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Approaches to the total synthesis of chaetochalasin A

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Eric J. Thomas*[a] and Mark Willis[a]

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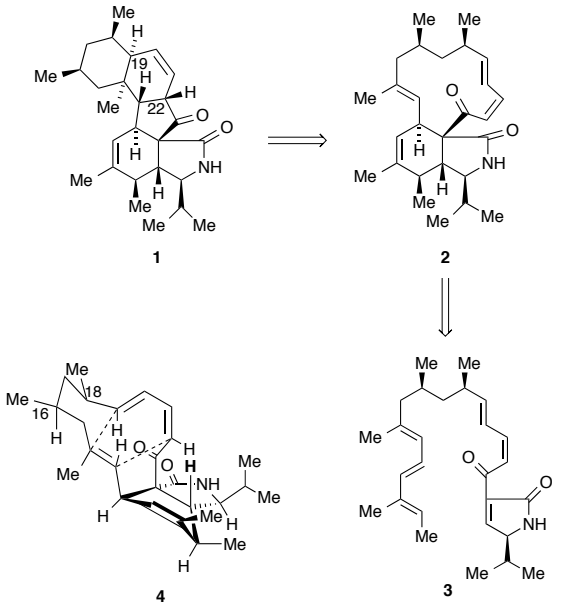
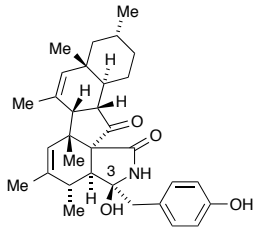
Chaetochalasin A is a complex natural product whose biosynthesis may involve two domino Diels-Alder reactions. Approaches to the total synthesis of chaetochalasin A using this approach have been studied. Methyl (6*R*,8*S*,2*Z*,4*E*,10*E*,12*E*,14*E*)-6,8,10,14-tetramethylhexadeca-2,4,10,12,14-pentaenoate was identified as a key intermediate and was synthesized from (*E*)-1-bromo-4-*tert*-butyldimethylsilyloxy-2-methylbut-2-ene using diastereoselective alkylations of derivatives of (+)-pseudoephedrine to introduce the stereogenic centres, a modified Julia reaction to prepare the conjugated triene and a phosphonate condensation to provide the (2*Z*)-alkene. However, during the synthesis, facile geometrical isomerisation of the (14*E*)-trisubstituted and (2Z)-double-bonds was observed and attempts to incorporate this pentaene into a synthesis of chaetochalasin A led to the formation of mixtures of products. The analogous ethyl 6,8,10,14-tetramethylhexadeca-4,10,12,14-tetraenoate [that lacks the (2Z)-double-bond] was incorporated into a Diels-Alder precursor by acylation of a valine-derived *N*-acylpyrrolidinone followed by oxidative elimination of the corresponding 3-(phenylselanyl)pyrrolidinone. However, preliminary studies of the macrocycle-forming Diels-Alder reaction for a synthesis of chaetochalasin A were complicated by (*E*,*Z*)-isomerisation of the (10*E*)-double-bond of the conjugated triene and three Diels-Alder adducts were isolated and characterised. Further studies of this approach to chaetochalasin A will require an alternative procedure for the generation of the acylpyrrolinone in the presence of the acid sensitive conjugated triene.

Introduction

The cytotoxic chaetochalasin A (**1**) was isolated from *Chaetomium brasiliense* and showed antibacterial activity against *Staphylococcus aureus* and *Bacillus substilis*.[1] It is structurally related to the cytochalasans that are believed to be biosynthesised by sequences that involve intramolecular Diels-Alder reactions of 3-acylpyrrolinones.[2] Although not really biomimetic, intramolecular Diels-Alder reactions of 3-acylpyrrolinones were used in an approach to the total synthesis of several cytochalasins and related compounds including an isomer of aspochalasin C.[3,4] By analogy, it was suggested that the biosynthesis of chaetochalasin A involves two Diels-Alder reactions with the 3-acylpyrrolinone **3** being identified as a potential precursor of the cyclisations. This Diels-Alder precursor is shown with the (2*Z*,4*E*)-hexadecapentaenoyl side-chain attached to the 3-position of the pyrrolinone to account for the relative configurations of chaetochalasin A at C(19) and C(22) (cytochalasan numbering). The conjugated triene fragment has the all (*E*)-stereochemistry. In the cyclisation of the 3-acylpyrrolinone **3** into chaetochalasin A **1**, by analogy with cytochalasan biosynthesis, it was proposed that the Diels-Alder reaction of the pyrrolinone and the terminal dienyl fragment occurs first.[1] If this proceeds *exo* with respect to the pyrrolinone, it would provide the macrocyclic intermediate **2** that could undergo a transannular, inverse electron demand, Diels-Alder reaction to give the intact framework of chaetochalasin A (**1**) with the concommitant introduction of the quaternary centre at C(14), *cf.* transition structure **4** for the second Diels-Alder reaction.

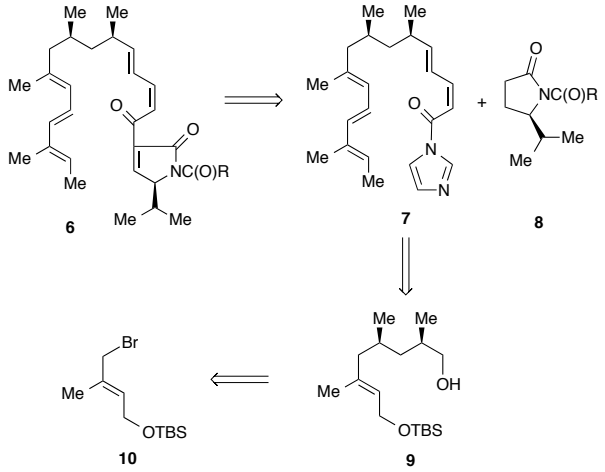


It should be noted that this biogenetic proposal for chaetochalasin A differs from that recently put forward for the biosynthesis of another polycyclic fungal metabolite, diaporthichalasin **5**.[5] On the basis of excellent synthetic studies and the elucidation of its absolute configuration, it is likely that in the biosynthesis of diaporthichalasin, the decalin-forming Diels-Alder reaction occurs first followed by the pyrrolinone mediated cyclisation that, in this case, also introduces a quaternary centre.[6]



Notwithstanding the different biogenetic proposals put forward for chaetochalasin A and diaporthichalasin, it is of interest to investigate the total synthesis of chaetochalasin A using a double Diels-Alder strategy related to that proposed for its biosynthesis. Studies of the synthesis of potential Diels-Alder precursors for a synthesis of chaetochalasin A and their cyclisations are reported herein.

At the onset on the work, it was decided to study the synthesis of the Diels-Alder precursor **6** by acylation of the *N*-acylpyrrolidinone **8** using the hexadecapentaenoyl imidazolide **7**. A subsequent phenylselenation – oxidative elimination sequence as used in the syntheses of cyclochalasans[3] would then complete the synthesis of the 3-acylpyrrolinone **6**. The octenol **9** was identified as a precursor of the long-chain intermediates and was to be synthesized from (*E*)-1-bromo-4-*tert*-butyldimethylsilyloxy-2-methylbut-2-ene (**10**) using chiral auxiliary chemistry.

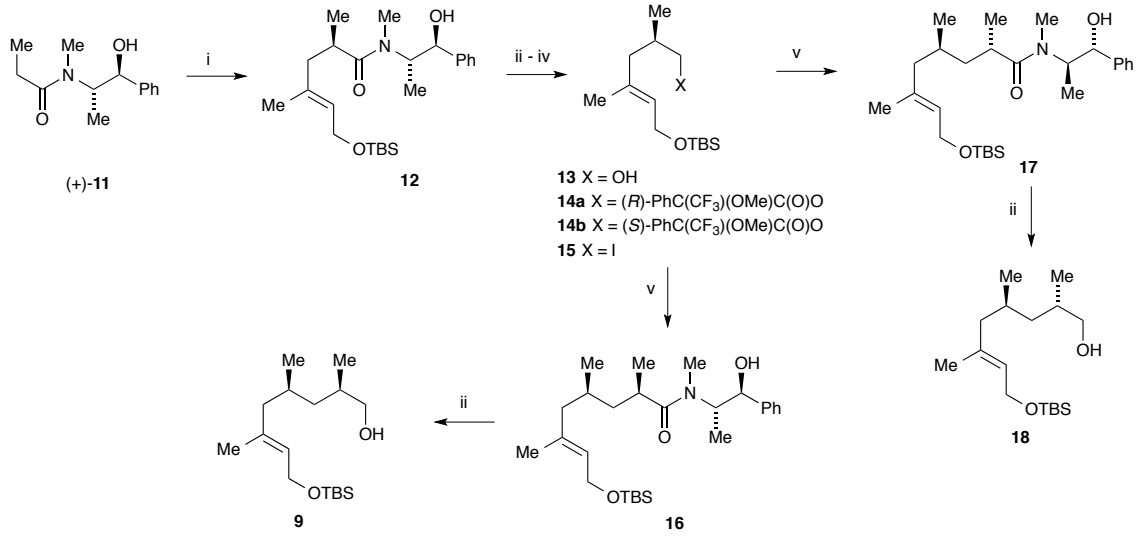


N-Acylpyrrolinones, i.e. **6**, were studied in this synthetic work since experience gained in the syntheses of the cytochalasans showed that *N*-acyl substituents prevent competing isomerism of pyrrolinones into their unstable hydroxypyrrole tautomers and facilitate the Diels-Alder reactions without appreciable racemisation at C(3).[3] Just how Nature controls this process is not clear.

Results and discussion

Use of hexadecapentaenoates

Myers chemistry using (+)-*N*-propionylpseudoephedrine (+)-**11** was used to convert the bromide **10** into the octenol **9**, see Scheme 1.[7] Alkylation of the amide (+)-**11** using the bromide **10**[8] gave the alkylated amide **12**. The ^{1}H NMR spectrum of this was broadened due to the presence of rotamers that were interconverting on the NMR time scale. Reduction of amide **12** gave the alcohol **13** that was converted into its (*R*)- and (*S*)-Mosher´s derivatives **14a** and **14b** to estimate its enantiomeric purity. In the event, both Mosher´s derivatives appeared to comprise (>99%) a single diastereoisomer (^{1}H and ^{19}F NMR) and so the optical purity of the alcohol **13** was judged to be high. This alcohol was then converted into the iodide **15** that was used to alkylate the amide (+)-**11**. By analogy with the literature, the product from this reaction was identified as the amide **16** although again its ^{1}H NMR spectrum was broadened by the interconversion of rotamers at room temperature. Reduction gave the required octenol **9**. The NMR spectra of octenol **9** indicated that it was mainly a single compound with a minor component present at the 3% level. To confirm the diastereoselectivity of the synthesis, the enantiomeric *N*-propionylpseudoephedrine (-)-**11** was alkylated using the iodide **15** and the alkylated amide **17** so formed reduced to give the octenol **18**.[7] Comparison of the ^{1}H NMR spectra of the alcohol **9** prepared from the amide **16** with the alcohol **18** prepared from **17** confirmed that the minor component present in the alcohol **9** was indeed its diastereoisomer **18**, **9** : **18** = 97 : 3.

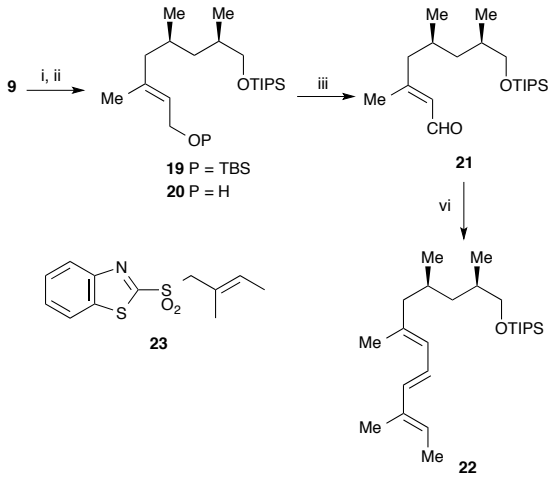


Scheme 1 Synthesis of (2*R*,6*S*,6*E*)-2,4,6-trimethyloct-6-en-1-ol (**9**) Reagents and conditions: i, LiCl, LDA, -78 °C, (+)-**11**, THF, -78 °C to r.t., 0 °C, add **10**, 0 °C, 40 min (89%); ii, LDA, $NH_3.BH_3$, THF, 0 °C to r.t., 0 °C, add **12** or **16** or **17**, r.t., 1.5 - 2 h (**13**, 80%; **9**, 84%; **18**, 75%); iii, (*S*)- or (*R*)-Mosher's acid chloride, DCM, DMAP, Et_3N, r.t. (**14a**, 74%; **14b**, 71%); iv, Ph_3P, imid., DCM, I_2, r.t., 1.5 h (83%); v, LiCl, LDA, -78 °C, (+)- or (-)-**11**, THF, -78 °C to r.t., add **15**, r.t., 19 h (**16**, 86%; **17**, 83%).

The minor product present in the mixture obtained by reduction of **16** will comprise (2*S*,4*S*)-octenol **18** and its enantiomer. However, the required (2*R*,4*S*)-octenol **9** was of very high optical purity since its enantiomer could only have been formed from the minor enantiomer of iodide **15** reacting in its less favoured mode with the amide (+)-**11**.

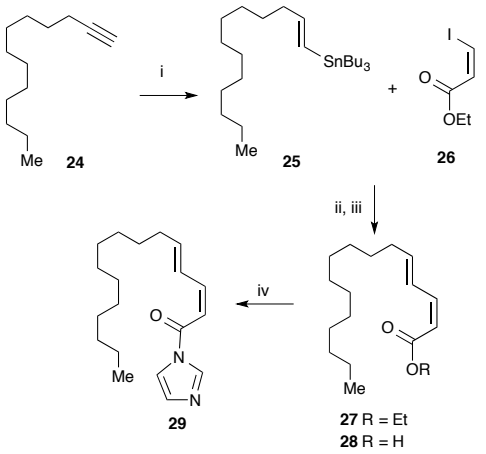
It was decided to check procedures for the introduction of the conjugated triene and the (2*Z*,4*E*)-dienyl ester. The alcohol **9** was protected as its tri-*iso*propylsilyl ether **19** and selective desilylation gave the alcohol **20** that was oxidised to the aldehyde **21**. The modified Julia reaction[9] with sulfone **23**, prepared from (*E*)-2-methylbut-2-en-1-ol via the corresponding sulfide, was then investigated.[10] Useful stereoselectivity was obtained if lithium hexamethyldisilazide was added to a mixture of the aldehyde **21** and the sulfone **23** at -78 °C. Under these conditions, the (6*E*,8*E*,10*E*)-isomer **22** was the major product with minor side-products provisionally identified as the (6*E*,8*Z*,10*E*)- and the (6*E*,8*E*,10*Z*)-isomers being formed at the 4-5% level, see Scheme 2. The *N*-phenyltetrazolyl sulfone analogous to the benzotriazolyl sulfone **23** gave lower yields.

