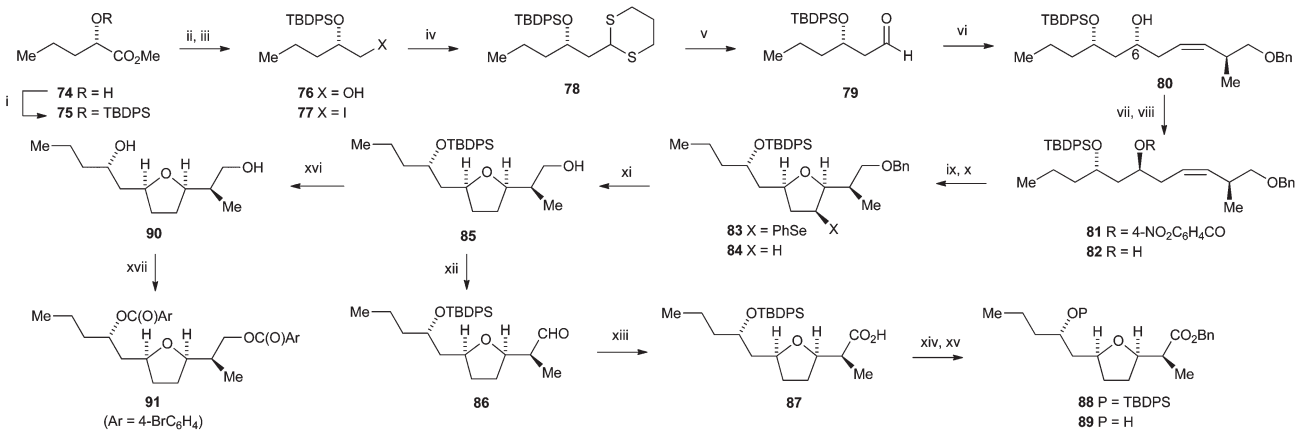
Oxidation of the alcohol **52** using Swern conditions gave the aldehyde **62**. The tin(IV) chloride promoted reaction of this aldehyde with the stannane **3** was again highly stereoselective and gave the required (*Z*)-2,6-*anti*-product **63** with no evidence of any other diastereoisomer (^1H, ^{13}C NMR). The next step was the crucial cyclisation of this alcohol to give the required 2,5-*cis*-disubstituted tetrahydrofuran, but this was regarded as a stern test of the methodology since this substrate was more hindered than the earlier substrates had been. In the event the best results were obtained using phenylselenenyl phthalimide with anhydrous zinc chloride as the Lewis acid. Under these conditions the bis-tetrahydrofuran **64** was obtained in an acceptable yield (54%) as the only diastereoisomer that could be isolated. The 2,5-*cis*-configuration of the newly formed tetrahydrofuran ring was consistent with nOe studies. Reduction using tributyltin hydride then removed the phenylselenenyl group to give the tetrahydrofuran **65**, see Scheme 7.

At this point, the toluene 4-sulfonyl group had completed its task of preventing interference by the *N*-substituent in the phenylselenenyl induced cyclisations. As its reductive removal would be incompatible with ester functionalities in later intermediates, it was removed using sodium naphthalenide to give the free secondary amine **66**. This was protected as its *tert*-butyloxycarbonyl derivative **67** and hydrogenolysis delivered the primary alcohol **68**. Oxidation *via* aldehyde **69** then gave the carboxylic acid **70** that corresponds to the intact C(1)–C(18) component of pamamycin 607 and is ready for incorporation into a final assembly of the natural product.

Structures were assigned to the intermediates in this scheme on the basis of the earlier work and were consistent with spectroscopic data. The acid **70** was also converted into the known methyl ester **73** with the dimethylamino substituent at C(15), by esterification using trimethylsilyl diazomethane to give the ester **71** that was treated with acid to remove the *tert*-butoxycarbonyl and *tert*-butyldimethylsilyl groups and reductive methylation of the resulting monomethylamine **72**. The methyl ester **73** had physical and spectroscopic properties consistent with those in the literature.[5l]

Synthesis of the C(1′)–C(11′) component of pamamycin 607

The C(1′)–C(11′) fragment of pamamycin 607 contains a 2,5-*cis*-disubstituted tetrahydrofuran with an α-methyl bearing side-chain at C(2), but the configuration of the methyl bearing stereogenic centre relative to the stereogenic centres in the tetrahydrofuran is the opposite of that in the C(1)–C(18) component. This necessitated an inversion step in the synthesis.



Scheme 8 Synthesis of the C(1′)–C(11′) fragment of pamamycin 607. Reagents and conditions: (i) TBDPSCl, imid., DCM, r.t., 16 h (92%); (ii) DIBAL-H, THF, −78 °C, 1 h, then r.t., 1 h (94%); (iii) I_2, Ph_3P, imid., THF, r.t., 2 h (97%); (iv) 1,3-dithiane, ^{n}BuLi, hexanes, THF, −20 °C, 1.5 h, added to **77**, THF, 0 °C, 16 h (88%); (v) HgO, THF, H_2O, r.t., $BF_3{\cdot}Et_2O$ 45 min (98%); (vi) (*R*)-**3**, $SnCl_4$, DCM, −78 °C, 5 min, add **79**, −78 °C, 50 min (90%); (vii) 4-$NO_2C_6H_4CO_2H$, Ph_3P, Et_2O, toluene, DEAD, r.t., 2 h (**81**, 70%; diene 12%); (viii) NaOH, MeOH, r.t., 2 h (94%); (ix) PhSePhth, $SnCl_4$, DCM, r.t., 40 min (81%); (x) Bu_3SnH, AIBN (cat.), benzene, reflux, 2.5 h (99%); (xi) 10% Pd/C, EtOH, AcOH, H_2, r.t., 15 h (89%); (xii) Dess–Martin periodinane, DCM, r.t., 1 h; (xiii) $NaClO_2$, ^{t}BuOH, H_2O, 2-methylbut-2-ene, NaH_2PO_4, r.t., 2 h; (xiv) BnBr, $^i Pr_2NEt$, MeCN, r.t., 15 h (76% from **85**); (xv) TFA, H_2O, r.t., 40 min (94%); (xvi) *c*HCl, MeOH, reflux, 2.5 h (99%); (xvii) 4-BrC_6H_4COCl, Et_3N, DMAP (cat.), DCM, r.t., 16 h (43%).

(*S*)-3-*tert*-Butyldiphenylsilyloxyhexanal (**79**) was prepared from the known methyl (*S*)-2-hydroxypentanoate (**74**)[22] by reduction of the corresponding silyl ether **75** using DIBAL-H to give the alcohol **76**. This was converted into the iodide **77** that was used to alkylate 1,3-dithiane to prepare the 2-alkyldithiane **78**. Hydrolysis of this gave the required aldehyde **79**.

The tin(IV) chloride promoted reaction of the (*R*)-stannane (*R*)-**3** with the (*S*)-3-*tert*-butyldiphenylsilyloxyhexanal (**79**) gave the homoallylic alcohol **80** with excellent stereoselectivity, just *ca.* 5% of the 1,5-*syn*-epimer being detected by ^{13}C NMR. At this point the configuration at C(6) had to be inverted. Treatment of the alcohol **80** with 4-nitrobenzoic acid under Mitsunobu conditions[23] gave the ester **81** with the desired inversion of configuration and 12% of a side-product provisionally identified as (2*S*,8*S*,3*Z*,5*EZ*)-1-benzyloxy-8-*tert*-butyldiphenylsilyloxy-2-methylundeca-3,5-diene. Saponification of the ester **81** gave the alcohol **82** that was cyclised using phenylselenenyl phthalimide and tin(IV) chloride to give the tetrahydrofuran **83**. Reductive removal of the phenylselenenyl group using tributyltin hydride then gave the 2,5-*cis*-disubstituted tetrahydrofuran **84**. This was debenzylated to give the primary alcohol **85** and oxidation *via* the aldehyde **86** gave the acid **87**. *O*-Alkylation using benzyl bromide under basic conditions gave the benzyl ester **88** and desilylation using trifluoroacetic acid provided the hydroxy ester **89** ready for incorporation into a pamamycin, see Scheme 8.

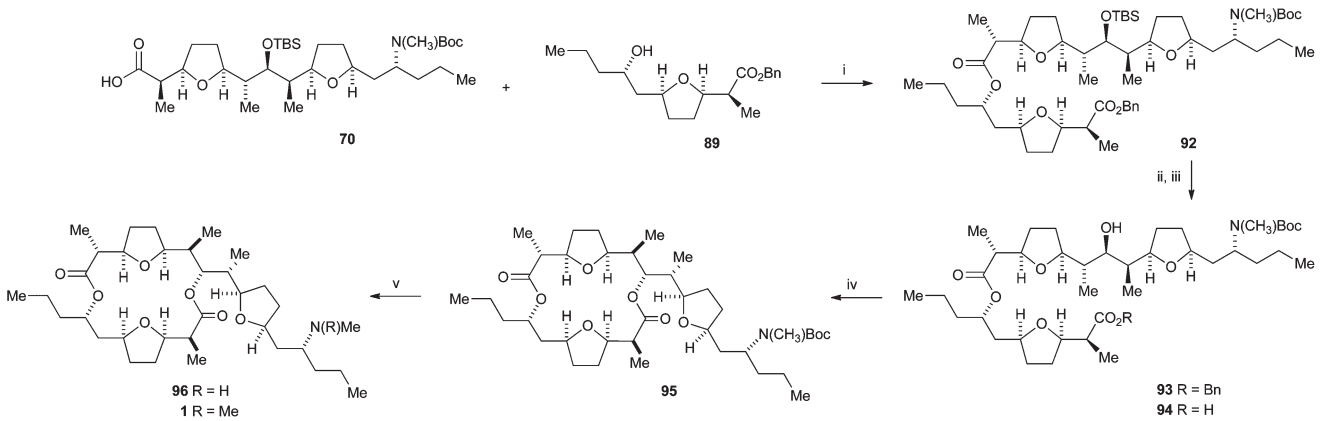
The structures of the compounds in this scheme were assigned by analogy with the earlier work. However, the tetrahydrofuran **83** contained a minor inseparable impurity, *ca.* 20%, that may have been a diastereoisomer of the major product, but this was not confirmed. It was removed during chromatography of the tetrahydrofurans **83** and **84**. The structure assigned to the tetrahydrofuran **85** was confirmed by desilylation to the known diol **90**[1c] that was bis-acylated to give the known 4-bromobenzoate **91** (Scheme 8).[5j]

Completion of a synthesis of pamamycin 607

Fortuitously, it was decided to join the C(1)–C(18) and C(1′)–C(11′) fragments by formation of the ester using the acid **70** of the C(1)–C(18)-component and the alcohol **89** of the C(1′)–C(11′) component.[24] Esterification of acid **70** using the alcohol **89** under Yamaguchi conditions[25] gave the ester **92**. Desilylation using tetrabutylammonium fluoride was complicated by base promoted tetrahydrofuran ring-opening and so had to be carried out under acidic conditions that led to loss of the *tert*-butoxycarbonyl group. This was reinstated to give the hydroxy-ester **93** that was hydrogenolysed to give the *seco*-acid **94**. Macrocyclisation was then achieved in a modest, albeit unoptimised, yield using the modified Yamaguchi conditions[25] to give the macrodiolide **95**. It remained to remove the *tert*-butoxycarbonyl group and to methylate the resulting secondary amine to complete a synthesis of a pamamycin. This was carried out using the conditions that had been used for the conversion of the monotetrahydrofuran **43** into the dimethylamine derivative **45**, see Scheme 5, namely acid catalysed removal of the Boc-group to give pamamycin 593 (**96**), which itself is a natural product,[1d] followed by reductive methylation using formalin and sodium cyanoborohydride.[18] This gave pamamycin 607 (**1**) that was compared directly with a sample of the natural material. The trifluoroacetate salts of the synthetic and natural pamamycin 607 (**1**)[1a] were shown to be identical by ^{1}H and ^{13}C NMR spectroscopy (Scheme 9).

Summary and conclusions

This synthesis of pamamycin 607 (**1**) features the use of remote stereocontrol using allylstannanes and the stereoselective Lewis acid promoted cyclisation of (*Z*)-homoallylic alcohols using phenylselenenyl electrophiles, both of these reactions being used successfully with complex chiral



Scheme 9 Completion of a synthesis of pamamycin 607 (**1**). Reagents and conditions: (i) DMAP, 2,4,6-trichlorobenzoyl chloride, DCM, r.t., 3.5 h (78%); (ii) (a) *c*HCl, EtOH, 55 °C, 3.5 h (b) (^{t}BuOCO)$_2$O, Et$_3$N, DCM, r.t., 16 h (93%); (iii) 10% Pd/C, EtOH, H$_2$, r.t., 16 h (97%); (iv) Et$_3$N, 2,4,6-trichlorobenzoyl chloride, xylene, r.t., 14 h, add DMAP, r.t., 24 h (25%); (v) (a) TFA, DCM, r.t., 45 min (82%) (b) formalin, NaBH$_3$CN, MeCN, r.t., 1.5 h, then AcOH, r.t. 21 h (70%).

substrates. In this synthesis, all the stereogenic centres, apart from those at C(15) and at C(8′) were derived from the allylstannanes or were induced from centres formed during allylstannane reactions. Indeed, the only chiral starting materials used in this synthesis were the (*R*)- and (*S*)-4-methylpent-2-enylstannanes (*R*)- and (*S*)-**3**, the ester **74** and (*R*)-*N*-benzyl-α-methylbenzylamine.

The synthesis of the C(1)–C(18)-component is a linear synthesis and perhaps convergent alternatives could be envisaged, but the use of the Felkin–Anh controlled *anti*-selective aldol reaction to introduce the required stereogenic centres at C(7) and C(8) directly did provide a concise assembly strategy. In this step it would have been possible to use a chiral aldol reagent for improved stereoselectivity, but the aldol reaction using the ester **61** made use of the chirality embedded in the substrate to control its stereoselectivity, in line with the philosophy of the synthesis.

In this work, some of the earlier steps involving the pent-2-enylstannanes (*R*)- and (*S*)-**3** were carried out successfully on multigramme scales on quite complex substrates, yet the remote stereocontrol introduced by the stannane dominated over any intrinsic stereochemical preference of the starting material. Moreover, the use of organotin reagents could be avoided by using the analogous organogermanium compounds that have been introduced more recently and which tend to react with even better stereoselectivity.[26]

The use of a Lewis acid to promote the phenylselenenyl induced cyclisations of the (*Z*)-homoallylic alcohols to give 2,5-*cis*-disubstituted tetrahydrofurans was not optimised.[27] However, the beneficial effect of having a Lewis acid present was observed for both phenylselenenyl chloride and phthalimide induced cyclisations. Tin(IV) chloride was usually used as the Lewis acid although the use of zinc chloride gave a better yield in a later example. However, studies to establish which Lewis acid–phenylselenenyl reagent combination was the optimum for a broad range of substrates, were not undertaken.

Experimental

General experimental procedures

^{1}H and ^{13}C NMR spectra were recorded on Varian Unity 500, Varian Unity Inova 400 and Varian Unity Inova 300 spectrometers with residual non-deuterated solvent as the internal standard. IR spectra were recorded on an ATI Mattson Genesis FTIR as thin films produced by evaporation of a DCM solution on sodium chloride plates unless otherwise stated. Mass spectra were recorded on Micromass VG Trio 200 and Kratos Concept IS spectrometers. Chemical ionisation (CI) was performed using ammonia. Typical clusters of isotope peaks were observed for bromine-, selenium- and tin-containing compounds. Only those corresponding to ^{79}Br, ^{80}Se and ^{120}Sn are reported. Chromatography refers to flash column chromatography using Merck silica gel 60H (40–60 nm, 26 230–300 mesh).

Tetrahydrofuran (THF) was dried and distilled from sodium metal using benzophenone as an indicator under an atmosphere of nitrogen. DCM (DCM) was dried and distilled from calcium hydride under an atmosphere of nitrogen. Ether refers to diethyl ether, which was dried and distilled from sodium metal using benzophenone as an indicator under an atmosphere of nitrogen. Light petroleum refers to the fraction of light petroleum ether distilled between 40–60 °C. Benzene and hexane were dried over sodium metal. Butyllithium (1.6 M in hexanes) was titrated against a solution of propan-2-ol in xylene with 2,2′-bipyridine as an indicator. Triethylamine and diisopropylamine were dried over potassium hydroxide pellets. Brine refers to saturated aqueous sodium chloride. Zinc(II) chloride was dried in Kugelrohr at 220 °C for 7 h at high vacuum, allowed to cool to 50 °C at the same pressure and then allowed to cool to room temperature in desiccator.

tert-Butyl (*E*)-hex-2-enoate (**20**)[16] was prepared as colourless liquid from butanal using *tert*-butoxycarbonylmethylene-(triphenyl)phosphorane (Found: M$^+$ + NH$_4$, 188.1648. C$_{10}$H$_{22}$NO$_2$ requires *M*, 188.1650); δ_H (CDCl$_3$, 300 MHz) 0.98 (3 H, t, *J* 7.4, 6-H$_3$), 1.52 [9 H, s, C(CH$_3$)$_3$], 1.45–1.60 (2 H, m, 5-H$_2$), 2.19

(2 H, dq, *J* 0.5, 7.3, 4-H_2), 5.78 (1 H, d, *J* 15.5, 2-H) and 6.90 (1 H, dt, *J* 15.5 and 6.9, 3-H); δ_C ($CDCl_3$, 75 MHz) 13.6, 21.3, 28.1, 34.0, 79.9, 123.0 and 147.8; *m*/*z* (CI) 188 (M^+ + 18, 100%), 171 (M^+ + 1, 90) and 132 (80).

(2*S*,3*S*,4*S*,6*R*)-1-Benzyloxy-3,6-epoxy-2-methyl-4-phenylselenononane (**7**). Phenylselenenyl chloride (112 mg, 0.58 mmol) and $SnCl_4$ (1 M in DCM, 80 μL, 0.08 mmol) were added slowly to the alkenol **6** (102 mg, 0.39 mmol) in DCM (2 mL) and the mixture stirred for 5 h. Aqueous sodium bicarbonate was added and the aqueous layer extracted with DCM. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 10 : 1 light petroleum : ether gave the *title compound* **7** (81 mg, 50%) as a colourless oil (Found: M^+, 418.1417. $C_{23}H_{30}O_2{}^{80}Se$ requires *M*, 418.1411); ν_{max}/cm^{-1} 3061, 3029, 1579, 1476, 1453, 1372, 1103, 1073, 1024, 735 and 694; δ_H ($CDCl_3$, 300 MHz) 0.97 (3 H, t, *J* 7.2, 9-H_3), 1.1 (3 H, d, *J* 6.7, 2-CH_3), 1.20–1.6 (3 H, m), 1.78 (1 H, m), 1.98 (1 H, ddd, *J* 13.8, 5.7 and 2.1, 5-H), 2.24 (1 H, m, 2-H), 2.63 (1 H, m, 5-H′), 3.58 (1 H, dd, *J* 9 and 6.9, 1-H), 3.65 (1 H, dd, *J* 9.6 and 4.2, 3-H), 3.74 (1 H, dd, *J* 9 and 3.3, 1-H′), 3.84 and 3.92 (each 1 H, m), 4.55 and 4.64 (each 1 H, d, *J* 12.2, PhHC*H*O) and 7.36–7.6 (10 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 14.1, 14.5, 19.6, 37.1, 38.6, 40.3, 46.3, 72.9, 73.0, 78.1, 83.8, 127.1, 127.2, 127.4, 128.2, 129.0, 130.2, 133.9 and 138.9; *m*/*z* (EI) 418 (M^+, 2%) and 91 (100).

(2*S*,3*R*,6*R*)-1-Benzyloxy-3,6-epoxy-2-methylnonane (**8**).[11] Tributyltin hydride (70 μL, 0.264 mmol) was added to the phenylselenide **7** (55 mg, 0.132 mmol) in thoroughly degassed benzene (10 mL) and the solution heated under reflux for 2 h. After concentration under reduced pressure, chromatography of the residue using 10 : 1 light petroleum : ether gave the title compound **8**[11] (29 mg, 85%) as a colourless oil (Found: M^+ + H, 263.2016. $C_{17}H_{27}O_2$ requires *M*, 263.2011); δ_H ($CDCl_3$ 300 MHz) 0.98 (6 H, m, 2-CH_3 and 9-H_3), 1.32–1.66 (7 H, m), 1.92 (2 H, m), 3.4 (1 H, dd, *J* 9 and 7.4, 1-H), 3.65 (1 H, dd, *J* 9 and 4.6, 1-H′), 3.73 (1 H, q, *J* 7.4, 3-H), 3.84 (1 H, m, 6-H), 4.55 (2 H, s, $PhCH_2$) and 7.37 (5 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 13.5, 14.2, 19.3, 28.4, 30.9, 38.2, 38.9, 72.9, 73.2, 78.9, 80.5, 127.2, 127.4, 128.2 and 138.8; *m*/*z* (CI) 263 (M^+ + 1, 100).

(2*S*,4*S*,8*R*,6*Z*)-9-Benzyloxy-2-*tert*-butyldiphenylsilyloxy-8-methylnon-6-en-4-ol (**11**). Tin(IV) chloride (0.18 mL, 1.0 M in DCM, 0.18 mmol) cooled to −78 °C was added to the stannane **3** (90 mg, 0.18 mmol) in DCM at −78 °C. After 5 min, the aldehyde **10**[13] (76 mg, 0.22 mmol) in DCM (1.5 mL) cooled at −78 °C was added and the solution was stirred for 45 min at −78 °C. Saturated aqueous sodium bicarbonate (7 mL) was added and the aqueous phase was extracted with DCM (3 × 5 mL). The organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue 4 : 1 light petroleum : ether gave the *title compound* **11** (80 mg, 82%) as a colourless oil, $[\alpha]_D^{21}$ −1.9 (*c* 1.7 in DCM) (Found: M^+ + H, 517.3123. $C_{33}H_{45}O_3Si$ requires *M*, 517.3138); ν_{max}/cm^{-1} 3429, 1643, 1428, 1110 and 702; δ_H ($CDCl_3$, 300 MHz) 0.87 (3 H, d, *J* 6, 8-CH_3), 0.96 [12 H, m, $SiC(CH_3)_3$ and 1-H_3), 1.45 (1 H, ddd, *J* 3, 6 and 14, 3-H), 1.56 (1 H, ddd, *J* 4, 9 and 14, 3-H′), 2.08 and 2.14 (each 1 H, m, 5-H), 2.74 (1 H, m, 8-H), 3.20 (2 H, m, 9-H_2), 3.23 (1 H, m, OH), 3.85 (1 H, m, 4-H), 4.05 (1 H, m, 2-H), 4.42 (2 H, s, $PhCH_2$), 5.21 (1 H, t, *J* 10, 7-H), 5.35 (1 H, m, 6-H), 7.06–7.40 (11 H, m, ArH) and 7.56–7.68 (4 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 17.5, 19.1, 23.0, 26.9, 32.3, 35.9, 44.9, 67.9, 68.4, 72.9, 74.9, 126.0, 127.4, 127.5, 128.2, 129.5, 129.6, 135.2 and 135.8; *m*/*z* (CI) 534 (M^+ + 18, 23%) and 517 (M^+ + 1, 100).

(2*S*,3*S*,4*S*,6*R*,8*S*)-1-Benzyloxy-8-*tert*-butyldiphenylsilyloxy-3,6-epoxy-2-methyl-4-phenylselenononane (**12**). *N*-Phenylselenophthalimide (1.7 g, 5.5 mmol) and tin(IV) chloride (0.74 mL, 1.0 M in DCM, 0.74 mmol) were added to the alcohol **11** (1.9 g, 3.7 mmol) in DCM (20 mL) at room temperature and the solution stirred for 20 h. Saturated aqueous sodium bicarbonate (30 mL) was added and the aqueous phase extracted with DCM (3 × 15 mL). The organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 20 : 1 light petroleum : ether (20 : 1) gave the *title compound* **12** (1.5 g, 62%) as a colourless oil, $[\alpha]_D^{21}$ +27 (*c* 1.8 in DCM) (Found: M^+, 672.2541. $C_{39}H_{48}O_3SiSe$ requires *M*, 672.2538); δ_H ($CDCl_3$, 300 MHz) 0.95 [15 H, m, $SiC(CH_3)_3$, 9-H_3 and 2-CH_3), 1.74 (3 H, m, 5-H and 7-H_2), 2.10 (1 H, m, 2-H), 2.45 (1 H, m, 5-H′), 3.36 (1 H, dd, *J* 7 and 9, 4-H), 3.41 (1 H, dd, *J* 4 and 9, 1-H), 3.61 (1 H, dd, *J* 3 and 9, 1-H′), 3.68 (1 H, m, 6-H), 4.00 (2 H, m, 3-H and 8-H), 4.41 and 4.46 (each 1 H, d, *J* 12, PhHC*H*), 7.16–7.37 (14 H, m, ArH), 7.42 (2 H, m, ArH) and 7.56–7.65 (4 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 14.4, 19.3, 24.2, 27.0, 37.0, 40.7, 46.2, 46.7, 67.6, 73.0, 73.1, 74.9, 83.9, 127.1, 127.3, 127.4, 128.2, 129.0, 129.3, 129.4, 130.1, 133,9, 134.3, 134.9, 135.8 and 138.9; *m*/*z* (CI) 690 (M^+ + 18, 100%) and 673 (M^+ + 1, 30).

