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A cross-metathesis approach to the tricyclic marine alkaloids (-)-fasicularin and (-)-lepadiformine A

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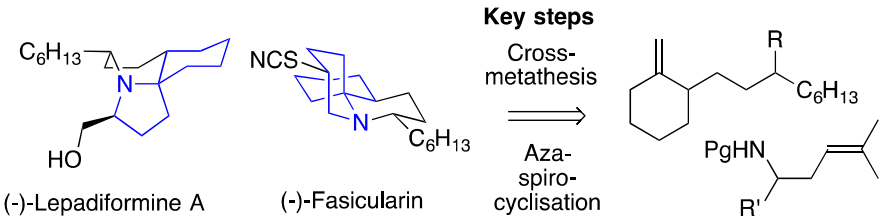
Supporting Information Placeholder



A cross-metathesis protocol has been developed to provide facile access to highly hindered tri-substituted α-branched olefins, which when coupled with a cationic aza-spirocyclisation reaction generates the marine alkaloids (-)-fasicularin **2** and a pro-forma synthesis of (-)-lepadiformine A **1**.

INTRODUCTION

Olefin metathesis has featured as a key transformation in natural product synthesis especially since its modern inception in the early 1990s.[1] Largely it appears in the ring-closing metathesis guise (RCM),[2] often utilized in the late stage construction of large unsaturated macrocycles. This is testament to the mild reaction conditions employed, wide substrate tolerance and low by-product formation when suitable conditions are applied.[3] Cross-metathesis (CM) however, is less utilised in the construction of advanced intermediates[4] even though *a priori* it is a highly attractive transformation that efficiently couples two components and rapidly generates synthetically useful olefinic products. The application of CM is often thwarted by unwanted homocoupled by-product formation which is circumvented only by the use of large excesses of reagents or by careful electronic or steric tuning which may not always be applicable during the course of a natural product synthesis.[3] Some of these issues have been addressed by employing our recently disclosed CM protocol for sterically demanding olefins, which gives rapid access to complex constructs bearing an α-substituted methylene cyclohexane core.[5] This, coupled with acid promoted aza-spirocyclisation,[6] delivers core architectures that are displayed by many alkaloids including (-)-lepadiformine A **1**, (-)-fasicularin **2**, (+)-cyclindricine A **3** and (-)-cephalotaxine **4** (Figure 1A).

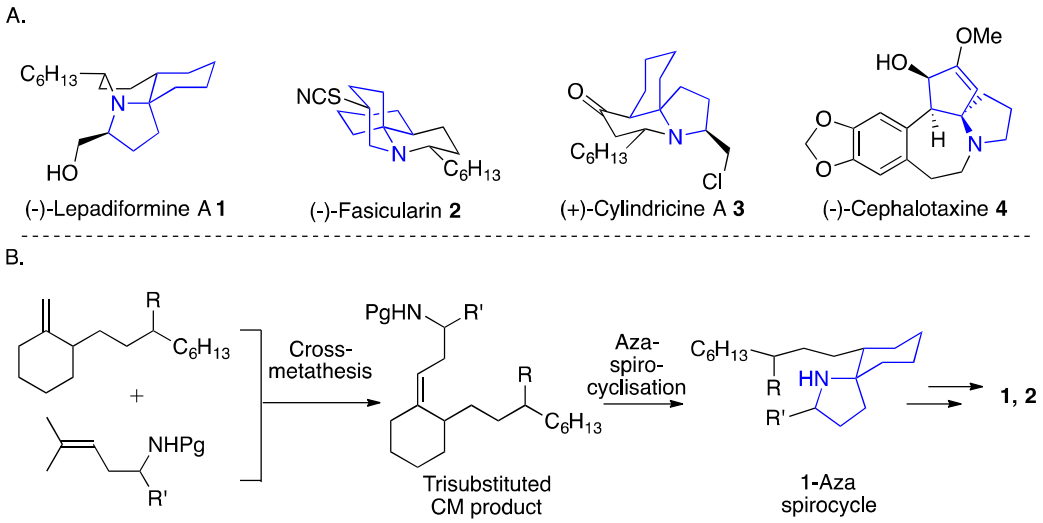


Figure 1: (A) Selected examples of natural products with an aza-spirocyclic core, (B) accessible using the cross-metathesis/cationic cyclisation methodology.