A Stille procedure[11] was initially investigated for the introduction of (2*Z*,4*E*)-dienyl ester fragment. Addition of tributyltin hydride to 1-tridecyne **24**[12] gave mainly the (*E*)-vinyl stannane **25** that was coupled with ethyl (*Z*)-3-iodopropenoate **26**[13] under Stille conditions. This gave the (2*Z*,4*E*)-dienyl ester **27** containing about 10% of its (2*Z*,4*Z*)-isomer. This mixture was converted into the acyl di-imidazolide **29** *via* the acid **28** since analogous imidazolides, *cf.* **7**, have been used in the synthesis of 3-acylated pyrrolidinones. In practice, the (2*Z*)-stereochemical integrity of the imidazolide **29** was found to be sensitive to the time allowed for the reaction between the acid



Scheme 2 Introduction of the conjugated triene Reagents and conditions: i, Et_3N, TIPSOTf, DCM, -78 °C to r.t., 30 min. (92%); ii, PPTS, DCM, MeOH, r.t., 4 h (86%); iii, Dess Martin periodinane, DCM, r.t., 1 h (92%); iv, **21** and **23,** add LiHMDS, -78 °C to r.t., 2 h [74%; (6*E*,8*E*,10*E*) : (6*E*,8*Z*,10*E*) : (6*E*,8*E*,10*Z*) = 91: 5 : 4].

28 and carbonyl di-imidiazole. A 5 : 1 mixture of the (2*Z*,4*E*)-isomer **29** and its (2*E*,4*E*)-isomer was obtained after 45 minutes but longer reaction times gave more (2*Z*)- to (2*E*)-isomerisation, (2*Z*,4*E*) : (2*E*,4*E*) = 3 : 1 after 2 h, and 1 : 1 after 16 h. In this sequence, products from the minor (2Z,4Z)-dienyl ester were not isolated. As this Stille chemistry had provided access to (2*Z*,4*E*)-dienyl esters, it was now applied to a synthesis of the ethyl hexadecapentaenoate **40** required for the synthesis of the Diels-Alder precursor **7**, see Scheme 4.



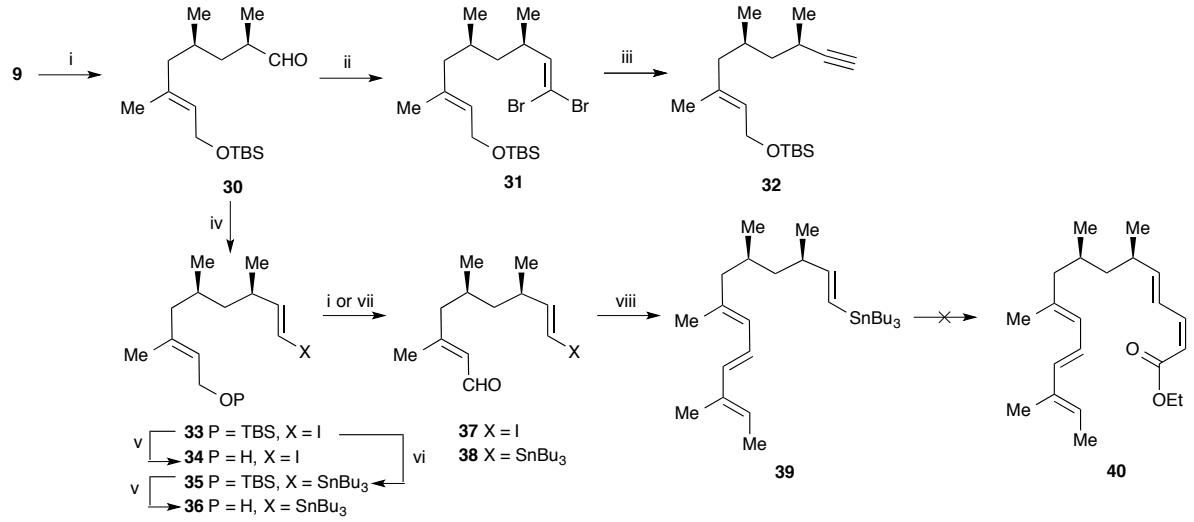
Scheme 3 Introduction of the (2*Z*,4*E*)-dienyl ester using a Stille reaction Reagents and conditions: i, Bu_3SnH, AIBN (cat.), benzene, heat, 4 h [79%; (*E*) : (*Z*) = 10 : 1]; ii, **26**, $PdCl_2(MeCN)_2$, DMF, r.t., 24 h [80%; (2*Z*,4*E*) : (2*Z*,4*Z*) = 10 : 1); iii, NaOH, EtOH, r.t., 3 h (99%); iv, $CO(imid)_2$, THF, r.t., 45 min [82%; (2*Z*,4*E*) : (2*E*,4*E*) = 5 : 1).

Aldehyde **30** was prepared by oxidation of the alcohol **9** and was converted into the alkyne **32** *via* the dibromide **31**[14] since direct conversion using the Ohira-Bestmann reagent[15] was accompanied by epimerisation at C(3). However, attempts to convert alkyne **32** into the corresponding (*E*)-vinylstannane by either free-radical or palladium catalysed[16] procedures gave mixtures of (*E*,*Z*) and regioisomers, respectively. The aldehyde **30** was then converted into the (*E*)-vinyl iodide **33**[17] that was deprotected to give the corresponding alcohol **34**. This was oxidised to the aldehyde **37** but, despite a precedent,[18] attempts to carry out a modified Julia reaction on this vinylic iodide led to mixtures of products that were not fully characterised.

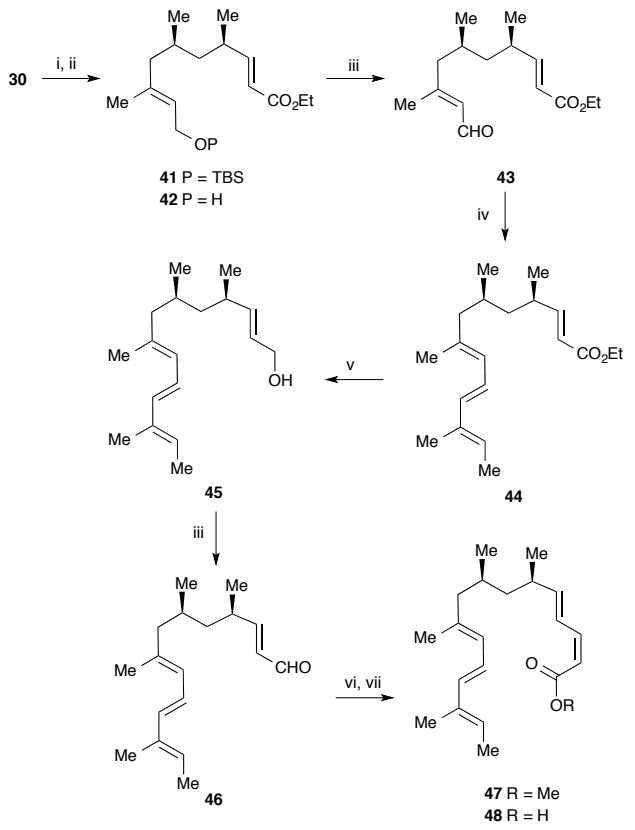
The vinyl iodide **33** was therefore converted into the stannane **35**.[19] Deprotection and oxidation of the resulting alcohol **36** then gave the aldehyde **38**. The modified Julia reaction of this with sulfone **23** was successful, albeit slightly less stereoselective than observed earlier, and gave mainly the required all-(*E*)-tetraene **39**, but attempts to effect a Stille reaction with ethyl (*Z*)-3-iodopropenoate **26** gave a mixture of products that could not easily be separated and properly characterised. In particular, the hexadecapentaenoate **40** could not be isolated, see Scheme 4. At this point it was decided to look at the use of phosphonate condensations for the synthesis of the long-chain pentenyl ester.

The aldehyde **30** was converted into the (2*E*)-unsaturated ester **41** using a Wittig reaction. This reaction was highly stereoselective, the (2*Z*)-isomer not being detected as a product. Following desilylation, oxidation of the resulting alcohol **42** gave the aldehyde **43** that was converted into the conjugated triene **44** by the modified Julia reaction using the sulfone **23**. This reaction was selective for the formation of the all (*E*)-tetraene **44** although small amounts of the (10*Z*)- and (12*Z*)-isomers were also formed, (2*E*,8*E*,10*E*,12*E*) : (2*E*,8*E*,10*Z*,12*E*) : (2*E*,8*E*,10*E*,12*Z*) = 87 : 6 : 7, see Scheme 5.

The mixture of tetraenes was not separated. Structures were assigned to components of the mixture by ^{1}H NMR. The geometries of the 10-double-bonds of all three products were established by their 10,11-vicinal coupling constants. Moreover, comparison of the ^{1}H NMR spectrum of the mixture with data published for (2*E*,4*E*)- and (2*Z*,4*E*)-3,7,11-trimethyldodeca-2,4,6,10-tetraenes and for aspochalasan precursors,[20,4] confirmed the all-(*E*)-stereochemistry assigned to the major product **44** and the (2*E*,8*E*,10*E*,12*Z*)-configuration assigned to the minor (10*E*)-product that had presumably formed by a small amount of (*E*,*Z*)-isomerisation of the lithiated sulfone.



Scheme 4 Attempts to prepare hexadecapentaenoate **40** using Stille reactions Reagents and conditions: i, Dess Martin periodinane, DCM, py., r.t., 15 min., add alcohol, r.t. 1 - 2 h (**30**, 97%; **37**, 78%); ii, Ph_3P, DCM, Zn, 0 °C, CBr_4, 0 °C to r.t., add **30**, r.t., 18 h (74%); iii, ^{n}BuLi, THF, -78 °C, 1.5 h (80%); iv, $CrCl_2$, THF, 0 °C, 15 min, add **30**, CHI_3, 0 °C, 3 h (76%); v, TBAF, THF, 0 °C to r.t., 1 h (**34**, 83%; **36**, 82%); vi, **33**, Bu_3SnCl, THF, -78 °C, add ^{t}BuLi, -78 °C, 2 h (84%); vii, MnO_2, **36**, DCM, r.t., 1 h (82%); viii, **38**, **23**, THF, -78 °C, LiHMDS, -78 °C to r.t., 2 h [75%, (1*E*,7*E*,9*E*,11*E*) : (1*E*,7*E*,9*Z*,11*E*) : (1*E*,7*E*,9*E*,11*Z*) = 88 : 7 : 5].



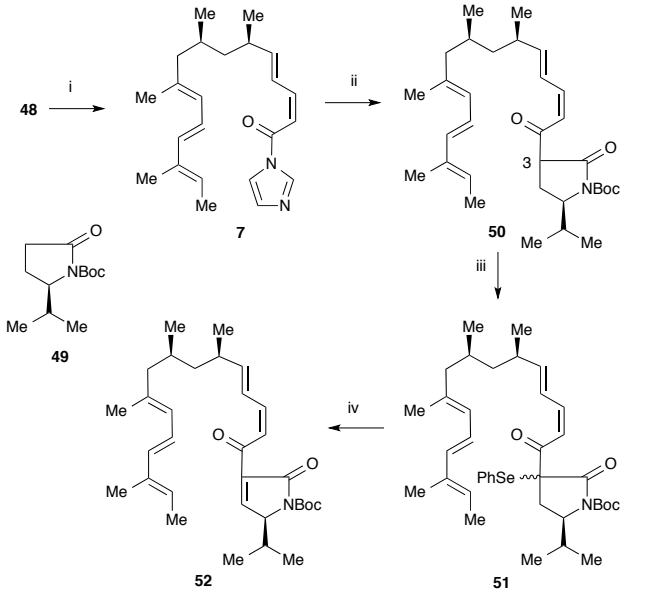
Scheme 5 Synthesis of hexadecapentaenoic acid **48** Reagents and conditions; i, Ph_3PCHCO_2Et, DCM, r.t., 14 h (73%); ii, PPTS, DCM, EtOH, r.t., 3 h (90%); iii, MnO_2, DCM, r.t., 2 - 4 h (**43**, 85%; **46**, 84%); iv, **43**, **23**, THF, add LiHMDS, -78 °C to r.t., 2 h [73%, (2*E*,8*E*,10*E*,12*E*) : (2*E*,8*E*,10*Z*,12*E*) : (2*E*,8*E*,10*E*,12*Z*) = 87 : 6 : 7]; v, DIBAL-H, THF, -78 °C, 1 h, r.t. (85%); vi, K_2CO_3, 18-*c*-6, r.t., 1 h, -20 °C, add $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ and **46**, 0 °C, 3 h (86%); vii, NaOH, EtOH, H_2O, r.t., 18 h [92%; (2*Z*,4*E*,10*E*,12*E*,14*E*) : (2*Z*,4*E*,10*E*,12*Z*,14*E*) : (2*Z*,4*E*,10*E*,12*E*,14*Z*) = 77 : 6 : 17].

Reduction of the ester **44**, still containing its (10*Z*)- and (12*Z*)-isomers as minor components, gave the alcohol **45**. This was oxidised and condensation of the resulting aldehyde **46** with bis-(2,2,2-trifluoroethyl) (methoxycarbonyl)methylphosphonate was selective for the formation of the (2*Z*)-hexadecapentaenoate **47**.[21] Hydrolysis of the ester then gave the acid **48**, ready for incorporation into a synthesis of the Diels-Alder precursor **7**, see Scheme 5.

Although this sequence provided the required (2*Z*,4*E*,10*E*,12*E*,14*E*)-isomer **48** as the major product, the amount of the (14*Z*)-isomer gradually increased along the reaction sequence so that the acid **48** was a mixture of geometrical isomers, in the ratio (2*Z*,4*E*,10*E*,12*E*,14*E*) : (2*Z*,4*E*,10*E*,12*Z*,14*E*) : (2*Z*,4*E*,10*E*,12*E*,14*Z*) = 77 : 6 : 17. This attrition of the stereochemical integrity of the 14-double-bond along the sequence was attributed to acid-catalysed isomerisation *via* resonance stabilised carbenium ions and could not be avoided despite precautions taken to minimize the exposure of the intermediates to acid, e.g. the use of base-extracted silica and glasswear. No isomerisation of the trisubstituted 10-double-bond was observed.