(2*S*,3*R*,6*S*,8*S*)-1-Benzyloxy-8-*tert*-butyldiphenylsilyloxy-3,6-epoxy-2-methylnonane (**13**). The tetrahydrofuran **12** (1.4 g, 2.2 mmol), tributyltin hydride (1.2 mL, 4.4 mmol) and azobis-*iso*butyronitrile (cat.) in benzene (25 mL) was degassed for 45 min and then heated under reflux for 2 h. After concentration under reduced pressure the residue was chromatographed 15 : 1 light petroleum : ether to give the *title compound* **13** (0.96 g, 85%) as a colourless oil, $[\alpha]_D^{21}$ −8.8 (*c* 0.9 in DCM) (Found: M^+, 516.3063. $C_{33}H_{44}O_3Si$ requires *M*, 516.3060); ν_{max}/cm^{-1} 3069, 3047, 1454, 1427, 1375, 1109, 1074, 821, 736 and 702; δ_H ($CDCl_3$, 300 MHz) 0.96 (3 H, d, *J* 6, 2-CH_3), 1.09 [12 H, m, $SiC(CH_3)_3$ and 9-H_3], 1.15–1.98 (7 H, m, 4-H_2, 5-H_2, 7-H_2 and 2-H), 3.36 (1 H, dd, *J* 7 and 9, 1-H), 3.61 (2 H, m, 3-H and 1-H′), 3.90 (1 H, m, 6-H), 4.08 (1 H, m, 8-H), 4.54 (2 H, s, $PhCH_2$), 7.36–7.48 (11 H, m, ArH) and 7.72–7.78 (4 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 13.7, 19.3, 24.13, 27.0, 28.6, 31.2, 39.0, 46.2, 67.8, 72.9, 73.3, 75.8, 80.6, 127.3, 127.4(2), 128.2, 129.3(2), 134.3, 135.0, 135.7, 135.8, 135.9 and 138.8; *m*/*z* (CI) 534 (M^+ + 18, 35%), 517 (M^+ + 1, 12) and 439 (100).

(2*S*,3*R*,6*S*,8*S*)-8-*tert*-Butyldiphenylsilyloxy-3,6-epoxy-2-methylnonan-1-ol (**14**). Palladium (0.03 g, 10% on carbon) was added to the benzyl ether **13** (0.23 g, 0.43 mmol) in ethanol (20 mL) and acetic acid (0.2 mL) at room temperature and the suspension stirred under an atmosphere of hydrogen for 52 h. The mixture was filtered through Celite® and the solid residue was washed with ethanol (2 × 20 mL). The filtrate was concentrated under

reduced pressure and the residue chromatographed 4 : 1 light petroleum : ether to give the *title compound* **14** (0.14 g, 73%) as a colourless oil, $[\alpha]_D^{21}$ +17.8 (*c* 1.8 in DCM) (Found: M^+, 427.2665. $C_{26}H_{38}O_3Si$ requires *M*, 427.2668); ν_{max}/cm^{-1} 3323, 1427, 1110, 821, 794, 739 and 703; δ_H ($CDCl_3$, 300 MHz) 0.72 (3 H, d, *J* 7, 2-CH_3), 0.88 (3 H, d, *J* 6, 9-H_3), 0.89 [9 H, s, SiC-$(CH_3)_3$], 1.22–1.95 (7 H, m, 4-H_2, 5-H_2, 7-H_2 and 2-H), 3.24 (1 H, br. s, OH), 3.46 (3 H, m, 6-H and 1-H_2), 3.92 (2 H, m, 3-H and 8-H), 7.26–7.34 (6 H, m, ArH) and 7.58–7.64 (4 H, m, Ar-H); δ_C ($CDCl_3$, 75 MHz) 13.7, 19.3, 24.2, 26.9, 30.4, 30.6, 40.9, 46.0, 67.6, 68.4, 76.7, 85.4, 127.3, 127.4, 129.3, 129.4, 134.8 and 135.8; *m*/*z* (CI) 427 (M^+, 8%), 349 (97) and 271(100).

Methyl (2*R*,3*R*,6*S*,8*S*)-8-*tert*-butyldiphenylsilyloxy-3,6-epoxy-2-methylnonanoate (**15**). Pyridinium dichromate (0.42 g, 1.12 mmol) was added to the alcohol **14** (0.14 g, 0.32 mmol) in *N*,*N*-dimethylformamide (3 mL) at room temperature and the reaction mixture stirred for 24 h. Water (3 mL) and saturated aqueous sodium carbonate (25 mL) were added and the aqueous phase was acidified to pH 1 using aqueous hydrogen chloride (50 mL, 3.5 M) then extracted with ethyl acetate (4 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue 2 : 1 light petroleum : ether (with 1% v/v of acetic acid) gave the corresponding acid (0.12 g, 82%) as a colourless oil, ν_{max}/cm^{-1} 1709, 1110 and 703; δ_H ($CDCl_3$, 300 MHz) 1.08 [12 H, m, SiC-$(CH_3)_3$ and 9-H_3], 1.22 (3 H, d, *J* 7, 2-CH_3), 1.40–2.18 (6 H, m, 4-H_2, 5-H_2 and 7-H_2), 2.47 (1 H, m, 2-H), 3.85 (1 H, m, 3-H), 4.04 (1 H, m, 6-H), 4.09 (1 H, m, 8-H), 7.43 (6 H, m, ArH), 7.70–7.66 (4 H, m, ArH) and 9.90 (1 H, br. s, OH).

Trimethylsilyldiazomethane (0.23 mL, 2.0 M in hexanes, 0.6 mmol) was added to the acid (0.1 g, 0.23 mmol) in benzene (4 mL) and methanol (1 mL) at room temperature and the solution stirred for 30 min. Water (5 mL) was added and the organic phase was washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed 6 : 1 light petroleum : ether to yield the *title compound* **15** (0.08 g, 78%) as a colourless oil, $[\alpha]_D^{21}$ −3.7 (*c* 1.8 in DCM) (Found: M^+ + H, 441.2468. $C_{26}H_{39}O_4Si$ requires *M*, 441.2461); ν_{max}/cm^{-1} 1740, 1108, 1462, 1430, 1376, 1260, 1196, 1065, 822, 736 and 703; δ_H ($CDCl_3$, 300 MHz) 1.07 [12 H, m, $SiC(CH_3)_3$ and 9-H_3], 1.13 (3 H, d, *J* 7, 2-CH_3), 1.20–1.80 (4 H, m, 4-H_2 and 5-H_2), 1.90 (2 H, m, 7-H_2), 2.51 (1 H, quin, *J* 7, 2-H), 3.68 (3 H, s, OCH_3), 4.00 (3 H, m, 3-H, 6-H and 8-H), 7.36–7.48 (6 H, m, ArH) and 7.69–7.76 (4 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 13.2, 19.3, 24.0, 26.9, 28.4, 31.2, 45.2, 46.1, 51.5, 67.8, 76.4, 80.0, 127.3, 127.4, 129.3, 134.3, 134.9, 135.8 and 175.2; *m*/*z*, (CI) 458 (M^+ + 18, 3%), 441 (M^+ + 1, 7) and 285 (100).

(−)-Methyl nonactate (**2**).[3] The silyl ether **15** (62 mg, 0.14 mmol) was added to tetrabutylammonium fluoride (0.7 mL 1.0 M in THF, 0.7 mmol) and the solution was stirred for 7 h at room temperature. Water (0.5 mL) was added and the organic phase washed with brine (0.5 mL) and then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using 2 : 1 light petroleum : ether gave the title compound **2** (23 mg, 78%) as a colourless oil, $[\alpha]_D^{21}$ −15.6 (*c* 1.4 in DCM), enantiomer lit.[3a] $[\alpha]_D^{21}$ +19.1 (*c* 0.45 in $CHCl_3$) (Found: M^+, 216.1359. $C_{11}H_{20}O_4$ requires *M*, 216.1362); ν_{max}/cm^{-1} 3421, 1736, 1461, 1374, 1266, 1201, 1163, 1089 and 1060; δ_H ($CDCl_3$, 300 MHz) 1.06 (3 H, d, *J* 8, 2-CH_3), 1.14 (3 H, d, J 6, 9-H_3), 1.52–1.64 (3 H, m, 5-H_2 and 7-H), 1.68 (1 H, ddd, *J* 4, 8 and 14, 7-H′), 1.94 (2 H, m, 4-H_2), 2.47 (1 H, m, 2-H), 2.95 (1 H, br. s, OH), 3.63 (3 H, s, OCH_3), 3.94 (2 H, m, 3-H and 8-H) and 4.06 (1 H, m, 6-H); δ_C ($CDCl_3$, 75 MHz) 13.5, 23.1, 28.8, 30.4, 42.5, 45.2, 51.6, 65.1, 77.2, 81.0 and 175.2; *m*/*z* (CI) 234 (M^+ + 18, 58%) and 217 (M^+ + 1, 100).

A solution of nonactin (25 mg, 0.035 mmol) in methanol (2.85 mL) and aqueous sulfuric acid (0.15 mL, 5% v/v) was heated under reflux for 48 h then allowed to cool to room temperature.[15] DCM (5 mL) was added and the organic phase was washed with a saturated aqueous sodium bicarbonate (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 1 : 1 light petroleum : ether gave racemic methyl nonactate (±)-(**2**) (20 mg, 66%) as a colourless oil (Found; M^+, 216.1359. $C_{11}H_{20}O_4$ requires *M*, 216.1362) with spectroscopic data identical to those of the (−)-enantiomer.

tert-Butyl (3*R*)-3-[*N*-benzyl-*N*-(*R*)-α-methylbenzyl]aminohexanoate (**21**). *N*-Butyllithium was added to (*R*)-*N*-benzyl-α-methylbenzylamine (29.5 g, 139.4 mmol) in anhydrous THF (200 mL) at −78 °C and the solution stirred at −78 °C for 30 min. *tert*-Butyl (*E*)-hex-2-enoate (**20**)[17] (15.8 g, 93 mmol) in THF (100 mL) was added and, after 2 h, aqueous ammonium chloride (50 mL) was added. The mixture was allowed to warm to ambient temperature and concentrated to approximately one third of its original volume under reduced pressure. Ether was added and the aqueous layer was extracted with ether. The organic extracts were washed with water and brine then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using 20 : 1 light petroleum : ether gave the *title compound* **21** (31.5 g, 89%) as a pale yellow liquid, $[\alpha]_D^{23}$ +12.4 (*c* 0.9 in $CHCl_3$) (Found: M^+, 381.2674. $C_{25}H_{35}NO_2$ requires *M*, 381.2668); δ_H ($CDCl_3$, 300 MHz) 0.9 (3 H, t, *J* 7.1, 6-H_3), 1.37 (3 H, d, *J* 7, CHCH_3), 1.2–1.7 [13 H, m, $C(CH_3)_3$, 4-H_2 and 5-H_2], 1.90 (1 H, dd, *J* 14.6, 9.1, 2-H), 2.0 (1 H, dd, *J* 14.6, 3.7, 2-H′), 3.36 (1 H, m, 3-H), 3.52 and 3.84 (each 1 H, d, *J* 15, PhCHCH), 3.86 (1 H, q, *J* 7, NCH) and 7.2–7.5 (10 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 14.0, 20.0, 20.4, 28.0, 35.7, 37.7, 50.0, 53.6, 58.2, 79.8, 126.4, 126.8, 127.9, 128.0(2), 128.1, 142.0, 143.1 and 172.2; *m*/*z* (EI) 382 (M^+ + 1, 5%), 381 (M^+, 5), 338 (50), 266 (45) and 105 (100).

tert-Butyl (*R*)-3-aminohexanoate (**22**). Methanol (100 mL) was added to $Pd(OH)_2$ on carbon (20%, 4 g) with gentle stirring. Ammonium formate (31.5 g, 0.5 mol) was added as a solid in batches (CAUTION gas evolved) over 30 min. After 15 min, the amine **21** (7.62 g, 19.97 mmol) in methanol (100 mL) was added over 5 min and the mixture was stirred for 1 h. Formic acid (12 mL, 0.319 mol) was added in batches (*ca.* 1 mL every 5 min) (CAUTION gas evolved rapidly). After the addition was completed, the mixture was stirred for 2 h at room temperature then filtered through a plug of Celite® that was washed with methanol and $CHCl_3$. The filtrate was concentrated under

reduced pressure to give a white solid that was dissolved in aqueous sodium hydroxide (10%, 150 mL). The aqueous solution was extracted with DCM (3 × 75 mL) and the organic layer washed with water and brine then dried ($MgSO_4$). Concentration under reduced pressure gave the *title compound* **22** (3.72 g, 91%) as colourless liquid, $[\alpha]_D^{24}$ −16.6 (*c* 1 in $CHCl_3$) (Found: M^+ + H, 188.1652. $C_{10}H_{22}NO_2$ requires *M*, 188.1650); ν_{max}/cm^{-1} 3300, 1726, 1459 1367, 1318, 1255, 1153 and 843; δ_H ($CDCl_3$, 300 MHz) 0.85 (3 H, t, *J* 5.9, 6-H_3), 1.39 [9 H, s, $C(CH_3)_3$], 1.2–1.46 (4 H, m, 4-H_2 and 5-H_2), 2.09 (1 H, dd, *J* 15.5, 8.8, 2-H), 2.30 (1 H, dd, *J* 15.5, 4.0, 2-H′) and 3.10 (1 H, m, 3-H); δ_C ($CDCl_3$, 75 MHz) 13.9, 19.0, 28.0, 39.6, 43.8, 47.9, 80.2 and 171.9; *m*/*z* (CI) 188 (M^+ + 1, 100%) and 132 (70).

tert-Butyl (*R*)-3-(*N*-benzyloxycarbonyl)aminohexanoate (**23**). Benzyl chloroformate (0.8 mL, 5.61 mmol) was added to the amine **22** (1.05 g, 5.61 mmol), potassium carbonate (3.87 g, 28.07 mmol), water (60 mL) and ether (60 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature and then stirred for a further 3 h. The aqueous layer was extracted with ether and the organic extracts were washed with water and brine then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using 15 : 1 light petroleum : ether gave the *title compound* **23** (1.58 g, 88%) as a colourless liquid, $[\alpha]_D^{21}$ +15.6 (*c* 1.14 in $CHCl_3$) (Found: M^+ + H, 322.2022. $C_{18}H_{28}NO_4$ requires 322.2018); ν_{max}/cm^{-1} 3333, 1725, 1532, 1455, 1367, 1255, 1161, 1102, 738 and 697; δ_H ($CDCl_3$, 300 MHz) 0.84 (3 H, t, *J* 7, 6-H_3), 1.2–1.48 [13 H, m, $C(CH_3)_3$, 4-H_2 and 5-H_2), 2.35 (2 H, m, 2-H_2), 3.89 (1 H, m, 3-H), 5.01 (2 H, s, $PhCH_2O$), 5.18 (1 H, br. d, *J* 6.5, NH) and 7.26 (5 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 13.7, 19.2, 28.0, 36.7, 40.2, 48.1, 66.4, 80.9, 127.9, 128.4, 136.0, 155.7 and 171.0; *m*/*z* (CI) 322 (M^+ + 1, 30%) and 266 (100).

(*R*)-3-(*N*-Benzyloxycarbonyl)aminohexan-1-ol (**24**). Lithium aluminium hydride (1 M in ether, 4.9 mL, 4.9 mmol) was added to the ester **23** (1.58 g, 4.92 mmol) in ether (8 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C, allowed to warm to room temperature and stirred for a further 2 h. The mixture was cooled to 0 °C and water (1 mL), aqueous sodium hydroxide (2 mL) and water (2 mL) were added. The mixture was warmed to room temperature, stirred for 45 min, then filtered through Celite®. The aqueous layer was extracted with ether and the organic extracts were washed with water and brine then dried ($MgSO_4$). Concentration under reduced pressure gave the *title compound* **24** (0.98 g, 80%) as a white solid, mp 61 °C, $[\alpha]_D^{21}$ −13.6 (*c* 0.89 in $CHCl_3$) (Found: M^+ + H, 252.1597. $C_{14}H_{22}NO_3$ requires *M*, 252.1600); ν_{max}/cm^{-1} 3309, 1688, 1544, 1264, 1050, 732 and 694; δ_H ($CDCl_3$, 300 MHz) 0.95 (3 H, t, *J* 7, 6−H_3), 1.44 (4 H, m, 4-H_2 and 5-H_2), 1.88 (2 H, m, 2-H_2), 3.26 (1 H, br. s, OH), 3.66 (2 H, m, 1-H_2), 3.86 (1 H, m, 3-H), 4.76 (1 H, br. m, NH), 5.13 and 5.14 (each 1 H, d, *J* 12.1, PhHC*H*) and 7.38 (5 H, ArH); δ_C ($CDCl_3$, 75 MHz) 13.8, 19.2, 37.6, 38.6, 47.8, 58.8, 66.9, 128.0, 128.1, 128.5, 136.3 and 157.3; *m*/*z* (CI) 252 (M^+ + 1, 20%), 161 (40) and 144 (100).

(*R*)-3-(*N*-Benzyloxycarbonyl)aminohexanal (**25**). DMSO (1.8 mL, 23.7 mmol) in DCM (5 mL) was added to oxalyl chloride (1.06 mL, 12.13 mmol) in DCM (17 mL) at −78 °C and the mixture stirred at −78 °C for 5 min. The hexanol **24** (2.89 g, 11.5 mmol) in DCM (9 mL) was added and the mixture stirred at −78 °C for 20 min. Et_3N (6.1 mL, 44 mmol) was added and the solution was stirred for 10 min then allowed to warm to room temperature. Water was added and the aqueous phase extracted with DCM. The organic extracts were washed with aqueous ammonium chloride, water and brine then dried ($MgSO_4$). Concentration under reduced pressure gave the *title compound* **25** (2.87 g, 99%) as a white solid that was used immediately (Found: M^+ + H, 250.1447. $C_{14}H_{20}NO_3$ requires *M*, 250.1443); ν_{max}/cm^{-1} 3327, 1722, 1693, 1530, 1455, 1257, 1229, 1085, 1027, 739 and 698; δ_H ($CDCl_3$, 300 MHz) 0.85 (3 H, t, *J* 7, 6-H_3), 1.2–1.5 (4 H, m, 4-H_2 and 5-H_2), 2.56 (2 H, m, 2-H_2), 4.02 (1 H, m, 3-H), 4.90 (1 H, br. m, NH), 5.01 (2 H, s, $PhCH_2$), 7.27 (5 H, m, ArH) and 9.68 (1 H, s, 1-H); δ_C ($CDCl_3$, 75 MHz) 13.7, 19.2, 36.9, 46.8, 48.8, 66.7, 128.0, 128.1, 128.4, 136.3, 155.8 and 200.9; *m*/*z* (CI) 250 (M^+ + 1, 100%).

(2*R*,6*S*,8*R*,3*Z*)-1-Benzyloxy-8-(*N*-benzyloxycarbonyl)amino-2-methylundec-3-en-6-ol (**26**). Tin(IV) chloride (1 M in DCM, 1.35 mL, 1.35 mmol) was added to the stannane **3** (0.65 g, 1.35 mmol) in DCM (15 mL) at −78 °C. After 5 min, a cooled (0 °C) solution of aldehyde **25** (307 mg, 1.23 mmol) in DCM (10 mL) was added and the mixture was stirred for 50 min at −78 °C. Methanol (0.75 mL) and aqueous sodium bicarbonate (3 mL) were added and the mixture was allowed to warm to room temperature and was stirred for 1 h. Water (5 mL) was added and the aqueous phase extracted with DCM. The organic extracts were washed with water (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (gradient elution 10 : 1 to 3 : 1) gave the *title compound* **26** (352 mg, 64%) as a colourless liquid, $[\alpha]_D^{21}$ +1.7 (*c* 1.87 in $CHCl_3$) (Found: M^+ + H, 440.2806. $C_{27}H_{38}NO_4$ requires *M*, 440.2800); ν_{max}/cm^{-1} 3404, 3327, 1698, 1530, 1453, 1255, 1233, 1091, 739 and 698; δ_H ($CDCl_3$, 500 MHz) 0.9 (6 H, m, 2-CH_3 and 11-H_3), 1.26–1.66 (6 H, m, 7-H_2, 9-H_2 and 10-H_2), 2.25 (2 H, m, 5-H_2), 2.87 (1 H, m, 2-H), 3.18 (1 H, t, *J* 9, 1-H), 3.2 (1 H, br. s, OH, exchangeable with D_2O), 3.36 (1 H, dd, *J* 9 and 5, 1-H′), 3.64 (1 H, m, 6-H), 3.76 (1 H, m, 8-H), 4.48 and 4.53 (each 1 H, d, *J* 12, PhHC*H*), 4.90 (1 H, br. m, NH), 5.09 (2 H, s, $PhCH_2OCO$), 5.34 (1 H, t, *J* 10, 3-H), 5.46 (1 H, m, 4-H) and 7.34 (10 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 13.9, 17.2, 18.8, 32.3, 36.0, 38.0, 42.5, 49.5, 66.4, 69.2, 73.0, 74.8, 126.0, 127.6, 127.7, 127.9, 128.3, 128.4, 136.5 and 156.2; *m*/*z* (CI) 440 (M^+ + 1, 15%) and 332 (100).

(2*S*,3*S*,4*S*,6*R*,8*R*)-1-Benzyloxy-8-(*N*-benzyloxycarbonylamino)-3,6-epoxy-2-methyl-4-phenylselenoundecane (**27**). Tin(IV) chloride (1 M in DCM, 113 μL, 0.113 mmol) and PhSeCl (200 mg, 1.05 mmol) were added to the alkenol **26** (482 mg, 1.13 mmol) in DCM (20 mL) at room temperature. After 3 h, more tin(IV) chloride (1 M in DCM, 113 μL, 0.113 mmol) and PhSeCl (60 mg, 0.31 mmol) were added and the mixture was stirred at room temperature for 15 h. Aqueous sodium bicarbonate was added and the aqueous phase was extracted with DCM. The organic extracts were washed with water and brine, then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using 10 : 1 light petroleum : ether

gave the *title compound* **27** (167 mg, 25%) as a colourless oil (Found: M^+, 595.2207. $C_{33}H_{41}NO_4{}^{80}Se$ requires *M*, 595.2204); ν_{max}/cm^{-1} 3333, 1704, 1536, 1454, 1260, 1231, 1089, 1072, 1023, 737 and 695; δ_H ($CDCl_3$, 300 MHz) 0.94 (3 H, t, *J* 7.1, 11-H_3), 1.08 (3 H, d, *J* 6.7, 2-CH_3), 1.38 and 1.50 (each 2 H, m), 1.82 (2 H, t, *J* 6.6), 2.0 (1 H, dd, *J* 13.8 and 4.2, 5-H), 2.19 (1 H, m, 2-H), 2.70 (1 H, m, 5-H′), 3.52 (1 H, m, 1-H), 3.64 (3 H, m), 3.8 and 4.01 (each 1 H, m), 4.40 and 4.51 (each 1 H, d, *J* 12.2, PhHC*H*), 4.89 (1 H, br. m, NH), 5.06 and 5.14 (each 1 H, d, *J* 12.2, PhHC*H*OCO), 7.32 (13 H, m, ArH) and 7.56 (2 H, m, ArH); δ_C ($CDCl_3$, 300 MHz) 13.9, 14.4, 18.8, 37.1, 38.1, 40.5, 41.5, 46.0, 49.9, 66.4, 72.8, 73.0, 76.1, 84.2, 127.3, 127.4, 127.9, 128.2, 128.4, 129.1 and 134.1; *m*/*z* (EI) 594 (M^+ − 1, 3%), 487 (5), 398 (8), 330 (15) and 91 (100).