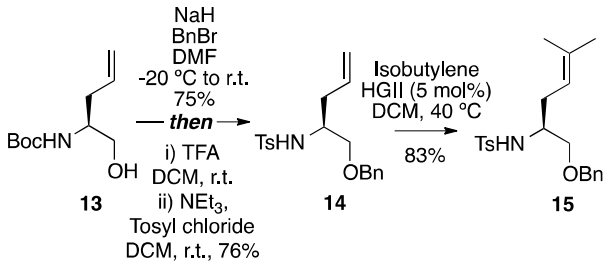
(-)-Lepadiformine A **1** and (-)-fasicularin **2** are spirocyclic marine alkaloids that have a rich history and their highly appealing structures have attracted the interest of the synthetic community for over two decades;[7] as such there are now many innovative and successful routes for their synthesis.[8,9,10] The key challenges facing our new synthetic approach were i) development of a highly efficient CM strategy with practical reagent stoichiometry, and ii) the development of chemo- and diastereoselective conditions for the acid-mediated cyclisation (Figure 1). Subsequent elaboration of the appropriately functionalised 1-azaspirocyclic core to (-)-lepadiformine A **1** involves deprotection, cyclodehydration and hydrogenolysis. To access (-)-fasicularin **2**, a diastereomeric series was required, in addition to [4.5]- to [5.5]-ring expansion, to generate the spiropiperidine core.

RESULTS AND DISCUSSION

Synthesis commenced with the construction of suitably functionalised metathesis partners. The readily available homochiral iodoalcohol **5**[11] underwent smooth TBS protection under basic conditions with TBSOTf to give the alkyl iodide **6** in excellent yield (Scheme 1). Next, reaction of the protected iodide **6** with commercially available allyl 2-oxocyclohexane-1-carboxylate **7** in DMF at 50 °C using Cs_2CO_3 gave the β-keto ester **8** in good yield as an inconsequential mixture of diastereoisomers.[12] The resulting β-keto ester **8** was subjected to the stereoselective, decarboxylative protonation protocol developed by Stoltz *et al.*.[13] The β-keto ester **8** gave the α-substituted ketone **9** in good yield, reasonable diastereoselectivity (8:1), and was routinely prepared on a gram scale. Wittig methenylation was effected using methyltriphenylphosphonium bromide and *n*-butyllithium which proceeded in excellent yield, and was followed by TBS deprotection with TBAF delivering the alcohol **10** in a concise number of chemical transformations (Scheme 1).[14] The intermediate **10** served as a point of divergence in this synthesis and could be readily protected using benzoyl chloride under basic conditions to give **11**, or epimerized under Mitsunobu's conditions to give the diastereomeric benzoyl ester **12**, both in good yield (Scheme 1).[15]

Our previous studies had shown that CM of α-branched 1,1-disubstituted olefins are problematic due to formation of nonproductive 1,3-metallocyclobutane intermediates and homocoupled by-products.[5] To overcome this, we developed a steric reversal strategy, employing prenylated cross-partners rather than allylated cross-partners, to facilitate formation of the productive 1,2-metallocyclobutane during the CM reaction. The result was a significant increase in yield of the desired cross-product. Therefore, we decided to adopt a similar strategy in our synthesis of spirocyclic marine alkaloids **1** and **2** by using the prenylated cross-partner **15** (Scheme 2). Synthesis of **15** began from the commercially available (*S*)-allylglycine derivative **13**. Suitable protection of the primary alcohol and amine functionalities delivered the tosylamide **14** in good yield. Prenylation to give **15** was affected using isobutylene and Hoveyda-Grubbs second generation catalyst.[16]

Scheme 2: Synthesis of the chiral prenyl amine **15**



With both cross-partners in hand, we next explored the key CM reaction. The conditions reported in our previous work required a large excess (30 equiv.) of the α-branched cross-partner. Using these conditions, we were able to deliver an excellent yield of tri-substituted olefin **16** (Table 1, entry 1). Although the cross-partner **11** could be recovered and recycled, it was considered to be a major drawback to our methodology and we saw an opportunity to seek conditions which required fewer equivalents of **11**.[17] Unfortunately, halving the number of equivalents of **11** led to a significant decrease in yield of olefin **16** (Table 1, entry 2) and reducing the equivalents to five (Table 1, entry 3) only provided negligible quantities of **16**. Extending the reaction time to 3 days led to a 61% yield of olefin **16** (Table 1, entry 4) but this was still considered to be unacceptable in terms of practicality. Eventually it was found that use of a higher catalyst loading and intermediate reaction time led to synthetically useful yields of **16** with only two equivalents of **11** (Table 1, entries 5 and 6). These reaction conditions were implemented at a 1 mmol scale (Table 1, entry 7) which could also be applied to the *S*-epimer **17** (Table 1, entry 8). Although the catalyst loading was high, it facilitated rapid, modular construction of the advanced target intermediates **16** and **17** under relatively mild conditions.

