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Approaches to the total synthesis of chaetochalasin A

Eric J. Thomas* and Mark Willis

Chactochalasin 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 (6R,8S,2Z,4E,10E,12E,14E)-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-tet-butylidimethylsilyloxy-2-methylbut-2-ene using diastereoselective alkylation of derivatives of (+)-pseudoephedrine to introduce the stereogenic centres, a modified Julia reaction to prepare the conjugated diene and a phosphonate condensation to provide the (2Z)-alkene. However, during the synthesis, facile geometrical isomerisation of the (14E)-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 (10E)-double-bond of the conjugated diene 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 diene.

Introduction

The cytotoxic chaetochalasin A (1) was isolated from Chaetomium brasiliense and showed antibacterial activity against Staphylococcus aureus and Bacillus subtilis. It is structurally related to the cytochalasans that are believed to be biosythesised by sequences that involve intramolecular Diels-Alder reactions of 3-acylpyrrolinones. Although not really biomimetic, intramolecular Diels-Alder reactions of 3-acylpyrrolinones were used in an approach to the total synthesis of several cytochalasans and related compounds including an isomer of aspochalasin C. 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 (2Z,4E)-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) (cytochalasin 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 cytochalasin biosynthesis, it was proposed that the Diels-Alder reaction of the pyrrolinone and the terminal dienyl fragment occurs first. 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 concomitant 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. 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.

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-acylpyrrolinone 8 using the hexadecapentaenoyl imidazolide 7. A subsequent phenylselenation – oxidative elimination sequence as used in the syntheses of cyclochalasans3 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 synthesised from (E)-1-bromo-4-tert-butyldimethylsilyloxy-2-methylbut-2-ene (10) using chiral auxiliary chemistry.

\[ R \rightarrow [\text{cyclisation}] \rightarrow 6 \]

\[ 6 \rightarrow 7 \]

\[ 7 \rightarrow 8 \]

\[ 8 \rightarrow 9 \]

\[ 9 \rightarrow 10 \]

\[ 10 \rightarrow 11 \]

\[ 11 \rightarrow 12 \]

\[ 12 \rightarrow 13 \]

\[ 13 \rightarrow 14a \]

\[ 14a \rightarrow 14b \]

\[ 14b \rightarrow 15 \]

\[ 15 \rightarrow 16 \]

\[ 16 \rightarrow 17 \]

\[ 17 \rightarrow 18 \]

\[ 18 \rightarrow 19 \]

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

**Results and discussion**

**Use of hexadecapentaenates**

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 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 $^{13}$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.
The minor product present in the mixture obtained by reduction of 16 will comprise (2S,4S)-octenol 18 and its enantiomer. However, the required (2R,4S)-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 (2Z,4E)-dieneyl ester. The alcohol 9 was protected as its tri-isopropylsilyl ether 19 and selective desilylation gave the alcohol 20 that was oxidised to the aldehyde 21. The modified Julia reaction with sulfone 23, prepared from (E)-2-methylbut-2-en-1-ol via the corresponding sultide, was then investigated. 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 (6E,8E,10E)-isomer 22 was the major product with minor side-products provisionally identified as the (6E,8Z,10E)- and the (6E,8E,10Z)-isomers being formed at the 4-5% level, see Scheme 2. The N-phenylethetrazolyl sulfone analogous to the benztotriazolyl sulfone 23 gave lower yields.

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

Scheme 1 Synthesis of (2R,6S,6E)-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, NH₂BH₃, 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, Et₃N, r.t. (14a, 74%; 14b, 71%); iv, Ph₃P, imid., DCM, i₂, 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%).

Scheme 2 Introduction of the conjugated triene Reagents and conditions: i, Et₃N, 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%; (6E,8E,10E) : (6E,8Z,10E) : (6E,8E,10Z) = 91: 5: 4]. 28 and carbonyl di-imidazole. A 5 : 1 mixture of the (2Z,4E)-isomer 29 and its (2E,4E)-isomer was obtained after 45 minutes but longer reaction times gave more (2Z)- to (2E)-isomerisation, (2Z,4E) : (2E,4E) = 3 : 1 after 2 h, and 1 : 1 after 16 h. In this sequence, products from the minor (2Z,4Z)-dieneyl ester were not isolated. As this Stille chemistry had provided access to (2Z,4E)-dieneyl 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.
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Scheme 3 Introduction of the (2Z,4E)-diene ester using a Stille reaction Reagents and conditions: i, Bu'SnH, AIBN (cat.), benzene, heat, 4 h [79%]; (E) : (Z) = 10 : 1; ii, 26, PdCl₂(MeCN)₂, DMF, r.t., 24 h [80%]; (2Z,4E) : (2Z,4Z) = 10 : 1; iii, NaOH, EtOH, r.t., 3 h (99%); iv, CO(imidaz)₂, THF, r.t., 45 min [82%]; (2Z,4E) : (2E,4E) = 5 : 1).

