Stereocontrolled synthesis of lepadiformine A

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In this paper we present results of a study into whether the tricyclic core of the lepadiformines A–C can be accessed *via* intramolecular hetero-Diels–Alder cycloaddition. We are able to demonstrate that such a process is possible and that the reaction proceeds in an *endo*-selective fashion, providing the correct relative stereochemistry for this family of natural products. By employing this approach we have been able to develop a short (7 step) synthesis of (±)-lepadiformine A, starting from commercially-available *trans*-2-nonenal.

Introduction

(−)-Lepadiformine A **1** is a tricyclic alkaloid that has been isolated from several species of sea squirt belonging to the Clavelina and Polycitoridae families.[1–3] It has been shown to be moderately cytotoxic towards various tumour cell lines, and is also an effective blocker of cardiac muscle K_{ir} (potassium ion) channels.[1,3] The original structure for this natural product, proposed on the basis of ^{1}H and ^{13}C NMR analysis,[1] was later shown be incorrect, and the correct relative and absolute stereochemistry was established by synthesis.[4–6] Lepadiformines B and C,[3] polycitorals A and B,[2] fasicularin,[7] and the cylindricines A–K,[8] are structurally-related tricyclic marine alkaloids that have also been isolated from marine ascidiacea (Fig. 1). Together, this family of natural products has attracted considerable interest from synthetic chemists,[4–6,9–19] culminating in a number of syntheses of lepadiformine A,[6,11–17] fasicularin,[11,18] and cylindricines A–E.[11,14,19]

Despite this considerable synthetic effort, as far as we are aware, there have been no reports of investigations into the use of an intramolecular hetero-Diels–Alder cycloaddition involving an imine dieneophile **19** (Scheme 1) as a means of accessing the tricyclic core **18** of the lepadiformines.

This study presents the results of our investigations using the hetero-Diels–Alder approach to prepare lepadiformine A **1**.

Results and discussion

Unconjugated imines tend to be poor dieneophiles, but can be activated towards Diels–Alder cycloaddition *via* protonation, especially if the reaction is carried out in a polar environment.[21–23] Thus we envisaged that it may be possible to access the lepadiformine A tricycle **24** from an α-carboxy imine precursor **20** (Scheme 2). We considered that under thermal conditions, internal protonation of the imine function may be sufficient to promote the desired cycloaddition, and if this proved not to be the case, Diels–Alder reaction may still be possible *via* the use of external acid catalysis. However, there are at least two other thermal processes that could compete with the desired Diels–Alder reaction; namely decarboxylation to give imine(s) **22**,[24] and ene-reaction to give bicyclic intermediates such as **23**.[25]

A further complication is that the Diels–Alder reaction, even if favoured,[26] could generate up to four diastereoisomeric products **24**. Inspection of simple transition state models leading to each isomer suggested that the diene should preferentially add *anti* to the carboxyl function leading to either **27** or **28** (Fig. 2).

It was less clear whether *endo*- or *exo*-mode of addition would be favoured, so in an effort to gain more insight into this, optimized transition state structures (gas-phase) for **25** and **26** (R = Me) were calculated using B3LYP/6-31G*.[27] These calculations predict that both *exo*- and *endo*-Diels–Alder reactions would proceed *via* highly asynchronous transition states (Fig. 3) and that the transition state leading to the *endo*-adduct would be slightly favoured. Although the predicted energy differences are unlikely to be accurate for reactions performed in polar media, this did provide an indication that the desired *endo*-adduct may be favoured with this type of substrate.

Encouraged by these results, we moved on to investigate preparation of the Diels–Alder precursor **20**. We considered that such an intermediate should be readily accessed *via* Michael addition of a glycine imine **30** to enone **31** (Scheme 3).

The desired enone **31** was prepared *via* the sequence outlined in Scheme 4. Starting from commercially-available *trans*-2-nonenal **32**, Wittig reaction gave diene **33** as a mixture of alkene isomers, slightly favouring the undesired (6*Z*,8*E*)-isomer. This geometrical mixture could be equilibrated by treatment with iodine and sunlight, and the pure (6*E*,8*E*)-isomer could then be obtained from the resulting 70 : 30 mixture by repeated crystallization from petroleum ether at −20 °C. In this way we were able to obtain (6*E*,8*E*)-**33** in 43% overall yield. This material was then converted into the desired enone **31** *via* formation of the Weinreb amide, followed by reaction with vinylmagnesium bromide. This four-step sequence provided useful quantities of enone **31**.