Scheme 1. Construction of the methylene cyclohexane cross partners **11** and **12**

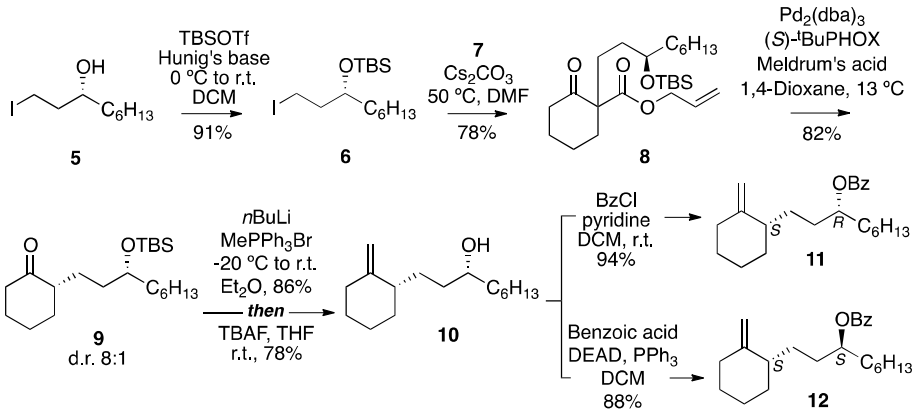
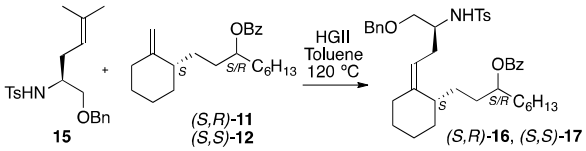


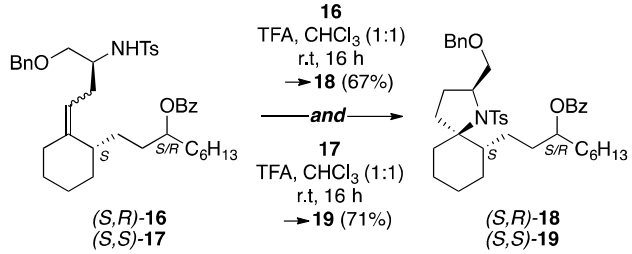
Table 1: Optimisation of key cross-metathesis reaction



Entry	Metathesis conditions[5]	Product	Yield
1	30 equiv. **11**, 5 mol% HGII, 16 h[5]	**16**	89
2	15 equiv. **11**, 5 mol% HGII, 16 h	**16**	45
3	5 equiv. **11**, 5 mol% HGII, 16 h	**16**	15
4	5 equiv. **11**, 5 mol% HGII, 72 h	**16**	61
5	2 equiv. **11**, 25 mol% HGII, 48 h	**16**	73
6	2 equiv. **12**, 25 mol% HGII, 48 h	**17**	67
7	Entry 5 1.64 mmol scale	**16**	70
8	Entry 6 1 mmol scale	**17**	74

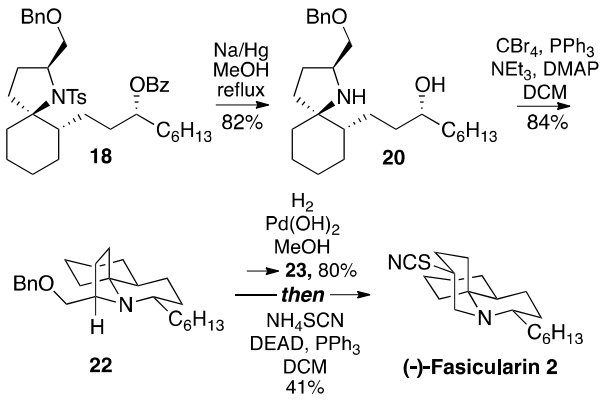
The cyclisation conditions reported by us[6] and Knight[18] were examined using a catalytic quantity of triflic acid (20 mol%) in both toluene and chloroform at room temperature. This approach was only moderately successful because the high reactivity of triflic acid resulted in decomposition. After extensive optimisation it was found that a 1:1 mixture of dry TFA and chloroform provided the target spirocycles **18** and **19** in good yield (Scheme 3). The observed high diastereoselectivity presumably arises from the pendent α-substituent directing facial-selection during the carbocationic cyclisation, resulting in a *trans*-relationship between the amide and the α-substituent. This cationic 5-*endo*-trig cyclisation is rarely applied to such complex systems[19] and could lend itself to more widespread use in the synthesis of spirocyclic alkaloids.