(2*S*,3*R*,6*S*,8*R*)-1-Benzyloxy-8-(benzyloxycarbonylamino)-3,6-epoxy-2-methylundecane (**28**). Tributyltin hydride (47 μL, 0.178 mmol) and AIBN (cat.) were added to the phenylselenide **27** (53 mg, 0.089 mmol) in degassed toluene (7 mL) and the mixture was heated under reflux for 1 h. After concentration under reduced pressure, chromatography of the residue using 3 : 1 light petroleum : ether gave the *title compound* **28** (25 mg, 64%) as a white solid, ν_{max}/cm^{-1} 3331, 1723, 1530, 1517, 1454, 1256, 1230, 1091, 1069, 737 and 698; δ_H ($CDCl_3$, 300 MHz) 0.94 (3 H, t, *J* 7, 11-H_3), 0.98 (3 H, d, *J* 6.7, 2-CH_3), 1.28–1.72 (8 H, m), 1.9 (2 H, m), 2.04 (1 H, m, 2-H), 3.38 (1 H, dd, *J* 9 and 7, 1-H), 3.62 (1 H, dd, *J* 9 and 4.5, 1-H′), 3.7 (2 H, m, 3-H, 6-H), 3.9 (1 H, quin, *J* 6.5, 8-H), 4.49 (2 H, s, $PhCH_2O$), 4.92 (1 H, br. m, NH), 5.12 (2 H, s, $PhCH_2OCO$) and 7.36 (10 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 13.7, 13.9, 18.8, 25.1, 28.4, 31.5, 38.1, 39.0, 41.0, 49.8, 66.3, 72.9, 73.1, 81.0, 127.3, 127.4, 127.9(2), 128.2, 128.4, 136.7, 138.8 and 156.1.

tert-Butyl (*R*)-3-(toluene-4-sulfonylamino)hexanoate (**29**). Toluene 4-sulfonyl chloride (3.35 g, 17.65 mmol) in DCM (10 mL), Et_3N (1.77 mL, 17.65 mmol) and DMAP (0.22 g) were added to the aminohexanoate **22** (2.20 g, 11.76 mmol) in DCM (20 mL) at 0 °C. The mixture was stirred at room temperature for 24 h before being diluted with water (10 mL). The aqueous layer was extracted with DCM (3 × 10 mL) and the organic extracts were washed with saturated aqueous sodium bicarbonate (25 mL) and water (25 mL), then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue with ether : light petroleum (gradient elution 1 : 10 to 4 : 10) gave the *title compound* **29** (3.80 g, 95%) as an oil, R_f = 0.41 (50% ether : light petroleum), $[\alpha]_D^{26}$ +35 (*c* 0.5 in $CHCl_3$) (Found: M^+ + H, 342.1740. $C_{17}H_{28}NO_4S$ requires *M*, 342.1739); ν_{max}/cm^{-1} 3289, 1727, 1455, 1368, 1329, 1160, 1093, 1034, 959 and 815; δ_H (300 MHz, $CDCl_3$) 0.84 (3 H, t, *J* 7.1, 6-H_3), 1.16–1.54 [13 H, m, 4-H_2, 5-H_2, C(CH_3)$_3$], 2.26 (1 H, dd, *J* 15.9, 5.5, 2-H), 2.34 (1 H, dd, *J* 15.9, 4.4, 2-H′), 2.46 (3 H, s, $ArCH_3$), 3.52 (1 H, m, 3-H), 5.32 (1 H, d, *J* 9.1, NH) and 7.33 and 7.80 (each 2 H, d, *J* 7.8, ArH); δ_C (75 MHz, $CDCl_3$) 13.5, 18.9, 21.4, 28.0, 36.6, 39.3, 50.5, 81.3, 126.9, 129.5, 138.2, 143.1, 170.7; *m*/*z* (CI) 359 (M^+ + 18, 23%), 342 (M^+ + 1, 6%) and 303 (100).

tert-Butyl (*R*)-3-[*N*-methyl-*N*-(toluene-4-sulfonyl)amino]hexanoate (**30**). The sulfonamide **29** (27.65 g, 81.18 mmol) in THF (500 mL) was added to a suspension of NaH (3.4 g, 85.13 mmol) in THF (500 mL) at room temperature and the mixture stirred for 2 h. MeI (46 g, 324 mmol) was added dropwise and the mixture stirred overnight. Water and ether were added and the aqueous phase was extracted with ether. The organic extracts were washed with water and brine then dried ($MgSO_4$). Concentration under reduced pressure gave the *title compound* **30** (28.7 g, 99%) as a colourless liquid, $[\alpha]_D^{22}$ −35.8 (*c* 1.23 in $CHCl_3$) (Found: M^+ + H, 356.1902. $C_{18}H_{30}NO_4S$ requires 356.1895); ν_{max}/cm^{-1} 1727, 1458, 1342, 1160, 1090, 939, 816 and 693; δ_H ($CDCl_3$, 300 MHz) 0.9 (3 H, t, *J* 7.3, 6-H_3), 1.22–1.42 (4 H, m, 4-H_2 and 5-H_2), 1.46 [9 H, s, C(CH_3)$_3$], 2.05 (1 H, dd, *J* 14.7, 5.2, 2-H), 2.2 (1 H, dd, *J* 14.7, 8.9, 2-H′), 2.42 (3 H, s, $ArCH_3$), 2.68 (3 H, s, NCH_3), 4.32 (1 H, m, 3-H) and 7.3 and 7.74 (each 2 H, d, *J* 8.3, ArH); δ_C (75 MHz, $CDCl_3$) 13.6, 19.2, 21.4, 27.9, 28.1, 34.1, 39.0, 53.9, 80.8, 127.1, 129.5, 136.8, 143.0 and 170.0; *m*/*z* (EI) 356 (M^+ + 1, 20%), 312 (30), 300 (90), 240 (90) and 144 (100).

(*R*)-3-[*N*-Methyl-*N*-(toluene-4-sulfonyl)amino]hexan-1-ol (**31**). Lithium aluminium hydride (1 M in Et_2O, 124 mmol, 124 mL) was added to the ester **30** (55 g, 155 mmol) in dry ether (400 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C at room temperature for 1 h and was then cooled to 0 °C. Water (10 mL) was added, followed by aqueous sodium hydroxide (10%, 10 mL) and water (50 mL). The reaction mixture was stirred at room temperature for 1 h, and then was filtered through Celite®. The aqueous phase was extracted with ether and the organic extracts were washed with water and brine, then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using 1 : 1 light petroleum : ether gave the *title compound* **31** (41.66 g, 94%) as a colourless oil, $[\alpha]_D^{22}$ −7.8 (*c* 1.22 in $CHCl_3$) (Found: M^+ + H, 286.1473. $C_{14}H_{24}NO_3S$ requires *M*, 286.1477); ν_{max}/cm^{-1} 3387, 1598, 1465, 1330, 1161, 1149, 1089, 1054, 942, 816 and 715; δ_H ($CDCl_3$, 300 MHz) 0.75 (3 H, t, *J* 7, 6-H_3), 0.82–1.36 (4 H, m, 4-H_2 and 5-H_2), 1.48 and 1.72 (each 1 H, m, 2-H), 2.44 (3 H, s, $ArCH_3$), 2.5 (3 H, s, NCH_3), 2.8 (1 H, br. s, OH), 3.62 and 3.77 (each 1 H, m 1-H), 4.02 (1 H, m, 3-H) and 7.32 and 7.72 (each 2 H, d, *J* 8.4, ArH); δ_C ($CDCl_3$, 75 MHz) 13.8, 19.6, 21.4, 27.4, 34.3 (2), 53.5, 58.5, 126.8, 129.5, 136.9 and 143.2; *m*/*z* (EI) 286 (M^+ + 1, 20%), 242 (95), 240 (85), 155 (80) and 91 (100).

(*R*)-3-[*N*-Methyl-*N*-(toluene-4-sulfonyl)amino]hexanal (**32**). DMSO (0.69 g, 8.78 mmol, 0.62 mL) was added to oxalyl chloride (0.67 g, 0.46 mL, 5.27 mmol) in DCM (20 mL) at −78 °C and the mixture stirred for 5 min. The alcohol **31** (1.01 g, 3.54 mmol) in DCM (10 mL) was added and the resulting mixture stirred at −78 °C for 20 min. Et_3N (1.77 g, 2.45 mL, 17.55 mmol) was added at −78 °C and the mixture stirred for a further 10 min at −78 °C and then for 1.5 h at room temperature. Water (10 mL) was added and the aqueous layer was extracted with DCM (3 × 10 mL). The organic extracts were washed with saturated aqueous ammonium chloride (20 mL), water (20 mL) and brine (20 mL). After drying ($MgSO_4$), concentration under reduced pressure gave the *title compound* **32** (0.99 g, 99%) as a pale oil, which was used immediately, R_f = 0.55 (50% ether : light petroleum); $[\alpha]_D^{26}$ −6.0 (*c* 1.0 in $CHCl_3$) (Found: M^+ + H, 284.1321. $C_{14}H_{22}NO_3S$ requires *M*, 284.1320];

ν_{max}/cm^{-1} 1723, 1598, 1462, 1383, 1335, 1213, 1162, 1089, 928, 817 and 714; δ_H ($CDCl_3$, 300 MHz) 0.87 (3 H, t, *J* 7.3, 6-H_3), 1.20–1.40 (4 H, m, 4-H_2 and 5-H_2), 2.34 (1 H, ddd, *J* 16, 8, 2, 2-H), 2.45 (3 H, s, $ArCH_3$), 2.47 (1 H, m, 2-H′), 2.7 (3 H, s, NCH_3), 4.48 (1 H, quin, *J* 7, 3-H), 7.32 and 7.7 (each 2 H, d, *J* 7.8, ArH) and 9.64 (1 H, m, 1-H); δ_C ($CDCl_3$, 75 MHz) 13.5, 19.3, 21.4, 28.0, 34.5, 46.3, 51.8, 127.0, 129.6, 136.6, 143.4 and 199.8; *m*/*z* (EI) 284 (M^+ + 1, 20%) and 240 (100).

(2*R*,6*S*,8*R*,3*Z*)-8-[*N*-Methyl-*N*-(toluene-4-sulfonyl)amino]-1-benzyloxy-2-methylundec-3-en-6-ol (**33**). Tin(IV) chloride (1 M in DCM, 19.6 mL, 19.6 mmol) was added to the stannane **3** (9.41 g, 19.64 mmol) in DCM (200 mL) at −78 °C. After 5 min, the aldehyde **32** (5.05 g, 17.86 mmol) in DCM (100 mL), cooled to 0 °C, was added and the solution was stirred for 50 min at −78 °C. Methanol (5 mL) and aqueous sodium bicarbonate (50 mL) were added and the mixture was allowed to warm to room temperature then stirred for 1 h. Water (100 mL) was added and the aqueous layer was extracted with DCM. The organic extracts were washed with water (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (gradient elution 10 : 1 to 3 : 1) gave the *title compound* **33** (5.4 g, 64%) as an oil, $[\alpha]_D^{21}$ −18.6 (*c* 1.53 in $CHCl_3$) (Found: M^+ + H, 474.2678. $C_{27}H_{40}NO_4S$ requires *M*, 474.2678); ν_{max}/cm^{-1} 3483, 1454, 1335, 1162, 1151, 1089, 928, 815, 718 and 699; δ_H ($CDCl_3$, 400 MHz) 0.83 (3 H, t, *J* 7, 11-H_3), 0.92 (3 H, d, *J* 6.5, 2-CH_3), 1.05–1.55 (6 H, m, 7-H_2, 9-H_2, 10-H_2), 2.21 (2 H, m, 5-H_2), 2.42 (3 H, s, $ArCH_3$), 2.67 (3 H, s, NCH_3), 2.85 (1 H, m, 2-H), 3.04 (1 H, br. s, OH), 3.18 (1 H, t, *J* 8.5, 1-H), 3.35 (1 H, dd, *J* 8.5 and 5, 1-H′), 3.6 (1 H, m, 6-H), 4.07 (1 H, quin, *J* 7, 8-H), 4.53 (2 H, s, $PhCH_2$), 5.33 (1 H, t, *J* 10, 3-H), 5.44 (1 H, m, 4-H), 7.28 and 7.72 (each 2 H, d, *J* 7.8, ArH) and 7.34 (5 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 13.8, 17.2, 19.6, 21.4, 27.7, 32.3, 34.0, 35.6, 39.3, 54.4, 68.1, 73.0, 74.7, 126.0, 127.2, 127.5, 127.7, 128.3, 129.4, 136.3, 137.1, 138.0 and 142.8; *m*/*z* (CI) 491 (M^+ + 18, 15%) and 474 (M^+ + 1, 100).

(2*S*,3*S*,4*S*,6*R*,8*R*)-1-Benzyloxy-8-[*N*-methyl-*N*-(toluene-4-sulfonyl)-amino]-3,6-epoxy-2-methyl-4-phenylselenoundecane (**34**). Tin(IV) chloride (1 M in DCM, 12.4 mL, 12.4 mmol) and PhSeCl (14.2 g, 74.33 mmol) were added in batches to the alkenol **33** (29.3 mg, 61.9 mmol) in DCM (1 L) at room temperature and the solution stirred for 6 h. Aqueous sodium bicarbonate was added and the mixture stirred for another 30 min. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (gradient elution 10 : 1 to 3 : 1) gave the *title compound* **34** (16.8 g, 42%) as a colourless liquid, $[\alpha]_D^{21}$ +51.5 (*c* 1.09 in $CHCl_3$) (Found: M^+, 629.2076. $C_{33}H_{43}NO_4S^{80}Se$ requires *M*, 629.2078); ν_{max}/cm^{-1} 3061, 3029, 1598, 1579, 1453, 1337, 1153, 1090, 927, 815, 736 and 695; δ_H ($CDCl_3$, 500 MHz) 0.86 (3 H, t, *J* 7, 11-H_3), 1.1 (3 H, d, *J* 6.7, 2-CH_3), 1.10–1.42 (4 H, m, 9-H_2 and 10-H_2), 1.61 and 1.76 (each 1 H, m, 7-H), 1.94 (1 H, ddd, *J* 14, 3.7, 1.6, 5-H), 2.19 (1 H, m, 2-H), 2.44 (3 H, s, $ArCH_3$), 2.70 (4 H, m, 5-H′ and NCH_3), 3.54 (1 H, dd, *J* 8.9 and 7.0, 1-H), 3.60 (1 H, dd, *J* 9.7 and 4, 3-H), 3.75 (1 H, dd, *J* 9.0 and 3.3, 1-H′), 3.79 (1 H, m, 4-H), 3.97 (2 H, m, 6-H and 8-H), 4.57 and 4.6 (each 1 H, d, *J* 12.1, PhHC*H*), 7.20–7.40 (10 H, m, ArH), 7.53 (2 H, m, ArH) and 7.72 (2 H, d, *J* 8.2, ArH); δ_C ($CDCl_3$, 75 MHz) 13.8, 14.4, 19.5, 21.5, 27.7, 33.9, 37.2, 38.6, 40.1, 46.3, 54.5, 72.9, 73.1, 75.1, 83.9, 127.0, 127.1, 127.3, 127.4, 128.2, 129.0, 129.4, 129.5, 133.8, 137.2, 138.8 and 142.7; *m*/*z* (EI) 629 (M^+, 0.25%), 474 (2), 240 (40) and 91 (100).

(2*S*,3*R*,6*S*,8*R*)-1-Benzyloxy-8-[*N*-methyl-*N*-(toluene-4-sulfonyl)-amino]-3,6-epoxy-2-methylundecane (**35**). Tributyltin hydride (18.2 mL, 67.63 mmol) and AIBN (cat.) were added to the phenylselenide **34** (21.27 g, 33.81 mmol) in benzene (1 L) and the mixture heated under reflux for 45 min. The mixture was allowed to cool to room temperature and was concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (gradient elution 10 : 1 to 3 : 1) gave the *title compound* **35** (15.03 g, 94%) as a colourless oil, $[\alpha]_D^{21}$ −24.5 (*c* 1.27 in $CHCl_3$) (Found: M^+ + H, 474.2683. $C_{27}H_{40}NO_4S$ requires *M*, 474.2678); ν_{max}/cm^{-1} 1598, 1495, 1454, 1337, 1152, 1090, 927 and 815; δ_H ($CDCl_3$, 500 MHz) 0.84 (3 H, t, *J* 7, 11-H_3), 0.96 (3 H, d, *J* 7, 2-CH_3), 1.15 (1 H, m), 1.25 (2 H, m), 1.30–1.50 (3 H, m), 1.56 and 1.87 (each 2 H, m), 2.02 (1 H, m, 2-H), 2.4 (3 H, s, $ArCH_3$), 2.67 (3 H, s, NCH_3), 3.36 (1 H, dd, *J* 9.3 and 7.5, 1-H), 3.63 (2 H, m, 1-H′ and 3-H), 3.76 and 3.99 (each 1 H, quin, *J* 7.0, 6-H or 8-H), 4.55 (2 H, s, $PhCH_2$), 7.26 (2 H, d, *J* 8.3, ArH), 7.34 (5 H, m, ArH) and 7.69 (2 H, d *J* 8.3, ArH); δ_C ($CDCl_3$, 125 MHz) 13.3, 13.6, 19.4, 21.1, 27.4, 28.2, 30.8, 33.8, 38.0, 38.8, 54.5, 72.7, 72.9, 75.8, 80.4, 126.9, 127.0, 127.2, 128.0, 129.2, 137.1, 138.6 and 142.5; *m*/*z* (CI) 491 (M^+ + 18, 30%) and 474 (M^+ + 1, 100%).

(2*S*,3*R*,6*S*,8*R*)-8-[*N*-Methyl-*N*-(toluene-4-sulfonyl)amino]-3,6-epoxy-2-methylundecan-1-ol (**36**). The benzyl ether **35** (7.2 g, 15.22 mmol) in ethanol (50 mL) and acetic acid (3 mL) was added to Pd/C (10%, 2.5 g) and ethanol (500 mL) and the solution stirred under an atmosphere of hydrogen for 15 h. The catalyst was removed by filtration through Celite® and the filtrate was evaporated to give the *title compound* **36** (5.7 g, 91%) as a colourless liquid, $[\alpha]_D^{25}$ −5.5 (*c* 1.73 in $CHCl_3$) (Found: M^+ + H, 384.2203. $C_{20}H_{34}NO_4S$ requires *M*, 384.2208); δ_H ($CDCl_3$, 500 MHz) 0.79 (3 H, t, *J* 7, 11-H_3), 0.82 (3 H, d, *J* 7, 2-CH_3), 1.00–1.20 (3 H, m), 1.28 (1 H, m), 1.44 (2 H, m), 1.56 (1 H, m), 1.71 (2 H, m), 2.0 and 2.08 (each 1 H, m), 2.41 (3 H, s, $ArCH_3$), 2.65 (3 H, s, NCH_3), 3.32 (1 H, br. s, OH, exchangeable with D_2O), 3.58 (3 H, m, 1-H_2 and 3-H), 3.86 and 3.91 (each 1 H, m, 6-H or 8-H) and 7.28 and 7.68 (each 2 H, d, *J* 8.3, ArH); δ_C ($CDCl_3$, 125 MHz) 13.6, 13.7, 19.6, 21.4, 27.5, 30.2(2), 34.0, 38.0, 40.9, 54.7, 68.2, 77.0, 85.1, 127.0, 129.4, 137.1 and 142.9; *m*/*z* (CI) 384 (M^+ + 1, 100%).

(2*R*,3*R*,6*S*,8*R*)-8-[*N*-Methyl-*N*-(toluene-4-sulfonyl)amino]-3,6-epoxy-2-methylundecanal (**37**). Following the procedure outlined for the preparation of aldehyde **32**, the alcohol **36** (144 mg, 0.376 mmol) was oxidised to the *title compound* **37** (129 mg, 90%) as an oil, that was used immediately without chromatography (Found: M^+ + H, 382.2047. $C_{20}H_{32}NO_4S$ requires *M*, 382.2052); δ_H ($CDCl_3$, 300 MHz) 0.74 (3 H, t, *J* 7, 11-H_3), 0.99 (3 H, d, *J* 7, 2-CH_3), 1.02–1.66 (8 H, m), 1.9–2.1 (2 H, m), 2.34 (4 H, m, 2-H and $ArCH_3$), 2.59 (3 H, s, NCH_3), 3.76 (1 H, m), 3.86 (2 H, m), 7.22 and 7.6 (each 2 H, d, *J* 8.1 ArH) and 9.67 (1 H, d, *J* 2.5, 1-H); δ_C ($CDCl_3$, 75 MHz) 10.5, 13.7, 19.6, 21.4, 27.6, 29.1,

30.6, 34.0, 38.0, 51.6, 54.6, 77.0, 79.4, 127.1, 128.2, 129.4, 142.8 and 204.3; *m*/*z* (CI) 399 (M^+ + 18, 45%) and 382 (M^+ + 1, 100).

(2*S*,3*R*,6*S*,8*R*)-1-Benzyloxy-3,6-epoxy-2-methyl-8-(methylamino)-undecane (**38**). Sodium (~150 mg) and naphthalene (900 mg) were added to dimethoxyethane (6 mL) and the mixture sonicated at room temperature for 10 min then added to the sulfonamide **35** (55 mg) in dimethoxyethane (2 mL) at −60 °C until a dark green colour persisted. The mixture was stirred with a glass covered magnetic bar for 1 h. Aqueous sodium bicarbonate and solid K_2CO_3 were added and the mixture was diluted by adding ether. The aqueous layer was extracted with ether and the organic extracts were dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using 1 : 1 light petroleum : ether (with 1% Et_3N) gave the *title compound* **38** (32 mg, 85%) as an oil, $[\alpha]_D^{21}$ −16.1 (*c* 1 in $CHCl_3$) (Found: M^+ + H, 320.2586. $C_{20}H_{34}NO_2$ requires *M*, 320.2589); ν_{max}/cm^{-1} 3353, 1454, 1363, 1096, 1071, 735 and 697; δ_H ($CDCl_3$, 500 MHz) 0.96 (3 H, t, *J* 7.0, 11-H_3), 0.98 (3 H, d, *J* 7.0, 2-CH_3), 1.25–1.35 (3 H, m), 1.40–1.50 (2 H, m), 1.55–1.65 (3 H, m), 1.80–2.00 (3 H, m), 2.40 (3 H, s, NCH_3), 2.58 (1 H, m, 8-H), 3.44 (1 H, dd, *J* 9 and 7, 1-H), 3.64 (1 H, dd, *J* 9 and 4.6, 1-H′), 3.77 (1 H, q, *J* 7.2, 3-H), 3.95 (1 H, m, 6-H), 4.57 (2 H, s, $PhCH_2$) and 7.38 (5 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 13.6, 14.3, 18.8, 28.3, 32.0, 33.5, 36.0, 39.0, 40.1, 58.5, 73.0, 73.1, 78.4, 81.1, 127.3, 127.4, 128.2 and 138.8; *m*/*z* (CI) 320 (M^+ + 1, 30%) and 86 (100).

(2*S*,3*R*,6*S*,8*R*)-1-Benzyloxy-8-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)-3,6-epoxy-2-methylundecane (**39**). Di-*tert*-butyl dicarbonate (0.11 g, 0.52 mmol) and Et_3N (0.07 mL, 0.71 mmol) were added to the secondary amine **38** (0.15 g, 0.47 mmol) in DCM (3 mL) at room temperature and the mixture stirred for 16 h. Water (5 mL) was added and the aqueous layer was extracted with DCM (3 × 5 mL). The organic extracts were washed with water (10 mL) and brine (10 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (gradient elution 5 : 1 to 2 : 1) gave the *title compound* **39** (0.176 g, 90%) as a colourless oil, a 40 : 60 mixture of rotamers, R_f = 0.36 (2 : 1 light petroleum : ether); $[\alpha]_D^{26}$ −8.2 (*c* 0.54 in $CHCl_3$) (Found: M^+ + H, 420.3115. $C_{25}H_{42}NO_4$ requires *M*, 420.3114); ν_{max}/cm^{-1} 1695, 1455, 1399, 1365, 1338, 1250, 1150, 1071, 875, 771 and 735; δ_H (300 MHz, $CDCl_3$) 0.80–1.02 (6 H, m, 1-CH_3, 11-H_3), 1.10–1.70 (7 H, m), 1.48 [9 H, s, $C(CH_3)_3$], 1.80–2.13 (4 H, m), 2.66 (1.2 H, s, NCH_3), 2.70 (1.8 H, s, NCH_3), 3.40 (1 H, m, 1-H), 3.66 (1 H, dd, *J* 9.2, 4.8, 1-H′), 3.68–3.81 (2 H, m, 2-H, 6-H), 4.10 (0.6 H, m, 8-H), 4.24 (0.4 H, m, 8-H), 4.55 (2 H, s, $PhCH_2$) and 7.30–7.40 (5 H, m, ArH); *m*/*z* (CI) 420 (M^+ + 1, 71%), 364 (10) and 320 (100).

(2*S*,3*R*,6*S*,8*R*)-8-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-3,6-epoxy-2-methylundecan-1-ol (**40**). The benzyl ether **39** (410 mg) and Pd/C (10%, cat.) in ethanol (10 mL) was stirred under an atmosphere of hydrogen for 16 h. The catalyst was removed by filtration through Celite® and the filtrate concentrated under reduced pressure. The residue was azeotroped with benzene to give the *title compound* **40** (286 mg, 89%) as an oil, a 40 : 60 mixture of rotamers, $[\alpha]_D^{26}$ +4.6 (*c* 1.1 in $CHCl_3$) (Found: M^+ + H, 330.2651. $C_{18}H_{36}NO_4$ requires *M*, 330.2644); ν_{max}/cm^{-1} 3465, 1692, 1478, 1455, 1400, 1366, 1341, 1150, 1045, 873 and 770; δ_H ($CDCl_3$, 300 MHz) 0.85 (3 H, m, 2-CH_3), 0.93 (3 H, t, *J* 7, 11-H_3), 1.20–2.02 (12 H, m), 2.47 [9 H, s, $C(CH_3)_3$], 2.66 (1.2 H, s, NCH_3), 2.69 (1.8 H, s, NCH_3), 3.62 (3 H, m), 3.79 (1 H, m), 4.09 (0.6 H, m, 8-H) and 4.24 (0.4 H, m, 8-H); δ_C ($CDCl_3$, 75 MHz) 13.7, 19.0(2), 28.4, 30.3, 34.9(2), 38.3, 38.7, 41.0, 52.4, 68.2, 68.4, 85.2, 85.4 and 156.0; *m*/*z* (CI) 330 (M^+ + 1, 5%), 286 (8) and 230 (100).

(2*R*,3*R*,6*S*,8*R*)-8-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-3,6-epoxy-2-methylundecanal (**41**). The Dess–Martin periodinane (0.254 g, 0.599 mmol) was added to the alcohol **40** (0.116 g, 0.353 mmol) in DCM (2.5 mL) and the mixture was stirred for 40 min at room temperature. Saturated aqueous sodium bicarbonate (3 mL) and saturated aqueous sodium bisulfite (3 mL) were added and the mixture stirred for 20 min. The aqueous layer was extracted with ether (3 × 10 mL) and the organic extracts were washed with saturated aqueous sodium bicarbonate (10 mL), water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure to give the aldehyde **41** (0.115 g, *ca.* 100%), as a colourless oil, a 60 : 40 mixture of rotamers, R_f = 0.46 (1 : 1 light petroleum : ether) (Found: M^+ + H, 328.2488. $C_{18}H_{34}NO_4$ requires *M*, 328.2488); ν_{max}/cm^{-1} 1729, 1691, 1458, 1398, 1366, 1151, 1063, 874 and 770; δ_H ($CDCl_3$, 300 MHz) 0.92 (3 H, t, *J* 7, 11-H_3), 1.09 (3 H, 2 × d, *J* 7, 2-CH_3), 1.18–1.74 (7 H, m), 1.47 [9 H, s, $C(CH_3)_3$], 1.88 (1 H, m), 2.06 (2 H, m), 2.47 (1 H, m, 2-H), 2.64 (1.2 H, s, NCH_3), 2.68 (1.8 H, s, NCH_3), 3.79 (1 H, m, 3-H), 3.98 (1 H, m, 6-H), 4.1 (0.6 H, m, 8-H), 4.25 (0.4 H, m, 8-H) and 9.78 (1 H, m, 1-H); *m*/*z* (CI) 328 (M^+ + 1, 3%), 272 (25) and 228 (100).