We next investigated the synthesis of potential Diels–Alder precursors (Scheme 5). Michael addition of glycine imines **30a** and **30b** was readily achieved using caesium carbonate in diisopropyl ether in conjunction with a quaternary ammonium catalyst.[28] Hydrolysis of the benzophenone imine, followed by basification[29] then led directly to the cyclic imines **35**.

We next attempted to perform Diels–Alder cyclizations of the cyclic imine esters **35a** and **35b**. Heating either of these substrates in toluene (up to 165 °C) led to slow isomerization of the 5′-alkene, but no cycloadducts were formed. Similar results

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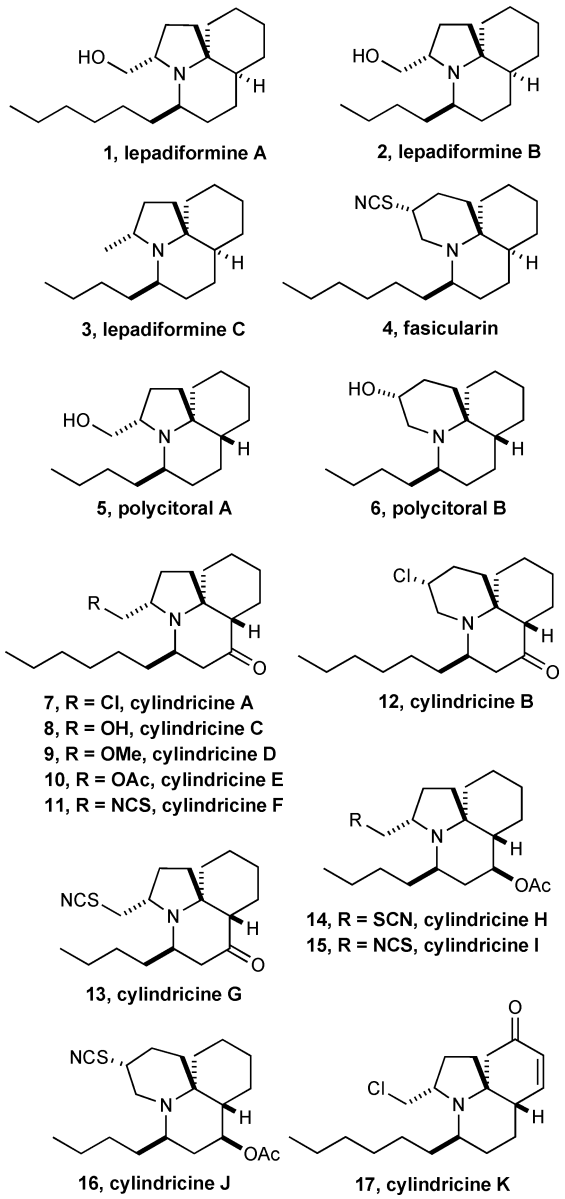
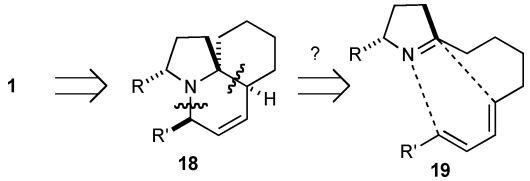


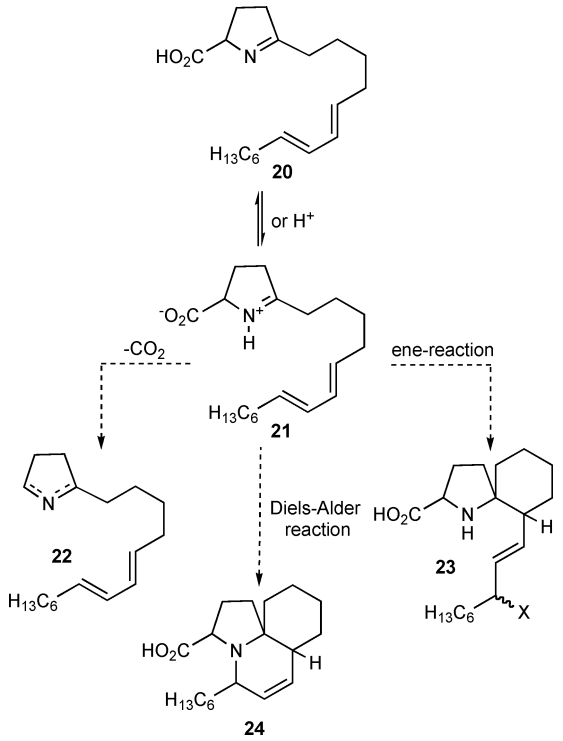
Fig. 1 Structures of tricyclic alkaloids isolated from marine ascidiacea.[20]



Scheme 1 Possible hetero-Diels–Alder approach to the lepadiformine tricycle **18**.

were obtained when the TFA salt **36** was heated in toluene (Scheme 6).