Aldehyde 30 was prepared by oxidation of the alcohol 9 and was converted into the alkyne 32 via the dibromide 31 since direct conversion using the Ohira-Bestmann reagent 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 procedures gave mixtures of (E,Z) and regioisomers, respectively. The aldehyde 30 was then converted into the (E)-vinyl iodide 33 that was deprotected to give the corresponding alcohol 34. This was oxidised to the aldehyde 37 but, despite a precedent, 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. Deprotection and oxidation of the resulting aldehyde 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 (2E)-unsaturated ester 41 using a Wittig reaction. This reaction was highly stereoselective, the (2Z)-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 (10Z)- and (12Z)-isomers were also formed, (2E,8E,10E,12E) : (2E,8E,10Z,12E) : (2E,8E,10E,12Z) = 87 : 6 : 7, see Scheme 5.

The mixture of tetaenes was not separated. Structures were assigned to components of the mixture by 1H 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 1H NMR spectrum of the mixture with data published for (2E,4E)- and (2Z,4E)-3,7,11-trimethyldeca-2,4,6,10-tetraenes and for aspochalasane precursors confirmed the all-(E)-stereochemistry assigned to the major product 44 and the (2E,8E,10E,12Z)-configuration assigned to the minor (10E)-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, pyridine, r.t., 15 min., add alcohol, r.t. - 2 h (30, 97%; 37, 78%); ii, Ph₃P, DCM, Zn, 0 °C, CBr₄, 0 °C to r.t., add 30, r.t., 18 h (74%); iii, tBuLi, THF, -78 °C, 1.5 h (80%); iv, CrCl₂, THF, 0 °C, 15 min, add 30, CH₃, 0 °C, 3 h (76%); v, TBAF, THF, 0 °C to r.t., 1 h (34, 83%; 36, 82%); vi, 33, Bu’SnCl, THF, -78 °C, add tBuLi, -78 °C, 2 h (84%); vii, MnO₂, 36, DCM, r.t., 1 h (82%); viii, 38, 23, THF, -78 °C, LiHMDS, -78 °C to r.t., 2 h [75%, (1E,7E,9E,11E) : (1E,7E,9Z,11E) : (1E,7E,9E,11Z) = 88 : 7 : 5].
Although this sequence provided the required (2Z,4E,10E,12E,14E)-isomer 48 as the major product, the amount of the (14Z)-isomer gradually increased along the reaction sequence so that the acid 48 was a mixture of geometrical isomers, in the ratio (2Z,4E,10E,12E,14E) : (2Z,4E,10E,12Z,14E) : (2Z,4E,10E,12E,14Z) = 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 carbonium 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 imidazolidine 7. This wasn’t purified but was used immediately to acylate the Boc-protected pyrrolidinone 49. 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 compounds prepared earlier. Phenylselenation gave the epimers of the 3-phenylselenylpyrrolidinone 51 and these were immediately subjected to oxidative elimination to generate the pyrrolinone 52 using conditions that had been successful 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 (14E,14Z)- and (2Z,2E)-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 (2Z)-double-bond. If successful, attempts would be made to introduce this double-bond after the macrocyclisation.

**Scheme 5** Synthesis of hexadecapentaenoic acid 48 Reagents and conditions; i, Ph₂PCHCO₂Et, DCM, r.t., 14 h (73%); ii, PPTS, DCM, EtOH, r.t., 3 h (90%); iii, MnO₂, DCM, r.t., 2 - 4 h (43, 85%; 46, 84%); iv, 43, THF, add LiHMDS, -78 °C to r.t., 2 h [73%, (2E,8E,10E,12E) : (2E,8E,10Z,12E) : (2E,8E,10E,12Z) = 87 : 6 : 7]; v, DIBAL-H, THF, -78 °C, 1 h, r.t. (85%); vi, K₂CO₃, 18-c-6, r.t., 1 h, -20 °C, add (CF₃CHO)₂P(O)CH₂CO₂Me and 46, 0 °C, 3 h (86%); vii, NaOH, EtOH, H₂O, r.t., 18 h (92%; (2Z,4E,10E,12E,14E) : (2Z,4E,10E,12Z,14E) : (2Z,4E,10E,12E,14Z) = 77 : 6 : 17).

Reduction of the ester 44, still containing its (10Z)- and (12Z)-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 (2Z)-hexadecapentaenoate 47. Hydrolysis of the ester then gave the acid 48, ready for incorporation into a synthesis of the Diels-Alder precursor 7, see Scheme 5.