Methyl (2*R*,3*R*,6*S*,8*R*)-8-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)-3,6-epoxy-2-methylundecanoate (**43**). 2-Methylbut-2-ene (2 M in THF, 3.68 mmol, 1.84 mL), sodium chlorite (80% tech. grade, 0.21 g, 2.30 mmol) and sodium dihydrogen phosphate (0.55 g, 4.60 mmol) were added to the aldehyde **41** (0.12 g, 0.367 mmol) in $^tBuOH : H_2O$ (1 : 1, 9 mL) and the mixture was stirred for 2 h at room temperature. Brine (3 mL) was added and the mixture diluted with EtOAc (3 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to leave the acid **42** as an oil, a 60 : 40 mixture of rotamers (Found: M^+ + H, 344.2439. $C_{18}H_{34}NO_5$ requires *M*, 344.2437); ν_{max}/cm^{-1} 1736, 1691, 1461, 1399, 1366, 1154, 1062, 939, 872 and 770; δ_H ($CDCl_3$, 300 MHz) 0.86 (3 H, t, *J* 7, 11-H_3), 1.13 (3 H, d, *J* 7.1, 2-CH_3), 1.16–1.70 (7 H, m), 1.40 [9 H, s, $C(CH_3)_3$], 1.74–2.1 (3 H, m), 2.47 (1 H, m, 2-H), 2.58 (1.2 H, s, NCH_3), 2.61 (1.8 H, s, NCH_3), 3.79 (1 H, m, 6-H), 3.95 (1 H, q, *J* 6.6, 3-H), 4.03 (0.6 H, m, 8-H) and 4.19 (0.4 H, m, 8-H); *m*/*z* (CI) 344 (M^+ + 1, 5%), 288 (20) and 244 (100).

This acid **42** was azeotroped with benzene then dissolved in benzene : methanol (4 : 1, 8 mL). (Trimethylsilyl)diazomethane (1 M in hexanes, 0.734 mmol, 0.37 mL) was added slowly at room temperature After 1.5 h, the mixture was concentrated under reduced pressure and chromatography of the residue using 3 : 1 light petroleum : ether gave the *title compound* **43**

(98 mg, 75%) as an oil, a 60 : 40 mixture of rotamers, R_f = 0.46 (1 : 1 light petroleum : ether); $[\alpha]_D^{26}$ −12.8 (*c* 1.0 in $CHCl_3$) (Found: M^+ + H, 358.2595. $C_{19}H_{36}NO_5$ requires *M*, 358.2593); ν_{max}/cm^{-1} 1741, 1691, 1458, 1398, 1365, 1340, 1256, 1150, 1063 and 769; δ_H (300 MHz, $CDCl_3$) 0.93 (3 H, t, *J* 7.1, 11-H_3), 1.15 (3 H, d, *J* 7.0, 2-CH_3), 1.21–1.70 (8 H, m), 1.46 [9 H, s, $C(CH_3)_3$], 1.81–2.16 (2 H, m), 2.55 (1 H, m, 2-H), 2.64 (1.2 H, s, NCH_3), 2.68 (1.8 H, s, NCH_3), 3.73 (3 H, s, OCH_3), 3.79 (1 H, m), 4.05 (1.4 H, m) and 4.21 (0.6 H, m, 8-H); δ_C (75 MHz, $CDCl_3$) 13.2, 13.4, 13.6, 13.8, 19.0, 19.2, 28.2, 28.3, 28.3, 30.8, 30.9, 34.9, 35.1, 38.2, 38.7, 45.1, 45.3, 51.5, 52.3, 77.0, 77.4, 78.8, 79.1, 80.1, 80.2, 155.9 and 175.1; *m*/*z* (CI) 358 (M^+ + 1, 48%) and 258 (100).

Methyl (2*R*,3*R*,6*S*,8*R*)-3,6-epoxy-2-methyl-8-(methylamino)undecanoate (**44**).[5κ] Concentrated aqueous hydrogen chloride (few drops) was added to the carbamate **43** (84 mg) in ethyl acetate (2 mL) and the mixture stirred for 15 h at room temperature. Aqueous sodium bicarbonate and ethyl acetate were added and the aqueous layer extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 1 : 1 light petroleum : ether (with 1% Et_3N) gave the title compound **44** (29 mg, 48%), as a colourless oil, $[\alpha]_D^{22}$ −26 (*c* 0.75 in $CHCl_3$) lit.[5k] $[\alpha]_D^{20}$ −28.2 (*c* 0.85 in $CHCl_3$); ν_{max}/cm^{-1} 3357, 1739, 1461, 1377, 1260, 1198, 1162, 1062, 854 and 760; δ_H ($CDCl_3$, 300 MHz) 0.90 (3 H, t, *J* 6.7, 11-H_3), 1.10 (3 H, d, *J* 7, 2-CH_3), 1.20–1.70 (7 H, m), 1.90–2.10 (3 H, m), 2.34 (3 H, s, NCH_3), 2.50 (2 H, m, 2-H and 8-H), 3.68 (3 H, s, OCH_3) and 3.96 (2 H, m, 3-H and 6-H); δ_C ($CDCl_3$, 75 MHz) 13.3, 14.3, 18.7, 28.3, 31.8, 33.4, 36.0, 40.0, 45.4, 51.5, 58.4, 78.8, 80.8 and 175.4.

Methyl (2*R*,3*R*,6*S*,8*R*)-8-(dimethylamino)-3,6-epoxy-2-methylundecanoate (**45**).[5κ] Formalin (85 μL, 1.13 mmol) and $NaBH_3CN$ (36 mg, 0.564 mmol) were added to the secondary amine **44** (29 mg, 0.113 mmol) in acetonitrile (1.5 mL) and the solution stirred for 1 h at room temperature. Acetic acid (12 mL) was added and the solution stirred for 1.5 h. After concentration under reduced pressure, chromatography using 1 : 1 light petroleum : ether (with 1% Et_3N) gave the title compound **45** (16 mg, 52%), as a colourless oil, $[\alpha]_D^{22}$ −19.2 (*c* 0.375 in $CHCl_3$) lit.[5k] $[\alpha]_D^{20}$ −23.9 (*c* 0.715 in $CHCl_3$); ν_{max}/cm^{-1} 1740, 1461, 1376, 1260, 1197, 1162, 1062, 890 and 855; δ_H ($CDCl_3$, 300 MHz) 0.90 (3 H, t, *J* 6.9, 11-H_3), 1.11 (3 H, d, *J* 7, 2-CH_3), 1.18–1.51 (6 H, m), 1.63 and 1.78 (each 1 H, m), 1.98 (2 H, m), 2.20 [6 H, s, $N(CH_3)_2$], 2.52 (2 H, m, 2-H and 8-H), 3.69 (3 H, s, OCH_3), 3.93 (1 H, quin, *J* 6.5, 6-H) and 4.02 (1 H, q, *J* 6.7, 3-H); δ_C ($CDCl_3$, 75 MHz) 13.3, 14.2, 20.1, 28.4, 31.1, 31.7, 35.5, 40.1, 45.5, 51.5, 60.6, 77.5, 80.1 and 175.4.

2,6-Dimethylphenyl (2*R*,3*R*,4*S*,5*R*,8*S*,10*R*)-, (2*S*,3*S*,4*S*,5*R*,8*S*,10*R*)- and (2*R*,3*S*,4*S*,5*R*,8*S*,10*R*)-2,4-dimethyl-5,8-epoxy-3-hydroxy-10-[*N*-methyl-*N*-(toluene-4-sulfonyl)amino]tridecanoates (**46**), (**48**) and (**50**). *n*-Butyllithium (2.05 M in hexanes, 16.3 mL, 33.4 mmol) was added to di-*iso*propylamine (3.37 mL, 33.4 mmol) in THF (15 mL) and the mixture cooled to 0 °C. After 15 min, the solution was cooled down to −78 °C and 2,6-dimethylphenyl propionate (5.95 g, 33.4 mmol) in THF (5 mL) was added. The solution was stirred for 1 h at −78 °C then the aldehyde **37** (2.87 g, 7.53 mmol) in THF (5 mL) cooled to 0 °C was added. The mixture was stirred for 1 h at −78 °C then saturated aqueous ammonium chloride was added. The mixture was allowed to warm to room temperature and was then stirred for 30 min. Ether was added and the aqueous layer was extracted with more ether. The organic extracts were washed with water and brine then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using light petroleum : ether (gradient elution 3 : 1 to 1 : 1) gave a mixture of the *title compounds* **46** and **48** (2.66 g, 63%) as a colourless liquid (Found: M^+ + NH_4, 577.3301. $C_{31}H_{49}N_2O_6S$ requires *M*, 577.3311); ν_{max}/cm^{-1} 3520, 1752, 1462, 1380, 1336, 1152, 1092, 922, 816, 759 and 719; δ_H ($CDCl_3$, 300 MHz) 0.84 (3 H, m, 13-H_3), 1.02 (3 H, d, *J* 7, 4-CH_3), 1.05–1.80 (8 H, m), 1.35 (3 H, d, *J* 7, 2-CH_3), 2.0–2.2 (3 H, m), 2.24 (6 H, s, 2 × $ArCH_3$), 2.44 (3 H, s, $ArCH_3$), 2.7 (3 H, s, NCH_3), 3.0 (1 H, dq, *J* 10. 7, 2-H), 3.15 (1 H, d, *J* 4.2, OH), 3.75–4.1 (3 H, m), 4.35 (1 H, ddd, *J* 10, 4, 2, 3-H), 7.09 (3 H, s, ArH) and 7.3 and 7.7 (each 2 H, d, *J* 8.3, ArH); *m*/*z* (CI) 577 (M^+ + 18, 90%) and 86 (100). The second fraction contained the *title compound* **50** (289 mg, 7%) as a white solid, $[\alpha]_D^{25}$ +1.96 (*c* 0.82 in $CHCl_3$) (Found: M^+ + NH_4, 577.3318. $C_{31}H_{49}N_2O_6S$ requires *M*, 577.3311); ν_{max}/cm^{-1} 3438, 1748, 1598, 1461, 1337, 1153, 1090, 1056, 927, 816 and 758; δ_H ($CDCl_3$, 300 MHz) 0.84–1.04 (3 H, m, 13-H_3), 1.14 (3 H, d, *J* 7.1, 4-CH_3), 1.15–2.20 (10 H, m), 1.58 (3 H, d, *J* 7, 2-CH_3), 1.95 (6 H, s, 2 × $ArCH_3$), 2.45 (3 H, s, $ArCH_3$), 2.71 (1 H, m, 4-H), 2.71 (3 H, s, NCH_3), 3.05 (1 H, dq, *J* 9.5 and 7.5, 2-H), 3.26 (1 H, d, *J* 3.3, OH), 3.74–4.14 (3 H, m), 4.24 (1 H, dt, *J* 9.5 and 2.8, 3-H), 7.09 (3 H, s, ArH), 7.32 and 7.73 (each 2 H, d, *J* 8.1, ArH); δ_C ($CDCl_3$, 75 MHz) 11.4, 13.7, 14.9, 16.4, 19.6, 21.4, 27.6, 29.0, 31.1, 34.3, 37.7, 40.0, 43.1, 55.0, 71.7, 77.0, 82.6, 125.7, 127.0, 127.1, 128.6, 129.4, 130.0 and 173.2; *m*/*z* (EI) 560 (M^+ + 1, 2%), 438 (10), 382 (70) and 240 (100).

2,6-Dimethylphenyl (2*R*,3*R*,4*R*,5*R*,8*S*,10*R*)- and (2*S*,3*S*,4*R*,5*R*,8*S*,10*R*)-3-*tert*-butyldimethylsilyloxy-2,4-dimethyl-5,8-epoxy-10-[*N*-methyl-*N*-(toluene-4-sulfonyl)amino]tridecanoates (**47**) and (**49**). 2,6-Lutidine (1.34 mL, 11.53 mmol) and *tert*-butyldimethylsilyl trifluoromethylsulfonate (1.76 mL, 7.69 mmol) were added to a mixture of the aldol products **46** and **48** (2.15 g, 3.84 mmol) in DCM (40 mL) at room temperature and the solution stirred for 16 h. Water was added and the aqueous layer extracted with DCM. The organic extracts were washed with water and brine then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 7 : 1 light petroleum : ether gave the *title compound* **49** (1.71 g, 66%) as a colourless liquid, $[\alpha]_D^{25}$ −2.67 (*c* 1.2 in $CHCl_3$) (Found: M^+, 673.3827. $C_{37}H_{59}NO_6SSi$ requires *M*, 673.3832); ν_{max}/cm^{-1} 1755, 1466, 1341, 1256, 1154, 1092, 1049, 934, 836 and 774; δ_H ($CDCl_3$, 500 MHz) 0.08 and 0.1 (each 3 H, s, $SiCH_3$), 0.81 (3 H, t, *J* 7, 13-H_3), 0.92 [12 H, m, $SiC(CH_3)_3$ and 4-CH_3], 1.05–1.20 (3 H, m), 1.25–1.45 (4 H, m), 1.38 (3 H, d, *J* 7.2, 2-CH_3), 1.64, 1.82, 1.92 and 2.02 (each 1 H, m), 2.16 (6 H, s, 2 × $ArCH_3$), 2.40 (3 H, s, $ArCH_3$), 2.66 (3 H, s, NCH_3), 3.04 (1 H, dq, *J* 5.0, 6.5, 2-H), 3.54 (1 H, dt, *J* 5.0 and 6.8, 5-H), 3.66 and 3.95 (each 1 H, quin, *J* 7.2, 8-H or 10-H), 4.54 (1 H, dd, *J* 6 and 2, 3-H), 7.03 (3 H, m, ArH) and 7.25 and 7.68 (each 2 H, d, *J* 8.1, ArH); δ_C ($CDCl_3$,

125 MHz) −5.0, −4.0, 10.6, 13.6, 13.8, 16.8, 18.5, 19.6, 21.4, 26.2, 27.6, 29.7, 31.0, 34.0, 38.1, 41.9, 46.1, 54.7, 71.8, 75.7, 80.2, 125.6, 127.1, 128.5, 129.4, 130.2, 137.3, 142.8, 148.2 and 172.1; *m*/*z* (CI) 691 (M^+ + 18, 2%), 674 (M^+ + 1, 1) and 86 (100). The second fraction contained the *title compound* **47** (0.44 g, 17%) as a colourless oil, $[\alpha]_D^{25}$ −4.83 (*c* 0.91 in $CHCl_3$) (Found: M^+ + NH_4, 691.4173. $C_{37}H_{63}N_2O_6SSi$ requires *M*, 691.4176); ν_{max}/cm^{-1} 1755, 1467, 1339, 1256, 1156, 1094, 1051, 931, 837 and 773; δ_H ($CDCl_3$, 500 MHz) 0.09 and 0.12 (each 3 H, s, $SiCH_3$), 0.84 (3 H, t, *J* 7, 13-H_3), 0.91 [9 H, m, $SiC(CH_3)_3$], 0.93 (3 H, d, *J* 7, 4-CH_3), 1.10–1.31 (3 H, m), 1.35 (2 H, m), 1.41 (3 H, d, *J* 7, 2-CH_3), 1.47, 1.56, 1.68 and 1.88 (each 1 H, m), 2.06 (2 H, m), 2.18 (6 H, s, 2 × $ArCH_3$), 2.41 (3 H, s, $ArCH_3$), 2.68 (3 H, s, NCH_3), 3.08 (1 H, dq, *J* 5.1, 7.9, 2-H), 3.76 (1 H, quin, *J* 7.5), 3.98 (2 H, m), 4.19 (1 H, dd, *J* 6.0 and 4.5, 3-H), 7.05 (3 H, m, ArH) and 7.27 and 7.7 (each 2 H, d, *J* 8.1, ArH); δ_C ($CDCl_3$, 125 MHz) −4.6, −4.2, 10.7, 13.7, 13.8, 16.8, 18.3, 19.7, 21.5, 26.0, 27.7, 27.9, 31.3, 34.0, 38.0, 42.5, 44.1, 54.8, 75.2, 75.9, 79.6, 125.6, 127.1, 128.6, 129.4, 130.2, 137.3, 142.8, 148.3 and 172.2; *m*/*z* (EI) 674 (M^+ + 1, 20%), 616 and 552 (100).

2,6-Dimethylphenyl (2*R*,3*S*,4*R*,5*R*,8*S*,10*R*)-3-*tert*-butyldimethylsilyloxy-2,4-dimethyl-5,8-epoxy-10-[*N*-methyl-*N*-(toluene-4-sulfonyl)amino]tridecanoate (**51**). Following the procedure used to prepare the silyl ethers **47** and **49**, the aldol product **50** (40 mg, 0.71 mmol) gave the *title compound* **51** (34 mg, 70%) as a colourless oil (Found: M^+ + NH_4, 691.4180. $C_{37}H_{63}N_2O_6SSi$ requires *M*, 691.4176); ν_{max}/cm^{-1} 1750, 1464, 1339, 1256, 1154, 1091, 1056, 931, 836 and 773; δ_H ($CDCl_3$, 500 MHz) 0.1 and 0.15 (each 3 H, s, $SiCH_3$), 0.82 (3 H, t, *J* 7, 13-H_3), 0.94 [12 H, m, $SiC(CH_3)_3$ and 4-CH_3], 1.06–1.41 (7 H, m), 1.43 (3 H, d, *J* 7, 2-CH_3), 1.58 (1 H, m), 1.69 (1 H, m, 4-H), 1.98 (2 H, m), 2.16 (6 H, s, 2 × $ArCH_3$), 2.33 (3 H, s, $ArCH_3$), 2.64 (3 H, s, NCH_3), 2.94 (1 H, dq, *J* 7.9, 6.9, 2-H), 3.48 (1 H, m, 5-H), 3.64 and 3.99 (each 1 H, quin, *J* 7.0, 8-H or 10-H), 4.43 (1 H, dd, *J* 9.0, 1.5, 3-H), 7.05 (3 H, m, ArH) and 7.2 and 7.68 (each 2 H, d, *J* 8.1, ArH); δ_C ($CDCl_3$, 125 MHz) −4.5, −3.7, 9.6, 13.9, 16.3, 16.7, 18.6, 19.6, 21.4, 26.2, 27.6, 30.5, 30.9, 33.9, 37.9, 43.9, 44.9, 54.8, 72.4, 75.7, 79.3, 125.7, 127.1, 128.6, 129.4, 130.2, 137.3, 142.7, 148.1 and 173.1; *m*/*z* (CI) 691 (M^+ + 18, 50%), 674 (M^+ + 1, 15) and 86 (100).

(2*R*,3*R*,4*R*,5*R*,8*S*,10*R*)-3-*tert*-Butyldimethylsilyloxy-2,4-dimethyl-5,8-epoxy-10-[*N*-methyl-*N*-(toluene-4-sulfonyl)amino]tridecan-1-ol (**52**). Di-isobutylaluminium hydride (1 M in DCM, 16.5 mL, 16.5 mmol) was added slowly to the ester **49** (4.45 g, 6.61 mmol) in DCM (55 mL) at −78 °C and the solution was stirred for 30 min at −78 °C then warmed to room temperature over a period of 1 h. The solution was then cooled to −78 °C and MeOH (*ca.* 3 mL) and saturated aqueous ammonium chloride (*ca.* 20 mL) were added. The mixture was allowed to warm to room temperature and was stirred for a further 45 min then filtered through Celite®, washed with water and brine then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using light petroleum : ether (gradient elution 4 : 1 to 2 : 1) gave the *title compound* **52** (2.93 g, 80%) as a colourless liquid, $[\alpha]_D^{23}$ −19.1 (*c* 1.05 in $CHCl_3$) (Found: M^+ + H, 556.3490. $C_{29}H_{54}NO_5SSi$ requires *M*, 556.3492); ν_{max}/cm^{-1} 3451, 1462, 1339, 1254, 1153, 1089, 1038, 837 and 773; δ_H ($CDCl_3$, 500 MHz) 0.08 and 0.12 (each 3 H, s, $SiCH_3$), 0.83 (3 H, t, *J* 7, 13-H_3), 0.86 (3 H, d, *J* 7, 4-CH_3), 0.88 (3 H, d, *J* 7, 2-CH_3), 0.92 [9 H, s, $SiC(CH_3)_3$], 1.12 (1 H, m), 1.2 (2 H, m), 1.34 (1 H, m), 1.42 (3 H, m), 1.6 and 1.92 (each 2 H, m), 2.04 (1 H, m), 2.42 (3 H, s, $ArCH_3$), 2.65 (3 H, s, NCH_3), 2.86 (1 H, dd, *J* 7.5 and 3.7, OH, D_2O exchangeable), 3.45–3.62 (3 H, m, 1-H_2 and 5-H), 3.77 and 4.01 (each 1 H, m, 8-H or 10-H), 4.12 (1 H, dd, *J* 6.2 and 1.8, 3-H), 7.28 and 7.70 (each 2 H, d, *J* 8.1, ArH); δ_C ($CDCl_3$, 125 MHz) −4.6, −4.2, 11.0, 13.0, 13.8, 18.3, 19.7, 21.5, 26.1, 27.7, 30.1, 30.8, 33.8, 38.2, 40.8, 41.4, 54.6, 65.8, 73.9, 75.6, 81.5, 127.2, 129.4, 137.2 and 142.9; *m*/*z* (CI) 556 (M^+ + 1, 50%) and 86 (100).

(2*R*,3*R*,4*R*,5*R*,8*S*,10*R*)-2,4-Dimethyl-5,8-epoxy-1,3-(1,3-bis-epoxycarbonyl)-10-[*N*-methyl-*N*-(toluene-4-sulfonyl)amino]tridecane (**54**). Tetrabutylammonium fluoride (1 M in THF, 270 μL, 0.27 mmol) was added to the silyl ether **52** (75 mg, 0.135 mmol) in THF (1 mL) at room temperature and the solution was stirred for 2 h. After concentration under reduced pressure, water and DCM were added and the aqueous phase was extracted with DCM. The organic extracts were washed with water and brine then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 1 : 2 light petroleum : ether gave the diol **53** (53 mg, 89%) as a colourless liquid, $[\alpha]_D^{21}$ −11.2 (*c* 0.3 in $CHCl_3$); ν_{max}/cm^{-1} 3432, 1598, 1461, 1383, 1335, 1154, 1090, 1037, 923, 816 and 758; δ_H ($CDCl_3$, 300 MHz) 0.76 (6 H, m, 13-H_3 and 2- or 4-CH_3), 0.97 (3 H, d, *J* 7, 4- or 2-CH_3), 1.04–1.3 (4 H, m), 1.36–1.76 (5 H, m), 1.9 (2 H, m), 2.1 (1 H, m), 2.39 (3 H, s, $ArCH_3$), 2.63 (3 H, s, NCH_3), 3.4–4.0 (8 H, m) and 7.25 and 7.65 (each 2 H, d, *J* 8.2, ArH); δ_C ($CDCl_3$, 75 MHz) 10.7, 13.4, 13.7, 19.6, 21.4, 27.5, 29.2, 31.1, 34.3, 37.0, 37.8, 39.2, 55.0, 69.2, 76.7, 77.0, 82.7, 127.0, 129.4, 137.5 and 142.9.

Carbonyl di-imidazole (97 mg, 0.6 mmol) was added to the diol **53** (53 mg, 0.12 mmol) in dry benzene (5 mL) and the solution was heated under reflux for 16 h. After concentration under reduced pressure, chromatography of the residue using 1 : 2 light petroleum : ether gave the *title compound* **54** (49 mg, 87%), as a colourless liquid, ν_{max}/cm^{-1} 1752, 1667, 1461, 1405, 1334, 1211, 1152, 1123, 1088, 924 and 761; δ_H ($CDCl_3$, 500 MHz) 0.84 (3 H, t, *J* 6.8, H-13), 0.92 (3 H, d, *J* 6.6, 4-CH_3), 0.98 (3 H, d, *J* 6.6, 2-CH_3), 1.19 (3 H, m), 1.38–1.62 (5 H, m), 1.75 (1 H, m, 4-H), 2.04 (2 H, m), 2.19 (1 H, m, 2-H), 2.43 (3 H, s, $ArCH_3$), 2.64 (3 H, s, NCH_3), 3.84 (2 H, m), 4.04 (1 H, t, *J* 11, 1-H), 4.08 (1 H, m), 4.28 (1 H, dd, *J* 10.7 and 4.8, 1-H′), 4.64 (1 H, dd, *J* 10.6 and 1.5, 3-H), 7.28 and 7.68 (each 2 H, d, *J* 8.2, ArH); δ_C ($CDCl_3$, 75 MHz) 8.5, 11.2, 13.6, 19.3, 21.2, 27.3, 27.9, 29.5, 30.8, 33.4, 39.0, 39.8, 54.2, 72.0, 75.6, 78.5, 83.8, 126.9, 129.1, 137.0, 142.7 and 150.0.