Reaction of the corresponding carboxylic acid **20** produced more interesting results. This substrate was stable towards heating to 100 °C in toluene, but when the temperature was increased to 165 °C (sealed tube), decarboxylation was observed, giving rise to a mixture of imine isomers **22**. Attempts to promote the Diels–Alder pathway by addition of trifluoroacetic acid were unsuccessful;



Scheme 2

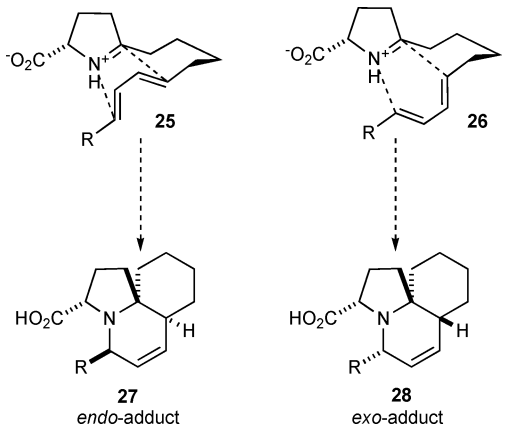


Fig. 2

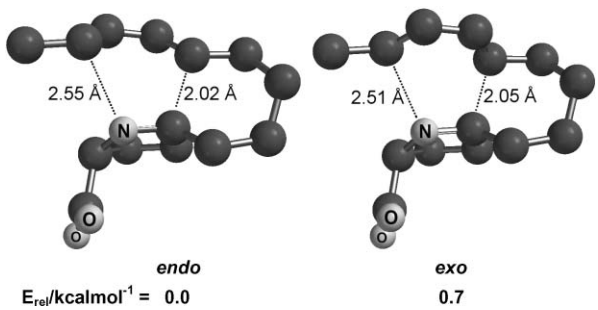
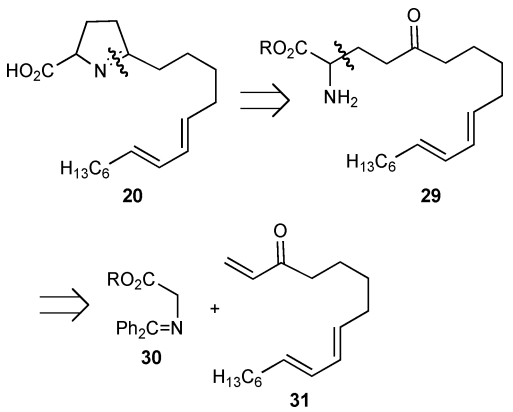
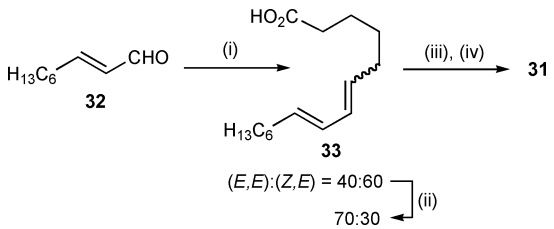


Fig. 3 B3LYP/6-31G* predicted structures for transition states **25** and **26** (R = Me).

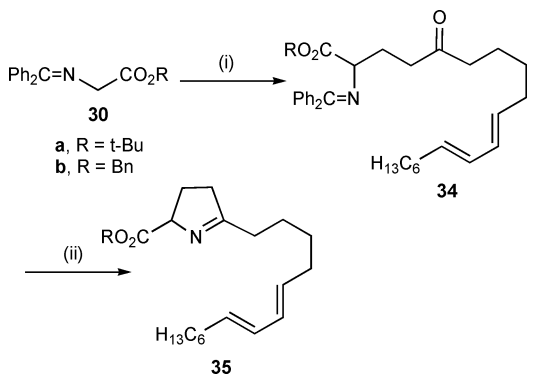
at lower temperatures no reaction occurred, and on heating to 165 °C the substrate degraded. We next investigated replacing toluene with hexafluoroisopropanol. We have previously found



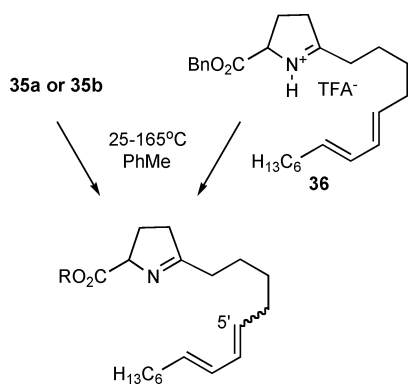
Scheme 3



Scheme 4 *Reagents and conditions:* (i) LDA (2.1 eq.), $BrPh_3P(CH_2)_5CO_2H$ (89%); (ii) I_2, hv; (iii) MeNHOMe, EDC, DMAP (94%); (iv) $H_2CCHMgBr$ (79%).