**Scheme 6** Formation of the 3-(hexadecapentaenoyl)pyrrolidinone 52 Reagents and conditions; i, CO(imid)₃, THF, r.t., 45 min; ii, 49, LiHMDS, THF, -78 °C, 1 h, add 7, 45 min, 2 h (-78 °C, 2 h [58%; (10E,12E,14E) : (10E,12Z,14E) : (10E,12E,14Z) = 73 : 5 : 22; (2Z,AE) : (2E,AE) = 90 : 10]; iii, LiHMDS, -78 °C, 30 min, add PhSeCl, THF, -78 °C, 4 h (60%); iv, (a) H₂O₂, -50 °C, m-CBPA, CDCl₃, -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-benzoylpyrrolidone was used in this synthesis. Following acid catalysed removal of the Boc-group from pyrrolidone 49, the enantiomeric purity of the resulting NH-pyrrolidone 53 was checked by comparison of the N-Mosher’s derivatives of the pyrrolidine 54 prepared by reduction of pyrrolidone 53 using lithium aluminium hydride. The Mosher’s derivatives appeared to be diastereomerically homogeneous and so the e.e. of the pyrrolidone 53 was >95%. Following N-benzoylation, the resulting imide 57 was acylated using hexanoyl imidazolide to give the 3-acetylpyrrolidone 58 as a mixture of 3-epimers with some enol present. This mixture was taken through to the 3-phenylselenyl derivative 59, again as a mixture of epimers at C(3). Oxidative elimination generated the pyrrolidone 60 that was heated in toluene in the presence of (1E3E)-1,4-diphenylbuta-1,3-diene. A single adduct 61 was isolated and the endo configuration with respect to the pyrrolidone was established by 31H NMR (nOe). Sodium hydrosyde gave the debenzyolated product 62.

Scheme 7 Pyrrolidone synthesis and an intermolecular Diels-Alder reaction Reagents and conditions: i, TFA, DCM, r.t., 1 h (94%); ii, LiAlH4, THF, 66 °C, 14 h (70%); iii, (S)- or (R)-PhC(CF3)(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, 2 h (57); vi, 57, THF, -78 °C, LiHMDS, -78 °C, 5 h (76%); vii, PhSeCl, -78 °C, 2 h (77%); vii, (a) H2O2, CHCl3, m-CPBA, -48 °C, 45 min, 0 °C, 10 min; (b) (2E,4E)-1,4-diphenylbuta-1,3-diene, toluene, heat, 4 days (43%); viii, NaOH, MeOH, H2O, r.t., 6 h (60%).

The synthesis of a Diels-Alder precursor lacking the (2Z)-double bond would require the assembly of a γδ-unsaturated ester. Such compounds can be prepared using Claisen rearrangements2 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 as its (E)-isomer. After desilylation, oxidation of the alcohol 65 gave the aldehyde 66 and a modified Julia reaction with the benzothiazolyl sulphonate 23 gave the hexadecatetraenoate 67 predominantly as its (E)-diastereoisomer, (4E,10E,12E,14E) : (4E,10E,12Z,14E) : (4E,10E,12E,14Z) = 91 : 4 : 5. This was taken through to the acyl imidazolide 69 via the acid 68, and acylation of the pyrrolidone 57 using this imidazolide gave the partly enolised 3-acetylpyrrolidinone 70 as a mixture of epimers. Phenylselenation then gave the 3-phenylselenylpyrrolidinone 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 (14Z)-isomer was present, (4E,10E,12E,14E) : (4E,10E,12Z,14E) : (4E,10E,12E,14Z) = 76 : 3 : 21.

Scheme 8 Synthesis of the ethyl hexadecatetraenoate 67 and Diels-Alder precursors; i, CH3=CHMgBr, THF, r.t., 50 min (74%; 2 : 1 mixture); ii, CH3C(OMe)2, CH3CH2CO2H, xylene, heat, 6 h (91%); iii, PPTS, DCM, EtOH, r.t., 24 h (95%); iv, MnO2, DCM, r.t., 1 h (85%); v, 66, 23, THF, -78 °C, add LiHMDS, THF, -78 °C, 1 h, r.t., 1 h [74%]; (4E,10E,12E,14E) : (4E,10E,12Z,14E) : (4E,10E,12E,14Z) = 91 : 4 : 5; vi, NaOH, EtOH, r.t., 1 h (99%); vii, CO(Imid)2, THF, r.t., 18 h [95%]; (4E,10E,12E,14E) : (4E,10E,12Z,14E) : (4E,10E,12E,14Z) = 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%]; (4E,10E,12E,14E) : (4E,10E,12Z,14E) : (4E,10E,12E,14Z) = 76 : 3 : 21.
Notwithstanding the partial isomerisation of the 14-double-bond, the mixture of phenylselenylpyrrolinones 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 \( \text{exo-(11E)} \) - and \( \text{endo-(11E)} \)-Diels-Alder adducts 73 and 74.\(^{24}\) The more polar fraction comprised a mixture of the analogous \( \text{exo-} \) and \( \text{endo-(11Z)} \)-isomers 75 and 76 (11%). (The \( \text{endo-} \) and \( \text{exo-} \)-nomenclature refers to the stereoselectivity with respect to the pyrrolinone.)