Methyl (4*S*,5*R*,8*S*,10*R*,2*E*)-10-[*N*-methyl-*N*-(toluene-4-sulfonyl)-amino]-5,8-epoxy-4-methyltridec-2-enoate (**55**). (Methoxycarbonylmethylene)triphenylphosphorane (188 mg, 0.564 mmol) was added to freshly prepared aldehyde **37** (from Swern oxidation of 144 mg, 0.376 mmol, of alcohol **36**) in DCM (1.5 mL) and the mixture stirred for 48 h. After concentration under reduced

pressure, chromatography using 3 : 1 light petroleum : ether) gave the *title compound* **55** (133 mg, 81% from **34**) as colourless oil (Found: M^+ + H, 438.2318. $C_{23}H_{36}NO_5S$ requires *M*, 438.2314); ν_{max}/cm^{-1} 1723, 1656, 1598, 1459, 1437, 1338, 1274, 1153, 1090, 1055, 1040, 989, 928, 817 and 719; δ_H ($CDCl_3$, 300 MHz) 0.85 (3 H, t, *J* 7, 13-H_3), 1.08 (3 H, d, *J* 6.9, 4-CH_3), 1.12–1.52 (6 H, m), 1.58, 1.70, 1.92 and 2.08 (each 1 H, m), 2.44 (4 H, m, $ArCH_3$ and 4-H), 2.70 (3 H, s, NCH_3), 3.70 (1 H, q, *J* 7, 5-H), 3.76 (3 H, s, OCH_3), 3.81 and 3.98 (each 1 H, m, 8-H or 10-H), 5.9 (1 H, dd, *J* 15.8 and 1.1, 2-H), 7.0 (1 H, dd, *J* 15.8 and 7.7, 3-H) and 7.31 and 7.72 (each 2 H, d, *J* 8.2, ArH); δ_C ($CDCl_3$, 75 MHz) 13.7, 15.4, 19.6, 21.4, 27.6, 28.6, 30.9, 34.1, 37.9, 41.6, 51.3, 54.7, 76.5, 81.7, 120.7, 127.1, 129.4, 137.3, 142.8, 151.3 and 167.0; *m*/*z* (EI) 438 (M^+ + 1, 4%), 394 (5), 282 (15), 240 (85) and 86 (100).

(4*S*,5*R*,8*S*,10*R*,2*E*)-10-[*N*-Methyl-*N*-(toluene-4-sulfonyl)amino]-5,8-epoxy-4-methyltridec-2-en-1-ol (**56**). Di-isobutylaluminium hydride (1 M in hexane, 0.99 μL, 0.99 mmol) was added to the ester **55** (122 mg, 0.279 mmol) in DCM (1 mL) at −78 °C. The solution was stirred for 30 min at −78 °C and at room temperature for 90 min. It was then cooled to −78 °C and methanol and aqueous sodium bicarbonate were added. After being allowed to warm to room temperature, the mixture was stirred for another 30 min and filtered through Celite®. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 1 : 1 light petroleum : ether gave the *title compound* **56** (84 mg, 74%) as a colourless liquid (Found: M^+ + H, 410.2361. $C_{22}H_{36}NO_4S$ requires *M*, 410.2365); ν_{max}/cm^{-1} 3402, 1598, 1461, 1336, 1154, 1091, 1051 and 816; δ_H ($CDCl_3$, 300 MHz) 0.86 (3 H, t, *J* 7, 13-H_3), 1.04 (3 H, d, *J* 6.9, 4-CH_3), 1.05–2.00 (9 H, m), 2.06 and 2.30 (each 1 H, m), 2.45 (3 H, s, $ArCH_3$), 2.69 (3 H, s, NCH_3), 3.66 (1 H, q, *J* 7.1, 5-H), 3.82 (1 H, quin, *J* 7.0, 8-H), 4.04 (1 H, quin, *J* 7.0, 10-H), 4.14 (2 H, m, 1-H_2), 5.75 (2 H, m, 2-H and 3-H) and 7.31 and 7.74 (each 2 H, d, *J* 8.2, ArH); δ_C ($CDCl_3$, 75 MHz) 13.8, 16.3, 19.6, 21.4, 27.6, 28.5, 31.1, 34.0, 38.2, 41.5, 54.7, 63.7, 76.2, 82.7, 127.1, 129.0, 129.3, 135.1, 137.3 and 142.7; *m*/*z* (CI) 427 (M^+ + 18, 97%), 410 (M^+ + 1, 100) and 392 (85).

(2*S*,3*S*,4*R*,5*R*,8*S*,10*R*)-10-[*N*-Methyl-*N*-(toluene-4-sulfonyl)amino]-2,3;5,8-bis-epoxy-4-methyltridecan-1-ol (**57**). The alkenol **56** (84 mg, 0.205 mmol) and diethyl L-(+)-tartrate (105 mg, 0.513 mmol) in dry DCM (1.5 mL) were added to titanium(IV) isopropoxide (146 mg, 0.513 mmol) in DCM (1 mL) at −23 °C. Anhydrous *tert*-butyl hydroperoxide (4.5 M in toluene, 0.32 mL, 1.43 mmol) was added slowly and the mixture was stirred at −23 °C for 2 h. Aqueous tartaric acid (2 mL) was added and the mixture stirred for 10 min. It was then warmed to room temperature and stirred for another 30 min. The aqueous layer was extracted with DCM and the organic extracts concentrated under reduced pressure then diluted with ether and cooled to 0 °C. Aqueous sodium hydroxide (1 N, 1 mL) was added and the mixture stirred for 1 h. The aqueous layer was extracted with DCM and the organic extracts dried ($MgSO_4$) then concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (gradient elution 3 : 1 to 1 : 1) gave the *title compound* **57** (61 mg, 70%) as a colourless liquid, 57 : 58 = 95 : 5 (^{1}H NMR) (Found: M^+ + H, 426.2316. $C_{22}H_{36}NO_5S$ requires *M*, 426.2314); ν_{max}/cm^{-1} 3425, 1598, 1462, 1380, 1335, 1151, 1089, 1058, 927, 898, 816, 759 and 718; δ_H ($CDCl_3$, 500 MHz) 0.85 (3 H, t, *J* 7, 13-H_3), 1.02 (3 H, d, *J* 6.8, 4-CH_3), 1.10–1.30 (4 H, m), 1.35–1.60 (5 H, m), 1.72 (1 H, br. s, OH), 1.98 and 2.06 (each 1 H, m), 2.42 (3 H, s, $ArCH_3$), 2.64 (3 H, s, NCH_3), 2.87 (1 H, dd, *J* 7.7 and 2.3, 3-H), 3.12 (1 H, m, 2-H), 3.65 (1 H, q, *J* 7.0, 5-H), 3.72 (1 H, dd, *J* 12.4 and 4.3, 1-H), 3.82 (1 H, quin, *J* 6.6, 8-H), 3.87 (1 H, dd, *J* 12.4 and 3.4, 1-H′), 4.10 (1 H, quin, *J* 6.9, 10-H) and 7.4 and 7.7 (each 2 H, d, *J* 8.2, ArH); δ_C ($CDCl_3$, 100 MHz) 13.8, 15.2, 19.6, 21.4, 27.5, 29.4, 30.9, 33.5, 38.7, 41.9, 54.6, 59.0, 62.2, 65.8, 76.1, 81.2, 127.1, 129.3, 137.2 and 142.9; *m*/*z* (EI) 426 (M^+ + 1, 8%), 240 (80) and 86 (100).

Methyllithium (1.6 M in ether, 1.42 mL, 2.27 mmol) was added to a suspension of copper(I) iodide (230 mg, 1.2 mmol) in ether (3.5 mL) at −10 °C. After 30 min, epoxide **57** (34 mg, 0.08 mmol) in ether (0.5 mL) was added slowly and the mixture was stirred for 5 h at −10 °C. The mixture was then poured onto a mixture of saturated aqueous ammonium chloride and aqueous ammonium hydroxide and the ensuing mixture was stirred for 10 min. The aqueous layer was extracted with DCM and the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (gradient elution 1 : 1 to 1 : 2) gave the diol **53** (20 mg, 57%) as a colourless liquid with spectroscopic data identical to those of the sample prepared earlier by desilylation of the silyl ether **52**.

(2*R*,3*R*,4*R*,5*R*,8*S*,10*R*)-10-[*N*-Methyl-*N*-(toluene-4-sulfonyl)amino]-2,3;5,8-bis-epoxy-4-methyltridecan-1-ol (**58**). Following the procedure outlined for the synthesis of epoxide **57** but using diethyl D-(−)-tartrate, the alkenol **56** (78 mg, 0.19 mmol) gave the *title compound* **58** (81 mg, 80%) as a colourless oil containing only traces, <2%, of **57** (^{1}H NMR) (Found: M^+ + H, 426.2312. $C_{22}H_{36}NO_5S$ requires *M*, 426.2314); δ_H ($CDCl_3$, 500 MHz) 0.84 (3 H, t, *J* 7, 13-H_3), 0.94 (3 H, d, *J* 6.8, 4-CH_3), 1.10–1.26 (3 H, m), 1.34, 1.42 and 1.49 (each 1 H, m), 1.69 and 1.92 (each 2 H, m), 2.08 (1 H, m), 2.42 (3 H, s, $ArCH_3$), 2.64 (3 H, s, NCH_3), 3.02 (1 H, m, 2-H), 3.06 (1 H, dd, *J* 6.8 and 2.3, 3-H), 3.68 (1 H, ddd, *J* 12.1, 7.2 and 4.5, 1-H), 3.72 (1 H, q, *J* 7.0, 5-H), 3.84 (1 H, quin, *J* 6.8), 3.89 (1 H, ddd, *J* 12.5, 6.1, 3.0, 1-H′), 4.0 (1 H, quin, *J* 7.1) and 7.4 and 7.7 (each 2 H, d, *J* 8.2, ArH); δ_C ($CDCl_3$, 125 MHz) 12.5, 13.8, 19.7, 21.5, 27.7, 28.7, 31.0, 34.2, 38.2, 39.6, 54.9, 55.8, 57.6, 62.0, 76.5, 81.3, 127.2, 129.4, 137.4 and 142.8; *m*/*z* (CI), 426 (M^+ + 1, 50%), 272 (40) and 86 (100).

(2*S*,3*S*,4*R*,5*R*,8*S*,10*R*)-2,4-Dimethyl-5,8-epoxy-1,3-(bis-1,3-epoxycarbonyl)-10-[*N*-methyl-*N*-(toluene-4-sulfonyl)amino]tridecane (**60**). Following the procedure outlined for the synthesis of diol **53** from the epoxide **57**, the epoxide **58** (58 mg, 0.136 mmol) gave the diol **59** (45 mg, 72%) as a colourless oil (Found: M^+ + H, 442.2631. $C_{23}H_{40}NO_5S$ requires *M*, 442.2627); ν_{max}/cm^{-1} 3440, 1598, 1462, 1335, 1154, 1089, 1040, 919, 816 and 732; δ_H ($CDCl_3$, 300 MHz) 0.83 (6 H, m, 2- or 4-CH_3 and 13-H_3),

0.85–1.25 (4 H, m), 1.10 (3 H, d, *J* 7.0, 4- or 2-CH_3), 1.30–1.94 (6 H, m), 2.13 (2 H, m), 2.4 (3 H, s, $ArCH_3$), 2.69 (3 H, s, NCH_3), 3.34–3.60 and 3.75–3.90 (each 3 H, m) and 7.32 and 7.71 (each 2 H, d, *J* 8.2, ArH); δ_C ($CDCl_3$, 75 MHz) 13.5, 13.7, 15.4, 19.6, 21.4, 27.6, 29.8, 30.9, 34.1, 35.2, 37.9, 42.4, 54.6, 64.5, 77.5, 82.0, 85.3, 127.0, 129.4, 137.1 and 143.0; *m*/*z* (EI) 442 (M^+ + 1, 20%), 240 (50) and 86 (100).

Reduction of the ester **47** (208 mg, 0.31 mmol) using DIBAL-H (1 M in hexanes, 0.775 mL, 0.775 mmol) following the procedure outlined for the reduction of ester **49**, gave the corresponding primary alcohol (65 mg, 38%); δ_H ($CDCl_3$, 300 MHz) 0.03 and 0.06 (each 3 H, s, $SiCH_3$), 0.73 (3 H, t *J* 6.8, 13-H_3), 0.82 [9 H, s, $C(CH_3)_3$], 0.86 and 0.90 (each 3 H, d, *J* 7.2, 2-CH_3 or 4-CH_3), 1.00–2.05 (12 H, m), 2.34 (3 H, s, $ArCH_3$), 2.58 (3 H, s, NCH_3), 2.94 (1 H, t, *J* 5.8, 3-H), 3.38–3.72 (4 H, m), 3.85–4.00 (2 H, m) and 7.19 and 7.61 (each 2 H, br. d, *J* 8.2, ArH). Desilylation of this monosilyl ether using TBAF following the procedure outlined for the synthesis of diol **53**, gave the diol **59** (35 mg, 70%) with NMR spectra identical to those of the sample of diol **59** prepared from the epoxide **58**.

Following the procedure outlined for the synthesis of the carbonate **54**, the diol **59** (20 mg, 0.045 mmol) was converted into the *title compound* **60** (14 mg, 67%) as a colourless liquid (Found: M^+ + H, 468.2428. $C_{24}H_{38}NO_6S$ requires *M*, 468.2420); ν_{max}/cm^{-1} 1754, 1463, 1404, 1335, 1212, 1152, 1122, 1087, 930, 817 and 759; δ_H ($CDCl_3$, 500 MHz) 0.93 (3 H, t, *J* 7, 13-H_3), 1.05 and 1.06 (each 3 H, d, *J* 7, 2-CH_3 or 4-CH_3), 1.13–1.27 (3 H, m), 1.33–1.44 (2 H, m), 1.45–1.53 (3 H, m), 1.90–2.04 (3 H, m), 2.42 (3 H, s, $ArCH_3$), 2.64 (3 H, s, NCH_3), 2.70 (1 H, m, 2-H), 3.73–3.82 (2 H, m), 3.94 (1 H, t, *J* 10.5, 1-H), 4.07 (1 H, m), 4.19 (1 H, dd, *J* 10 and 1.8, 3-H), 4.26 (1 H, dd, *J* 10.5 and 4.3, 1-H′) and 7.3 and 7.7 (each 2 H, d, *J* 8.2, ArH); δ_C ($CDCl_3$, 125 MHz) 12.4, 13.7, 14.0, 19.6, 21.4, 27.7, 29.1, 30.2, 30.6, 33.4, 38.9, 40.5, 54.5, 72.3, 76.1, 78.9, 88.4, 127.2, 129.4, 137.6, 142.9 and 149.9; *m*/*z* (CI) 485 (M^+ + 18, 15%), 468 (M^+ + 1, 20) and 314 (100).

(2*S*,3*S*,4*R*,5*R*,8*S*,10*R*)-3-*tert*-Butyldimethylsilyloxy-2,4-dimethyl-5,8-epoxy-10-[*N*-methyl-*N*-(toluene-4-sulfonyl)amino]tridecanal (**62**). Following the procedure outlined for the synthesis of aldehyde **32**, the alcohol **52** (3 g, 5.41 mmol) gave the aldehyde **62** (2.84 g, 95%) as a light brown coloured liquid that was used immediately without chromatography, $[\alpha]_D^{23}$ −7.2 (*c* 0.89 in $CHCl_3$) (Found: M^+ + H, 554.3337. $C_{29}H_{52}NO_5SSi$ *M*, 554.3335); ν_{max}/cm^{-1} 1727, 1463, 1341, 1254, 1153, 1090, 1041, 927, 838 and 776; δ_H ($CDCl_3$, 500 MHz) 0.07 (6 H, s, 2 × $SiCH_3$), 0.88 [15 H, m, $SiC(CH_3)_3$, 4-CH_3 and 13-H_3], 1.08 (3 H, d, *J* 7, 2-CH_3), 1.16–1.46 (7 H, m), 1.50–1.65 and 1.90–2.05 (each 2 H, m), 2.42 (3 H, s, $ArCH_3$), 2.55 (1 H, m, 2-H), 2.66 (3 H, s, NCH_3), 3.48 (1 H, m, 5-H), 3.71 (1 H, m, 8-H), 4.07 (1 H, m, 10-H), 4.4 (1 H, dd, *J* 6.2 and 2.3, 3-H), 7.28 and 7.70 (each 2 H, d, *J* 8.1, ArH) and 9.76 (1 H, d, *J* 3, 1-H); δ_C ($CDCl_3$, 125 MHz) −4.5, −4.2, 10.0, 11.5, 13.9, 18.4, 19.6, 21.5, 26.0, 27.6, 30.2, 30.9, 33.7, 38.5, 42.8, 51.5, 54.5, 72.8, 75.5, 79.5, 127.2, 129.4, 137.4, 142.8 and 205.4; *m*/*z* (CI) 571 (M^+ + 18, 2%), 554 (M^+ + 1, 2%) and 86 (100).

(2*R*,6*S*,7*R*,8*R*,9*R*,10*R*,13*S*,15*R*,3*Z*)-1-Benzyloxy-8-*tert*-butyldimethylsilyloxy-10,13-epoxy-15-[*N*-methyl-*N*-(toluene-4-sulfonyl)-amino]-2,7,9-trimethyloctadec-3-en-6-ol (**63**). Tin(IV) chloride (1 M in DCM, 7.4 mL, 7.4 mmol) was added to the alkenylstannane **3** (3.55 g, 7.4 mmol) in DCM (35 mL) at −78 °C. After 5 min, a cooled (0 °C) solution of the aldehyde **62** (2.75 g, 4.93 mmol) in DCM (35 mL) was added and the solution was stirred for 50 min at −78 °C. MeOH (2 mL) and aqueous sodium bicarbonate (25 mL) were added and the mixture was allowed to warm to room temperature and stirred for 1 h. Water (50 mL) was added and the organic layer was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (gradient elution 10 : 1 to 2 : 1) gave the *title compound* **63** (3.04, 83%), $[\alpha]_D^{21}$ −22.9 (*c* 1.15 in $CHCl_3$) (Found: M^+ + NH_4, 761.4980. $C_{42}H_{73}N_2O_6SSi$ requires *M*, 761.4958); ν_{max}/cm^{-1} 3477, 1457, 1340, 1253, 1153, 1093, 1042, 1005, 834 and 774; δ_H ($CDCl_3$, 500 MHz) 0.06 and 0.13 (each 3 H, s, $SiCH_3$), 0.84 (3 H, t, *J* 7.2, 18-H_3), 0.86 (3 H, d, *J* 6.8, 9-CH_3), 0.91 [9 H, s, $SiC(CH_3)_3$], 0.93 (3 H, d, *J* 7, 7-CH_3), 0.95 (3 H, d, *J* 7, 2-CH_3), 1.10–1.28 (3 H, m), 1.30–1.44 (4 H, m), 1.50–1.60 (2 H, m), 1.68, 1.90 and 2.0 (each 1 H, m), 2.14 and 2.37 (each 1 H, m, 5-H), 2.38 (3 H, s, $ArCH_3$), 2.65 (3 H, s, NCH_3), 2.86 (1 H, m, 2-H), 3.09 (1 H, br. s, OH), 3.26 (2 H, m, 1-H_2), 3.51 (1 H, m, 10-H), 3.7 (1 H, m, 13-H), 3.96–4.08 (2 H, m, 6-H and 15-H), 4.15 (1 H, dd, *J* 5.9 and 1.9, 8-H), 4.5 (2 H, s, $PhCH_2$), 5.27 (1 H, t, *J* 10.8, 3-H), 5.46 (1 H, dt, *J* 10.8 and 7.5, 4-H), 7.27 and 7.70 (each 2 H, d, *J* 8.2, ArH) and 7.32 (5 H, m, ArH); δ_C ($CDCl_3$, 125 MHz) −4.3, −4.2, 10.0, 10.6, 13.7, 17.5, 18.4, 19.5, 21.4, 26.2, 27.6, 29.9, 31.0, 32.3, 33.7, 33.9, 38.3, 42.3, 42.4, 54.6, 70.2, 72.8, 74.8, 75.0, 75.5, 80.7, 126.8, 127.1, 127.3, 127.5, 128.2, 129.3, 134.7, 137.2, 138.5 and 142.6; *m*/*z* (CI), 762 (M^+ + 19, 2%) and 86 (100).

(2*S*,3*S*,4*S*,6*S*,7*R*,8*S*,9*R*,10*R*,13*S*,15*R*)-1-Benzyloxy-8-*tert*-butyldimethylsilyloxy-3,6;10,13-bis-epoxy-15-[*N*-methyl-*N*-(toluene-4-sulfonyl)amino]-4-phenylseleno-2,7,9-trimethyloctadecane (**64**). $ZnCl_2$ (*ca*. 500 mg) was added to the alkenol **63** (703 mg, 0.946 mmol) in DCM (16 mL). *N*-Phenylselenyl phthalimide (430 mg, 1.42 mmol) in DCM (5 mL) was added over a period of 10 min and the mixture stirred for 2 h. Aqueous sodium bicarbonate was added and the aqueous layer was extracted with DCM. The organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 6 : 1 light petroleum : ether gave the *title compound* **64** (460 mg, 54%) as a colourless liquid, $[\alpha]_D^{21}$ +12.6 (*c* 1.27 in $CHCl_3$) (Found: M^+ + NH_4, 917.4434. $C_{48}H_{77}N_2O_6SSi^{80}Se$ requires *M*, 917.4436); ν_{max}/cm^{-1} 1598, 1578, 1495, 1472, 1456, 1382, 1341, 1250, 1207, 1153, 1091, 1042, 933, 920, 877, 830, 814, 774, 734, 718, 693 and 657; δ_H ($CDCl_3$, 500 MHz) 0.03 and 0.06 (each 3 H, s, $SiCH_3$), 0.79 (3 H, d, *J* 7, 9-CH_3), 0.88 [12 H, m, $SiC(CH_3)_3$ and 18-H_3), 1.01 and 1.03 (each 3 H, d, *J* 7, 2-CH_3 or 7-CH_3), 1.14–1.44 (8 H, m), 1.50–1.73 and 1.86–1.98 (each 2 H, m), 2.05 (1 H, ddd, *J* 13.7, 7.5 and 1.9, 5-H), 2.14 (1 H, m, 2-H), 2.42 (3 H, s, $ArCH_3$), 2.61 (1 H, m, 5-H′), 2.65 (3 H, s, NCH_3), 3.48 (2 H, m, 10-H and 1-H), 3.54 (1 H, dd, *J* 9.4 and 4.4, 3-H), 3.66

(2 H, m), 3.86 (1 H, m, 4-H), 3.98 (1 H, m, 6-H), 4.1 (2 H, m), 4.48 (2 H, s, $PhCH_2$), 7.22–7.36 (10 H, m, ArH), 7.54 (2 H, m, ArH) and 7.73 (2 H, d, *J* 8.2, ArH); δ_C ($CDCl_3$, 125 MHz) −4.6 (2), 9.8, 10.8, 13.9, 14.6, 18.5, 19.6, 21.5, 26.3, 27.7, 30.1, 31.0, 33.7, 37.0, 38.3, 39.6, 41.7, 42.4, 46.5, 54.6, 72.5, 72.8, 73.0, 75.3, 78.0, 80.3, 83.6, 126.8, 127.1, 127.2, 127.5, 128.1, 129.0, 129.4, 130.7, 133.5, 137.4, 139.1 and 142.7; *m*/*z* (CI) 917 (M^+ + 18, 1%) and 106 (100).

(2*S*,3*R*,6*S*,7*R*,8*S*,9*R*,10*R*,13*S*,15*R*)-1-Benzyloxy-8-*tert*-butyldimethylsilyloxy-3,6;10,13-bis-epoxy-15-[*N*-methyl-*N*-(toluene-4-sulfonyl)amino]-2,7,9-trimethyloctadecane (**65**). Following the procedure outlined for the deselenation of selenide **34**, the selenide **64** (750 mg, 0.834 mmol) gave the *title compound* **65** (527 mg, 85%) as a colourless liquid, $[\alpha]_D^{19}$ −9.13 (*c* 4.6 in $CHCl_3$) (Found: $M^+ + NH_4$, 761.4955. $C_{42}H_{73}N_2O_6SSi$ requires *M*, 761.4958); ν_{max}/cm^{-1} 1599, 1495, 1462, 1384, 1343, 1251, 1154, 1092, 1042, 963, 921, 878, 832, 815, 774, 734, 718, 698 and 657; δ_H ($CDCl_3$, 500 MHz) 0.05 and 0.09 (each 3 H, s, $SiCH_3$), 0.81 (3 H, d, *J* 6.7, 7-CH_3 or 9-CH_3), 0.87 (3 H, t, *J* 7.1, 18-H_3), 0.91 [9 H, s, $SiC(CH_3)_3$], 0.92 (3 H, d, *J* 6.7, 9-CH_3 or 7-CH_3), 0.94 (3 H, d, *J* 6.7, 2-CH_3), 1.15–1.68 (12 H, m), 1.82–1.98 (5 H, m), 2.41 (3 H, s, $ArCH_3$), 2.65 (3 H, s, NCH_3), 3.36 (1 H, dd, *J* 8.7 and 7.5, 1-H), 3.46 (1 H, dt, *J* 6.2, 8.7, 10-H), 3.56–3.68 (3 H, m, 1-H′, 3-H and 13-H or 15-H), 3.9 (1 H, m, 6-H), 4.09 (1 H, m, 15-H or 13-H), 4.13 (1 H, dd, *J* 7.5 and 1.2, 8-H), 4.46 (2 H, s, $PhCH_2$), 7.27 (3 H, m, ArH), 7.73 (4 H, m, ArH) and 7.72 (2 H, d, *J* 8.2, ArH); δ_C ($CDCl_3$, 125 MHz) −4.6, −4.5, 10.1, 10.5, 13.9, 18.6, 19.7, 21.5, 25.2, 26.3, 27.7, 29.1, 29.3, 30.2, 31.1, 33.7, 38.3, 38.9, 41.6, 42.9, 54.7, 72.6, 72.9, 73.4, 75.2, 78.5, 80.4, 80.5, 127.2, 127.3, 127.5, 128.2, 129.4, 137.4, 139.1 and 142.7; *m*/*z* (CI) 761 (M^+ + 18, 1%), 240 (10) and 86 (100).