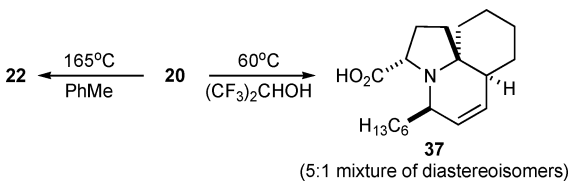


Scheme 5 *Reagents and conditions:* (i) **31**, Cs_2CO_3, i-Pr_2O, $PhCH_2NMe_3Br$; (ii) 15% aq. citric acid, THF; K_2CO_3 (**35a**, 77%; **35b**, 55%).



Scheme 6

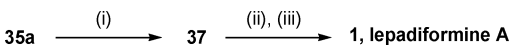
this to be a highly effective solvent for Diels–Alder chemistry,[30] and envisaged that it might provide a sufficiently acidic medium so as to promote cycloaddition whilst also stabilizing any potential carboxylate intermediates, such as **21**, towards decarboxylation. This change proved successful; heating imine **20** to 60 °C in this solvent led to formation of the desired cycloadduct **37**, along with a minor diastereoisomer (Scheme 7). At this point we were unable to unambiguously determine the stereochemistry of the major product, but subsequent studies (*vide infra*) have established that this was the *endo*-cycloadduct **37** with the correct relative stereochemistry for lepadiformine A **1**. We were unable to isolate the minor diastereoisomer, consequently this product has not been fully characterized, but ^{1}H NMR analysis of mixtures containing this component suggest that it is most probably the *exo*-adduct **28** ($R = C_6H_{13}$).



Scheme 7

Interestingly, when the cyclic imine ester **35b** or the corresponding TFA salt **36** are heated to 60 °C in hexafluoroisopropanol, only very low conversions (>10% after 10 days) to the cycloadducts are observed. In addition, when acid **20** is heated in less acidic protic solvents (H_2O, MeOH, i-PrOH), no cycloadducts are observed. This suggests that the combination of the α-carboxyl group and hexafluoroisopropanol are crucial to the success of this transformation.

A further advantage of employing hexafluoroisopropanol as the solvent is that it promotes cleavage of the *tert*-butyl ester **35a** to give the corresponding acid **20** under the same conditions required for the cycloaddition. Thus, simply by heating ester **35a** in hexafluoroisopropanol at 60 °C we were able to obtain the tricyclic acid **37** in 53% overall yield. This material was readily converted into (±)-lepadiformine A **1** by hydrogenation of the alkene followed by reduction of the carboxylic acid using lithium aluminium hydride (Scheme 8).



Scheme 8 *Reagents and conditions:* (i) $(CF_3)_2CHOH$, 60 °C (53%, 5 : 1 mixture of diastereoisomers); (ii) H_2, Pd/C, EtOH; (iii) $LiAlH_4$, THF (52% over two steps).

This study has established that the tricyclic core of lepadiformine can be readily accessed *via* intramolecular cycloaddition of diene precursor **20**. The stereochemical outcome of this process is consistent with the reaction proceeding *via* an *endo*-selective Diels–Alder reaction. By employing this approach we have been able to develop a short (7 step) synthesis of (±)-lepadiformine A **1** starting from commercially-available *trans*-2-nonenal.

Experimental

General details

Unless otherwise stated, all solvents and chemicals were used as provided by the supplier. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F_{254} precoated glass TLC plates, visualised using UV light and then basic potassium permanganate solution. Flash chromatography was performed using Merck silica gel (230–400 mesh) as the stationary phase. Melting points were determined using a Kopfler hot-stage apparatus and are uncorrected.

Infrared spectra were recorded using either a Perkin-Elmer FT 1600 or a Nicolet Avatar 360 FT-IR infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AV400 or DRX500 spectrometers at ambient temperature. Chemical shifts are quoted relative to residual solvent and *J* values are given in Hz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br., broad; m, multiplet. Mass spectra were obtained on Micromass Autospec or Micromass LCT instruments using electron impact (EI) or +ve electrospray (ES+).