Despite this partial isomerisation, following the procedure used earlier, the acid **48** was converted into the imidazolide **7**. This wasn´t purified but was used immediately to acylate the Boc-protected pyrrolidinone **49**.[22] The product obtained was a complex mixture of products including both epimers of the 3-acylated pyrrolidinone **50**, the corresponding enol, and minor components corresponding to geometrical isomers along the hexadecapentaenoyl chain. It was identified on the basis of spectroscopic data and by comparison with analogous conpounds prepared earlier. Phenylselanation gave the epimers of the 3-phenylselanylpyrrolidinone **51** and these were immediately subjected to oxidative elimination to generate the pyrrolinone **52** using conditions that had been successsful during syntheses of cytochalasans.[3] However, after heating the reaction mixture derived from the oxidative elimination, a mixture of products was isolated in only a low yield and no discrete product could be identified, see Scheme 6.

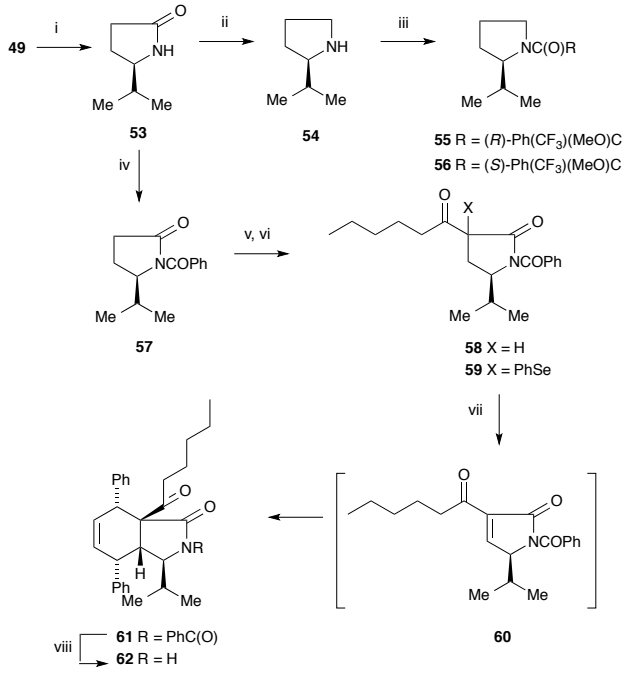
This work had been complicated by (14*E*,14*Z*)- and (2*Z*,2*E*)-isomerisation and by the extensive enolisation of the 3-acylated pyrrolidinone **50**. To avoid this problem, it was decided to synthesize Diels-Alder precursors that lacked the (2*Z*)-double-bond. If successful, attempts would be made to introduce this double-bond after the macrocyclisation.



Scheme 6 Formation of the 3-(hexadecapentaenoyl)pyrrolinone **52** Reagents and conditions; i, $CO(imid)_2$, THF, r.t., 45 min; ii, **49**, LiHMDS, THF, -78 °C, 1 h, add **7**, -78 °C, 2 h [58%; (10*E*,12*E*,14*E*) : (10*E*,12*Z*,14*E*) : (10*E*,12*E*,14*Z*) = 73 : 5 : 22; (2*Z*,4*E*) : (2*E*,4*E*) = 90 : 10]; iii, LiHMDS, -78 °C, 30 min, add PhSeCl, THF, -78 °C, 4 h (60%); iv, (a) H_2O_2, -50 °C, *m*-CPBA, $CDCl_3$, -50 °C, 40 min, 0 °C, 15 min; (b) benzene, reflux, 5 h.

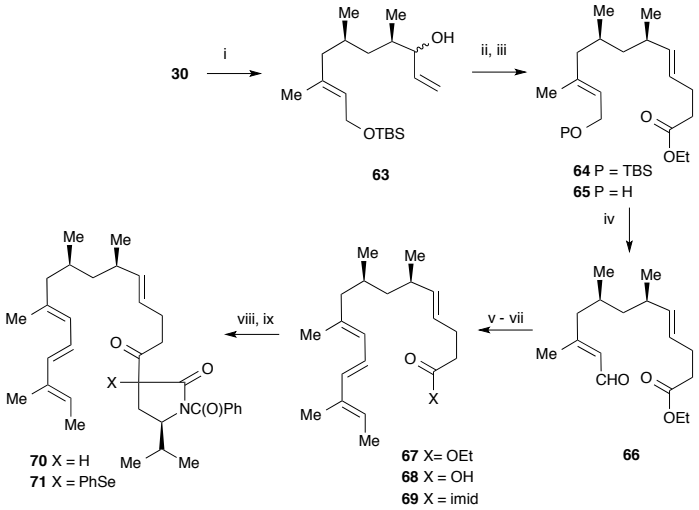
Use of hexadecatetraenoates

It was decided to check the reactivity of valine-derived pyrrolinones in a simple intermolecular Diels-Alder reaction, see Scheme 7. As *N*-benzoylpyrrolinones rather than *N*-Boc-pyrrolinones had been used in the earlier syntheses of cytochalasans,[3] an *N*-benzoylpyrrolidinone was used in this synthesis. Following acid catalysed removal of the Boc-group from pyrrolidinone **49**, the enantiomeric purity of the resulting NH-pyrrolidinone **53** was checked by comparison of the *N*-Mosher´s derivatives of the pyrrolidine **54** prepared by reduction of pyrrolidinone **53** using lithium aluminium hydride. The Mosher´s derivatives appeared to be diastereomerically homogeneous and so the e.e of the pyrrolidinone **53** was >95%. Following *N*-benzoylation, the resulting imide **57** was acylated using hexanoyl imidazolide to give the 3-acylpyrrolidinone **58** as a mixture of 3-epimers with some enol present. This mixture was taken through to the 3-phenylselanyl derivative **59**, again as a mixture of epimers at C(3). Oxidative elimination generated the pyrrolinone **60** that was heated in toluene in the presence of (1*E*,3*E*)-1,4-diphenylbuta-1,3-diene. A single adduct **61** was isolated and the *endo* configuration with respect to the pyrrolinone was established by ^{1}H NMR (nOe). Sodium hydroxide gave the debenzoylated product **62**.

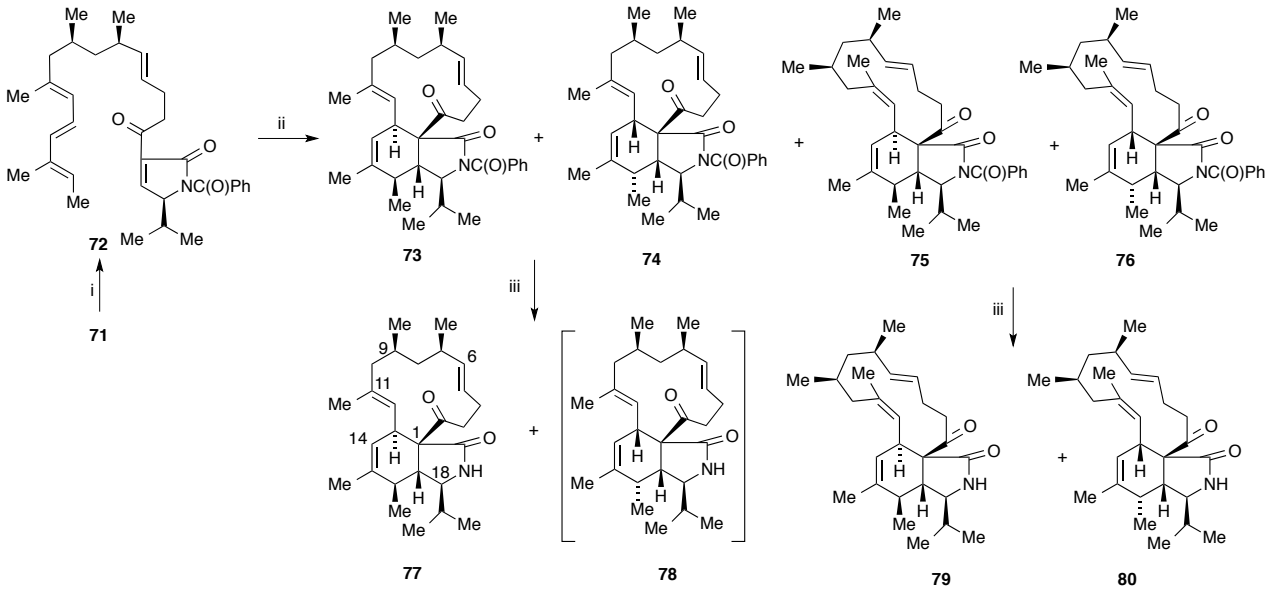


Scheme 7 Pyrrolinone synthesis and an intermolecular Diels-Alder reaction Reagents and conditions: i, TFA, DCM, r.t., 1 h (94%); ii, $LiAlH_4$, THF, 66 °C, 14 h (70%); iii, (*S*)- or (*R*)-PhC(CF_3)(OMe)COCl, DCM, py., r.t. 16 h (**55**, 70%; **56**, 75%); iv, PhCOCl, py., r.t., 4 h (84%); v, **57**, THF, -78 °C, LiHMDS, -78 °C, 1 h, $CH_3(CH_2)_4CO(C_3N_2H_3)$, -78 °C, 5 h (76%); vi, LiHMDS, -78 °C, 1 h, PhSeCl, -78 °C, 2 h (77%); vii, (a) H_2O_2, $CHCl_3$, *m*-CPBA, -48 °C, 45 min, 0 °C, 10 min; (b) (2*E*,4*E*)-1,4-diphenylbuta-1,3-diene, toluene, heat, 4 days (43%); viii, NaOH, MeOH, H_2O, r.t., 6 h (60%).

The synthesis of a Diels-Alder precursor lacking the (2*Z*)-double-bond would require the assembly of a γδ-unsaturated ester. Such compounds can be prepared using Claisen rearrangements[23] and this strategy was adopted for the present work, see Scheme 8. Addition of vinylmagnesium bromide to the aldehyde **30** gave the alcohol **63** as a mixture of epimers. Heating this mixture with triethyl orthoacetate and a catalytic amount of propanoic acid in xylene gave the γδ-unsaturated ester **64** predominantly as its (*E*)-isomer. After desilylation, oxidation of the alcohol **65** gave the aldehyde **66** and a modified Julia reaction with the benzothiazolyl sulfone **23** gave the hexadecatetraenoate **67** predominantly as its all (*E*)-diastereoisomer, (4*E*,10*E*,12*E*,14*E*) : (4*E*,10*E*,12*Z*,14*E*) : (4*E*,10*E*,12*E*,14*Z*) = 91 : 4 : 5. This was taken through to the acyl imidazolide **69** *via* the acid **68**, and acylation of the pyrrolidinone **57** using this imdazolide gave the partly enolised 3-acylpyrrolidinone **70** as a mixture of epimers. Phenylselanation then gave the 3-phenylselanylpyrrolidinone **71** also a mixture of epimers. During his sequence there was some attrition in the stereochemical homogeneity of the conjugated triene so that, although the hexadecatetraenoyl side chain of the major pyrrolidinone **71** had retained the all (*E*)-configuration, more of the (14*Z*)-isomer was present, (4*E*,10*E*,12*E*,14*E*) : (4*E*,10*E*,12*Z*,14*E*) : (4*E*,10*E*,12*E*,14*Z*) = 76 : 3 : 21.



Scheme 8 Synthesis of the ethyl hexadecatetraenoate **67** and Diels-Alder precursors; i, CH_2=CHMgBr, THF, r.t., 50 min (74%; 2 : 1 mixture); ii, $CH_3C(OEt)_3$, $CH_3CH_2CO_2H$, xylene, heat, 6 h (91%); iii, PPTS, DCM, EtOH, r.t., 24 h (95%); iv, MnO_2, DCM, r.t., 1 h (85%); v, **66**, **23**, THF, -78 °C, add LiHMDS, THF, -78 °C, 1 h, r.t., 1 h [74%; (4*E*,10*E*,12*E*,14*E*) : (4*E*,10*E*,12*Z*,14*E*) : (4*E*,10*E*,12*E*,14*Z*) = 91 : 4 : 5]; vi, NaOH, EtOH, r.t., 18 h (99%); vii, $CO(imid)_2$, THF, r.t., 18 h [95%; (4*E*,10*E*,12*E*,14*E*) : (4*E*,10*E*,12*Z*,14*E*) : (4*E*,10*E*,12*E*,14*Z*) = 88 : 4 : 12]; viii, **57**, THF, -78 °C, LiHMDS, -78 °C, 1 h, add **69**, -78 °C, 6 h (79%); ix, LiHMDS, -78 °C, 30 min., PhSeCl, -78 °C, 2.5 h [92%; (4*E*,10*E*,12*E*,14*E*) : (4*E*,10*E*,12*Z*,14*E*) : (4*E*,10*E*,12*E*,14*Z*) = 76 : 3 : 21].



Scheme 9 Diels Alder cyclisation of the hexadecatetraenoylpyrrolinone **72** Reagents and conditions: i, H_2O_2, $CHCl_3$, *m*CPBA, -48 °C, 50 min, 0 °C, 10 min; ii, toluene, 90 °C, 10 h (**73** + **74**, 12%; **75** + **76**, 11%); iii, NaOH, MeOH, r.t., 3 h (**77**, 32%; **78**, 11% not pure; **79**, 38%; **80**, 29%).

Notwithstanding the partial isomerisation of the 14-double-bond, the mixture of phenylselanylpyrrolidinones **71** was subjected to oxidative elimination to generate the pyrrolinone **72** and the resulting product heated in toluene to attempt the intramolecular Diels-Alder reaction. Repeated chromatography of the product mixture gave two fractions. The less polar was identified as a mixture of the *exo*-(11*E*)- and *endo*-(11*E*)-Diels-Alder adducts **73** and **74**.[24] The more polar fraction comprised a mixture of the analogous *exo*- and *endo*-(11Z)-isomers **75** and **76** (11%). (The *endo*- and *exo*-nomenclature refers to the stereoselectivity with respect to the pyrrolinone.)