\( \text{N-Debenzylation of the exo/endo-mixture of the (11E)-isomers 73 and 74 gave the exo-(11E)-NH-adduct 77 but the endo-(11E)-isomer 78 could not be separated from other products. The exo-(11E)-NH-adduct 77 has the same configuration at each of its seven stereogenic centres as chaetochalasin A (1). N-Debenzylation of the mixture of the (11Z)-isomers 75 and 76 gave the exo- and endo-(11Z)-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 \( \text{endo-} \) and \( \text{exo-} \)-adducts from pyrrolinones can be distinguished by their 13,14-coupling constants. These are typically 6.5 Hz for \( \text{exo-} \)-adducts and significantly smaller, typically 0 – 1 Hz, for \( \text{endo-} \)-adducts.\(^{3,4}\) On this basis, the adducts 77 and 79 were assigned the \( \text{exo-} \)-configuration with the adduct 80, the \( \text{endo-} \)-configuration.

The relative configuration at C(13) and C(17) was confirmed for the adduct 77 by nOe studies.\(^{22}\) 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-(11Z)-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-(11Z)-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 (\( \text{Z,} \text{E} \))-isomerisation of the (2Z)-double-bonds in intermediates that contained the hexadecapenta-2,4,10,12,14-enoate moiety. Morover the (14E)-hexadecapenta- and -hexadecatetra-enoates have a tendency to equilibrate with their (14Z)-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 (11Z)-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 aspochalasin synthesis was attributed to the use of a mixture of (E-) and (Z-)isomers in the starting material for the Diels-Alder reaction.\(^6\)

It may be that the (10E,10Z)-isomerisation observed in the present work leading to products with both the (11E)- and (11Z)-geometry, is catalysed by the acidic side-products of the selenoxide elimination although the solution of the pyrrolone 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 pyrroline from an aldehyde precursor under mildly basic conditions. No products were isolated that had been derived from (14Z)-isomers of the Diels-Alder precursors. However only modest yields of Diels-Alder products were observed and it may be that the (14Z)-isomers were less disposed to Diels-Alder cyclisations because of steric hinderance in the conformation of the conjugated diene required for cyclisation.

Notwithstanding these complications, substantial progress towards a total synthesis of chaetocinaphalasin A \(^1\) has been made. Future work will be to develop the Knoevenagel approach to the N-acylated pyrroliones 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 (3Z)-double-bond into the N-deacylated (11E)-exo-Diels-Alder product \(^7\) in order to complete a synthesis of chaetocinaphalasin A \(^1\).