(6*E*,8*E*)-Pentadeca-6,8-dienoic acid 33. A solution of freshly distilled *i*-Pr_2NH (10.7 mL, 76.0 mmol) in dry THF (100 mL) was placed under an atmosphere of nitrogen, then cooled to −30 °C. n-BuLi (32 mL, 76.0 mmol, 2.4 M) was added dropwise and the mixture was stirred for 30 min at −30 °C. The resulting LDA solution was added dropwise *via* cannula to a stirred suspension of (5-carboxypentyl)triphenylphosphonium bromide (17.4 g, 36.0 mmol) in dry THF (100 mL) at −30 °C under an atmosphere of nitrogen. The mixture was stirred at RT for 30 min before re-cooling to −30 °C. A solution of freshly distilled *trans*-2-nonenal **32** (4.5 mL, 27.0 mmol) in dry THF (50 mL) was then added dropwise at −30 °C. The mixture was then allowed to warm to RT and stirred for 18 h. An ice-cold solution of 10% aq. $NaHSO_4$ (200 mL) was added to the mixture and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 100 mL) and the combined organics were washed with brine (100 mL) then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue extracted with Et_2O. Insoluble Ph_3PO was filtered off and the solution was then passed through a large pad of silica using Et_2O (R_f 1), then concentrated under reduced pressure to give diene **33** (5.6 g, 89%, 60 : 40 mixture of (6*Z*,8*E*)- and (6*E*,8*E*)-isomers) as a yellow oil. This material was then dissolved in chloroform (170 mL), iodine (770 mg, 3.0 mmol) was added, and the mixture was left in natural sunlight for 4 h. The mixture was washed with saturated aq. $Na_2S_2O_3$ (2 × 100 mL), the combined organics were dried ($MgSO_4$) and the solvent removed under reduced pressure to give the crude diene **33** as a 30 : 70 mixture of (6*Z*,8*E*)- and (6*E*,8*E*)-isomers. Repeated recrystallization from petroleum ether (cooling to −20 °C and then filtering the crystals ice cold) gave the (6*E*,8*E*)-isomer **33** (2.4 g, 43%) as a low-melting solid (found: C, 75.6; H, 10.95. $C_{15}H_{26}O_2$ requires C, 75.6; H, 11.00%); ν_{max}(neat)/cm^{-1} 3014, 2955, 2920, 2848, 1712, 1444, 1308, 1254, 1202, 980, 902; δ_H (500 MHz, $CDCl_3$) 6.04–5.97 (2H, m, 2 × C=CH), 5.61–5.52, (2H, m, 2 × C=CH), 2.37 (2H, t, *J* 7.5, C*H*$_2$CO$_2$H), 2.11–2.03 (4H, m), 1.69–1.63 (2H, m), 1.48–1.40 (2H, m), 1.38–1.24 (8H, m), 0.89 (3H, t, *J* 7.0, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 179.8 (C), 132.9 (CH), 131.3 (CH), 130.9 (CH), 130.1 (CH), 33.8 (CH_2), 32.6 (CH_2), 32.1 (CH_2), 31.7 (CH_2), 29.4 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 24.2 (CH_2), 22.6 (CH_2), 14.1 (CH_3); *m*/*z* (EI) 238.1933 (M^+ $C_{15}H_{26}O_2$ requires 238.1933), 238 (100%), 94 (60) and 67 (95).