N-Debenzoylation of the *exo*/*endo*-mixture of the (11*E*)-isomers **73** and **74** gave the *exo*-(11*E*)-NH-adduct **77** but the *endo*-(11*E*)-isomer **78** could not be separated from other products. The *exo*-(11*E*)-NH-adduct **77** has the same configuration at each of its seven stereogenic centres as chaetochalasin A (**1**). *N*-Debenzoylation of the mixture of the (11*Z*)-isomers **75** and **76** gave the *exo*- and *endo*-(11*Z*)-NH adducts **79** and **80** that could be separated and were characterised separately.

Structures were assigned to these debenzoylated Diels-Alder adducts on the basis of ^{1}H NMR data and by comparison with earlier work. In all cases Diels-Alder addition to 5-substituted pyrrolinones is known to take place on the less hindered face of the pyrrolinone away from the bulky 5-substituent.[3] This was assumed to be the case here and so the configuration at C(1), C(17) and C(18) of all the adducts was assigned as shown. Intramolecular *endo*- and *exo*-adducts from pyrrolinones can be distinguished by their 13,14-coupling constants. These are typically 6.5 Hz for *exo*-adducts and significantly smaller, typically 0 – 1 Hz, for *endo*-adducts.[3,4] On this basis, the adducts **77** and **79** were assigned the *exo*-configuration with the adduct **80**, the *endo*-configuration.

The relative configuration at C(13) and C(17) was confirmed for the adduct **77** by nOe studies.[23] These showed a significant interaction between H(12) and H(17). Moreover, significant nOe enhancements of H(16) on irradiation of H(18) and the lack of any observable nOe interactions between the 16-methyl group and H(18) confirmed the configuration of adduct **77** at C(16). Similar studies confirmed the configurational assignment of the *exo*-(11*Z*)-isomer **79** with the (*Z*)-configuration of the 11-double-bond being established by a strong nOe enhancement of the 11-methyl group on irradiation of H(12). Complementary nOe observations established the stereochemistry of the *endo*-(11*Z*)-isomer **80**.

Summary and conclusions

This work on studies into the synthesis of chaetochalasin A (**1**) using intramolecular Diels-Alder reaction will help to direct further work in this area. Syntheses of the macrocyclic Diels-Alder precursors were complicated by (*Z*,*E*)-isomerisation of the (2*Z*)-double-bonds in intermediates that contained the hexadecapenta-2,4,10,12,14-enoate moiety. Morover the (14*E*)-hexadecapenta- and -hexadecatetra-enoates have a tendency to equilibrate with their (14*Z*)-isomers. As the 2- and 14-double-bonds were introduced separately it was difficult to prepare intermediates without partial isomerisation of one or other of these double-bonds during the synthesis. For this reason later studies were carried out on hexadecatetraenoates to evaluate the macrocycle-forming Diels-Alder reaction first.

In contrast to the isomerisation of the 14-double-bond observed during the assembly of the Diels-Alder precursors, it appeared that significant isomerisation of the 10-double-bond took place during the Diels-Alder itself leading to the (11*Z*)-products **75** and **76**. This isomerisation had not been observed

during syntheses of cytochalasans using intramolecular Diels-Alder reactions but the corresponding double-bonds were (*E*)-disubstituted so (*E*)-(*Z*)-isomerisation was not expected. The formation of an (*E*,*Z*)-mixture of Diels-Alder products isolated during the study of aspochalasan synthesis was attributed to the use of a mixture of (*E*)- and (*Z*)-isomers in the starting material for the Diels-Alder reaction.[4]

It may be that the (10*E*,10*Z*)-isomerisation observed in the present work leading to products with both the (11*E*)- and (11*Z*)-geometry, is catalysed by the acidic side-products of the selenoxide elimination although the solution of the pyrrolinone was extracted with base before heating. In future work, the selenoxide elimination should be avoided perhaps by using a biomimetic Knoevenagel condensation to assemble the pyrrolinone from an aldehyde precursor under mildly basic conditions. No products were isolated that had been derived from (14*Z*)-isomers of the Diels-Alder precursors. However only modest yields of Diels-Alder products were observed and it may be that the (14*Z*)-isomers were less disposed to Diels-Alder cyclisations because of steric hindrance in the conformation of the conjugated diene required for cyclisation.

Notwithstanding these complications, substantial progress towards a total synthesis of chaetochalasin A **1** has been made. Future work will be to develop the Knoevenagel approach to the *N*-acylated pyrrolinones to see whether the isomerisation of the trisubstituted double-bonds during the Diels-Alder step can be avoided and to study the introduction of the (3*Z*)-double-bond into the *N*-deacylated (11*E*)-*exo*-Diels-Alder product **77** in order to complete a synthesis of chaetochalasin A **1**.

Experimental

(2*R*,4*E*)-*N*-[(1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl]-*N*-methyl-6-*tert*-butyldimethylsilyloxy-2,4-dimethylhex-4-enamide (12). Lithium di-*iso*propylamide (1.8 M in THF/heptane/ethylbenzene, 1.72 g, 16.1 mmol, 8.94 mL) was added to LiCl (1.95 g, 46.4 mmol) in THF (11 mL) and the solution cooled to −78 °C. The amide (+)-**11** (1.70 g, 7.74 mmol) in THF (20 mL) cooled to 0 °C, was added dropwise with stirring at −78 °C for 1 h before being allowed to warm to r.t.. The mixture was cooled 0 °C before the dropwise addition of the bromide **10** (3.24 g, 11.6 mmol) in THF (11 mL) with stirring at 0 °C for 40 min. Saturated aqueous ammonium chloride (360 mL) was added and the aqueous layer was extracted with ethyl acetate (144 mL × 6). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate : light petroleum (1 : 2) as eluent gave the *title compound* **12** as a light yellow oil (2.89 g, 89%), R_f = 0.17 (2 : 1, ether : petrol), as a 3 : 1 mixture of rotamers (^{1}H and ^{13}C NMR), $[\alpha]_D^{19}$ +37 (*c* 0.4, $CHCl_3$) (Found: M^+ + Na, 442.2750. $C_{24}H_{41}O_3NNaSi$ requires *M*, 442.2748); ν_{max}/cm^{-1} 3371(br), 2929, 2856, 2361, 1620, 1462, 1407, 1378, 1253, 1196, 1074, 1053, 1005, 939, 833, 774, 700, 667 and 614; δ_H (400 MHz, $CDCl_3$) major rotamer 0.04 (6 H, s, 2 × $SiCH_3$), 0.88 [9 H, s, $SiC(CH_3)_3$], 1.07 (6 H, m, 2-CH_3 and 2′-CH_3), 1.59 (3 H, s, 4-CH_3), 2.00 (1 H, dd, *J* 14.0, 7.5, 3-H), 2.30 (1 H, dd, *J* 14.0, 7.0, 3-H′), 2.81 (1 H, m, 2-H), 2.89 (3 H, s, N-CH_3), 4.17 (2 H, m, 6-H_2), 4.34 (1 H, br. s, OH), 4.45 (1 H, m, 2′-H), 4.61 (1 H, m, 1′-H), 5.30 (1 H, tq, *J* 7.5, 1.0, 5-H) and 7.35 (5 H, m, Ar); minor rotamer 0.06 (6 H, s, 2 × $SiCH_3$), 0.89 [9 H, s, $Si(CH_3)_3$], 0.99 (3 H, d, *J* 7.0, 2′-CH_3), 1.68 (3 H, s, 4-CH_3), 2.08 (1 H, dd, *J* 13.5, 8.0, 3-H), 2.52 (1 H, dd, *J* 13.5, 6.5, 3-H′), 2.74 (1 H, br. s, OH), 2.90 (3 H, s, N-CH_3), 3.06 (1 H, m, 2-H), 4.08 (1 H, m, 2′-H), 4.54 (1 H, m, 1′-H), 5.42 (1 H, m, 5-H) and 7.27 (5 H, m, Ar); δ_C (100 MHz, $CDCl_3$) major rotamer −5.3, 14.3, 16.5, 16.8, 18.2, 25.8, 25.9, 33.6, 34.6, 43.1, 60.0, 76.1, 126.2, 126.3, 127.4, 128.1, 134.2, 142.4, and 178.3; minor rotamer −5.2, 15.5, 16.5, 17.2, 18.3, 27.0, 32.4, 43.1, 58.0, 75.1, 126.7, 128.0, 128.5, 135.0, 141.4 and 177.3; *m*/*z* (ES+) 442 (M^+ + 23, 100%).

(4*E*,2*R*)-6-*tert*-Butyldimethylsilyloxy-2,4-dimethylhex-4-en-1-ol (13). The borane-ammonia complex (90%, 0.328 g, 9.52 mmol) in THF (3 mL) was added to lithium di-*iso*propylamide (1.8 M in THF/heptane/ethylbenzene; 1.02 g, 9.52 mmol, 5.29 mL) at 0 °C with stirring at 0 °C for 15 min and then at r.t. for 15 min. The solution was then cooled to 0 °C before the addition of the amide **12** (1.00 g, 2.38 mmol) in THF (7 mL) with subsequent stirring at r.t. for 1.5 h. Aqueous hydrogen chloride (1.0 M, 50 mL) was added and the aqueous layer was extracted with ethyl acetate (50 mL × 4). The organic extracts were extracted with saturated aqueous sodium hydrogen carbonate (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 1) gave the *title compound* **13** as a clear liquid (0.49 g, 80%), R_f = 0.47 (1 : 1, ether : light petroleum), $[\alpha]_D^{20}$ +4.6 (*c* 1.1, $CHCl_3$) (Found: M^+ + Na, 281.1914. $C_{14}H_{30}O_2SiNa$ requires *M*, 281.1907); ν_{max}/cm^{-1} 3350(br), 2954, 2928, 2857, 2364, 1668, 1462, 1382, 1361, 1253, 1081, 1040, 1005, 938, 833, 813, 773 and 665; δ_H (400 MHz, $CDCl_3$) 0.07 (6 H, s, 2 × $SiCH_3$), 0.89 (3 H, d, *J* 6.5, 2-CH_3), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.54 (1 H, br. s, OH), 1.64 (3 H, m, 4-CH_3), 1.79-1.92 (2 H, m, 3-H_2), 2.12 (1 H, m, 2-H), 3.43 and 3.50 (each 1 H, dd, *J* 10.5, 5.5, 1-H), 4.19 (2 H, m, 6-H_2) and 5.35 (1 H, tq, *J* 6.5, 1.0, 5-H); δ_C (100 MHz, $CDCl_3$) −5.1, 16.2, 16.6, 18.4, 26.0, 33.7, 44.1, 60.1, 68.4, 126.2 and 135.7; *m*/*z* (ES+) 281 (M^+ + 23, 100%).

(2*R*,4*E*)-6-*tert*-Butyldimethylsilyloxy-1-iodo-2,4-dimethylhex-4-ene (15). Triphenylphosphine (0.51 g, 1.94 mmol) and imidazole (0.132 g, 1.94 mmol) were added to the alcohol **13** (0.32 g, 1.25 mmol) in dichloromethane (13 mL) with stirring for 10 min. Iodine (0.434 g, 1.71 mmol) was added and the reaction mixture was stirred for 1.5 h at r.t. Saturated aqueous sodium bisulfite (14 mL) was added and the aqueous layer was extracted with dichloromethane (40 mL × 4). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum then light petroleum : ether (99 : 1) as eluent gave the *title compound* **15** as a clear liquid (0.38 g, 83%), R_f = 0.44 (20 : 1, hexane : ether), $[\alpha]_D^{20}$ −8.8 (*c* 1.6, $CHCl_3$) (Found: M^+ − C_4H_9, 311.0313. $C_{10}H_{20}OISi$ requires *M*, 311.0323); ν_{max}/cm^{-1} 2955, 2927, 2885, 2856, 1670, 1638, 1472, 1461, 1380, 1360, 1314, 1253, 1221, 1194, 1151, 1101, 1055, 1005, 938, 833, 813, 773 and 665; δ_H (400 MHz, $CDCl_3$) 0.08 (6 H, s, 2 × $SiCH_3$), 0.91 [9 H, s, $SiC(CH_3)_3$], 0.97 (3 H, d, *J* 6.5, 2-CH_3), 1.61 (3 H, m, 4-CH_3), 1.68 (1 H, m, 2-H), 1.88 and 2.10 (each 1 H, dd, *J* 13.5, 7.0, 3-H), 3.10 (1 H, dd, *J* 9.5, 6.0, 1-H), 3.24 (1 H, dd, *J* 9.0, 4.5, 1-H′), 4.20 (2 H, m, 6-H_2)

and 5.37 (1 H, tq, *J* 6.5, 1.0, 5-H); δ_C (100 MHz, $CDCl_3$) −5.1, 16.2, 17.2, 18.4, 20.6, 26.0, 32.7, 46.5, 60.1, 127.1, and 134.2; *m*/*z* (EI/CI) 311 (M^+ - 57, 4%).