**Experimental**

\((2\text{RAE})-N-[\{1S,2S\}-1\text{-Hydroxy}-1\text{-phenylpropan}-2\text{-yl}]\text{-N-methyl-} 6\text{-tert-butyl(dimethyl)silyloxy}-2,4\text{-dimethylhex-4-ene}\) (12). Lithium di-isopropylamide (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 \(78^\circ\)C. The amide (-)-11 (1.70 g, 7.74 mmol) in THF (20 mL) cooled to \(0^\circ\)C was added dropwise with stirring at \(-78^\circ\)C for 1 h before being allowed to warm to r.t. The mixture was cooled to \(0^\circ\)C before the dropwise addition of the bromide 10 (3.24 g, 11.6 mmol) in THF (11 mL) with stirring at \(0^\circ\)C for 40 min. Saturated aqueous ammonium chloride (360 mL) was added and the aqueous layer was extracted with ethyl acetate (144 mL \(\times\) 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 \textit{title compound} 12 as a light yellow oil (2.89 g, 89%), \(R\_s = 0.17\) (2 : 1, ether : petrol), as a 3 : 1 mixture of rotamers (1H and 1\(^{13}\)C NMR), \([\alpha]_D^{\text{26.0}} +37\) (c 0.4, CHCl\(_3\)) (Found: \(M^+ +\) Na, 442.2750. \(C_{22}H_{34}O_N\) requires M, 442.2748; \(\nu_{\text{max/cm}}^{-1}\) 3371(br), 2929, 2856, 2361, 1620, 1426, 1407, 1378, 1253, 1196, 1074, 1053, 1005, 939, 833, 774, 700, 667 and 614; \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) major rotamer 0.04 (6 H, s, 2 \(\times\) SiCH\(_3\)), 0.88 (9 H, s, Si(CCH\(_3\)), 0.74 (6 H, m, 2-CH\(_3\) and 2-CH\(_2\)), 1.59 (3 H, s, 4-CH\(_3\)), 2.00 (1 H, dd, \(J 14.0, 7.5, 3-\text{H}\)), 2.30 (1 H, dd, \(J 14.0, 7.0, 3-\text{H}\)), 2.81 (1 H, m, 2-H), 2.89 (3 H, s, N-CH\(_3\)), 4.17 (2 H, m, 6-H), 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, tj, \(J 7.5, 1.0, 5-\text{H}\)) and 7.35 (5 H, m, Ar); minor rotamer 0.06 (6 H, s, 2 \(\times\) SiCH\(_3\)), 0.89 (9 H, s, Si(CCH\(_3\)), 0.99 (3 H, d, \(J 7.0, 2-\text{CH}_2\)), 1.68 (3 H, s, 4-CH\(_3\)), 2.08 (1 H, dd, \(J 13.5, 8.0, 3-\text{H}\)), 2.52 (1 H, dd, \(J 13.5, 6.5, 3-\text{H}\)), 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); \(\delta_\text{C}(100\text{ MHz, CDCl}_3)\) major rotamer \(-5.3, 14.3, 16.5, 16.8, 18.2, 25.8, 32.0, 32.6, 43.6, 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; \(m/\varepsilon\) (ES+)) 442 (M\(^+\) 23%, 100%).

**Future work** will be to develop the Knoevenagel approach to the N-acylated pyrroliones 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 (3Z)-double-bond into the N-deacylated (11E)-exo-Diels-Alder product \(^7\) in order to complete a synthesis of chaetocinaphalasin A \(^1\).
and 5.37 (1 H, t, J 6.5, 1.0, 5-H); δC (100 MHz, CDCl3) −5.1, 16.2, 17.2, 18.4, 20.6, 26.0, 32.7, 46.5, 50.1, 62.1, 127.1, and 134.2; m/z (El/CI) 311 (M+ − 57, 4%).

**Table 1: Spectroscopic Data for the Title Compounds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>δH (6.60 g, 28.1 mmol) in DMSO-d6</th>
<th>δC (100 MHz, CDCl3)</th>
<th>m/z (El/CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H5NO2</td>
<td>1.83 (3 H, s, H3-1)</td>
<td>135.2, 135.2, 135.2</td>
<td>323 (M+ + 23, 100%)</td>
</tr>
</tbody>
</table>

**Table 2: Analytical Data for the Title Compounds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rf</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H5NO2</td>
<td>0.48</td>
<td>78%</td>
</tr>
</tbody>
</table>

**Table 3: Comparison of Spectroscopic Data**

<table>
<thead>
<tr>
<th>Compound</th>
<th>δH (6.60 g, 28.1 mmol) in DMSO-d6</th>
<th>δC (100 MHz, CDCl3)</th>
<th>m/z (El/CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H5NO2</td>
<td>1.83 (3 H, s, H3-1)</td>
<td>135.2, 135.2, 135.2</td>
<td>323 (M+ + 23, 100%)</td>
</tr>
</tbody>
</table>

**Table 4: Analytical Data for the Title Compounds**

<table>
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<tr>
<th>Compound</th>
<th>Rf</th>
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<td>C6H5NO2</td>
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<td>78%</td>
</tr>
</tbody>
</table>

**Table 5: Comparison of Spectroscopic Data**

<table>
<thead>
<tr>
<th>Compound</th>
<th>δH (6.60 g, 28.1 mmol) in DMSO-d6</th>
<th>δC (100 MHz, CDCl3)</th>
<th>m/z (El/CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H5NO2</td>
<td>1.83 (3 H, s, H3-1)</td>
<td>135.2, 135.2, 135.2</td>
<td>323 (M+ + 23, 100%)</td>
</tr>
</tbody>
</table>

**Table 6: Analytical Data for the Title Compounds**

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<tr>
<th>Compound</th>
<th>Rf</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>C6H5NO2</td>
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<td>78%</td>
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</tbody>
</table>

**Table 7: Comparison of Spectroscopic Data**

<table>
<thead>
<tr>
<th>Compound</th>
<th>δH (6.60 g, 28.1 mmol) in DMSO-d6</th>
<th>δC (100 MHz, CDCl3)</th>
<th>m/z (El/CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H5NO2</td>
<td>1.83 (3 H, s, H3-1)</td>
<td>135.2, 135.2, 135.2</td>
<td>323 (M+ + 23, 100%)</td>
</tr>
</tbody>
</table>