(6*E*,8*E*)-Pentadeca-6,8-dienoic acid methoxymethyl amide. (6*E*,8*E*)-Diene **33** (3.6 g, 15.0 mmol) was dissolved in dry CH_2Cl_2 (75 mL) and cooled to 0 °C and placed under an atmosphere of nitrogen. *N*,*O*-Dimethylhydroxylamine hydrochloride (2.2 g, 22.6 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) (4.4 g, 23.0 mmol) and DMAP (2.8 g, 23.0 mmol) were added to the solution and the mixture was stirred for 2 h at RT. The reaction was quenched with brine (50 mL) and the phases separated. The aqueous phase was extracted with EtOAc (2 × 50 mL) and the combined organics were washed with 1 M HCl (50 mL), saturated aq. $NaHCO_3$ (50 mL), brine (50 mL) and dried ($MgSO_4$). The solvent removed under reduced pressure and the residue was purified by flash chromatography on silica gel (4 : 1, petroleum ether–EtOAc) to give the Weinreb amide (3.9 g, 94%) as a yellow oil (found: C, 72.7; H, 11.1; N, 4.6. $C_{17}H_{31}NO_2$ requires C, 72.55; H, 11.1; N, 5.0%); ν_{max}(neat)/cm^{-1} 3013, 2959, 2854, 1732, 1670, 1462, 1383, 1177, 1109, 988; δ_H (500 MHz, $CDCl_3$) 6.00–5.97 (2H, m, 2 × C=C*H*), 5.56–5.52 (2H, m, 2 × C=C*H*), 3.66 (3H, s, OC*H*$_3$), 3.17 (3H, s, NC*H*$_3$), 2.41 (2H, t, *J* 7.5, C*H*$_2$CO), 2.10–2.01 (4H, m), 1.66–1.60 (2H, m), 1.45–1.36 (2H, m), 1.36–1.23 (8H, m), 0.87 (3H, t, *J* 7.0, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 174.5 (C), 132.5 (CH), 131.5 (CH), 130.7 (CH), 130.1 (CH), 61.1 (CH_3), 32.5 (CH_2), 32.2 (CH_3), 32.1 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 24.1 (CH_2), 22.5 (CH_2), 14.1 (CH_3); *m*/*z* (ES+) 282.2437 (M + H^+ $C_{17}H_{32}NO_2$ requires 282.2433), 282 (100%).

(6*E*,8*E*)-Heptadeca-1,8,10-triene-3-one 31. (6*E*,8*E*)-Pentadeca-6,8-dienoic acid methoxymethyl amide (3.9 g, 14.0 mmol) was dissolved in dry THF (200 mL), placed under an atmosphere of nitrogen, and cooled to −78 °C. Vinylmagnesium bromide (41 mL of a 1 M solution in Et_2O, 41.0 mmol) was added dropwise. The mixture was stirred for 30 min then allowed to warm to RT and stirred for a further 4 h. Aqueous HCl (200 mL, 1 M) was added and the phases separated. The aqueous phase was extracted with EtOAc (2 × 150 mL) and the combined organics were washed with brine (150 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (6 : 1, petroleum ether–EtOAc) to give the enone **31** (2.7 g, 79%) as a yellow oil (found: C, 82.2; H, 11.3. $C_{17}H_{28}O$ requires C, 82.2; H, 11.4%); ν_{max}(neat)/cm^{-1} 3014, 2926, 2855, 1703, 1683, 1615, 1456, 1401, 987, 725; δ_H (500 MHz, $CDCl_3$) 6.34 (1H, dd, *J* 17.5, 10.5, C*H*=CH$_2$), 6.21 (1H, dd, *J* 17.5, 1.0, C=C*H*$_a$H$_b$), 6.03–5.95 (2H, m, 2 × C=C*H*), 5.81 (1H, dd, *J* 10.5, 1.0, C=CH$_a$*H*$_b$), 5.59–5.51 (2H, m, 2 × C=C*H*), 2.58 (2H, t, *J* 7.5, C*H*$_2$CO), 2.17–2.02 (4H, m), 1.66–1.60 (2H, m), 1.44–1.22 (10H, m), 0.88 (3H, t, *J* 7.0, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 200.8 (C), 136.6 (CH), 132.8 (C), 131.5 (C), 130.8 (C), 130.1 (C), 127.9 (C), 39.5 (CH_2), 32.6 (CH_2), 32.3 (CH_2), 31.7 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 23.5 (CH_2), 22.6 (CH_2), 14.1 (CH_3); *m*/*z* (EI) 248.2143 (M^+ $C_{17}H_{28}O$ requires 248.2140), 248 (40%), 207 (20), 123 (25), 79 (80), 67 (100).

(5*E*,7*E*)-5-Tetradeca-5′,7′-dienyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid *tert*-butyl ester 35a. Enone **31** (208 mg, 0.84 mmol) was added to a solution of glycine imine **30a** (247 mg, 0.84 mmol)