(2*R*,4*S*,6*E*)-*N*-[(1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl]-*N*-methyl-8-*tert*-butyldimethylsilyloxy-2,4,6-trimethyloct-6-enamide (16). Lithium di-isopropylamide (1.8 M in THF/heptane/ethylbenzene; 0.92 g, 8.6 mmol, 4.78 mL) was added to LiCl (1.15 g, 27.3 mmol) in THF (4 mL) and the solution cooled to -78 °C. The amide (+)-**11** (1.00 g, 4.52 mmol) in THF (13 mL) cooled to -78 °C was added dropwise and the mixture stirred at −78 °C for 1 h, 0 °C for 15 min and at r.t. for 10 min. The iodide **15** (0.79 g, 2.15 mmol) in THF (8 mL) was then added and the mixture stirred at r.t. for 19 h. Saturated aqueous ammonium chloride (280 mL) was added and the aqueous layer extracted with ethyl acetate (240 mL × 5). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate : light petroleum (1 : 2) as eluent gave the *title compound* **16** as a clear oil (0.85 g, 86%) as a 5 : 1 mixture of rotamers, R_f = 0.24 (2 : 1, light petroleum : ethyl acetate), $[\alpha]_D^{19}$ +41 (*c* 1.6, $CHCl_3$) (Found: M^+ + Na, 484.3230. $C_{27}H_{47}O_3NNaSi$ requires *M*, 484.3217); ν_{max}/cm^{-1} 3378 (br), 2955, 2928, 2856, 1620, 1462, 1408, 1378, 1360, 1300, 1253, 1197, 1083, 1051, 1005, 938, 843, 813, 774, 700 and 665; δ_H (400 MHz, $CDCl_3$) major rotamer 0.06 (6 H, s, 2 × $SiCH_3$), 0.71 (3 H, d, *J* 6.5, 4-CH_3), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.02 (1 H, m, 3-H), 1.04 (3 H, d, *J* 7.0, 2-CH_3), 1.14 (3 H, d, *J* 7.0, 2′-CH_3), 1.56 (1 H, m, 4-H), 1.60 (3 H, s, 6-CH_3), 1.67 (1 H, m, 3-H′), 1.73 (1 H, dd, *J* 13.0, 8.5, 5-H), 1.97 (1 H, dd, *J* 13.0, 6.0, 5-H′), 2.69 (1 H, m, 2-H), 2.83 (3 H, s, NCH_3), 4.19 (2 H, m, 8-H_2), 4.37 (1 H, m, 2′-H), 4.61 (1 H, t, *J* 7.0, 1′-H), 5.27 (1 H, tq, *J* 6.0, 1.0, 7-H) and 7.33 (5 H, m, ArH); minor rotamer 0.86 (3 H, d, *J* 6.5, 4-CH_3), 1.60 (3 H, s, 6-CH_3), 1.73 (1 H, m, 5-H), 1.88 (1 H, m, 3-H′), 2.06 (1 H, dd, *J* 13.0, 5.5, 5-H′), 2.88 (3 H, s, NCH_3), 3.01 (1 H, m, 2-H), 4.08 (1 H, m, 2′-H), 4.55 (1 H, m, 1′-H) and 5.30 (1 H, m, 7-H); δ_C (100 MHz, $CDCl_3$) major rotamer -5.1, 14.3, 16.0, 16.0, 17.9, 18.3, 18,3, 19.4, 25.9, 28.1, 33.9, 41.1, 47.8, 60.2, 76.3, 126.1, 126.1, 127.4, 128.2, 135.4, 142.6 and 178.8; minor rotamer −5.4, 15.4, 18.7, 19.7, 26.9, 28.3, 33.1, 41.3, 57.9, 60.2, 75.1, 125.9, 126.9, 128.3, 128.6, 135.8, 141.3 and 177.5; *m*/*z* (ES+) 484 (M^+ + 23, 100%).

(2*R*,4*S*,6*E*)-8-*tert*-Butyldimethylsilyloxy-2,4,6-trimethyloct-6-en-1-ol (9). Borane-ammonia complex (1.52 g, 44.2 mmol) was added at 0 °C to LDA (1.8 M in THF/heptane/ethylbenzene; 4.73 g, 44.2 mmol, 24.5 mL) in THF (13 mL) with stirring at 0 °C for 15 min and at r.t. for 15 min. The solution was cooled to 0 °C before the amide **16** (5.10 g, 11.0 mmol) was added in THF (37 mL) and the solution stirred at r.t. for 2 h. Aqueous hydrogen chloride (1.0 M; 10 mL) was added and the aqueous layer extracted with ethyl acetate (4 × 10 mL). The organic extracts were extracted with saturated aqueous sodium hydrogen carbonate (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate : light petroleum (1 : 10) as eluent gave the *title compound* **9** as a clear liquid (2.79 g, 84%), R_f = 0.18 (1 : 3, ether : light petroleum), $[\alpha]_D^{22}$ +7.5 (*c* 2.4, $CHCl_3$) (Found: M^+ + Na, 323.2365. $C_{17}H_{36}O_2NaSi$ requires *M*, 323.2377); ν_{max}/cm^{-1} 3348(br), 2953, 2927, 2856, 2360, 1668, 1462, 1379, 1361, 1253, 1092, 1042, 1005, 938, 833, 813, 773, 734 and 665; δ_H (400 MHz, $CDCl_3$) 0.07 (6 H, s, 2 × $SiCH_3$), 0.84 (3 H, d, *J* 6.0, 4-CH_3), 0.90 [9 H, s, $SiC(CH_3)_3$], 0.93 (3 H, d, *J* 6.0, 2-CH_3), 0.94 and 1.33 (each 1 H, m, 3-H), 1.53 (1 H, br. s, OH), 1.59 (3 H, m, 6-CH_3), 1.65-1.78 (3 H, m, 2-H, 4-H and 5-H), 2.02 (1 H, m, 5-H′), 3.38 (1 H, dd, *J* 10.5, 6.5, 1-H), 3.50 (1 H, dd, *J* 10.5, 5.5, 1-H′), 4.19 (2 H, m, 8-H_2) and 5.30 (1 H, tq, *J* 6.5, 1.0, 7-H); δ_C (100 MHz, $CDCl_3$) −5.1, 16.2, 17.4, 18.4, 20.4, 26.0, 28.0, 33.2, 40.9, 47.5, 60.2, 68.2, 125.9 and 135.8; *m*/*z* (ES+) 323 (M^+ + 23, 100%).

(2*E*)-2-(2-methylbut-2-en-1-yl)sulfonylbenzo[*d*]thiazole (23). 2-Mercaptobenzothiazole (0.606 g, 3.63 mmol) and triphenylphosphine (0.951 g, 3.63 mmol) were added sequentially to (*E*)-2-methylbut-2-en-1-ol (0.208 g, 2.42 mmol) in THF (8 mL) and the reaction mixture cooled down to 0 °C before the addition of di-isopropyl azodicarboxylate (0.733 g, 3.63 mmol, 0.71 mL). The mixture was stirred at 0 °C for 10 min and at r.t. for 3 h, and then concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 30) as eluent, gave (2*E*)-2-(2-methylbut-2-en-1-yl)thiobenzo[*d*]thiazole as a light yellow liquid (0.442 g, 78%), R_f = 0.37 (20 : 1, light petroleum : ether) (Found: M^+ + Na, 258.0383. $C_{12}H_{13}NNaS_2$ requires *M*, 258.0382); ν_{max}/cm^{-1} 3059, 2978, 2913, 2856, 2289, 1939, 1901, 1822, 1782, 1667, 1558, 1455, 1425, 1380, 1308, 1274, 1237, 1205, 1158, 1125, 1076, 1018, 990, 933, 879, 850, 828, 780, 725, 704 and 666; δ_H (400 MHz, $CDCl_3$) 1.64 (3 H, dq, *J* 7.0, 1.0, 4-H_3), 1.79 (3 H, m, 2-CH_3), 4.01 (2 H, s, 1-H_2), 5.66 (1 H, qq, *J* 7.0, 1.5, 3-H), 7.30 (1 H, ddd, *J* 8.5, 7.5, 1.5, 6′-H), 7.42 (1 H, ddd, *J* 8.5, 7.5, 1.5, 5′-H), 7.76 (1 H, dd, *J* 8.5, 1.5, 7′-H) and 7.89 (1 H, dd, *J* 8.5, 1.5, 4′-H); δ_C (100 MHz, $CDCl_3$) 13.7, 15.0, 43.0, 120.9, 121.5, 124.1, 124.9, 125.9, 130.0, 135.2, 153.1 and 167.2; *m*/*z* (ES+) 258 (M^+ + 23, 100%).

Ammonium molybdate tetrahydrate (16.3 g, 13.2 mmol) in aqueous hydrogen peroxide (28%; 287.0 mL) was to a chilled solution of the benzothiazolyl sulphide (6.60 g, 28.1 mmol) in ethanol (200 mL) and the mixture stirred at 0 °C for 15 min and at r.t. for 30 min. Ethyl acetate (2000 mL) was added, the mixture was cooled to 0 °C and saturated aqueous sodium bisulfite (400 mL) and water (1000 mL) were added. The aqueous layer was washed with ethtl acetate (4 × 1000 mL) and the organic extracts were dried ($MgSO_4$) and concentred under reduced pressure. Chromatography of the residue using gradient elution, ether : light petroleum (1 : 10) to ether as eluent, gave the *title compound* **23** as a white solid (5.74 g, 77%), R_f = 0.11 (5 : 1, light petroleum : ether), m.p 90.1-91.4 °C; (Found: M^+ + Na, 290.0271. $C_{12}H_{13}O_2NNaS_2$ requires 290.0280; Found: C, 53.72; H, 4.97; N, 5.21; S, 23.53. $C_{12}H_{13}O_2NS_2$ requires C, 53.91; H, 4.90; N, 5.24; S, 23.99); ν_{max}/cm^{-1} 2927, 2855, 1667, 1553, 1466, 1403, 1311, 1235, 1197, 1143, 1124, 1084, 1022, 850, 771, 732, 692 and 641; δ_H (400 MHz, $CDCl_3$) 1.55 (3 H, dq, *J* 7.0, 1.0, 4-H_3), 1.83 (3 H, s, 2-CH_3), 4.15 (2 H, s, 1-H_2), 5.45 (1 H, qq, *J* 7.0, 1.0, 3-H), 7.59 (1 H, ddd, *J* 8.5, 7.5, 1.5, 6′-H), 7.64 (1 H, ddd, *J* 8.5, 7.5, 1.5, 5′-H), 8.01 (1 H, dd, *J* 8.5, 1.5, 7′-H) and 8.23 (1 H, dd, *J* 8.5, 1.5, 4′-H); δ_C (100 MHz, $CDCl_3$) 14.1, 16.6, 64.4, 122.2, 122.5, 125.4, 127.5, 127.9, 132.1, 136.9, 152.6 and 165.8; *m*/*z* (ES+) 557 (100%) and 290 (M^+ + 23, 56%).

(5*R*)-5-(Prop-2-yl)pyrrolidin-2-one (53). Trifluoroacetic acid (0.122 g, 1.07 mmol, 0.08 mL) was added to the pyrrolidinone **49** (0.122 g, 0.537 mmol) in dichloromethane (4 mL) at r.t. and the solution stirred at r.t. for 1 h. Saturated aqueous sodium hydrogen carbonate (20 mL) was added, the aqueous layer was extracted with dichloromethane (4 × 20 mL) and the organic extracts were dried (Na_2SO_4). After concentration under reduced pressure, chromatography of the residue using ether and methanol as eluent (gradient elution, ether to 1 : 10 methanol : ether) gave the *title compound* **53** as a white solid (0.57 g, 94%), R_f = 0.46 (1 : 10, MeOH : ether), m.p. 57.0-60.0 °C, $[\alpha]_D^{18}$ +12 (*c* 0.4, benzene) (Found: $M^+ - C_3H_7$, 84.0441. C_4H_6ON requires *M*, 84.0444); ν_{max}/cm^{-1} 3198, 3092, 2960, 2934, 2892, 2875, 1682, 1658, 1470, 1451, 1392, 1371, 1346, 1315, 1291, 1269, 1214, 1168, 1140, 1076, 1033, 995, 975, 956, 922, 885, 766, 681 and 626; δ_H (400 MHz, $CDCl_3$) 0.89 and 0.94 (each 3 H, d, *J* 7.0, CHCH_3), 1.62 (1 H, m, 5-CH), 1.74 and 2.15 (each 1 H, m, 4-H), 2.25-2.38 (2 H, m, 3-H_2), 3.37 (1 H, q, *J* 7.0, 5-H) and 7.13 (1 H, br. s, NH); δ_C (100 MHz, $CDCl_3$) 18.0, 18.7, 24.5, 30.6, 33.4, 60.8 and 179.1; *m*/*z* (EI/CI) 127 (M^+, 1%) and 84 ($M^+ - 43$, 100).

(4*R*,6*S*,8*E*)-10-*tert*-Butyldimethylsilyloxy-4,6,8-trimethyldeca-1,8-dien-3-ol (63). Vinyl magnesium bromide (1.0 M in THF; 5.19 g, 39.6 mmol, 39.6 mL) was added to the aldehyde **30** (7.40 g, 24.8 mmol) in THF (120 mL) at −78 °C and the mixture was allowed to warm to room temperature and was stirred for 50 min. Saturated aqueous ammonium chloride (300 mL) was added and the mixture stirred at r.t. for 5 min. The aqueous layer was extracted with ether (4 × 400 mL) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 10) as eluent gave the *title compound* **63** as a clear liquid (5.99 g, 74%), a 2 : 1 mixture of epimers at C(3), R_f = 0.28/0.25 (1 : 5, ether : light petroleum), $[\alpha]_D^{22}$ +16, (*c* 0.3, benzene) (Found: M^+ + Na, 349.2527. $C_{19}H_{38}O_2NaSi$ requires *M*, 349.2534); ν_{max}/cm^{-1} 3396(br), 2954, 2927, 2856, 2361, 1667, 1641, 1461, 1379, 1361, 1252, 1199, 1088, 1054, 1004, 920, 833, 813, 773 and 665; δ_H (400 MHz, C_6D_6) major epimer 0.12 (6 H, s, 2 × $SiCH_3$), 0.84 (3 H, d, *J* 6.5, 6-CH_3), 0.88 (3 H, d, *J* 7.0, 4-CH_3), 0.94 (1 H, m, 5-H), 1.01 [9 H, s, $SiC(CH_3)_3$], 1.09 (1 H, br. s, OH), 1.46 (1 H, m, 5-H′), 1.52 (3 H, s, 8-CH_3), 1.62-1.71 (3 H, m, 4-H, 6-H and 7-H), 2.02 (1 H, m, 7-H′), 3.83 (1 H, m, 3-H), 4.23 (2 H, d, *J* 6.5, 10-H_2), 5.03 (1 H, dt, *J* 10.5, 1.5, 1-H), 5.16 (1 H, dt, *J* 17.0, 1.5, 1-H′), 5.50 (1 H, m, 9-H) and 5.73 (1 H, ddd, *J* 17.0, 10.5, 5.5, 2-H); minor epimer 0.85 (3 H, m, 6-CH_3), 0.88 (3 H, d, *J* 7.0, 4-CH_3), 1.06 (1 H, br. s, OH), 1.40 (1 H, m, 5-H′), 1.50 (3 H, s, 8-CH_3), 3.77 (1 H, t, *J* 5.0, 3-H), 5.13 (1 H, dt, *J* 17.0, 1.5, 1-H′), 5.50 (1 H, m, 9-H), and 5.74 (1 H, ddd, *J* 17.0, 10.5, 6.0, 2-H); δ_C (100 MHz, C_6D_6) major epimer −4.5, 15.3, 16.6, 18.9, 21.0, 26.6, 28.7, 36.5, 41.1, 47.9, 60.7, 76.1, 114.8, 127.0, 136.3 and 141.2; minor epimer −4.5, 16.1, 16.6, 18.9, 21.1, 26.5, 28.8, 36.7, 40.9, 47.7, 60.7, 77.2, 115.6, 127.1, 136.1 and 140.0; *m*/*z* (ES+) 349 (M^+ + 23, 100%).