**Table 8: Analytical Data for the Title Compounds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rf</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>C6H5NO2</td>
<td>0.48</td>
<td>78%</td>
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</table>

**Table 9: Comparison of Spectroscopic Data**

<table>
<thead>
<tr>
<th>Compound</th>
<th>δH (6.60 g, 28.1 mmol) in DMSO-d6</th>
<th>δC (100 MHz, CDCl3)</th>
<th>m/z (El/CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H5NO2</td>
<td>1.83 (3 H, s, H3-1)</td>
<td>135.2, 135.2, 135.2</td>
<td>323 (M+ + 23, 100%)</td>
</tr>
</tbody>
</table>

**Table 10: Analytical Data for the Title Compounds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rf</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H5NO2</td>
<td>0.48</td>
<td>78%</td>
</tr>
</tbody>
</table>

**Table 11: Comparison of Spectroscopic Data**

<table>
<thead>
<tr>
<th>Compound</th>
<th>δH (6.60 g, 28.1 mmol) in DMSO-d6</th>
<th>δC (100 MHz, CDCl3)</th>
<th>m/z (El/CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H5NO2</td>
<td>1.83 (3 H, s, H3-1)</td>
<td>135.2, 135.2, 135.2</td>
<td>323 (M+ + 23, 100%)</td>
</tr>
</tbody>
</table>

**Table 12: Analytical Data for the Title Compounds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rf</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H5NO2</td>
<td>0.48</td>
<td>78%</td>
</tr>
</tbody>
</table>
(5R)-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 (Na2SO4). After concentration under reduced pressure, chromatography of the residue using ether and methanol as eluent (gradient elution, eluent 1 to 10 methanol : ether) gave the title compound 53 as a white solid (0.57 g, 94%), Rf = 0.46 (1 : 10, MeOH : ether), m.p. 57.0-60.0 °C, [α]D20 18 +12 (c 0.4, benzene) (Found: M+ – C2H2, 84.0441. C4H5ON requires M+, 84.0444); νmax/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; δH (400 MHz, CDCl3) 0.89 and 0.94 (each 3 H, d, J 7.0, CH2CH3), 1.62 (1 H, m, 5-CH3), 1.74 and 2.15 (each 1 H, m, 4-CH3), 2.25-2.38 (2 H, m, 3-CH3), 3.37 (1 H, q, J 7.0, 5-H) and 7.13 (1 H, br. s, NH); δC (100 MHz, CDCl3) 18.0, 18.7, 24.5, 30.6, 33.4, 60.8 and 179.1; m/z (EI/Cl) 127 (M+, 1%) and 84 (M– 43, 100).

(4R,6S,8E)-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 stirred to 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 (Na2SO4) 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), Rf = 0.28/0.25 (1 : 5, ether : light petroleum), [α]D372 +16. (c 0.3, benzene) (Found: M+ + Na+, 349.2527. C19H24O2Na requires M+, 349.2534); νmax/cm–1 3396(br), 2954, 2927, 2856, 1261, 1667, 1641, 1461, 1379, 1361, 1252, 1199, 1088, 1054, 1004, 920, 833, 813, 773 and 665; δH (400 MHz, CDCl3) major epimer 0.12 (6 H, s, 2 × SiCH3), 0.84 (3 H, d, J 6.5, 6-CH3), 0.88 (3 H, d, J 7.0, 4-CH3), 0.94 (1 H, m, 5-H), 1.01 [9 H, s, Si(C2H5)3], 1.09 (1 H, br. s, OH), 1.46 (1 H, m, 5-H), 1.52 (3 H, s, 8-CH3), 1.62-1.71 (3 H, m, 4-6- 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), 5.03 (1 H, dt, J 10.5, 1.5-H), 5.16 (1 H, t, J 17.0, 1.5, 1.5-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-CH3), 0.88 (3 H, d, J 7.0, 4-CH3), 1.06 (1 H, br. s, OH), 1.40 (1 H, m, 5-H), 1.50 (3 H, s, 8-CH3), 1.77 (1 H, t, J 5.0, 3-H), 5.13 (1 H, dt, J 17.0, 1.5, 1.5-H), 5.50 (1 H, m, 9-H) and 5.74 (1 H, ddd, J 17.0, 10.5, 6.0, 2-H); δC (100 MHz, CDCl3) 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 (ESI+) 349 (M+ 23, 100%).