and benzyltrimethylammonium bromide (19 mg, 0.08 mmol) in diisopropyl ether (15 mL). Cs_2CO_3 (547 mg, 1.68 mmol) was then added and the mixture stirred at RT overnight. The reaction mixture was filtered through $MgSO_4$ and then concentrated under reduced pressure the give the crude imine **34a** (484 mg) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 7.84–7.21 (10H, m, Ar*H*), 6.04–5.96 (2H, m, 2 x C*H*=CH), 5.62–5.50 (2H, m, 2 x C*H*=CH), 3.96 (1H, apparent t, *J* 7.0, CH_2), 2.60–2.46 (2H, m), 2.41 (2H, apparent t, *J* 7.5, CH_2), 2.25–2.03 (6H, m), 1.46 (9H, s, C(CH_3)$_3$), 1.61–1.25 (12H, m), 0.85 (3H, t, *J* 6.5, CH_3). This material was dissolved in a mixture of THF (10 mL) and 15% aq. citric acid (10 mL) and stirred at room temperature for 3 h. The mixture was basified with solid K_2CO_3 and stirred for a further 30 min. CH_2Cl_2 (30 mL) was then added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (30 mL) and the combined organics dried ($MgSO_4$) and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (4 : 1, petroleum ether–Et_2O) to give the cyclic imine **35a** (235 mg, 77%) as a pale yellow oil; ν_{max}(neat)/cm^{-1} 2926, 2855, 1734, 1642, 1457, 1367, 1256, 1211, 1155, 987; δ_H (400 MHz, $CDCl_3$) 6.02–5.94 (2H, m, 2 x C*H*=CH), 5.57–5.46 (2H, m, 2 x C*H*=CH), 4.55 (1H, apparent t, *J* 7.0, C*HN*), 2.68–2.41 (2H, m), 2.38 (2H, m), 2.18–1.81 (6H, m), 1.46 (9H, s, C(CH_3)$_3$), 1.46–1.25 (12H, m), 0.85 (3H, t, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 181.5 (C), 172.6 (C), 132.7 (CH), 131.7 (CH), 130.7 (CH), 130.2 (CH), 80.9 (C), 74.8 (CH), 37.5 (CH_2), 33.7 (CH_2), 32.6 (CH), 32.3 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 28.9 (CH_2), 28.0 (CH_3), 26.7 (CH_2), 26.0 (CH_2), 22.7 (CH_2), 14.1 (CH_3); *m*/*z* (ES+) 362.3064 (M + H$^+$ $C_{23}H_{40}NO_2$ requires 362.3059) 362 (100%), 306 (50).

(5*E*,7*E*)-5-Tetradeca-5′,7′-dienyl-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid benzyl ester 35b. Glycine imine **30b** (257 mg, 0.78 mmol) was reacted with enone **31** following the above procedure to give the cyclic imine **35b** (170 mg, 55%) as a pale yellow oil; (found: C, 78.8; H, 9.3; N, 3.4. $C_{26}H_{37}NO_2$ requires C, 78.9; H, 9.4; N, 3.5%); ν_{max}(neat)/cm^{-1} 3013, 2926, 2855, 1741, 1640, 1456, 1379, 1342, 1264, 1171, 988, 735, 697; δ_H (400 MHz, $CDCl_3$) 7.37–7.30 (5H, m, Ar*H*), 6.01–5.94 (2H, m, 2 x C*H*=CH), 5.60–5.49 (2H, m, 2 x C*H*=CH), 5.22 (1H, d, *J* 12.0, CH_aH$_b$Ph), 5.19 (1H, d, *J* 12.0, CH$_a$$H_b$Ph), 4.74–4.69 (1H, m, C*H*N), 2.65–2.60 (1H, m), 2.56–2.49 (1H, m), 2.41 (2H, apparent t, *J* 7.5, CH_2), 2.23–2.13 (1H, m), 2.14–2.00 (5H, m), 1.64–1.58 (2H, m), 1.46–1.26 (10H, m), 0.88 (3H, t, *J* 7.5, CH_3); δ_C (100 MHz, $CDCl_3$) 182.3, 172.9, 135.8, 132.8, 131.6, 130.8, 130.2, 128.6, 128.5, 128.2, 128.2, 73.9, 66.6, 37.6, 33.6, 32.6, 32.3, 31.8, 29.4, 29.1, 28.9, 26.4, 25.9, 22.6, 14.1; *m*/*z* (ES+) 396.2904 (M + H$^+$ $C_{26}H_{38}NO_2$ requires 396.2903) 396 (100%), 306 (50).