(2*S*,3*R*,6*S*,7*R*,8*S*,9*R*,10*R*,13*S*,15*R*)-1-Benzyloxy-8-*tert*-butyldimethylsilyloxy-3,6;10,13-bis-epoxy-15-(*N*-methylamino)-2,7,9-trimethyloctadecane (**66**). Following the procedure outlined for the preparation of the secondary amine **38**, the sulfonamide **65** (0.15 g, 0.20 mmol) was deprotected to give, after chromatography using light petroleum : ether containing 1% v/v Et_3N (gradient elution 3 : 1 to 1 : 1), the *title compound* **66** (0.10 g, 83%), R_f = 0.03 (2 : 1 light petroleum : ether); $[\alpha]_D^{26}$ −4.0 (*c* 0.5 in $CHCl_3$) (Found: M^+ + H, 590.4598. $C_{35}H_{64}NO_4Si$ requires *M*, 590.4604); ν_{max}/cm^{-1} 3358, 1461, 1383, 1360, 1251, 1096, 1046, 835, 774 and 734; δ_H (300 MHz, $CDCl_3$) 0.09 (6 H, s, 2 × $SiCH_3$), 0.81 and 0.89 (each 3 H, d, *J* 6.9, 7-CH_3 or 9-CH_3), 0.90–0.95 [12 H, m, $SiC(CH_3)_3$, 18-H_3), 0.98 (3 H, d, *J* 6.7, 2-CH_3), 1.12–1.69 (12 H, m), 1.80–2.07 (5 H, m), 2.41 (3 H, s, NCH_3), 2.55 (1 H, br. t, *J* 4.5, 15-H), 3.39 (1 H, dd, *J* 8.9, 7.3, 1-H), 3.48–3.62 (2 H, m), 3.66 (1 H, dd, *J* 8.9, 4.4, 1-H′), 3.77–3.95 (2 H, m), 4.08 (1 H, d, *J* 7.9, 8-H), 4.52 (2 H, s, $ArCH_2$) and 7.26–7.40 (5 H, m, ArH); δ_C (75 MHz, $CDCl_3$) −4.4, −4.3, 10.1, 10.9, 14.1, 14.7, 18.8, 19.3, 26.5, 29.3, 29.4, 30.2, 32.2, 34.2, 36.3, 39.0, 40.5, 41.9, 42.8, 59.5, 72.9, 73.3, 73.6, 78.5, 78.6, 80.5, 81.1, 127.6, 127.7, 128.5 and 139.2; *m*/*z* (CI) 590 (M^+ + 1, 53%), 342 (22), 228 (41), 219 (50), 108 (82) and 86 (100).

(2*S*,3*R*,6*S*,7*R*,8*S*,9*R*,10*R*,13*S*,15*R*)-1-Benzyloxy-8-*tert*-butyldimethylsilyloxy-3,6;10,13-bis-epoxy-15-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino)-2,7,9-trimethyloctadecane (**67**). Following the procedure outlined for the synthesis of the Boc-protected amine **39**, the amine **66** (41 mg, 0.069 mmol), after chromatography using 15 : 1 light petroleum : ether, gave the *title compound* **67** (45 mg, 95%) as a pale yellow oil, a 60 : 40 mixture of rotamers, R_f = 0.14 (5 : 1 light petroleum : ether); $[\alpha]_D^{27}$ −5.1 (*c* 1.1 in $CHCl_3$) (Found: M^+, 689.5043. $C_{40}H_{71}NO_6Si$ requires *M*, 689.5050); ν_{max}/cm^{-1} 1692, 1461, 1389, 1365, 1251, 1149, 1097, 1065, 1044, 835 and 772; δ_H (500 MHz, $CDCl_3$) 0.04 and 0.05 (each 3 H, s, $SiCH_3$), 0.78 (3 H, d, *J* 6.5, 7-CH_3 or 9-CH_3), 0.82–0.93 [15 H, m, $SiC(CH_3)_3$, 18-H_3, 9-CH_3 or 7-CH_3], 0.96 (3 H, d, *J* 7.0, 2-CH_3), 1.19–1.64 (12 H, m), 1.45 [9 H, s, $C(CH_3)_3$], 1.79–2.09 (5 H, m), 2.64 (1.2 H, s, NCH_3), 2.68 (1.8 H, s, NCH_3), 3.37 (1 H, t, *J* 7.5, 1-H), 3.48 (1 H, m), 3.55–3.68 (3 H, m), 3.83 (1 H, m), 3.97–4.09 (1.4 H, m, 8-H, 15-H), 4.17 (0.6 H, br. s, 15-H), 4.51 (2 H, s, $ArCH_2$) and 7.22–7.40 (5 H, m, ArH); δ_C (125 MHz; $CDCl_3$) −4.4, −4.2, 10.4, 10.8, 14.0, 18.7, 19.5, 19.7, 26.5, 28.8, 29.2, 29.5, 30.3, 30.6, 31.1, 31.4, 35.2, 35.3, 38.8, 39.1, 39.2, 41.6, 41.7, 43.3, 43.4, 52.0, 52.6, 72.7, 73.3, 73.7, 76.0, 76.4, 79.0, 79.1, 79.5, 80.5, 80.6, 127.6, 127.7, 128.5, 139 and 156.4; *m*/*z* (EI) 689 (M^+, 2%), 617 (22), 253 (74) and 213 (100).

(2*S*,3*R*,6*S*,7*R*,8*S*,9*R*,10*R*,13*S*,15*R*)-8-*tert*-Butyldimethylsilyloxy-3,6;10,13-bis-epoxy-15-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino)-2,7,9-trimethyloctadecan-1-ol (**68**). Following the procedure outlined for the synthesis of alcohol **40**, the benzyl ether **67** (37 mg, 0.054 mmol) was hydrogenolysed to give, after chromatography using 5 : 1 light petroleum : ether, the *title compound* **68** (26 mg, 82%), as a colourless oil, a 60 : 40 mixture of rotamers, R_f = 0.29 (2 : 1 light petroleum : ether), $[\alpha]_D^{28}$ +6.8 (*c* 1.0 in $CHCl_3$) (Found: M^+ + H, 600.4663. $C_{33}H_{66}NO_6Si$ requires *M*, 600.4659); ν_{max}/cm^{-1} 3499, 1693, 1462, 1391, 1365, 1251, 1152, 1042, 869, 836 and 723; δ_H (500 MHz, $CDCl_3$) 0.03 and 0.05 (each 3 H, s, $SiCH_3$), 0.76 (3 H, m, 18-H_3), 0.81 and 0.86 (each 3 H, d, *J* 7.1, 7-CH_3 or 9-H_3), 0.87–0.95 [12 H, m, $SiC(CH_3)_3$, 2-CH_3], 1.10–2.10 (17 H, m), 1.44 [9 H, s, $C(CH_3)_3$], 2.62 (1.2 H, s, NCH_3), 2.67 (1.8 H, s, NCH_3), 3.45 (1 H, m), 3.49–3.64 (5 H, m), 3.94 (1 H, m), 3.98–4.06 (1.4 H, m, 8-H and 15-H) and 4.10–4.21 (0.6 H, m, 15-H); δ_C (125 MHz, $CDCl_3$) −4.4, 10.1, 10.7, 10.8, 14.0(2), 14.2, 18.7, 19.4, 19.6, 26.5, 28.8, 30.4, 31.1, 35.2, 35.4, 38.7, 39.0, 40.1, 41.7, 41.8, 42.8, 51.9, 52.6, 69.0, 72.6, 76.2, 76.4, 79.0, 79.4, 79.9, 80.3, 85.8 and 156.4; *m*/*z* (CI) 600 (M^+ + 1, 10%), 500 (72), and 86 (100).

(2*R*,3*R*,6*S*,7*R*,8*S*,9*R*,10*R*,13*S*,15*R*)-8-*tert*-Butyldimethylsilyloxy-3,6;10,13-bis-epoxy-15-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino)-2,7,9-trimethyloctadecanoic acid (**70**). Following the procedure outlined for the oxidation of alcohol **40**, the alcohol **68** (35 mg, 0.058 mmol) was oxidised to give the aldehyde **69** (35 mg, *ca.* 100%) as an oil, a 50 : 50 mixture of rotamers; ν_{max}/cm^{-1} 1729, 1693, 1462, 1390, 1366, 1257, 1150, 1043, 870, 836 and 773; δ_H (300 MHz, $CDCl_3$) 0.05 and 0.06 (each 3 H, s, $SiCH_3$), 0.77 and 0.87 (3 H, d, *J* 6.6, 7-CH_3 or 9-CH_3), 0.89–0.96 [12 H, m, $SiC(CH_3)_3$ and 18-H_3], 1.08 (3 H, d, *J* 7.0, 2-CH_3), 1.18–1.73 (20 H, m), 1.78–2.11 (5 H, m), 2.46 (1 H, m, 2-H), 2.66 and 2.70 (each 1.5 H, s, NCH_3), 3.47 and 3.62 (each 1 H, m), 3.81–4.00 (2 H, m), 4.01–4.11 (1.5 H, m), 4.19 (0.5 H, m, 15-H) and 9.81 (1 H, s, 1-H); *m*/*z* (CI) 598 (M^+ + 1, 2%), 497 (16) and 86 (100).

Following the procedure outlined for the oxidation of the aldehyde **41**, the aldehyde **69** (35 mg, 0.058 mmol), after chromatography 4 : 1 hexane : ether, gave the *title compound* **70** (32 mg, 90%) as a colourless oil, a 50 : 50 mixture of rotamers, R_f = 0.36 (2 : 1 light petroleum : ether); $[\alpha]_D^{25}$ +2.2 (*c* 1.0, $CHCl_3$) (Found: M^+ + H, 614.4450. $C_{33}H_{64}NO_7Si$ requires *M*, 614.4452); ν_{max}/cm^{-1} 3414, 1736, 1692, 1462, 1365, 1251, 1154, 1039, 834 and 772; δ_H (500 MHz, $CDCl_3$) 0.04 and 0.07 (each 3 H, s, $SiCH_3$), 0.76 (3 H, t, *J* 7.0, 18-H_3), 0.82–0.96 [15 H, m, 2 × CH_3, $SiC(CH_3)_3$,], 1.13–1.36 (8 H, m), 1.37–1.75 (15 H, m), 1.81–2.06 (5 H, m), 2.50 (1 H, m, 2-H), 2.63 and 2.68 (each 1.5 H, s, NCH_3), 3.49, 3.64 and 3.84 (each 1 H, m), 3.94–4.14 (2.5 H, m) and 4.31 (0.5 H, m, 15-H); δ_C (125 MHz, $CDCl_3$) −4.6, −4.5, 9.5, 9.8, 10.1, 10.3, 13.3, 13.6, 13.8, 14.0, 18.5, 18.6, 19.2, 26.2, 26.3, 27.6, 28.5, 28.7, 29.6, 29.7, 30.0, 30.1, 31.2, 31.3, 33.9, 35.3, 39.1, 39.2, 41.5, 41.9, 42.1, 44.6, 44.9, 51.7, 53.1, 72.6, 75.7, 76.3, 79.2, 79.3, 79.8, 79.9, 80.1, 80.2, 80.4, 156.0, 156.2, 176.4 and 176.6; *m*/*z* (CI) 614 (M^+ + 1, 2%) and 86 (100).

Methyl (2*R*,3*R*,6*S*,7*R*,8*S*,9*R*,10*R*,13*S*,15*R*)-8-*tert*-butyldimethylsiloxy-3,6;10,13-bis-epoxy-15-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino)-2,7,9-trimethyloctadecanoate (**71**). Following the procedure outlined for the synthesis of the methyl ester **43**, a sample of the acid **70** prepared from the aldehyde **69** (28 mg, 0.0047 mmol) was converted into the *title compound* **71** (22 mg, 73%), a colourless oil, a 60 : 40 mixture of rotamers (Found: M^+ + H, 628.4606. $C_{34}H_{66}NO_7Si$ requires *M*, 628.4608); δ_H ($CDCl_3$, 300 MHz) 0.00 and 0.025 (each 3 H, s, $SiCH_3$), 0.74 (3 H, d, *J* 6.7, CH_3), 0.86 [15 H, m, $SiC(CH_3)_3$ and 2 × CH_3), 1.08 (3 H, d, *J* 7.1, 2-CH_3), 1.16–1.64 (20 H, m), 1.88 (5 H, m), 2.52 (1 H, m, 2-H), 2.61 (1.2 H, s, NCH_3), 2.65 (1.8 H, s, NCH_3), 3.44 and 3.58 (each 1 H, m), 3.65 (3 H, s, OCH_3), 3.82 and 3.91 (each 1 H, m), 4.0 (1.6 H, m, 8-H and 15-H) and 4.14 (0.4 H, m, 15-H); δ_C (125 MHz, $CDCl_3$) −4.8, −4.5, 10.1, 10.5, 10.6, 13.2, 13.8, 13.9, 18.5, 19.2, 19.4, 26.2, 28.5, 28.7, 29.2, 30.0, 30.8, 31.1, 35.0, 38.5, 38.9, 41.3, 41.4, 43.0, 43.2, 45.0, 51.5, 52.4, 72.3, 75.8, 76.1, 79.2, 79.4, 79.9, 80.3, 80.4, 156.1 and 175.4; *m*/*z* (EI) 628 (M^+ + 1, 2%) and 514 (100).

Methyl (2*R*,3*R*,6*S*,7*R*,8*S*,9*R*,10*R*,13*S*,15*R*)-15-dimethylamino-3,6;10,13-bis-epoxy-8-hydroxy-2,7,9-trimethyloctadecanoate (**73**).[5*l*] Concentrated aqueous hydrogen chloride (3 drops) was added to the carbamate **71** (30 mg, 0.048 mmol) in ethanol (1 mL) and the mixture was stirred for 16 h at room temperature. Saturated aqueous sodium bicarbonate and ethyl acetate were added and the aqueous layer was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether with 1% Et_3N (gradient elution 2 : 1 to 1 : 1) gave the secondary amine **72** (10 mg, 50%); δ_H ($CDCl_3$, 300 MHz) 0.69 and 0.79 (each 3 H, d, *J* 7, 7-CH_3 or 9-CH_3), 0.84 (3 H, t, *J* 6.7, 18-H_3), 1.05 (3 H, d, *J* 7, 2-CH_3), 1.22 (3 H, m), 1.48 (6 H, m), 1.64–1.98 (7 H, m), 2.29 (3 H, s, NCH_3), 2.47 (2 H, m, 2-H and 15-H), 3.61 (3 H, s, OCH_3), 3.76 (1 H, m), 3.85 (3 H, m) and 4.04 (1 H, m); δ_C ($CDCl_3$, 75 MHz) 9.3, 12.2, 13.5, 14.3, 18.8, 25.9, 28.6, 29.2, 32.0, 33.4, 35.9, 37.5, 40.2, 40.4, 44.6, 51.6, 58.5, 71.7, 78.1, 80.4, 81.7, 82.5 and 175.2.

Formalin (18 μL) and $NaCNBH_3$ (8 mg) were added to this amine (10 mg, 0.024 mmol) in acetonitrile (0.3 mL), and the reaction was stirred for 1 h at room temperature. Acetic acid (5 μL) was added and the mixture stirred overnight at room temperature. After concentration under reduced pressure, chromatography of the residue using 1 : 1 light petroleum : ether with 1% Et_3N gave the title compound **73** (5 mg, 48%) as an oil, $[\alpha]_D^{22}$ −25.7 (*c* 0.28 in CH_2Cl_2), lit.[5*l*] $[\alpha]_D^{30}$ −33.4 (*c* 0.99 in CH_2Cl_2) (Found: M^+, 427.3292. $C_{24}H_{45}NO_5$ requires *M*, 427.3298); ν_{max}/cm^{-1} 3480, 1736, 1462, 1380, 1268, 1215, 1166, 1358, 963, 885, 856, 837, 757 and 666; δ_H (acetone-d_6 with CF_3COOD, 400 MHz) 0.79 and 0.88 (each 3 H, d, *J* 7, 7-CH_3 or 9-CH_3), 0.98 (3 H, t, *J* 7.2, 18-H_3), 1.1 (3 H, d, *J* 7, 2-CH_3), 1.43 (2 H, m), 1.5–1.8 (8 H, m), 1.7–2.2 (6 H, m), 2.53 (1 H, m, 2-H), 2.94 and 3.11 (each 3 H, s, NCH_3), 3.61 (1 H, m, 15-H), 3.63 (3 H, s, OCH_3), 3.75 (1 H, dd, *J* 9.5 and 1.8, 8-H), 3.86–3.94 (2 H, m, 3-H and 10-H), 4.14 (1 H, m, 13-H) and 4.25 (1 H, m, 6-H); *m*/*z* (CI) 428 (M^+, 100%).

Methyl (*S*)-2-*tert*-butyldiphenylsilyloxypentanoate (**75**). *tert*-Butyldiphenylsilyl chloride (19.6 g, 71.3 mmol) and imidazole (14.2 g, 20.7 mmol) were added to the hydroxy ester **74** (7.8 g, 59.4 mmol) in DCM (30 mL) and the mixture stirred at room temperature for 16 h. Water (10 mL) was added and the aqueous phase was extracted with ether (2 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (15 : 1) gave the *title compound* **75** (20.3 g, 92%) as an oil, $[\alpha]_D^{22}$ −27 (*c* 0.9 in $CHCl_3$) (Found: M^+ + NH_4, 388.2307. $C_{22}H_{34}NO_3Si$ requires *M*, 388.2308); ν_{max}/cm^{-1} 1753, 1736, 1110, 1047 and 737; δ_H ($CDCl_3$, 300 MHz) 0.88 (3 H, t, *J* 7, 5-H_3), 1.13 [9 H, s, $SiC(CH_3)_3$], 1.30–1.52 (2 H, m, 4-H_2), 1.65–1.82 (2 H, m, 3-H_2), 3.50 (3 H, s OCH_3), 4.27 (1 H, t, *J* 6, 2-H), 7.37–7.50 (6 H, m, ArH) and 7.66–7.73 (4 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 13.8, 17.8, 19.3, 26.8, 37.2, 51.2, 72.5, 127.4, 127.5, 129.6(2) 133.2, 133.4, 135.7, 135.9 and 173.7; *m*/*z* (CI) 388 (M^+ + 18, 100%) and 293 (99).

(*S*)-2-*tert*-Butyldiphenylsilyloxypentan-1-ol (**76**). Following the procedure outlined for the synthesis of the alcohol **56**, the ester **75** (8.7 g, 23.5 mmol) and DIBAL-H (47 mL, 1 M in hexanes, 47 mmol), after chromatography using light petroleum : ether (4 : 1), gave the *title compound* **76** (7.6 g, 94%) as an oil, $[\alpha]_D^{22}$ +16.0 (*c* 0.3 in $CHCl_3$) (Found: M^+ + NH_4, 360.2357. $C_{21}H_{34}NO_2Si$ requires *M*, 360.2359); ν_{max}/cm^{-1} 3453, 1472, 1463, 1111, 1044, 1005, 822, 740 and 701; δ_H ($CDCl_3$, 300 MHz) 0.76 (3 H, t, *J* 7, 5-H_3), 1.10 [9 H, s, $SiC(CH_3)_3$], 1.14–1.32 (2 H, m, 4-H_2), 1.38–1.58 (2 H, m, 3-H_2), 1.84 (1 H, br. m, OH), 3.54 (2 H, m, 1-H_2), 3.86 (1 H, m, 2-H), 7.36–7.52 (6 H, m, ArH) and 7.69–7.78 (4 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 14.0, 18.3, 19.3, 27.0, 35.7, 65.9, 73.8, 127.5, 127.7, 129.7(2), 133.8, 134.0, 135.6 and 135.8; *m*/*z* (CI) 360 (M^+ + 18, 70%), 282 (70) and 265 (100).

(*S*)-2-*tert*-Butyldiphenylsilyloxy-1-iodopentane (**77**). Imidazole (1.0 g, 14.6 mmol), triphenylphosphine (1.9 g, 7.3 mmol) and iodine (1.9 g, 7.6 mmol) were added to the alcohol **76** (1.0 g, 2.9 mmol) in THF (5 mL) and the solution stirred at room temperature for 2 h. Saturated aqueous sodium thiosulfate was

added until the colour of the iodine had disappeared. Ether (10 mL) was added and the aqueous phase extracted with ether (10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Hexane (15 mL) was added and the suspension filtered. Concentration gave the *title compound* **77** (1.3 g, 97%) as a yellow oil, $[\alpha]_D^{22}$ −23.3 (*c* 3.3 in $CHCl_3$) (Found: $M^+ + NH_4$, 470.1369. $C_{21}H_{33}NOSi$ requires *M*, 470.1378); ν_{max}/cm^{-1} 3071, 3047, 1472, 1427, 1112, 1044, 822, 740 and 701; δ_H ($CDCl_3$, 300 MHz) 0.83 (3 H, t, *J* 7, 5-H_3), 1.12 [9 H, s, $SiC(CH_3)_3$], 1.26 (2 H, m, 4-H_2), 1.60 (2 H, m, 3-H_2), 3.18 (2 H, d, *J* 4, 1-H_2), 3.49 (1 H, m, 2-H), 7.39–7.52 (6 H, m, ArH) and 7.68–7.78 (4 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 13.8, 14.5, 17.8, 19.3, 26.9, 38.9, 71.1, 127.5(2), 129.6, 129.7, 133.7 and 135.8(2); *m*/*z* (CI) 470 (M^+ + 18, 21%) and 196 (100).

2-[(*S*)-2-*tert*-Butyldiphenylsilyloxypent-1-yl]-1,3-dithiane (**78**). *n*-Butyllithium (18.4 mL, 1.6 M in hexanes, 29.3 mmol) was added to 1,3-dithiane (4.4 g, 36.7 mmol) in THF (50 mL) at −20 °C. The solution was stirred at −20 °C for 1.5 h, then allowed to warm to 0 °C and added to the iodide **77** (6.6 g, 14.7 mmol) in THF (40 mL) at 0 °C. The mixture was stirred at 0 °C for 16 h before water (20 mL) and ether (40 mL) were added. The aqueous layer was extracted with ether (2 × 20 mL) and the organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (50 : 1) gave the *title compound* **78** (5.7 g, 88%) as an oil, $[\alpha]_D^{22}$ −2.3 (*c* 1.7 in $CHCl_3$); ν_{max}/cm^{-1} 1719, 1686, 1474, 1369 and 1109; δ_H ($CDCl_3$, 400 MHz) 0.69 (3 H, t, *J* 7, 5′-H_3), 1.07 [9 H, s, $SiC(CH_3)_3$], 1.12–1.30 (2 H, m, 4′-H_2), 1.40 (2 H, m, 3′-H_2), 1.73–1.85 (2 H, m, 1′-H and 5-H), 1.93 (1 H, ddd, *J* 14, 8, 5, 1′-H′), 2.03 (1 H, m, 5-H′), 2.55–2.74 (4 H, m, 2 × SCH_2), 4.05 (2 H, m, 1-H and 2′-H), 7.36–7.46 (6 H, m, ArH) and 7.69–7.74 (4 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 14.0, 17.9, 19.6, 26.0, 27.2, 30.0, 30.5, 39.3, 42.4, 44.2, 69.9, 127.4, 129.4, 134.3 and 135.9; *m*/*z* (CI) 387 (M^+ − 57, 15%) and 367 (100).

(*S*)-3-*tert*-Butyldiphenylsilyloxyhexanal (**79**). Red mercury(II) oxide (3.0 g, 11.7 mmol) was added to the dithiane **78** (2.7 g, 60.1 mmol) in THF (36 mL) containing water (4 mL). Boron trifluoride diethyl etherate (3.7 mL, 30.6 mmol) was added and the mixture stirred for 45 min. After partial concentration under reduced pressure, ether (100 mL) was added and the mixture filtered. The filtrate was washed with saturated aqueous sodium hydrogen carbonate (3 × 30 mL) and then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using light petroleum : ether (15 : 1) gave the *title compound* **79** (1.9 g, 98%) as a colourless oil $[\alpha]_D^{22}$ +4.0 (*c* 0.9 in $CHCl_3$) (Found: $M^+ + NH_4$, 372.2358. $C_{22}H_{34}NO_2Si$ requires *M*, 372.2359); ν_{max}/cm^{-1} 1725, 1463, 1427, 1365, 1109 and 1039; δ_H ($CDCl_3$, 300 MHz) 0.76 (3 H, t, *J* 7, 6-H_3), 1.09 [9 H, s, $SiC(CH_3)_3$], 1.28 (2 H, m, 5-H_2), 1.51 (2 H, m, 4-H_2), 2.50 (2 H, m, 2-H_2), 4.24 (1 H, quin, *J* 5.8, 3-H), 7.37–7.52 (6 H, m, ArH), 7.60–7.8 (4 H, m, ArH) and 9.75 (1 H, t, *J* 3, 1-H); δ_C ($CDCl_3$, 75 MHz) 13.8, 18.1, 19.2, 26.9, 39.5, 50.1, 69.0, 127.5, 127.6, 129.6, 129.7, 133.6, 133.8, 135.8(2) and 202.2; *m*/*z* (CI) 372 (M^+ + 18, 100%) and 355 (41).