Ethyl (6R,8S,4E,10E)-6,8,10-trimethyl-12-oxodeca-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 azetropede 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%); Rf = 0.28 (1 : 10, ether : light petroleum), [α]D372 2.7 (c 0.6, benzene) (Found: M+ + Na+, 49.2957. C3H5NO4Na requires M+, 49.2952); νmax/cm–1 2954, 2928, 2857, 2360, 1737, 1666, 1462, 1374, 1252, 1163, 1086, 1054, 1006, 971, 939, 834, 813, 774 and 665; δH (400 MHz, CDCl3) 0.09 (6 H, s, 2 × SiCH3), 0.81 (3 H, d, J 6.5, 8-CH3), 0.91 (1 H, m, 7-H), 0.93 (2 H, d, J 6.5, 6-CH3), 0.98 (3 H, t, J 7.0, CH2CH3), 0.99 [9 H, s, Si(CH3)3], 1.23 (1 H, ddd, J 13.5, 10.0, 4.5, 7-H), 1.51 (3 H, s, 10-CH3), 1.63 (1 H, m, 8-H), 1.76 (1 H, ddd, J 13.0, 8.0, 9-H), 1.91 (1 H, ddd, 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-H2 or 3-H2), 3.95 (2 H, q, J 7.0, CH2CH3), 4.21 (2 H, d, J 6.5, 12-H), 5.19 (1 H, dt, J 15.5, 8.0, 10.5, 5-H), 5.32 (1 H, dt, J 15.5, 6.5, 4-H) and 5.46 (1 H, qt, J 6.5, 1.0, 11-H); δC (100 MHz, CDCl3) –4.5, 25.0, 25.6, 26.6, 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 (ESI+) 420 (10%) and 265 (100%).
(6R,8R,10E,12E,14E)-8,6,8,10,14-tetramethylhexadec-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 (0.65 g, 1.10 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 (Na2SO4) 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, (4E,10E,12E,14E) : (4E,10E,12Z,14E) = 89 : 1 : Rf = 0.37 (1 : 2 ether : light petroleum); [α]D19 +21 (c 0.6, benzene) (Found: M+ = 353.2319. C20H34O4 requires M+, 353.2329); νmax/cm−1 3036, 2953, 2912, 2868, 2831, 1706, 1462, 1439, 1410, 1376, 1295, 1267, 1209, 1023, 958, 789 and 676; δH (400 MHz, CD30) (4E,10E,12E,14E)-isomer 68 0.87 (3 H, d, J 6.5, 7-H), 1.89 (5 H, m, 6-H, 10-H, 12-H); δC (100 MHz, CD30) 14.7, 17.1, 19.5, 22.3, 25.8, 28.8, 34.8, 35.0, 44.6, 49.2, 60.4, 127.9, 129.5, 135.7, 161.2, 172.7 and 190.1. m/z (ES+) 303 (M+ + 23, 100%).
(5R)-1-Benzoyl-5-prop-2-yl-3-[6R,8S,4E,10E,12E,14E]-6,8,10,14-tetramethylhexadeca-4,10,12,14-tetraenoylpyrrolidin-2-one (70). Lithium hexamethyldisilazide (1.0 M in THF; 0.50 g, 29.9 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 at –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 (Na2SO4) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 7) eluent gave the *title compounds* 70 as a light orange liquid (0.069 g, 79%), a partly enolised mixture of isomers, (4E,10E,12E,14E)-: (4E,10E,12E,14Z)-: (4E,10E,12E,14Z) – 84 : 4 : 12, as 1 : 1 mixtures of epimers at C(3), keto-tautomers : enol tautomer = 2 : 1, Rf = 0.46 (1 : 2, ether : light petroleum), [α]D20 +130 (c 0.6, benzene) (Found: M+ + 1, 518.8662. C32H42NO2 requires M, 518.3629); m/z by electrospray mass spectrometry, 518 (M+, 100), 492 (M+ - 15), 477 (M+ - 30), 462 (M+ - 45), 447 (M+ - 60), 432 (M+ - 75), 417 (M+ - 90), 402 (M+ - 105), 387 (M+ - 120), 372 (M+ - 135), 357 (M+ - 150), 342 (M+ - 165), 327 (M+ - 180), 312 (M+ - 195), 297 (M+ - 210), 282 (M+ - 225), 267 (M+ - 240), 252 (M+ - 255), 237 (M+ - 270), 222 (M+ - 285), 207 (M+ - 300), 192 (M+ - 315), 177 (M+ - 330), 162 (M+ - 345), 147 (M+ - 360), 132 (M+ - 375), 117 (M+ - 390), 102 (M+ - 405), 87 (M+ - 420), 72 (M+ - 435), 57 (M+ - 450), 42 (M+ - 465), 27 (M+ - 480), 12 (M+ - 505) 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 phenylselenyl 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 (Na2SO4) 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), (4E,10E,12E,14E) : (4E,10E,12Z,14E) : (4E,10E,12E,14Z) = 76 : 3 : 21, Rf = 0.37 (1 : 4, ether : light petroleum); [α]D20 +130 (c 0.6, benzene) (Found: M+ + 1, 696.2937, C32H42NO2SeNa requires M, 696.2927); m/z by electrospray mass spectrometry, 785 (M+, 100), 760 (M+ - 25), 735 (M+ - 50), 710 (M+ - 75), 685 (M+ - 100), 660 (M+ - 125), 635 (M+ - 150), 610 (M+ - 175), 585 (M+ - 200), 560 (M+ - 225), 535 (M+ - 250), 510 (M+ - 275), 485 (M+ - 300), 460 (M+ - 325), 435 (M+ - 350), 410 (M+ - 375), 385 (M+ - 400), 360 (M+ - 425), 335 (M+ - 450), 310 (M+ - 475), 285 (M+ - 500), 260 (M+ - 525), 235 (M+ - 550), 210 (M+ - 575), 185 (M+ - 600), 160 (M+ - 625), 135 (M+ - 650), 110 (M+ - 675), 85 (M+ - 700), 65 (M+ - 725), 45 (M+ - 750), 25 (M+ - 775), 15 (M+ - 800), 5 (M+ - 825).
cooling bath and allowed to warm up to 0 °C over the period of 10 min with vigorous stirring. Chilled chloroform-\(d_2\) (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\(_2\)SO\(_4\)), 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 (11E)-Diels-Alder products 73 and 74 as a clear oil (34 mg, 11%), 73: \(\delta = 7.4: 5.4\) (Found: M\(^+\) + H, 516.3486. C\(_{33}\)H\(_{26}\)NO\(_2\) requires M, 516.3473); \(\nu_{\text{max}}\) cm\(^{-1}\) 2958, 2919, 2360, 2341, 1731, 1706, 1693, 1601, 1448, 1373, 1275, 1214, 1127, 1132, 908, 790 and 751; m/z (ES\(^+\)) 538 (M\(^+\) + 23, 100%). The second fraction was a mixture of the (11Z)-Diels-Alder adducts 75 and 76 as a clear oil (38 mg, 12%), 75: \(\delta = 7.5: 5.4\) (Found: M\(^+\) + H, 516.3464. C\(_{33}\)H\(_{26}\)NO\(_2\) requires M, 516.3473); \(\nu_{\text{max}}\) cm\(^{-1}\) 2957, 2919, 2360, 2340, 1734, 1682, 1600, 1448, 1373, 1275, 1217, 1178, 1140, 908, 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%).