Diels–Alder reaction of 35a. A solution of the cyclic imine **35a** (29 mg, 0.08 mmol) in degassed (5 freeze–thaw cycles) 1,1,1,3,3,3-hexafluoropropan-2-ol (1.5 mL) in a sealed tube was placed under an atmosphere of argon and heated at 60 °C for 9 days and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (9 : 1, CH_2Cl_2–MeOH) to give the cycloadduct **37** (13 mg, 53%, 5 : 1, mixture diastereoisomers) as a pale yellow oil; δ_H (500 MHz, CD_3OD, peaks for major diastereoisomer only) 6.21–6.18 (1H, m, C*H*=CH), 6.04–5.93 (1H, m, C*H*=CH), 3.95–3.94 (1H, m, C*H*N), 3.66 (1H, dd, *J* 12.0, 7.0, C*H*CO$_2$H), 2.43–2.39 (1H, m, C*H*CN), 2.34–2.29 (1H, m, CH_aH$_b$), 2.25 (1H, dd, *J* 13.0, 6.0, CH_aH$_b$), 2.05–1.28 (20 H, m), 0.92 (3H, t, *J* 7.0, CH_3); δ_C (100 MHz, CD_3OD, peaks for major diastereoisomer only) 172.8 (C), 139.4 (CH), 126.8 (CH), 79.0 (CH), 67.7 (CH), 58.6 (C), 42.7 (CH_2), 33.0 (CH_2), 31.3 (CH_2), 30.4 (CH_2), 28.8 (CH_2), 28.2 (CH_2), 28.0 (CH_2), 27.1 (CH_2), 25.9 (CH_2), 24.6 (CH_2), 23.3 (CH_2), 22.2 (CH_2), 13.0 (CH_3); *m*/*z* (ES+) 306.2425 (M + H$^+$ $C_{19}H_{32}NO_2$ requires 306.2433) 306 (100%).

Hydrogenation of cycloadduct 37. A solution of the alkene **37** (30 mg, 0.097 mmol) in EtOH (4 mL) was treated with 10% Pd/C (30 mg) and the mixture stirred at RT overnight under an atmosphere of hydrogen (balloon). The mixture was then filtered through Celite and then concentrated under reduced pressure to give the crude acid (30 mg, 100%) as a white solid; ν_{max}(neat)/cm^{-1} 3404, 2929, 2858, 1629, 1466; δ_H (400 MHz, CD_3OD, peaks for major diastereoisomer only) 4.07 (1H, apparent t, *J* 10.0, C*H*CO$_2$H), 3.75–3.72 (1H, m, C*H*N), 2.55–2.38 (1H, m), 2.20–1.15 (26H, m), 0.93–0.87 (3H, m); δ_C (100 MHz, CD_3OD, peaks for major diastereoisomer only) 76.7 (CH), 63.7 (C), 57.6 (CH), 36.2 (CH_2), 34.5 (CH_2), 31.3 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 28.9 (CH_2), 27.8 (CH_2), 27.4 (CH_2), 25.7 (CH_2), 25.0 (CH_2), 23.1 (CH_2), 22.2 (CH_2), 21.6 (CH_2), 19.0 (CH_2), 13.0 (CH_3); *m*/*z* (ES+) 308.2582 (M + H$^+$ $C_{19}H_{34}NO_2$ requires 308.2584) 308 (100%). This material was used directly in the next step without further purification.

Lepadiformine A 1. The crude acid from above (30 mg, 0.097 mmol) was dissolved in THF (4 mL) and placed under an atmosphere of nitrogen. $LiAlH_4$ (0.24 mL of a 2.4 M solution in THF, 0.59 mmol) was added dropwise and the reaction heated at reflux for 4 h. The reaction was then cooled to 0 °C and water saturated diethyl ether added (5 mL, 0.58 M water in Et_2O), the reaction was then allowed to warm to RT and water added (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organics dried ($MgSO_4$) and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (75 : 4.5 : 1, CH_3Cl–CH_3OH–NH_4OH) to give the lepadiformine A **1** (15 mg, 52%) as a clear oil; δ_H (400 MHz, $CDCl_3$) 3.43–3.32 (2H, m), 3.24 (1H, d, *J* 8.5), 3.20–3.13 (1H, m), 1.86–1.14 (27H, m), 1.10–0.97 (1H, m), 0.89 (3H, t, *J* 6.5, CH_3); δ_C (100 MHz, $CDCl_3$) 67.5 (C), 62.3 (CH), 58.5 (CH), 53.4 (CH), 40.0 (CH_2), 38.3 (CH_2), 34.1 (CH_2), 31.9 (CH_2), 30.6 (CH_2), 29.6 (CH_2), 28.2 (CH_2), 27.7 (CH_2), 27.6 (CH_2), 26.3 (CH_2), 24.3 (CH_2), 23.3 (CH_2), 22.7 (CH_2), 14.1 (CH_3); *m*/*z* (ES+) 294.2769 (M + H$^+$ $C_{19}H_{36}NO$ requires 294.2793) 294 (100%). The above ^{1}H NMR and ^{13}C NMR data is in agreement with that previously reported.[12]

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