Ethyl (6*R*,8*S*,4*E*,10*E*)-12-*tert*-Butyldimethylsilyloxy-6,8,10-trimethyldodeca-4,10-dienoate (64). Propionic acid (0.05 mL) was added to the alcohol **63** (4.64 g, 14.2 mmol) and triethyl orthoacetate (6.90 g, 42.6 mmol, 7.80 mL) in xylene (46 mL) and the solution heated under reflux for 6 h. After concentration under reduced pressure using benzene to azeotrope the xylene and triethylorthoacetate, chromatography of the residue using ether : light petroleum (1 : 40) as the eluent gave the *title compound* **64** as a clear liquid (5.11 g, 91%); R_f = 0.28 (1 : 10, ether : light petroleum), $[\alpha]_D^{20}$ −2.7 (*c* 0.6, benzene) (Found: M^+ + Na, 419.2957. $C_{23}H_{44}O_3NaSi$ requires *M*, 419.2952); ν_{max}/cm^{-1} 2954, 2928, 2857, 2360, 1737, 1666, 1462, 1374, 1252, 1163, 1086, 1054, 1006, 971, 939, 834, 813, 774 and 665; δ_H (400 MHz, C_6D_6) 0.09 (6 H, s, 2 × $SiCH_3$), 0.81 (3 H, d, *J* 6.5, 8-CH_3), 0.91 (1 H, m, 7-H), 0.92 (3 H, d, *J* 6.5, 6-CH_3), 0.98 (3 H, t, *J* 7.0, CH_2CH_3), 0.99 [9 H, s, $SiC(CH_3)_3$], 1.23 (1 H, ddd, *J* 13.5, 10.0, 4.5, 7-H′), 1.51 (3 H, s, 10-CH_3), 1.63 (1 H, m, 8-H), 1.76 (1 H, dd, *J* 13.0, 8.0, 9-H), 1.91 (1 H, dd, *J* 13.0, 7.0, 9-H′), 2.12 (1 H, m, 6-H), 2.16-2.20 and 2.23-2.29 (each 2 H, m, 2-H_2 or 3-H_2), 3.95 (2 H, q, *J* 7.0, CH_2CH$_3$), 4.21 (2 H, d, *J* 6.5, 12-H_2), 5.19 (1 H, ddt, *J* 15.5, 8.0, 1.0, 5-H), 5.32 (1 H, dt, *J* 15.5, 6.5, 4-H) and 5.46 (1 H, tq, *J* 6.5, 1.0, 11-H); δ_C (100 MHz, C_6D_6) −4.5, 14.7, 16.5, 18.9, 19.9, 22.5, 26.6, 28.6, 28.7, 34.9, 35.2, 44.9, 48.8, 60.3, 60.7, 127.2, 127.6, 136.0, 137.9 and 172.6; *m*/*z* (ES+) 420 (10%) and 265 (100).

Ethyl (6*R*,8*S*,4*E*,10*E*)-12-Hydroxy-6,8,10-trimethyldodeca-4,10-dienoate (65). Pyridinium toluene 4-sulfonate (0.32 g, 1.29 mmol) was added to the silyl ether **64** (5.11 g, 12.9 mmol) in dichloromethane (50 mL) and ethanol (50 mL) at r.t. and the mixture stirred at r.t. for 24 h. Saturated sodium hydrogen carbonate (250 mL) was added and the mixture extracted with ether (4 × 500 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 3) as eluent gave the *title compound* **65** as a clear liquid (3.45 g, 95%), R_f = 0.32 (1 : 1, ether : light petroleum), $[\alpha]_D^{20}$ −8.0 (*c* 0.5, benzene) (Found: M^+ + Na, 305.2075. $C_{17}H_{30}O_3Na$ requires *M*, 305.2088); ν_{max}/cm^{-1} 3358(br), 2956, 2913, 2868, 2359, 1735, 1668, 1445, 1373, 1345, 1296, 1255, 1163, 1096, 1067, 1008, 971, 856 and 777; δ_H (400 MHz, C_6D_6) 0.82 (3 H, d, *J* 6.5, 8-CH_3), 0.94 (1 H, m, 7-H), 0.94 (3 H, d, *J* 6.5, 6-CH_3), 0.97 (3 H, t, *J* 7.0, CH_2CH_3), 1.08 (1 H, br. s, OH), 1.24 (1 H, ddd, *J* 13.5, 10.0, 4.5, 7-H′), 1.49 (3 H, s, 10-CH_3), 1.64 (1 H, m, 8-H), 1.76 (1 H, dd, *J* 13.5, 8.0, 9-H), 1.92 (1 H, dd, *J* 13.5, 6.5, 9-H′), 2.14 (1 H, m, 6-H), 2.18-2.21 and 2.25-2.30 (each 2 H, m, 2-H_2 or 3-H_2), 3.96 (2 H, q, *J* 7.0, CH_2CH$_3$), 4.04 (2 H, d, *J* 6.5, 12-H_2), 5.21 (1 H, ddt, *J* 15.5, 8.0, 1.0, 5-H), 5.34 (1 H, dt, *J* 15.5, 6.5, 4-H) and 5.42 (1 H, dq, *J* 6.5, 1.0, 11-H); δ_C (100 MHz, C_6D_6) 14.7, 16.5, 19.9, 22.4, 28.6, 28.8, 34.9, 35.2, 44.9, 48.8, 59.7, 60.5, 126.9, 127.5, 137.2, 137.9 and 172.9; *m*/*z* (ES+) 305 (M^+ + 23, 100%).

Ethyl (6*R*,8*S*,4*E*,10*E*)-6,8,10-trimethyl-12-oxododeca-4,10-dienoate (66). Activated manganese dioxide (4.25 g, 48.8 mmol) was added to the alcohol **65** (0.46 g, 1.63 mmol) in dichloromethane (50 mL) and the mixture stirred at r.t. for 1 h. The reaction mixture was then filtered through celite and the celite washed with ether (4 × 40 mL) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 5) as eluent gave the *title compound* **66** as a light yellow liquid (0.39 g, 85%), R_f = 0.56 (1 : 1, ether : light petroleum), $[\alpha]_D^{22}$ +3.0 (*c* 0.4, benzene) (Found: M^+

+ Na, 303.1937. $C_{17}H_{28}O_3Na$ requires *M*, 303.1931); ν_{max}/cm^{-1} 2956, 2925, 2868, 1732, 1671, 1629, 1445, 1374, 1345, 1296, 1248, 1195, 1162, 1124, 1094, 1038, 972, 889, 859 and 808; δ_H (400 MHz, C_6D_6) 0.64 (3 H, d, *J* 6.5, 8-CH_3), 0.80 (1 H, ddd, *J* 13.5, 9.0, 4.5, 7-H), 0.87 (3 H, d, *J* 6.5, 6-CH_3), 0.98 (3 H, t, *J* 7.0, CH_2CH_3), 1.01 (1 H, ddd, *J* 13.5, 10.0, 4.0, 7-H′), 1.50-1.60 (2 H, m, 8-H and 9-H), 1.59 (3 H, d, *J* 1.0, 10-CH_3), 1.74 (1 H, m, 9-H′), 2.01 (1 H, m, 6-H), 2.16-2.30 and 2.23-2.28 (each 2 H, m, 2-H_2 or 3-H_2), 3.96 (2 H, q, *J* 7.0, CH_2CH_3), 5.11 (1 H, ddt, *J* 15.5, 8.5, 1.0, 5-H), 5.29 (1 H, dt, *J* 15.5, 6.0, 4-H), 5.83 (1 H, dq, *J* 8.0, 1.0, 11-H) and 9.90 (1 H, d, *J* 8.0, 12-H); δ_C (100 MHz, C_6D_6) 14.7, 17.1, 19.5, 22.3, 28.5, 28.8, 34.8, 35.0, 44.6, 49.2, 60.4, 127.9, 129.5, 137.4, 161.2, 172.7 and 190.1; *m*/*z* (ES+) 303 (M^+ + 23, 100%).

Ethyl (6*R*,8*S*,4*E*,10*E*,12*E*,14*E*)-6,8,10,14-tetramethylhexadeca-4,10,12,14-tetraenoate (67). Lithium hexamethyldisilazide (1.0 M in THF; 0.408 g, 2.44 mmol, 2.44 mL) was added to a solution of the aldehyde **66** (0.456 g, 1.63 mmol) and sulphone **23** (0.653 g, 2.44 mmol) in THF (50 mL) at −78 °C and the mixture stirred at −78 °C for 1 h and at r.t. for 1 h. Saturated aqueous sodium hydrogen carbonate (50 mL) and ether (100 mL) were added and the aqueous layer was extracted with ether (4 × 100 mL). The organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 40) as eluent gave the *title compound* **67** as a clear liquid (0.401 g, 74%), a mixture of geometrical isomers, (4*E*,10*E*,12*E*,14*E*) : (4*E*,10*E*,12*Z*,14*E*) : (4*E*,10*E*,12*E*,14*Z*) = 91 : 4 : 5, R_f = 0.43 (1 : 10 ether : light petroleum), $[\alpha]_D^{18}$ +29 (*c* 0.4, benzene) (Found: M^+ + Na, 355.2613. $C_{22}H_{36}O_2Na$ requires *M*, 355.2608); ν_{max}/cm^{-1} 2954, 2913, 2868, 1736, 1642, 1444, 1373, 1344, 1296, 1246, 1161, 1096, 1034, 958, 855, 795 and 619; δ_H (400 MHz, C_6D_6) (4*E*,10*E*,12*E*,14*E*)-isomer **67** 0.86 (3 H, d, *J* 6.5, 8-CH_3), 0.93 (3 H, d, *J* 7.0, 6-CH_3), 0.96 (1 H, m, 7-H), 0.97 (3 H, t, *J* 7.0, CH_2CH_3), 1.27 (1 H, ddd, *J* 13.5, 10.0, 4.5, 7-H′), 1.60 (3 H, d, *J* 7.0, 16-H_3), 1.68-1.76 (7 H, m, 14-CH_3, 10-CH_3 and 8-H), 1.89 (1 H, dd, *J* 13.5, 8.0, 9-H), 2.04 (1 H, dd, *J* 13.5, 7.0, 9-H′), 2.14 (1 H, m, 6-H), 2.18-2.21 and 2.25-2.30 (each 2 H, m, 2-H_2 or 3-H_2), 3.96 (2 H, q, *J* 7.0, CH_2CH_3), 5.19 (1 H, dd, *J* 15.5, 8.0, 5-H), 5.34 (1 H, dt, *J* 15.5, 6.0, 4-H), 5.53 (1 H, q, *J* 7.0, 15-H), 6.05 (1 H, d, *J* 11.0, 11-H), 6.34 (1 H, d, *J* 15.5, 13-H) and 6.53 (1 H, dd, *J* 15.5, 11.0, 12-H); (4*E*,10*E*,12*Z*,14*E*)-isomer 5.67 (1 H, q, *J* 7.0, 15-H), 5.91 (1 H, d, *J* 11.5, 11-H) and 6.24 (1 H, t, *J* 11.5, 12-H); (4*E*,10*E*,12*E*,14*Z*)-isomer 6.10 (1 H, d, *J* 11.0, 11-H), 6.62 (1 H, dd, *J* 15.5, 11.0, 12-H) and 6.75 (1 H, d, *J* 15.5, 13-H); δ_C (100 MHz, C_6D_6) (4*E*,10*E*,12*E*,14*E*)-isomer **67** 12.6, 14.4, 14.7, 17.1, 20.0, 22.5, 28.6, 29.2, 34.9, 35.2, 45.0, 49.4, 60.4, 123.2, 126.6, 127.6, 128.3, 135.8, 136.6, 136.8, 137.9 and 172.7; *m*/*z* (ES+) 355 (M^+ + 23, 100%).

(6*R*,8*S*,4*E*,10*E*,12*E*,14*E*)-6,8,10,14-Tetramethylhexadeca-4,10,12,14-tetraenoic acid (68). Sodium hydroxide (0.18 g, 4.51 mmol) in water (5 mL) was added to the ester **67** (0.365 g, 1.10 mmol) in ethanol (10 mL) at r.t. and the solution stirred at r.t. for 18 h. The reaction mixture was then acidified to pH 5 by adding it to a solution of tartaric acid (1.65 g, 11.0 mmol) in water (60 mL) at 0 °C, with vigorous stirring for 2 min. The mixture was extracted with ether (4 × 100 mL) and the organic extracts were washed with chilled water (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford the *title compound* **68** as a light yellow liquid (0.33 g, 99%), a mixture of geometrical isomers, (4*E*,10*E*,12*E*,14*E*) : (4*E*,10*E*,12*Z*,14*E*) : (4*E*,10*E*,12*E*,14*Z*) = 89 : 4 : 7, R_f = 0.37 (1 : 2 ether : light petroleum), $[\alpha]_D^{18}$ +21 (*c* 0.6, benzene) (Found: M^+ − H, 303.2319. $C_{20}H_{31}O_2$ requires *M*, 303.2329); ν_{max}/cm^{-1} 3036, 2953, 2912, 2868, 2831, 1706, 1642, 1439, 1410, 1376, 1295, 1267, 1209, 1023, 958, 789 and 676; δ_H (400 MHz, C_6D_6) (4*E*,10*E*,12*E*,14*E*)-isomer **68** 0.87 (3 H, d, *J* 6.5, 8-CH_3), 0.93 (3 H, d, *J* 6.5, 6-CH_3), 0.96 (1 H, ddd, *J* 13.5, 9.5, 5.0, 7-H), 1.27 (1 H, ddd, *J* 13.5, 10.0, 4.5, 7-H′), 1.60 (3 H, d, *J* 7.0, 16-H_3), 1.70 (1 H, m, 8-H), 1.74 (6 H, m, 14-CH_3 and 10-CH_3), 1.91 (1 H, dd, *J* 13.5, 8.0, 9-H), 2.05 (1 H, dd, *J* 13.5, 7.0, 9-H′), 2.12-2.20 (5 H, m, 6-H, 3-H_2 and 2-H_2), 5.16 (1 H, dd, *J* 15.5, 8.0, 5-H), 5.26 (1 H, dt, *J* 15.5, 6.0, 4-H), 5.54 (1 H, q, *J* 7.0, 15-H), 6.06 (1 H, d, *J* 11.0, 11-H), 6.36 (1 H, d, *J* 15.0, 13-H), (1 H, dd, *J* 15.0, 11.0, 12-H) and 12.1 (1 H, br. s, OH); (4*E*,10*E*,12*Z*,14*E*)-isomer 5.68 (1 H, q, *J* 7.0, 15-H), 5.92 (1 H, d, *J* 11.5, 11-H) and 6.26 (1 H, t, *J* 11.5, 12-H); (4*E*,10*E*,12*E*,14*Z*)-isomer 5.36 (1 H, q, *J* 7.5, 15-H), 6.11 (1 H, d, *J* 11.0, 11-H), 6.64 (1 H, dd, *J* 15.5, 11.0, 12-H) and 6.76 (1 H, d, *J* 15.5, 13-H); δ_C (100 MHz, C_6D_6) (4*E*,10*E*,12*E*,14*E*)-isomer **68** 12.6, 14.4, 17.1, 20.0, 22.4, 28.2, 29.2, 34.7, 35.2, 44.9, 49.4, 123.2, 126.7, 127.0, 128.2, 135.8, 136.6, 136.8, 138.2 and 180.6; *m*/*z* (ES−) 341 (40%) and 339 (M^+ + 35, 100).