(2*S*,6*R*,8*S*,3*Z*)-1-Benzyloxy-8-*tert*-butyldiphenylsilyloxy-2-methylundec-3-en-6-ol (**80**). Following the procedure outlined for the synthesis of alkenol **11**, but using the enantiomeric stannane (*R*)-**3** (0.29 g, 0.6 mmol), the aldehyde **79** (0.2 g, 0.6 mmol) and tin(IV) chloride (0.6 mL, 1.0 M in DCM, 0.6 mmol), after chromatography using 5 : 1 light petroleum : ether with 1% v/v of triethylamine, gave the *title compound* **80** (0.28 g, 90%) as a colourless oil containing <10% of its epimer at C(6) (^{13}C NMR), $[\alpha]_D^{25}$ +16 (*c* 0.1 in $CHCl_3$) (Found: M^+ + H, 545.3443. $C_{35}H_{49}O_3Si$ requires *M*, 545.3451); ν_{max}/cm^{-1} 3424, 1642, 1111, 1089 and 1049; δ_H ($CDCl_3$, 400 MHz) 0.65 (3 H, t, *J* 7, 11-H_3), 0.93 (3 H, d, *J* 7, 2-CH_3), 1.07 [9 H, s, $SiC(CH_3)_3$], 1.07–1.47 (4 H, m, 9-H_2 and 10-H_2), 1.50–1.70 (2 H, m, 7-H_2), 2.08 (1 H, m, 5-H), 2.19 (1 H, m, 5-H′), 2.80 (1 H, m, 2-H), 3.10 (1 H, br. s, OH), 3.21 (1 H, dd, *J* 8 and 9, 1-H), 3.30 (1 H, dd, *J* 6 and 9, 1-H′), 3.76 (1 H, m, 6-H), 3.96 (1 H, m, 8-H), 4.50 (2 H, s, $PhCH_2$), 5.30 (l H, dd, *J* 10.9, 9.7, 3-H), 5.39 (1 H, m, 4-H), 7.26–7.46 (11 H, m, ArH) and 7.70 (4 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) major isomer 13.9, 17.4, 18.0, 19.3, 27.0, 32.3, 35.9, 39.3, 43.2, 69.2, 72.6, 72.9, 74.8, 126.1, 127.4, 127.5, 127.6(2), 128.3, 129.5, 129.6, 135.7 and 135.9; minor isomer 17.7, 18.4, 19.2, 32.5, 35.7, 38.1, 40.6, 68.0, 72.3 and 75.1; *m*/*z* (CI) 545 (M^+ + 1, 14%) and 106 (100).

(2*S*,6*S*,8*S*,3*Z*)-1-Benzyloxy-8-*tert*-butyldiphenylsilyloxy-2-methylundec-3-en-6-yl 4-nitrobenzoate (**81**). 4-Nitrobenzoic acid (2.8 g, 16.7 mmol) and triphenylphosphine (5.0 g, 19.1 mmol) were added to the alcohol **80** (2.0 g, 3.9 mmol) in a mixture of ether (120 mL) and toluene (40 mL) at room temperature. Diethyl azodicarboxylate (3.0 mL, 19.1 mmol) was added dropwise and the mixture was stirred for 2 h. After concentration under reduced pressure, chromatography of the residue using light petroleum : ether (gradient elution 50 : 1 to 15 : 1) gave the *title compound* **81** (1.9 g, 70%) as a colourless oil, $[\alpha]_D^{25}$ +3.2 (*c* 1.5 in $CHCl_3$) (Found: $M^+ + NH_4$, 711.3819. $C_{46}H_{52}N_2O_6Si$ requires *M*, 711.3829); ν_{max}/cm^{-1} 1723, 1661, 1528, 1349, 1273 and 1108; δ_H ($CDCl_3$, 300 MHz) 0.68 (3 H, t, *J* 7, 11-H_3), 0.93 (3 H, d, *J* 7, 2-CH_3), 1.01 [9 H, s, $SiC(CH_3)_3$], 1.29 (2 H, m, 10-H_2), 1.44 (2 H, m, 9-H_2), 1.82 (1 H, ddd, *J* 4, 8 and 14, 7-H), 1.91 (1 H, m, 7-H′), 2.35 (1 H, m, 5-H), 2.47 (1 H, m, 5-H′), 2.75 (1 H, m, 2-H), 3.25 (2 H, d, *J* 7, 1-H_2), 3.79 (1 H, m, 8-H), 4.43 and 4.48 (each 1 H, d, *J* 12, PhHC*H*), 5.24 (1 H, m, 6-H), 5.35 (2 H, m, 3-H and 4-H), 7.14–7.43 (11 H, m, ArH), 7.61 (4 H, m, ArH) and 8.03 and 8.23 (each 2 H, d, *J* 8, ArH); *m*/*z* (CI) 712 (30%) and 106 (100). (2*S*,8*S*,3*Z*,5*EZ*)-1-Benzyloxy-8-*tert*-butyldiphenylsilyloxy-2-methylundeca-3,5-diene (0.25 g, 12%) was also isolated as a 6 : 4 mixture of *E* : *Z*-isomers, a colourless oil, $[\alpha]_D^{25}$ −20 (*c* 0.6 in $CHCl_3$) (Found: $M^+ + NH_4$, 544.3615. $C_{35}H_{50}O_2NSi$ requires *M*, 544.3611); ν_{max}/cm^{-1} 1471, 1454, 1389, 1040, 1110, 822 and 738; δ_H ($CDCl_3$, 500 MHz) 0.68 (3 H, t, *J* 7, 11-H_3), 0.92 [12 H, m, 2-CH_3 and $SiC(CH_3)_3$], 1.20 (2 H, m, 10-H_2), 1.34 (2 H, m, 9-H_2), 2.14 (1 H, m, 7-H), 2.22 (1 H, m, 7-H′), 2.84 (1 H, m, 2-H), 3.24 (2 H, m, 1-H_2), 3.69 (1 H, m, 8-H), 4.40 and 4.45 (each 1 H, d, *J* 12, Ph*H*CH), 5.05 (0.6 H, t, *J* 10, 3-H), 5.12 (0.4 H, t, *J* 10, 3-H), 5.34 (0.4 H, m, 6-H), 5.50 (0.6 H, dt, *J* 7 and 15, 6-H), 5.83 (0.6 H, t, *J* 11, 4-H), 5.91 (0.4 H, t, *J* 11, 4-H), 6.10 (0.6 H, dd, *J* 11 and 13, 5-H), 6.18 (0.4 H, t, *J* 11, 5-H), 7.17–7.36 (11 H, m, ArH) and 7.60 (4 H, m, ArH); δ_C ($CDCl_3$ 75 MHz) 14.1, 17.7, 17.9, 18.1, 19.3, 27.0, 32.4, 32.7, 34.6, 38.4, 38.5, 40.0, 72.7,

72.8, 75.1, 123.9, 125.0, 127.4(2), 127.7, 128.2, 128.3, 128.9, 129.4, 131.2, 132.3, 134.3, 134.5, 135.8 and 135.9; *m*/*z* (CI) 544 (M^+ + 18, 80%) and 271 (100).

(2*S*,6*S*,8*S*,3*Z*)-1-Benzyloxy-8-*tert*-butyldiphenylsilyloxy-2-methylundec-3-en-6-ol (**82**). Solid sodium hydroxide (0.9 g, 22.5 mmol) was added to a suspension of the ester **81** (2.0 g, 2.9 mmol) in methanol (10 mL) and the mixture was stirred at room temperature for 2 h then concentrated under reduced pressure. Ether (20 mL) and saturated aqueous ammonium chloride (50 mL) were added and the aqueous phase was extracted with ether (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 5 : 1 light petroleum : ether gave the *title compound* **82** (1.4 g, 94%) as a colourless oil, $[\alpha]_D^{25}$ +24 (*c* 0.2 in $CHCl_3$) (Found: M^+ + H, 545.3453. $C_{35}H_{49}O_3Si$ requires *M*, 545.3451); ν_{max}/cm^{-1} 3516, 1723, 1606, 1529, 1349, 1273, 1107, 873 and 703; δ_H ($CDCl_3$, 400 MHz) 0.65 (3 H, t, *J* 7, 11-H_3), 0.98 (3 H, d, *J* 7, 2-CH_3), 1.07 [9 H, s, SiC$(CH_3)_3$], 1.35–1.71 (6 H, m, 7-H_2, 9-H_2 and 10-H_2), 2.15–2.30 (2 H, m, 5-H_2), 2.81 (1 H, m, 2-H), 3.29 (1 H, br. s, OH), 3.30 (2 H, m, 1-H_2), 3.92–4.01 (2 H, m, 6-H and 8-H), 4.49 and 4.52 (each 1 H, d, *J* 14, PhHC*H*), 5.34 (1 H, dd, *J* 10.8, 9.6, 3-H), 5.37 (1 H, dt, *J* 11.2, 7.0, 4-H), 7.24–7.47 (11 H, m, ArH) and 7.68–7.74 (4 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 14.0, 17.8, 18.5, 19.4, 27.1, 32.6, 35.8, 38.2, 40.7, 68.1, 72.3, 72.9, 75.2, 125.6, 127.4, 127.5, 127.6, 128.2, 129.6, 129.7, 133.5, 133.9, 135.2, 135.9 and 138.5; *m*/*z* (CI) 545 (M^+ + 1, 32%) and 106 (100).

(2*R*,3*S*,4*S*,6*R*,8*S*)-1-Benzyloxy-8-*tert*-butyldiphenylsilyloxy-3,6-epoxy-2-methyl-4-phenylselenoundecane (**83**). *N*-Phenylselenophthalimide (0.25 g, 0.84 mmol) was added to the alcohol **82** (0.3 g, 0.56 mmol) in DCM (6 mL) at room temperature followed by tin(IV) chloride (0.11 mL, 1.0 M in DCM, 0.11 mmol). The mixture was stirred for 40 min before saturated aqueous sodium bicarbonate (10 mL) was added. The aqueous phase was extracted with DCM (3 × 10 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (gradient elution 50 : 1 to 25 : 1) gave the *title compound* **83** (0.32 g, 81%) as a yellow oil containing *ca.* 20% of a side-product that was not separated, $[\alpha]_D^{25}$ +19 (*c* 0.4 in $CHCl_3$) (Found: M^+ + NH_4, 718.3181. $C_{41}H_{56}NO_3Si^{80}Se$ requires *M*, 718.3194); ν_{max}/cm^{-1} 1732, 1455, 1427, 1362, 1286, 1110, 1073, 737 and 701; δ_H ($CDCl_3$, 300 MHz) 0.68 (3 H, t, *J* 7, 11-H_3), 1.06 [9 H, s, SiC$(CH_3)_3$], 1.09 (3 H, d, *J* 7, 2-CH_3), 1.18–2.48 (9 H, m, 2-H, 5-H_2, 7-H_2, 9-H_2 and 10-H_2), 3.38 (1 H, dd, *J* 6 and 9, 1-H), 3.45 (1 H, dd, *J* 5 and 9, 1-H′), 3.51–4.06 (4 H, m, 3-H, 4-H, 6-H and 8-H), 4.42 and 4.48 (each 1 H, d, *J* 12, PhHC*H*), 7.22–7.48 (16 H, m, ArH) and 7.68–7.40 (4 H, m, ArH); *m*/*z* (CI) 718 (M^+ + 18, 2.5%) and 106 (l00).

(2*R*,3*R*,6*S*,8*S*)-1-Benzyloxy-8-*tert*-butyldiphenylsilyloxy-3,6-epoxy-2-methylundecane (**84**). Tributyltin hydride (76 mg, 0.26 mmol) and α-azobis-*iso*butyronitrile (cat.) were added to the phenylselenide **83** (90 mg, 0.013 mmol) in benzene (5 mL). The reaction mixture was degassed for 20 min, heated under reflux for 2.5 h then concentrated under reduced pressure. Chromatography of the residue using 20 : 1 light petroleum : ether gave the *title compound* **84** (70 mg, 99%) as a colourless oil containing *ca.* 20% of a side-product that was not separated, $[\alpha]_D^{25}$ +14 (*c* 0.4 in $CHCl_3$); (Found: M^+, 544.3386. $C_{35}H_{48}O_3Si$ requires *M*, 544.3373); ν_{max}/cm^{-1} 1730, 1284, 1122, 1073 and 833; δ_H ($CDCl_3$, 400 MHz) 0.68 (3 H, t, *J* 7, 11-H_3), 0.95 (3 H, d, *J* 7, 2-CH_3), 1.05 [9 H, s, SiC$(CH_3)_3$], 1.16–1.82 (11 H, m, 2-H, 4-H_2, 5-H_2, 7-H_2, 9-H_2 and 10-H_2), 3.30 (1 H, dd, *J* 7 and 9, 1-H), 3.43 (1 H, dd, *J* 6 and 9, 1-H′), 3.65, 3.82 and 3.93 (each 1 H, m, 3-H, 6-H or 8-H), 4.43 and 4.51 (each 1 H, d, *J* 12, PhHC*H*), 7.30–7.42 (11 H, m, ArH) and 7.67–7.73 (4 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 13.1, 14.0, 17.6, 19.4, 27.1, 28.7, 31.5, 38.5, 39.4, 43.0, 71.1, 73.0, 73.6, 75.6, 80.2, 127.3, 128.2, 129.3, 134.5, 134.9, 135.9(2) and 138.7; *m*/*z* (CI) 545 (M^+ + 1, 2%) and 91 (100).

(2*R*,3*R*,6*S*,8*S*)-8-*tert*-Butyldiphenylsilyloxy-3,6-epoxy-2-methylundecan-1-ol (**85**). Palladium (0.02 g, 10% wt on activated carbon) was added to the benzyl ether (**84**) (0.21 g, 0.39 mmol) in ethanol (10 mL) at room temperature. The suspension was stirred under one atmosphere of hydrogen overnight then filtered through Celite® and the filtrate was concentrated under reduced pressure. Chromatography of the residue using 8 : 1 light petroleum : ether gave the *title compound* **85** (0.16 g, 89%) as a colourless oil, $[\alpha]_D^{25}$ +12 (*c* 0.4 in $CHCl_3$) (Found: M^+ + H, 455.2974. $C_{28}H_{43}O_3Si$ requires *M*, 455.2981); δ_H ($CDCl_3$, 400 MHz) 0.69 (3 H, t, *J* 8, 11-H_3), 0.84 (3 H, d, *J* 7, 2-CH_3), 1.06 [9 H, s, SiC$(CH_3)_3$], 1.18–1.40 (4 H, m, 9-H_2 and 10-H_2), 1.54–1.88 (6 H, m, 4-H_2, 5-H_2 and 7-H_2), 1.96 (1 H, m, 2-H), 3.53 (1 H, dd, *J* 4 and 12, 1-H), 3.62 (1 H, dd, *J* 7 and 12, 1-H′), 3.83 (2 H, m, 3-H and 6-H), 3.92 (1 H, dq, *J* 7.0 and 5.5, 8-H), 7.35–7.45 (6 H, m, ArH) and 7.68–7.72 (4 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 12.0, 14.1, 17.8, 19.6, 26.7, 27.2, 31.5, 37.8, 39.7, 42.8, 66.3, 71.0, 76.2, 82.4, 127.3(2), 129.3, 129.4, 134.3, 134.7, 135.8, 135.9; *m*/*z* (CI) 455 (M^+ + 1, 3%), 377 (65) and 299 (100).

Benzyl (2*S*,3*R*,6*S*,8*S*)-8-*tert*-butyldiphenylsilyloxy-3,6-epoxy-2-methylundecanoate (**88**). The Dess–Martin periodinane (1.2 g, 2.9 mmol) was added to the alcohol **85** (0.44 g, 0.96 mmol) in DCM (15 mL) and the suspension stirred at room temperature for 1 h. Saturated aqueous sodium bicarbonate (15 mL) and saturated aqueous sodium thiosulfate (15 mL) were added and the mixture was stirred at room temperature for an extra 30 min. The aqueous phase was extracted with ether (2 × 15 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield the aldehyde **86**; δ_H ($CDCl_3$, 300 MHz) 0.62 (3 H, t, *J* 7.2, 11-H_3), 0.96 [12 H, m, 2-CH_3 and SiC$(CH_3)_3$], 1.06–1.62 (8 H, m), 1.70–1.98 (2 H, m), 2.39 (1 H, m, 2-H), 3.72–3.92 (3 H, m, 3-H, 6-H and 8-H), 7.20–7.40 (6 H, m, ArH), 7.55–7.65 (4 H, m, ArH) and 9.60 (1 H, d, *J* 1.2, 1-H).

This aldehyde **86** was taken up in *tert*-butanol : water (50 : 50, 30 mL). 2-Methyl-2-butene (7 mL), sodium chlorite (0.54 g, tech. 80%, 4.8 mmol) and sodium dihydrogen phosphate (1.2 g, 9.7 mmol) were added and the reaction mixture was stirred at room temperature for 2 h. Brine (30 mL and ethyl acetate (50 mL) were added and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The organic extracts

were dried ($MgSO_4$) and concentrated under reduced pressure to give the carboxylic acid **87**; δ_H ($CDCl_3$, 300 MHz) 0.64 (3 H, t, *J* 7.2, 11-H_3), 0.97 [9 H, s, $SiC(CH_3)_3$], 1.06 (3 H, d, *J* 7.1, 2-CH_3), 0.70–1.64 (10 H, m), 2.59 (1 H, dq, *J* 5.4, 7.2, 2-H), 3.72 (1 H, m), 3.85 (2 H, m), 7.20–7.40 (6 H, m, ArH) and 7.55–7.65 (4 H, m, ArH).

This acid **87** was dissolved in acetonitrile (12 mL) and benzyl bromide (0.23 mL, 1.9 mmol) and *N*,*N*-di-*iso*propylethylamine (0.4 mL, 2.4 mmol) were added. The resulting solution was stirred at room temperature for 16 h. Water (15 mL) and ether (15 mL) were added and the aqueous phase was extracted with ether (2 × 15 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 50 : 1 light petroleum : ether gave the *title compound* **88** (0.41 g, 76% overall) as a colourless oil, $[\alpha]_D^{25}$ 12.7 (*c* 4.2 in $CHCl_3$) (Found: $M^+ + NH_4$, 576.3504. $C_{35}H_{50}NO_4Si$ requires *M*, 576.3509); ν_{max}/cm^{-1} 1734, 1461, 1273, 1108 and 1067; δ_H ($CDCl_3$, 400 MHz) 0.60 (3 H, t, *J* 7, 11-H_3), 0.97 [9 H, s, $SiC(CH_3)_3$], 1.16 (3 H, d, *J* 7, 2-CH_3), 1.18 (2 H, m, 10-H_2), 1.27 (2 H, m, 9-H_2), 1.42–1.80 (6 H, m, 4-H_2, 5-H_2 and 7-H_2), 2.39 (1 H, m, 2-H), 3.73–3.88 (3 H, m, 3-H, 6-H and 8-H), 5.00 and 5.04 (each 1 H, d, *J* 12, PhHC*H*), 7.22–7.38 (11 H, m, ArH) and 7.60–7.68 (4 H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 14.0, 14.2, 17.7, 19.5, 27.1, 29.3, 31.3, 39.5, 43.1, 45.5, 66.1, 71.1, 76.2, 79.7, 127.4, 128.1(2), 128.5, 128.8, 129.4, 130.9, 134.4, 134.9, 135.9, 136.0 and 174.5; *m*/*z* (CI) 576 ($M^+ + 18$, 2%) and 91 (l00).

Benzyl (2*S*,3*R*,6*S*,8*S*)-3,6-epoxy-8-hydroxy-2-methylundecanoate (**89**). The silyl ether **88** (26 mg, 0.047 mmol) was dissolved in trifluoromethanesulfonic acid and water (1.0 mL, 9 : 1) and the solution was stirred at room temperature for 40 min. Ether (3 mL) and saturated aqueous sodium hydrogen carbonate (5 mL) were added cautiously and the aqueous phase was extracted with ether (3 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 6 : 1 light petroleum : ether gave the *title compound* **89** (14 mg, 94%) as a colourless oil, $[\alpha]_D^{25}$ +16.6 (*c* 0.7 in $CHCl_3$) (Found: $M^+ + H$, 321.2067. $C_{19}H_{29}O_4$ requires *M*, 321.2066); ν_{max}/cm^{-1} 3445, 1732, 1459, 1376, 1158, 1056 and 746; δ_H ($CDCl_3$, 400 MHz) 0.94 (3 H, t, *J* 7, 11-H_3), 1.26 (3 H, d, *J* 7, 2-CH_3), 1.30–1.96 (10 H, m, 4-H_2, 5-H_2, 7-H_2, 9-H_2 and 10-H_2), 2.62 (1 H, quin, *J* 7.1, 2-H), 3.84 (1 H, m, 8-H), 4.01 (1 H, q, *J* 7.1, 3-H), 4.11 (1 H, m, 6-H), 5.12 and 5.15 (each 1 H, d, *J* 12, PhHC*H*), and 7.31–7.40 (5 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 14.1, 14.2, 19.1, 29.1, 30.9, 39.6, 41.2, 45.1, 66.3, 68.9, 77.2, 80.5, 128.1(2), 128.5, 135.9 and 174.1; *m*/*z* (CI) 338 ($M^+ + 18$, 33%), 321 ($M^+ + 1$, 100) and 320 (4).

(2*R*,3*R*,6*S*,8*S*)-3,6-Epoxy-2-methylundecan-1,8-diol (**90**).[1c] Concentrated aqueous hydrogen chloride (50 μL) was added dropwise to the silyl ether **85** (25 mg, 0.055 mmol) in methanol (0.7 mL) and the mixture heated under reflux for 2.5 h. After cooling to room temperature, saturated aqueous sodium bicarbonate (1 mL) was added and the mixture concentrated under reduced pressure. Chromatography of the residue using 1 : 1 light petroleum : ether gave the title compound **90** (12 mg, 99%) as a colourless oil, $[\alpha]_D^{25}$ +4.4 (*c* 1.2 in $CHCl_3$), lit.[1c] +7.2 (*c* 2.0 in benzene); (Found: $M^+ + H$, 217.1807. $C_{12}H_{25}O_3$ requires *M*, 217.1803); ν_{max}/cm^{-1} 3338, 1662, 1464, 1374 and 1038; δ_H ($CDCl_3$, 400 MHz) 0.91 (6 H, m, 11-H_3 and 2-CH_3), 1.30–1.78 (8 H, m, 4-H_2, 5-H_2, 9-H_2 and 10-H_2), 1.84–2.04 (3 H, m, 2-H and 7-H_2), 2.52 (2 H, br. s, 2 × OH), 3.56 (1 H, dd, *J* 4 and 11, 1-H), 3.66 (1 H, dd, *J* 7 and 11, 1-H′), 3.83 (1 H, m, 6-H or 8-H), 3.97 (1 H, dt, *J* 4.4, 7.6, 3-H), 4.09 (1 H, dq, *J* 4.0, 7.6, 6-H or 8-H); δ_C ($CDCl_3$, 100 MHz) 12.2, 14.2, 19.0, 27.4, 31.2, 38.6, 39.8, 41.6, 66.0, 68.9, 76.8 and 82.3; *m*/*z* (CI) 234 ($M^+ + 18$, 20%) and 217 ($M^+ + 1$, 100).

(2*R*,3*R*,6*S*,8*S*)-1,8-bis-(4-Bromobenzoyloxy)-3,6-epoxy-2-methylundecane (**91**).[5j] 4-Bromobenzoyl chloride (0.36 mL, 2.8 mmol), triethylamine (0.46 mL, 3.3 mmol) and DMAP (cat.) were added to the diol **90** (12 mg, 0.055 mmol) in DCM (0.5 mL) and the mixture stirred for 16 h. Water (1 mL) was added and the aqueous phase extracted with DCM (3 × 2 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 5 : 1 light petroleum : ether gave the title compound **91** (14 mg, 43%) as a colourless oil, $[\alpha]_D^{25}$ +27 (*c* 4 in $CHCl_3$), lit.[5j] +25 (*c* 0.28 in $CHCl_3$) (Found: $M^+ + H$, 581.0544. $C_{26}H_{31}O_5{}^{79}Br_2$ requires *M*, 581.0539); ν_{max}/cm^{-1} 1719, 1590, 1270, 1103, 1011 and 755; δ_H ($CDCl_3$, 400 MHz) 0.93 (3 H, t, *J* 7, 11-H_3), 1.05 (3 H, d, *J* 7, 2-CH_3), 1.33–1.76 (6 H, m, 4-H, 5-H, 9-H_2 and 10-H_2), 1.86–2.00 (4 H, m, 4-H′, 5-H′ and 7-H_2), 2.04 (1 H, m, 2-H), 3.80 (1 H, q, *J* 5.5, 3-H), 3.91 (1 H, quin, *J* 6.5, 6-H), 4.19 (1 H, dd, *J* 7, 11, 1-H), 4.29 (1 H, dd, *J* 6 and 11, 1-H′), 5.28 (1 H, quin, *J* 6.2, 8-H) and 7.56–7.62 and 7.87–7.92 (each 4 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 13.1, 14.1, 18.5, 28.7, 31.8, 37.0, 37.6, 40.5, 67.7, 73.3, 76.0, 80.1, 127.7, 127.9, 129.2, 129.5, 131.0, 131.6, 165.3 and 165.7; *m*/*z* (CI) 585, 583, 581 ($M^+ + 1$, 25, 50, 25%) and 183 (100).