\[ \text{(7R,9S,13R,16R,17R,18S,5E,11Z,14E)-7,9,11,15,16-Pentamethyl-18-(prop-2-yl)-19-aza-20-oxocticryloyl[15.3.0] cicos-5,11,14-trien-2-one (77)} \]

(7R,9S,13R,16R,17R,18S,5E,11Z,14E)-7,9,11,15,16-Pentamethyl-18-(prop-2-yl)-19-aza-20-oxocticryloyl[15.3.0] cicos-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 (11E)-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\(_2\)SO\(_4\)) and concentrated under reduced pressure. Chromatography of the residue using ether: light petroleum (1: 4) as eluent gave the (11E)-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\(_{22}\)H\(_{24}\)NO\(_2\) requires M, 412.3211); \(\nu_{\text{max}}\) 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 (13Z,16R)- and (13S,16S)-isomers 77 and 78 (6 mg, 32%), the second product was the (11E)-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\(_{22}\)H\(_{24}\)NO\(_2\) requires M, 412.3221); \(\nu_{\text{max}}\) cm\(^{-1}\) 3205, 2957, 2914, 2869, 2360, 2341, 2247, 1691, 1455, 1376, 1287, 1260, 1153, 1047, 1000, 968, 907, 811, 728 and 646; \(\delta_1\) (500 MHz, CDCl\(_3\)) 8.13 (3 H, d, J 6.5, 18-CH\(_2\)CH\(_2\)); 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-CH\(_2\)CH\(_2\)); 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\(_3\)); 1.41 (1 H, dd, J 12.5, 11.0, 10-CH\(_3\)); 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, 15.0, 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); \(\delta_1\) (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, 100%).

Acknowledgements

We thank the EPSRC for a studentship (to M. W.).

Notes and references
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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-y1)-19-aza-20-oxotricyclo[15.3.0.0[19,24]14]icosa-5,11,14-trien-2-ones. For the numbering scheme used see 77 and 1.