(6*R*,8*S*,4*E*,10*E*,12*E*,14*E*)-6,8,10,14-Tetramethylhexadeca-4,10,12,14-tetraenoyl (1H)-imidazolide (69). 1,1′-Carbonyldiimidazole (0.536 g, 3.31 mmol) was added to the acid **68** (0.50 g, 1.66 mmol) in THF (20 mL) and the solution stirred at r.t. for 18 h. Chilled ether (150 mL) was added and the solution was washed with chilled water (2 × 50 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated under reduced pressure to afford the *title compound* **69** as a light yellow liquid (0.366 g, 95%), a mixture of geometrical isomers, (4*E*,10*E*,12*E*,14*E*) : (4*E*,10*E*,12*Z*,14*E*) : (4*E*,10*E*,12*E*,14*Z*) = 88 : 4 : 8, R_f = 0.18 (3 : 1, ether : light petroleum), $[\alpha]_D^{18}$ +23 (*c* 0.6, benzene) (Found: M^+ + H, 355.2757. $C_{23}H_{35}N_2O$ requires *M*, 355.2744); ν_{max}/cm^{-1} 3125, 3038, 2953, 2913, 2866, 1737, 1640, 1526, 1473, 1380, 1296, 1270, 1221, 1110, 1085, 1062, 1022, 958, 895, 797, 751, 663, 648 and 618; δ_H (400 MHz, C_6D_6) (4*E*,10*E*,12*E*,14*E*)-isomer **69** 0.87 (3 H, d, *J* 6.5, 8-CH_3), 0.94 (3 H, d, *J* 6.5, 6-CH_3), 0.98 (1 H, ddd, *J* 13.5, 9.5, 5.0, 7-H), 1.28 (1 H, ddd, *J* 13.5, 10.0, 4.5, 7-H′), 1.60 (3 H, d, *J* 7.0, 16-H_3), 1.67 (1 H, m, 8-H), 1.74 (6 H, m, 14-CH_3 and 10-CH_3), 1.88-1.96 (3 H, m, 9-H and 3-H_2), 2.05 (1 H, dd, *J* 13.5, 7.0, 9-H′), 2.09-2.18 (3 H, m, 6-H and 2-CH_2), 5.15 (1 H, dd, *J* 15.5, 7.0, 5-H), 5.20 (1 H, dt, *J* 15.5, 6.0, 4-H), 5.54 (1 H, q, *J* 7.0, 15-H), 6.07 (1 H, d, *J* 11.0, 11-H), 6.36 (1 H, d, *J* 15.5, 13-H), 6.54 (1 H, dd, *J* 15.5, 11.0, 12-H), 6.97 (1 H, m, 3′-H), 7.08 (1 H, s, 5′-H) and 7.72 (1 H, s, 6′-H); (4*E*,10*E*,12*Z*,14*E*)-isomer 5.68 (1 H, q, *J* 7.0, 15-H), 5.92 (1 H, d, *J* 11.5, 11-H) and 6.25 (1 H, t, *J* 11.5, 12-H); (4*E*,10*E*,12*E*,14*Z*)-isomer 5.36 (1 H, q, *J* 7.5, 15-H), 6.12 (1 H, d, *J* 11.0, 11-H), 6.64 (1 H, dd, *J* 15.5, 11.0, 12-H) and 6.76 (1 H, d, *J* 15.5, 13-H); δ_C (100 MHz, C_6D_6) (4*E*,10*E*,12*E*,14*E*)-isomer **69** 12.6, 14.4, 17.2, 20.1, 22.3, 27.5, 29.3, 35.1, 35.2, 44.9, 49.4, 116.2, 123.2, 126.4, 126.8,

128.3, 128.5, 131.6, 135.8, 136.6, 136.7, 138.7 and 168.9; *m*/*z* (ES+) 355 (M^+ + 1, 100%).

(5*R*)-1-Benzoyl-5-(prop-2-yl)-3-[(6*R*,8*S*,4*E*,10*E*,12*E*,14*E*)-6,8,10,14-tetramethylhexadeca-4,10,12,14-tetraenoyl]pyrrolidin-2-one (70). Lithium hexamethyldisilazide (1.0 M in THF; 0.50 g, 2.99 mmol, 2.99 mL) cooled to −78 °C was added to the pyrrolidinone **57** (0.69 g, 2.99 mmol) in THF (20 mL) at −78 °C and the solution was stirred −78 °C for 1 h. A solution of the imidazolide **69** (0.53 g, 1.50 mmol) in THF (5 mL) at −78 °C was added and the solution stirred at −78 °C for 6 h. Saturated aqueous ammonium chloride (20 mL) was added and the mixture allowed to warm to r.t. More saturated aqueous ammonium chloride (40 mL) was added and the aqueous layer was extracted with ether (4 × 120 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 7) as eluent gave the *title compounds* **70** as a light orange liquid (0.609 g, 79%), a partly enolised mixture of isomers, (4*E*,10*E*,12*E*,14*E*) : (4*E*,10*E*,12*Z*,14*E*) : (4*E*,10*E*,12*E*,14*Z*) = 84 : 4 : 12, as 1 : 1 mixtures of epimers at C(3), keto-tautomers : enol tautomer = 2 : 1, R_f = 0.46 (1 : 2, ether : light petroleum), $[\alpha]_D^{18}$ +130 (*c* 0.6, benzene) (Found: M^+ + H, 518.3629. $C_{34}H_{48}NO_3$ requires *M*, 518.3629); ν_{max}/cm^{-1} 2959, 2915, 2871, 2360, 1737, 1716, 1673, 1633, 1602, 1449, 1378, 1279, 1236, 1177, 1134, 1117, 1077, 1028, 960, 888, 799, 738, 710, 693, 657 and 635; δ_H (400 MHz, C_6D_6) (4*E*,10*E*,12*E*,14*E*)-isomers **70** 0.68-0.74 (6 H, overlap. d, *J* 7.0, 2 × 5-CHC*H*$_3$), 0.85 and 0.94 (each 3 H, overlap. d, *J* 7.0, 6′-CH$_3$ or 8′-CH$_3$), 0.98 and 1.27 (each 1 H, m, 7′-H), 1.39 (1 H, m, 8′-H), 1.60 (3 H, d, *J* 7.0, 16′-H$_3$), 1.65-1.76 (7 H, m, 14′-CH$_3$, 10′-CH$_3$ and 6′-H), 1.89 (1 H, m, 4-H), 1.99-2.12 (2 H, m, 9′-H and 4-H′), 2.16 (1 H, m, 2′-H), 2.21-2.32 (3 H, m, 9′-H′ and 3′-H$_2$), 2.36 (1 H, m, 5-CH), 2.48 (1 H, m, 2′-H′), 2.89 and 3.24 (each 0.5 H, dd, *J* 10.5, 9.0, 3-H), 4.42 (1 H, m, 5-H), 5.21 (1 H, m, 5′-H), 5.32 (1 H, m, 4′-H), 5.52 (1 H, q, *J* 7.0, 15′-H), 6.04 (1 H, d, *J* 10.5, 11′-H), 6.33 (1 H, d, *J* 15.0, 13′-H), 6.51 and 6.52 (each 0.5 H, dd, *J* 15.0, 10.5, 12′-H), 7.00-7.20 (3 H, m, ArH) and 7.76 (2 H, m, ArH); enol-tautomer 0.60 (3 H, d, *J* 7.0, CHC*H*$_3$), 2.94 (1 H, m), 4.10 (1 H, m, 5-H) and 12.29 (1 H, s, OH); (4*E*,10*E*,12*Z*,14*E*)-isomer 5.65 (1 H, q, *J* 7.0, 15′-H), 5.90 (1 H, d, *J* 12.0, 11′-H) and 6.22 and 6.23 (each 0.5 H, t, *J* 11.5, 12′-H); (4*E*,10*E*,12*E*,14*Z*)-isomer 6.09 (1 H, d, *J* 11.0, 11′-H), 6.59 and 6.63 (each 0.5 H, dd, *J* 15.5, 11.0, 12′-H) and 6.72 (1 H, d, *J* 15.5, 13′-H); δ_C (100 MHz, C_6D_6) (4*E*,10*E*,12*E*,14*E*)-isomers **70** and enol-tautomer 12.6, 12.6, 14.4, 15.0, 15.1, 15.9, 17.1, 17.1, 18.7, 18.7, 19.0, 19.4, 19.4, 20.0, 20.1, 20.2, 20.3, 21.1, 21.1, 22.4, 27.0, 27.8, 29.1, 29.2, 29.3, 29.4, 29.8, 33.8, 35.2, 35.2, 35.3, 43.2, 43.7, 44.9, 45.0, 49.4, 49.4, 55.3, 56.3, 60.0, 60.0, 60.5, 100.3, 123.2, 123.2, 123.3, 126.6, 126.6, 126.7, 127.4, 127.6, 127.6, 128.2, 128.6, 129.9, 130.1, 130.6, 132.2, 132.4, 133.0, 135.3, 135.7, 135.8, 135.8, 135.8, 136.3, 136.5, 136.5, 136.7, 136.9, 137.0, 137.8, 138.2, 170.8, 170.8, 171.1, 171.4, 171.6, 171.7, 173.6, 202.7 and 203.1; *m*/*z* (ES+) 518 (M^+ + 1, 100%).

(5*R*)-1-Benzoyl-5-(prop-2-yl)-3-(phenylselanyl)-3-[(6*R*,8*S*,4*E*,10*E*,12*E*,14*E*)-6,8,10,14-tetramethylhexadeca-4,10,12,14-tetraenoyl]pyrrolidin-2-one (71). A cooled solution of lithium hexamethyldisilazide (1.0 M in THF; 0.203 g, 1.22 mL, 1.22 mmol) was added to the pyrrolidinone **70** (0.573 g, 1.11 mmol) in THF (18 mL) at −78 °C and the solution stirred at −78 °C for 30 min. Cooled phenylselanyl chloride (0.234 g, 1.22 mmol) in THF (6 mL) was added and the solution stirred at −78 °C for 2.5 h. Saturated aqueous sodium hydrogen carbonate (50 mL) was added and the mixture allowed to warm to r.t. before the addition of more saturated sodium hydrogen carbonate (50 mL). The aqueous layer was extracted with ether (4 × 200 mL) and the organic extracts dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 10) gave the *title compound* **71** as a clear liquid (0.687 g, 92%), a mixture of geometrical isomers and epimers at C(3), (4*E*,10*E*,12*E*,14*E*) : (4*E*,10*E*,12*Z*,14*E*) : (4*E*,10*E*,12*E*,14*Z*) = 76 : 3 : 21, C(3)-epimers 2 : 1, R_f = 0.37 (1 : 4, ether : light petroleum); $[\alpha]_D^{18}$ +192 (*c* 0.6, benzene) (Found: M^+ + Na, 696.2939. $C_{40}H_{51}NO_3SeNa$ requires *M*, 696.2927); ν_{max}/cm^{-1} 2959, 2912, 2360 1725, 1686, 1600, 1438, 1362, 1273, 1235, 1177, 1130, 1105, 1022, 1000, 960, 890, 798, 740 and 691; δ_H (400 MHz, C_6D_6) (4*E*,10*E*,12*E*,14*E*)-isomers **71** 0.54 (2 H, d, *J* 7.0, CHC*H*$_3$), 0.55 and 0.57 (each 1 H, d, *J* 7.0, CHC*H*$_3$), 0.58 (2 H, d, *J* 7.0, CHC*H*$_3$′), 0.85 (1 H, d, *J* 6.5, 8′-CH$_3$), 0.87 (2 H, d, *J* 6.5, 8′-CH$_3$), 0.92 (1 H, d, *J* 6.5, 6′-CH$_3$), 0.95 (2 H, d, *J* 6.5, 6′-CH$_3$), 0.99 (1 H, m, 7′-H), 1.26 (0.33 H, m, 7′-H′), 1.29 (0.67 H, ddd, *J* 13.5, 9.5, 4.5, 7′-H′), 1.60 (3 H, d, *J* 7.0, 16′-H$_3$), 1.66-1.78 (6.7 H, m, 14′-CH$_3$, 10′-CH$_3$, 8′-H), 1.83 (0.67 H, dd, *J* 16.0, 7.5, 9′-H), 1.86-1.91 (1.33 H, m, 8′-H and 4-H), 1.99 (0.33 H, dd, *J* 14.0, 8.0, 4-H′), 2.05 (1 H, m, 9′-H′), 2.18 (1 H, m, 6′-H), 2.31 (0.67 H, m, 3′-H$_2$), 2.44-2.54 (3 H, m, 4-H′, 5-CH and 3′-H$_2$), 2.83 (0.33 H, dt, *J* 18.0, 7.0, 2′-H), 2.89 (0.33 H, dd, *J* 12.0, 7.0, 9′-H), 3.12 (0.67 H, dt, *J* 18.0, 7.0, 2′-H), 3.27 (0.33 H, dt, *J* 17.5, 7.5, 2′-H′), 3.50 (0.67 H, dt, *J* 17.5, 7.5, 2′-H′), 4.31 (0.33 H, m, 5-H), 4.41 (0.67 H, m, 5-H), 5.19-5.36 (1.67 H, m, 4′-H and 5′-H), 5.42-5.55 (1.33 H, m, 4′-H and 15′-H), 6.05 (1 H, d, *J* 11.0, 11′-H), 6.34 (1 H, d, *J* 15.0, 13′-H), 6.52 (0.67 H, dd, *J* 15.0, 11.0, 12′-H), 6.53 (0.33 H, dd, *J* 15.0, 11.0, 12′-H), 6.89-7.00 (3 H, m, ArH), 7.05-7.15 (3 H, m, ArH), 7.39 (1.33 H, m, ArH), 7.53 (0.67 H, m, ArH) and 7.75-7.81 (2 H, m, ArH); (4*E*,10*E*,12*Z*,14*E*)-isomer 5.67 (1 H, q, *J* 7.0, 15′-H), 5.91 (1 H, d, *J* 12.0, 11′-H) and 6.24 (1 H, t, *J* 12.0, 12′-H); (4*E*,10*E*,12*E*,14*Z*)-isomer 6.10 (1 H, d, *J* 11.0, 11′-H), 6.61 (0.67 H, dd, *J* 15.5, 11.0, 12′-H), 6.62 (0.33 H, dd, *J* 15.5, 11.0, 12′-H) and 6.74 (1 H, d, *J* 15.5, 13′-H); δ_C (100 MHz, C_6D_6) (4*E*,10*E*,12*E*,14*E*)-isomers **71** major 3-epimer 12.6, 14.4, 15.3, 17.1, 18.5, 20.2, 22.3, 27.1, 27.3, 28.3, 29.2, 35.2, 39.6, 45.1, 49.4, 58.8, 60.9, 123.3, 126.6, 127.1, 127.9, 128.5, 129.9, 130.5, 130.7, 133.0, 135.3, 135.8, 136.5, 137.0, 137.8, 138.0, 138.2, 171.5, 171.6, and 201.7; minor 3-epimer 13.6, 14.2, 15.1, 16.7, 18.6, 20.1, 21.1, 27.1, 27.6, 28.3, 29.2, 35.1, 39.1, 45.0, 49.4, 60.6, 61.9, 123.4, 126.5, 127.1, 127.9, 128.5, 129.8, 130.4, 130.7, 133.3, 135.0, 135.9, 136.5, 137.1, 137.8, 138.0, 138.1, 171.4, 171.7 and 200.4; *m*/*z* (ES+) 691 (M^+ + 18, 100%).