Benzyl (2*S*,3*R*,6*S*,8*S*)-8-{(2*R*,3*R*,6*S*,7*R*,8*S*,9*R*,10*R*,13*S*,15*R*)-8-*tert*-butyldimethylsilyloxy-3,6;10,13-bis-epoxy-15-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino)-2,7,9-trimethyloctadecanoyloxy}-3,6-epoxy-2-methylundecanoate (**92**). DMAP (43 mg, 0.355 mmol) and 2,4,6-trichlorobenzoyl chloride (19 μL, 0.122 mmol) were added to the undecanol **89** (30 mg, 0.094 mmol) and the octadecanoic acid **70** (57 mg, 0.094 mmol) in DCM (0.92 mL) and the mixture stirred at room temperature for 3.5 h. Aqueous citric acid (10%, 1.5 mL) was added and the aqueous layer was extracted with DCM (3 × 5 mL). The organic extracts were washed with saturated aqueous sodium bicarbonate (10 mL), water (10 mL) and brine (10 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 5 : 1 light petroleum : ether gave the *title compound* **92** (67 mg, 78%), as an oil, a 40 : 60 mixture of rotamers, R_f = 0.60 (1 : 1 light petroleum : ether), $[\alpha]_D^{25}$ +1.5 (*c* 1.1 in $CHCl_3$) (Found: $M^+ + NH_4$, 933.6593. $C_{52}H_{93}N_2O_{10}Si$ requires *M*, 933.6594); ν_{max}/cm^{-1} 1734, 1692, 1460, 1389, 1365, 1338, 1253, 1156, 1049, 836, 773 and 698; δ_H (500 MHz, $CDCl_3$,) 0.03 and 0.05 (each 1.5 H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.78 (3 H, br. d, *J* 6.5, CH_3), 0.85–0.96 [18 H, m, $SiC(CH_3)_3$ and 3 × CH_3), 1.09 (3 H, d, *J* 7.0, CH_3), 1.25 (3 H, d, *J* 7, CH_3), 1.48 [9 H, s, $C(CH_3)_3$], 1.18–2.05 (26 H, m), 2.48–2.57 (2 H, m, 2-H and 2′-H), 2.63 (1.2 H, s, NCH_3), 2.67 (1.8 H, s, NCH_3), 3.45, 3.59, 3.73

and 3.85 (each 1 H, m), 3.91–4.00 (2 H, m), 4.01–4.08 (1.4 H, m, 8′-H and 15′-H), 4.18 (0.6 H, m, 15′-H), 4.99 (1 H, m, 8-H), 5.12 (2 H, s, $PhCH_2$) and 7.30–7.39 (5 H, m, ArH); δ_C (125 MHz, $CDCl_3$) −4.8, −4.4, 10.4, 11.1(2), 12.9, 13.0, 13.8, 13.9, 14.0, 14.1, 18.3, 18.4, 19.2, 19.4, 26.1, 28.2, 28.3, 28.4, 28.5, 29.2, 29.5, 29.9, 30.3(2), 30.7, 31.0, 31.5, 35.0, 36.9, 38.4, 38.8, 40.6, 41.2, 41.3, 43.8, 43.9, 45.1, 45.2, 45.4, 51.6, 52.3, 66.1, 72.0, 72.1, 75.8, 76.1, 76.7, 79.2, 79.5, 79.9, 80.0, 80.1, 80.5, 80.6, 128.1(2), 128.5, 136.0, 174.4 and 174.6; *m/z* ($APCI^+$) 916 (M^+ + 1, 6%) and 120 (100).

Benzyl (2*S*,3*R*,6*S*,8*S*)-8-{(2*R*,3*R*,6*S*,7*S*,8*S*,9*S*,10*R*,13*S*,15*R*)-3,6;10,13-bis-epoxy-15-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino)-8-hydroxy-2,7,9-trimethyloctadecanoyloxy}-3,6-epoxy-2-methylundecanoate (**93**). Concentrated aqueous hydrogen chloride (3 drops) was added to the silyl ether **92** (56 mg, 0.061 mmol) in ethanol (3 mL) and the mixture heated at 55 °C for 3.5 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue dissolved in ethyl acetate (3 mL). Saturated aqueous sodium bicarbonate (3 mL) was added and the aqueous fraction extracted with ethyl acetate (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in DCM (1.6 mL) and di-*tert*-butyl dicarbonate (0.027 g, 0.122 mmol) was added followed by Et_3N (0.184 mmol, 0.18 μL). The mixture was stirred for 16 h at room temperature then water (2 mL) was added. The aqueous layer was extracted with DCM (3 × 5 mL) and the organic extracts were washed with water (10 mL) and brine (10 mL). After drying ($MgSO_4$) and concentration under reduced pressure, chromatography of the residue using light petroleum : ether (gradient elution 2 : 1 to 1 : 1) gave the *title compound* **93** (46 mg, 93%), as an oil, a 40 : 60 mixture of rotamers, R_f = 0.11 (1 : 1 light petroleum : ether), $[\alpha]_D^{27}$ −8.2 (*c* 1.1 in $CHCl_3$) (Found: $M^+ + NH_4$, 819.5727. $C_{46}H_{79}N_2O_{10}$ requires *M*, 819.5729); ν_{max}/cm^{-1} 3499, 1732, 1691, 1457, 1365, 1254, 1154, 1057 and 751; δ_H (500 MHz, $CDCl_3$) 0.78 (3 H, d, *J* 7.0, CH_3), 0.85–0.95 (9 H, m, 3 × CH_3), 1.10 and 1.25 (each 3 H, d, *J* 7.0, CH_3), 1.25–1.80 (18 H, m), 1.45 [9 H, s, $C(CH_3)_3$], 1.81–2.04 (9 H, m), 2.49–2.58 (2 H, m, 2-H and 2′-H), 2.63 (1.2 H, br. s, NCH_3), 2.66 (1.8 H, s, NCH_3), 3.71 (1 H, m), 3.75–3.86 (2 H, m), 3.88 (1 H, br. d, *J* 8.5), 3.94 (2 H, m), 4.02–4.12 (1.4 H m, 8′-H and 15′-H), 4.22 (0.6 H m, 15′-H), 4.99 (1 H, m, 8-H), 5.12 (2 H, s, $ArCH_2$) and 7.30–7.39 (5 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 9.2, 12.1, 13.2, 13.7, 14.0, 14.1, 18.3, 19.1, 26.6(2), 28.5(2), 29.0, 29.2, 30.3, 31.1, 31.5, 35.1, 36.8, 37.8, 38.7, 40.5, 45.0, 45.4, 51.6, 66.1, 71.8, 72.3, 76.6, 79.2, 79.9, 80.2, 81.6, 82.1, 128.1(2), 128.5, 136.0, 174.44, 174.52; *m/z* (CI) 819 (M^+ + 18, 100%) and 802 (M^+ + 1, 5).

(2*S*,3*R*,6*S*,8*S*)-8-{(2*R*,3*R*,6*S*,7*S*,8*S*,9*S*,10*R*,13*S*,15*R*)-3,6;10,13-bis-Epoxy-15-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino)-8-hydroxy-2,7,9-trimethyloctadecanoyloxy}-3,6-epoxy-2-methylundecanoic acid (**94**). Palladium (10% wt. on activated carbon, 8 mg) was added to the benzyl ester **93** (44 mg, 0.055 mmol) in ethanol (2 mL) and the suspension stirred under an atmosphere of hydrogen for 16 h. The mixture was filtered through celite® and the residue washed with ethanol (10 mL). Concentration under reduced pressure gave the *title compound* **94** (38 mg, 97%), as an oil, a 40 : 60 mixture of rotamers, R_f = 0.11 (1 : 2 light petroleum : ether) (Found: M^+ + Na, 734.4814. $C_{39}H_{69}NO_{10}Na$ requires *M*, 734.4819); ν_{max}/cm^{-1} 3474, 1732, 1691, 1460, 1365, 1255, 1153, 1058, 956, 875 and 770; δ_H (300 MHz, $CDCl_3$,) 0.79 (3 H, d, *J* 6.9, CH_3), 0.84–1.00 (9 H, m, 3 × CH_3), 1.12 (3 H, d, *J* 7.2, CH_3), 1.20 (3 H, d, *J* 6.9, CH_3), 1.22–2.15 (28 H, m), 1.45 [9 H, s, $C(CH_3)_3$], 2.54 (1 H, m, 2-H or 2′-H), 2.64 (1.2 H, s, NCH_3), 2.68 (1.8 H, s, NCH_3), 2.74 (1 H, m, 2-H or 2′-H), 3.63–4.28 (8 H, m) and 5.03 (1 H, m, 8-H); *m/z* ($APCI^+$) 734 (M^+ + 23, 100%), 612 (16%), 528 (17), 427 (49), 330 (48), 267 (40), 211 (47) and 196 (86).

N-*tert*-Butoxycarbonyl-*N*-desmethylpamamycin 607 (**95**). Triethylamine (8 mg, 0.079 mmol) and 2,4,6-trichlorobenzoyl chloride (12.0 μL, 0.079 mmol) were added to the *seco*-acid **94** (40 mg, 0.056 mmol) in xylene (3.9 mL) and the mixture stirred at room temperature for 14 h. DMAP (20 mg) in xylene (6 mL) was added and the mixture stirred at room temperature for 24 h. Saturated aqueous ammonium chloride was added and the mixture extracted into ethyl acetate. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (2 : 1) gave the *title compound* **95** (10 mg, 25%), as an oil, a 40 : 60 mixture of rotamers, R_f = 0.50 (1 : 2 light petroleum : ether) (Found: M^+ + H, 694.4900. $C_{39}H_{68}NO_9$ requires *M*, 694.4889); δ_H (400 MHz, $CDCl_3$,) 0.81 (3 H, t, *J* 7.5, 18-H_3 or 11-H_3), 0.85–0.96 (12 H, m, 4 × CH_3), 1.08 (3 H, d, *J* 7.0, CH_3), 1.45 [9 H, s, $C(CH_3)_3$], 1.18–2.08 (26 H, m), 2.35 (1 H, m, 2-H or 2′-H), 2.59 (1 H, qd, *J* 7.1, 3.0, 2′-H or 2-H), 2.64 (1.2 H, s, NCH_3), 2.67 (1.8 H, s, NCH_3), 3.59–3.73 (1 H, m), 3.74–3.88 and 3.90–4.20 (each 3 H, m) and 4.85–4.99 (2 H, m, 8-H and 8′-H); *m/z* ($APCI^-$) 692 (M^+ − 1, 28%), 434 (21), 212 (60) and 174 (100); (ES^+) 716 (M^+ + 23, 100). A less polar compound (12 mg) was also isolated and identified as a dimer, *m/z* (ES^+) 1410 (M^+ + 23, 100%), but was not fully charactered.

Pamamycin 607 (**1**).[1a] Trifluoroacetic acid in DCM (6.5 M, 0.1 mL, 0.65 mmol) was added to the carbamate **95** (10 mg, 0.014 mmol) at room temperature and the solution stirred for 45 min. DCM (5 mL) and saturated aqueous sodium hydrogen carbonate (5 mL) were added and the aqueous phase, now with pH *ca.* 7, was extracted with DCM (5 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to leave desmethyl pamamycin 607 (**96**);[1d] δ_H (400 MHz, $CDCl_3$,) 0.78 (3 H, d, *J* 7.0, CH_3), 0.85 (3 H, d, *J* 6.5, CH_3), 0.89 (3 H, t, *J* 7.3, 18-H_3 or 11′-H_3), 0.96 (3 H, t, *J* 7.4, 18-H_3 or 11′-H_3), 1.07 (6 H, d *J* 7.0, 2 × CH_3), 1.20–2.07 (26 H, m), 2.28 (1 H, dq, *J* 9.8, 7.0, 2-H or 2′-H), 2.61 (1 H, dq, *J* 2.4, 6.8, 2-H or 2′-H), 2.87 (3 H, br. s, NCH_3), 3.13 and 3.45 (each 1 H, m), 3.65 (1 H, dt, *J* 3.9, 10.3), 3.78, 3.89, 4.00 and 4.21 (each 1 H, m), 4.30 (1 H, br. m, NH), 4.90 (1 H, d, *J* 10.6, 8-H), 4.92 (1 H, m, 8′-H); *m/z* (ES^+) 594 (M^+ + 1, 100%). This was taken up in acetonitrile (0.2 mL) and formalin (0.3 mL, 0.01 mmol) and sodium cyanoborohydride (3.8 mg, 0.060 mmol) were added. The mixture was stirred at room temperature for 1.5 h, acetic acid (6 μL, 0.11 mmol) was added and the mixture was stirred an additional 21 h. Ether (5 mL) and saturated aqueous

sodium carbonate (5 mL) were added and the mixture stirred for 15 min before being extracted with ether (3 × 2.5 mL), DCM (3 × 2.5 mL) and ethyl acetate (2.5 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using hexane : ethyl acetate (8 : 1.5 with triethylamine 5%) gave the title compound **1** (4.6 mg, 70%) as a clear viscous oil, $[\alpha]_D^{25}$ +13.3 (*c* 0.3 in $CHCl_3$), lit.[1a] +22.8 (*c* 0.26 in MeOH); δ_H (400 MHz, acetone-d_6 – TFA,) 0.85 (6 H, d, *J* 6.6, 7-CH_3 and 9-CH_3), 0.87 (3 H, t, *J* 7.3, 11′-H_3), 1.04 (3 H, t, *J* 7.3, 18-H_3), 1.05 (3 H, d *J* 6.8, 2′-CH_3), 1.09 (3 H, d *J* 7.1, 2-CH_3), 1.24–2.08 (26 H, m), 2.27 (1 H, dq, *J* 10.0. 7.2, 2-H), 2.75 (1 H, dq, *J* 2.0, 7.0, 2′-H), 2.98 and 3.22 (each 3 H, t, *J* 2.5, NCH_3), 3.38 (1 H, m, 10-H), 3.62 (1 H, m, 15-H), 3.72 (1 H, dt, *J* 10.8, 4.0, 3-H), 3.81–3.93 (2 H, m, 13-H, 6′-H), 4.10 (1 H, ddd, *J* 9.2, 6.8, 2.0, 3′-H), 4.29 (1 H, m, 6-H), 4.92 (1 H, m, 8′-H) and 4.98 (1 H, dd, *J* 11.2, 1.2, 8-H); *m*/*z* (ES^+) 608 (M^+ + 1, 100); δ_C (125 MHz, acetone-d_6 – TFA,) 8.7 (12′-C), 9.8 (20-C), 10.4 (21-C), 14.0 (2; 18-C and 19-C), 14.3 (11′-C), 18.8 (10′-C), 20.3 (17-C), 27.9 (4′-C), 28.1 (5-C), 29.0 (16-C), 30.0 (11-C), 31.1 (4-C), 31.6 (12-C), 32.1 (5′-C), 34.2 (14-C), 36.5 (22-C), 37.9 (2; 9′-C and 7-C), 39.4 (7′-C), 41.5 (9-C), 42.1 (2′-C), 43.7 (23-C), 47.9 (2-C), 68.7 (15-C), 71.5 (8′-C), 75.2 (2; 8-C and 6′-C), 77.3 (6-C), 79.2 (3′-C), 80.0 (13-C), 81.1 (10-C), 83.2 (3-C), 173.7 (1′-C) and 175.0 (1); *m*/*z* (EI) 607 (M^+, 5%), 564 (30) and 100 (100).

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Notes and references

1 (*a*) S. Kondo, K. Yasui, M. Katayama, S. Marumo, T. Kondo and H. Hattori, *Tetrahedron Lett.*, 1987, **28**, 5861; (*b*) M. Natsume, K. Yasui, S. Kondo and S. Marumo, *Tetrahedron Lett.*, 1991, **32**, 3087; (*c*) M. Natsume, S. Kondo and S. Marumo, *J. Chem. Soc., Chem. Commun.*, 1989, 1911; (*d*) I. Kozone, N. Chikamoto, H. Abe and M. Natsume, *J. Antibiot.*, 1999, **52**, 329.

2 (*a*) P. A. McCann and B. M. Pogell, *J. Antibiot.*, 1979, **32**, 673; (*b*) S. Kondo, K. Yasui, M. Natsume, M. Katayama and S. Marumo, *J. Antibiot.*, 1988, **41**, 1196; (*c*) M. Natsume, A. Honda, Y. Oshima, H. Abe, S. Kondo, F. Tanaka and S. Marumo, *Biosci. Biotechnol. Biochem.*, 1995, **59**, 1766; (*d*) M. Natsume, J. Tazawa, K. Yaki, H. Abe, S. Kondo and S. Marumo, *J. Antibiot.*, 1995, **48**, 1159.

3 (*a*) M. Ahmar, C. Duyck and I. Fleming, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2721; (*b*) I. Fleming and S. K. Ghosh, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2733; (*c*) P.-F. Deschenaux and A. Jacot-Guillarmod, *Helv. Chim. Acta*, 1990, **73**, 1861; (*d*) K. M. Sun and B. Fraser-Reid, *Can. J. Chem.*, 1980, **58**, 2732; (*e*) K. Takatori, N. Tanaka, K. Tanaka and M. Kajiwara, *Heterocycles*, 1993, **36**, 1489; (*f*) K. Bratt, A. Garavelas, P. Perlmutter and G. Westman, *J. Org. Chem.*, 1996, **61**, 2109; (*g*) J. W. Jeong, B. W. Woo, D.-C. Ha and Z. No, *Synlett*, 2003, 393; (*h*) U. Meiners, E. Cramer, R. Fröhlich, B. Wibbeling and P. Metz, *Eur. J. Org. Chem.*, 1998, **10**, 2073; (*i*) G. Mandville, C. Girard and R. Bloch, *Tetrahedron*, 1997, **53**, 17079.

4 (*a*) P. Metz, *Top. Curr. Chem.*, 2005, **244**, 215; (*b*) P. Fischer, M. Gruner, A. Jäger, O. Kataeva and P. Metz, *Chem.–Eur. J.*, 2011, **17**, 13334; (*c*) G.-B. Ren, Y.-X. Huang, Y.-P. Sun, Z.-H. Li and Y. Wu, *J. Org. Chem.*, 2010, **75**, 5048; (*d*) G.-B. Ren and Y. Wu, *Org. Lett.*, 2009, **11**, 5638; (*e*) P. Fischer, A. B. G. Segovia, M. Gruner and P. Metz, *Angew. Chem., Int. Ed.*, 2005, **44**, 6231; (*f*) E. J. Jeong, E. J. Kang, L. T. Sung, S. K. Hong and E. Lee, *J. Am. Chem. Soc.*, 2002, **124**, 14655; (*g*) S. H. Kang, J. W. Jeong, Y. S. Hwang and S. B. Lee, *Angew. Chem., Int. Ed.*, 2002, **41**, 1392; (*h*) Y. Wang, H. Bernsmann, M. Gruner and P. Metz, *Tetrahedron Lett.*, 2001, **42**, 7801; (*i*) E. Lee, E. J. Jeong, E. J. Kang, L. T. Sung and S. K. Hong, *J. Am. Chem. Soc.*, 2001, **123**, 10131; (*j*) S. Lanners, H. Norouzi-Arasi, X. J. Salom-Roig and G. Hanquet, *Angew. Chem., Int. Ed.*, 2007, **46**, 7086.

5 (*a*) A. Miura, S.-y. Takigawa, Y. Furuya, Y. Yokoo, S. Kuwahara and H. Kiyota, *Eur. J. Org. Chem.*, 2008, **29**, 4955; (*b*) B. H. Fraser, R. J. Mulder and P. Perlmutter, *Tetrahedron*, 2006, **62**, 2857; (*c*) A. Miura, H. Kiyota and S. Kuwahara, *Tetrahedron*, 2005, **61**, 1061; (*d*) S. Nagumo, Y. Ischii, S. Kanno and N. Kawahara, *Heterocycles*, 2003, **59**, 101; (*e*) S. Nagumo, Y. Ishii, Y.-i. Kakimoto and N. Kawahara, *Tetrahedron Lett.*, 2002, **43**, 5333; (*f*) S. H. Kang and J. W. Jeong, *Tetrahedron Lett.*, 2002, **43**, 3613; (*g*) H. Bernsmann, M. Gruner, R. Fröhlich and P. Metz, *Tetrahedron Lett.*, 2001, **42**, 5377; (*h*) G. Solladie, X. J. Salom-Roig and G. Hanquet, *Tetrahedron Lett.*, 2000, **41**, 551; (*i*) M. A. Calter and F. C. Bi, *Org. Lett.*, 2000, **2**, 1529; (*j*) G. Solladie, X. J. Salom-Roig and G. Hanquet, *Tetrahedron Lett.*, 2000, **41**, 2737; (*k*) G. Mandeville and R. Bloch, *Eur. J. Org. Chem.*, 1999, **9**, 2303; (*l*) H. Bernsmann, M. Gruner and P. Metz, *Tetrahedron Lett.*, 2000, **41**, 7629; (*m*) R. D. Walkup and Y. S. Kim, *Tetrahedron Lett.*, 1995, **36**, 3091.

6 Preliminary communication: O. Germay, N. Kumar and E. J. Thomas, *Tetrahedron Lett.*, 2001, **42**, 4969.

7 (*a*) J. S. Carey, S. MacCormick, S. J. Stanway, A. Teerawutgulrag and E. J. Thomas, *Org. Biomol. Chem.*, 2011, **9**, 3896; (*b*) L. A. Hobson and E. J. Thomas, *Org. Biomol. Chem.*, 2012, **10**, 7510; (*c*) D. J. Hallett, N. Tanikkul

and E. J. Thomas, *Org. Biomol. Chem.*, 2012, **10**, 6130; (*d*) K. Dorling and E. J. Thomas, *Org. Biomol. Chem.*, 2012, **10**, 6995.

8 (*a*) F. Bennett, S. B. Bedford, K. E. Bell, G. Fenton, D. W. Knight and D. Shaw, *Tetrahedron Lett.*, 1992, **33**, 6507; (*b*) S. B. Bedford, K. E. Bell, G. Fenton, C. J. Hayes, D. W. Knight and D. Shaw, *Tetrahedron Lett.*, 1992, **33**, 6511; (*c*) J. M. Barks, D. W. Knight, C. J. Seaman and G. G. Weingarten, *Tetrahedron Lett.*, 1994, **35**, 7259; (*d*) S. P. Bew, J. M. Barks, D. W. Knight and R. J. Middleton, *Tetrahedron Lett.*, 2000, **41**, 4447; (*e*) S. P. Bew, D. W. Knight and R. J. Middleton, *Tetrahedron Lett.*, 2000, **41**, 4453; (*f*) D. W. Knight and E. R. Staples, *Tetrahedron Lett.*, 2002, **43**, 6771.

9 (*a*) S. H. Kang, T. S. Hwang, W. J. Kim and J. K. Lim, *Tetrahedron Lett.*, 1991, **32**, 4015; (*b*) S. V. Ley and B. Lygo, *Tetrahedron Lett.*, 1982, **23**, 4625; (*c*) G. Brussani, S. V. Ley, J. L. Wright and D. J. Williams, *J. Chem. Soc., Perkin Trans 1*, 1986, 303; (*d*) B. H. Lipshutz and T. Gross, *J. Org. Chem.*, 1995, **60**, 3572.

10 D. Mihelich and G. A. Hite, *J. Am. Chem. Soc.*, 1992, **114**, 7318.

11 L. A. Hobson, L. W. Singh and E. J. Thomas, *ARKIVOC*, 2001, **viii**, 59.

12 For an analogous transition structure proposed for the cyclisations induced by iodonium ion formation, see: S. B. Bedford, K. E. Bell, F. Bennett, C. J. Hayes, D. W. Knight and D. E. Shaw, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2143.

13 M. M. Claffey and C. H. Heathcock, *J. Org. Chem.*, 1996, **61**, 7646.

14 D. M. Ashworth, C. A. Clark and J. A. Robinson, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1461.

15 (*a*) S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1991, **2**, 183; (*b*) S. G. Davies and I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1129; (*c*) S. G. Davies, O. Ichihara and I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1141; (*d*) M. E. Bunnage, A. J. Burke, S. G. Davies and C. J. Goodwin, *Tetrahedron: Asymmetry*, 1995, **6**, 165.

16 (*a*) U. Widmer, *Synthesis*, 1983, 135; (*b*) M. P. Cooke Jr. and D. L. Busman, *J. Org. Chem.*, 1982, **47**, 4955.

17 D. Boger, J.-H. Chen and K. W. Scionz, *J. Am. Chem. Soc.*, 1996, **118**, 1629.

18 (*a*) H. M. L. Davies, J. J. Matasi, L. M. Hodges, N. J. S. Huby, C. Thornley, N. Kong and J. W. Houser, *J. Org. Chem.*, 1997, **62**, 1095.

19 M. C. Pirrung and C. H. Heathcock, *J. Org. Chem.*, 1980, **45**, 1727.

20 (*a*) J. G. Hill, K. B. Sharpless, C. M. Exon and R. Regenye, *Org. Synth.*, 1985, **63**, 66; (*b*) T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974; (*c*) B. E. Rossiter, T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 464; (*d*) R. M. Hanson and K. B. Sharpless, *J. Org. Chem.*, 1986, **51**, 1922; (*e*) Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765.

21 (*a*) M. Cherest, H. Felkin and N. Prudent, *Tetrahedron Lett.*, 1968, **9**, 2199; (*b*) N. T. Anh and O. Eisenstein, *Tetrahedron Lett.*, 1976, **17**, 155.

22 (*a*) P. Raddatz, K.-O. Minck, F. Rippmann and C.-J. Schmitges, *J. Med. Chem.*, 1994, **37**, 486; (*b*) K. Mori and H. Takaishi, *Tetrahedron*, 1989, **45**, 1639.

23 (*a*) O. Mitsunobu, *Synthesis*, 1981, 1; (*b*) D. L. Hughes, *Org. React.*, 1992, **42**, 335.

24 Preliminary attempts were made to join the two fragments together by esterification of the more hindered 8-hydroxyl group of the C(1)–C(18)-fragment followed by macrocyclisation but this gave confusing results. Other laboratories had problems with this alternative assembly; see ref. 4*h*.

25 (*a*) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989; (*b*) J. D. White, R. G. Carter and K. F. Sundermann, *J. Org. Chem.*, 1999, **64**, 684.

26 (*a*) P. Casteno, E. J. Thomas and A. Weston, *Tetrahedron Lett.*, 2007, **48**, 337; (*b*) E. J. Thomas and A. Weston, *Tetrahedron Lett.*, 2007, **48**, 341.

27 V. M. Divac and Z. M. Bugarčič, *Synthesis*, 2009, 3684.