Generation of pyrrolinone 72 and its intramolecular Diels-Alder reaction. A chilled solution of aqueous hydrogen peroxide (30%; 0.71 g, 6.27 mmol) in water (5 mL) was added to the selenide **71** (0.40 g, 0.597 mmol) in chloroform-d_1 (40 mL) at −48 °C followed by a chilled solution of *m*-chloroperoxybenzoic acid (77%; 0.16 g, 0.716 mmol) in chloroform-d_1 (18 mL) and the mixture stirred at −48 °C for 50 min. The reaction mixture was then removed from the

cooling bath and allowed to warm up to 0 °C over the period of 10 min with vigorous stirring. Chilled chloroform-d_1 (30 mL) was added and the solution washed with chilled saturated aqueous sodium carbonate (2 × 20 mL) and chilled water (20 mL). The organic layer was dried (Na_2SO_4), diluted with toluene (400 mL) and deoxygenated by purging with nitrogen for 30 min at 40 °C before being heated at 90 °C for 10 h. After concentration under reduced pressure, chromatography of the residue using ether : light petroleum (gradient elution 1 : 80 to 1 : 15) as eluent gave a mixture of the (11*E*)-Diels-Alder products **73** and **74** as a clear oil (34 mg, 11%), **73** : **74** = 5 : 4 (Found: M^+ + H, 516.3486. $C_{34}H_{46}NO_2$ requires *M*, 516.3473); ν_{max}/cm^{-1} 2958, 2919, 2360, 2341, 1731, 1706, 1693, 1601, 1448, 1373, 1275, 1214, 1177, 1132, 1098, 970 and 751; *m*/*z* (ES+) 538 (M^+ + 23, 100%). The second fraction was a mixture of the (11*Z*)-Diels-Alder adducts **75** and **76** as a clear oil (38 mg, 12%), **75** : **76** = 5 : 4 (Found: M^+ + H, 516.3464. $C_{34}H_{46}NO_2$ requires *M*, 516.3473); ν_{max}/cm^{-1} 2957, 2913, 2360, 2340, 1734, 1682, 1600, 1448, 1373, 1275, 1217, 1178, 1140, 1098, 972, 911, 801 and 730; *m*/*z* (ES+) 538 (M^+ + 23, 100%). A mixed fraction was seen as an off-white liquid (5 mg, 2%).

(7*R*,9*S*,13*R*,16*R*,17*R*,18*S*,5*E*,11*E*,14*Z*)-7,9,11,15,16-Pentamethyl-18-(prop-2-yl)-19-aza-20-oxotricyclo[15.3.0^{1,17}]icosa-5,11,14-trien-2-one (77). Sodium hydroxide (38 mg, 0.94 mmol) in methanol (1.4 mL) and water (0.05 mL) was added to the mixture of the (11*E*)-Diels-Alder adducts **73** and **74** (24 mg, 0.047 mmol) in methanol (1.4 mL) and the solution stirred at r.t. for 3 h. Water (10 mL) was added and the mixture extracted with ether (4 × 15 mL). The organic extracts were then washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 4) as eluent gave the (11*E*)-endo-isomer **78** as a clear oil (2 mg, 11%), but only as an impure mixture, R_f = 0.4 (2 : 1, ether : light petroleum) (Found: M^+ + H, 412.3211. $C_{27}H_{42}NO_2$ requires *M*, 412.3211); ν_{max}/cm^{-1} 3201, 2959, 2919, 2360, 1686, 1457, 1374, 1154, 972, 908 and 731; *m*/*z* (ES+) 434 (M^+ + 23, 100%). After mixed fractions of the (13*R*,16*R*)- and (13*S*,16*S*)-isomers **77** and **78** (6 mg, 32%), the second product was the (11*E*)-exo-isomer of the *title compound* **77** isolated as a clear liquid (6 mg, 32%), R_f = 0.33 (2 : 1, ether : light petroleum) (Found: M^+ + H, 412.3222. $C_{27}H_{42}NO_2$ requires *M*, 412.3211); ν_{max}/cm^{-1} 3205, 2957, 2914, 2869, 2360, 2341, 2247, 1691, 1455, 1376, 1287, 1260, 1153, 1101, 1047, 1000, 968, 907, 811, 728 and 646; δ_H (500 MHz, $CDCl_3$) 0.83 (3 H, d, *J* 6.5, 18-CHCH_3), 0.86 (3 H, d, *J* 6.5, 9-CH_3), 0.92 (3 H, d, *J* 7.0, 7-CH_3), 0.95 (1 H, m, 8-H), 1.00 (3 H, d, *J* 6.5, 18-CHCH_3′), 1.18 (3 H, d, *J* 7.5, 16-CH_3), 1.26-1.36 (3 H, m, 8-H′, 9-H and 18-CH), 1.41 (1 H, dd, *J* 12.5, 11.0, 10-H), 1.67 (3 H, s, 15-CH_3), 1.80 (3 H, d, *J* 1.5, 11-CH_3), 1.89-2.00 (4 H, m, 4-H, 7-H, 10-H′ and 16-H), 2.37 (1 H, m, 4-H′), 2.57 (1 H, ddd, *J* 20.0, 5.0, 2.0, 3-H), 2.64 (1 H, d, *J* 9.5, 18-H), 2.89 (1 H, ddd, *J* 20.0, 12.5, 2.5, 3-H′), 3.02 (1 H, dd, *J* 3.0, 1.5, 17-H), 3.77 (1 H, dd, *J* 9.5, 6.5, 13-H), 4.84 (1 H, dt, *J* 9.5, 1.5, 12-H), 5.36-5.38 (2 H, m, 5-H and 6-H), 5.45 (1 H, d, *J* 6.5, 14-H) and 5.93 (1 H, s, NH); δ_C (125 MHz, $CDCl_3$) 19.4, 19.5, 20.6, 21.8, 22.3, 22.6, 24.3, 30.3, 32.2, 34.0, 35.0, 37.2, 40.0, 41.5, 43.2, 44.0, 46.1, 63.7, 70.1, 121.4, 125.0, 127.5, 136.5, 137.0, 137.5, 175.7 and 206.0; *m*/*z* (ES+) 434 (M^+ + 23, 72%) and 412 (M^+ + 1, 100).

(7*R*,9*S*,13*R*,16*R*,17*R*,18*S*,5*E*,11*Z*,14*Z*)- And (7*R*,9*S*,13*S*,16*S*,17*R*,18*S*,5*E*,11*Z*,14*Z*)-7,9,11,15,16-pentamethyl-18-(prop-2-yl)-19-aza-20-oxotricyclo[15.3.0^{1,17}]icosa-5,11,14-trien-2-ones (79) and (80). Sodium hydroxide (33 mg, 0.82 mmol) in methanol (1.4 mL) and water (0.05 mL) was added to the mixture of Diels-Alder adducts **75** and **76** (26 mg, 0.05 mmol) in methanol (1.4 mL) and the solution stirred at r.t. for 3 h. Water (10 mL) was added and the mixture extracted with ether (4 × 15 mL). The organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 4) as eluent gave the (11*Z*)-endo-isomer of the *title compound* **80**, a clear liquid (6 mg, 29%), R_f = 0.53 (2 : 1, ether : light petroleum) (Found: M^+ + H, 412.3213. $C_{27}H_{42}NO_2$ requires *M*, 412.3211); ν_{max}/cm^{-1} 3201, 2960, 2916, 2364, 1688, 1457, 1384, 1338, 1306, 1223, 1144, 1098, 970, 909 and 733; δ_H (500 MHz, $CDCl_3$) 0.90-0.99 (14 H, m, 7-CH_3, 8-H, 9-H, 9-CH_3, 2 × 18-CHCH_3), 1.15 (3 H, d, *J* 7.0, 16-CH_3), 1.29 (1 H, m, 8-H′), 1.62 (1 H, m, 18-CH), 1.66 (3 H, d, *J*, 1.5, 11-CH_3), 1.69-1.80 (5 H, m, 7-H, 10-H and 15-CH_3), 1.90 (1 H, m, 10-H′), 2.10 (1 H, m, 4-H), 2.27 (1 H, ddd, *J* 16.0, 6.0, 2.5, 3-H), 2.29 (1 H, m, 17-H), 2.51-2.61 (2 H, m, 4-H′ and 16-H), 2.88 (1 H, t, *J* 4.5, 18-H), 3.04 (1 H, ddd, *J* 16.0, 12.0, 2.5, 3-H′), 3.72 (1 H, br. d, *J* 10.5, 13-H), 5.32 (1 H, dt, *J* 16.0, 6.0, 5-H), 5.43 (1 H, br. s, 14-H), 5.49 (1 H, dd, *J* 16.0, 6.0, 6-H), 5.62 (1 H, d, *J* 10.5, 12-H) and 6.02 (1 H, s, NH); δ_C (125 MHz, $CDCl_3$) 14.5, 16.7, 16.9, 20.1, 20.7, 22.3, 23.5, 26.4, 30.9, 33.5, 34.4, 34.6, 38.4, 39.1, 45.4, 49.1, 51.4, 59.8, 67.1, 123.5, 125.4, 127.7, 135.9, 136.9, 138.1, 176.1 and 209.3; *m*/*z* (ES+) 434 (M^+ + 23, 100%) and 412 (M^+ + 1, 47). After a mixed fraction (2 mg, 9%), the second product to be eluted was the (11*Z*)-exo-isomer of the *title compound* **79** isolated as a clear liquid (8 mg, 38%), R_f = 0.28 (2 : 1, ether : light petroleum) (Found: M^+ + H, 412.3219. $C_{27}H_{42}NO_2$ requires *M*, 412.3211); ν_{max}/cm^{-1} 3211, 2957, 2916, 2866, 2360, 1693, 1455, 1386, 1284, 1260, 1117, 972, 910, 800, 732, 667 and 648; δ_H (500 MHz, $CDCl_3$) 0.83 (3 H, d, *J* 6.5, 18-CHCH_3), 0.94 (3 H, d, *J* 7.0, 9-CH_3), 0.96 (3 H, d, *J* 7.0, 7-CH_3), 0.99 (3 H, d, *J* 6.5, 18-CHCH_3′), 1.02 (1 H, ddd, *J* 13.5, 8.5, 2.5, 8-H), 1.21 (3 H, d, *J* 7.5, 16-CH_3), 1.31 (1 H, m, 8-H′), 1.38-1.43 (2 H, m, 9-H and 18-CH), 1.66 (1 H, m, 10-H), 1.69 (3 H, s, 11-CH_3), 1.70 (3 H, s, 15-CH_3), 1.80-1.89 (2 H, m, 7-H and 10-H′), 1.92-1.99 (2 H, m, 4-H and 16-H), 2.45 (1 H, m, 4-H′), 2.58 (1 H, ddd, *J* 19.5, 5.5, 2.0, 3-H), 2.70 (1 H, d, *J* 9.0, 18-H), 2.85 (1 H, ddd, *J* 19.5, 12.0, 2.5, 3-H′), 2.86 (1 H, dd, *J* 4.0, 2.0, 17-H), 3.76 (1 H, dd, *J* 9.5, 6.0, 13-H), 4.81 (1 H, d, *J* 9.5, 12-H), 5.35-5.41 (2 H, m, 5-H and 14-H), 5.52 (1 H, dd, *J* 16.0, 7.5, 6-H) and 5.94 (1 H, br. s, NH); δ_C (125 MHz, $CDCl_3$) 16.7, 19.1, 19.4, 20.7, 22.2, 22.4, 23.8, 24.5, 30.5, 32.5, 34.8, 38.8, 39.6, 40.8, 44.5, 46.9, 48.9, 63.8, 68.6, 122.4, 122.7, 126.5, 136.2, 137.5, 137.8, 175.8 and 206.3; *m*/*z* (ES+) 434 (M^+ + 23, 100%).

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Notes and references

[a] The School of Chemistry, The University of Manchester, Manchester, M13 9PL, UK.

Electronic Supplementary Information (ESI) available: this includes copies of 13C and 1H NMR spectra of key compounds. See DOI: 10.1039/b000000x/

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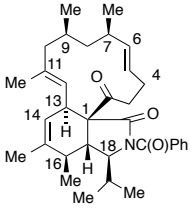
24 In the discussion and the experimental, the Diels-Alder products **73** – **76** and their debenzoyl derivatives **77** – **80** are named as 7,9,11,15,16-pentamethyl-18-(prop-2-yl)-19-aza-20-oxotricyclo[15.3.0^{1,17}]icosa-5,11,14-trien-2-ones. For the numbering scheme used see **77** and **i**.



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