Scheme 3. Cationic cyclisation of tri-substituted olefins **16** and **17** leading to spirocycles **18** and **19**.



After examining several conditions, selective deprotection of the tosylamide and benzoyl ester of **18** and **19** was effected with Na/Hg (10%) in methanol to give amino alcohols **20** and **21** respectively in good yield (Scheme 4). Annulation of the amino alcohol **20** was effected using the Zhao modification[8l,9o] of the Kibayashi[8c] cyclodehydration protocol to give the protected tricycle **22**. Final hydrogenation of the benzyl ether **22** and ring expansion of alcohol **23** under the Mitsunobu protocol delivered (-)-fasicularin **2** in respectable yield in 13 steps from readily available starting materials. Difficulties were encountered obtaining interpretable NMR spectra due to peak broadening of tricycles **22** and **23** even when rigorous deacidification of deuterated chloroform was carried out. However, clear ^{1}H and ^{13}C spectra for **2** were obtained in 5% KOH/d_4-methanol or d_5-pyridine. The spectra of **18**-**22** showed peaks at the same frequencies as those reported by Kibayashi[9c] but clear resolution of multiplets varied with solvent. The spectra of (-)-fasicularin in d_5-pyridine was identical in all aspects to those in the literature.[10]

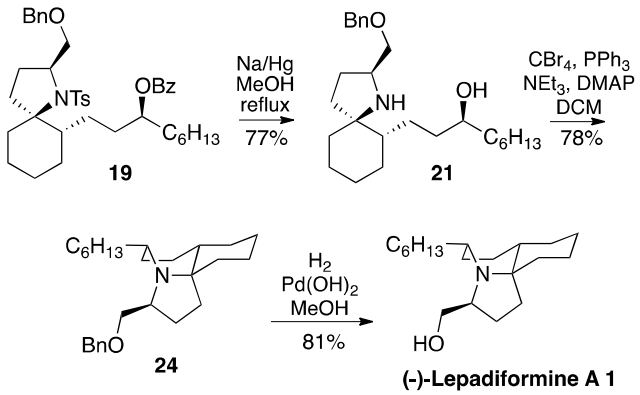
Scheme 4: Synthesis of (-)-fasicularin **2**



The epimeric alcohol **21** was also subjected to the same cyclodehydration protocol to give the tricyclic benzyl ether **24** which was followed by hydrogenolysis to give (-)-lepadiformine A **1** in 12 steps from readily available starting materials (Scheme 5).[8c,8l] Again problems were encountered in obtaining clear spectra for **1** which was in stark contrast to the behavior of its precursor **24** which generated a well resolved spectrum in 5% KOH/d_4-methanol. Because of the difficulties in obtaining a pure sample we can only claim a formal synthesis

of (-)-lepadiformine A from the unambiguously characterized precursor **24**.

Scheme 5. Formal synthesis of (-)-lepadiformine A **1**



CONCLUSION

This chemistry demonstrates the power of our cross-metathesis/aza-spirocyclisation methodology through the total synthesis of two spirocyclic marine alkaloid natural products, (-)-fasicularin **2** and (-)-lepadiformine A **1**. The tandem methodology allows for rapid construction of advanced intermediates in good chemical yield and diastereoselectivity from comparatively simple components thus facilitating the short asymmetric synthesis of two complex molecular architectures. The methodology could also be applied to the synthesis of other spirocyclic systems such as cephalotaxine **4.**

EXPERIMENTAL SECTION

General Experimental Information

Instrumentation

Melting points (m.p.) were determined using a Reichert hot-stage melting point apparatus and are uncorrected.

Infrared spectra (IR) were recorded on a Perkin-Elmer 1600 series Fourier Transform infrared spectrophotometer as thin films between sodium chloride plates. IR absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}) with the relative intensities expressed as s (strong), m (medium) or prefixed b (broad).

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on Bruker DPX300, AV400 or AV600 spectrometers operating at 300, 400 or 600 MHz respectively, as solutions in deuterated solvents as specified. Each resonance was assigned according to the following convention: chemical shift; multiplicity; observed coupling constants (*J* Hz); number of protons. Chemical shifts (δ), measured in parts per million (ppm), are reported relative to the residual proton peak in the solvent used as specified. Multiplicities are denoted as singlet (s), doublet (d), triplet (t), quartet (q), apparent quintet, multiplet (m) or prefixed broad (b), or a combination where necessary.

Carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on Bruker DPX300, AV400 or AV600 spectrometers operating at 75, 100 or 125 MHz respectively, as solutions in deuterated solvents as specified. Chemical shifts (δ), measured in parts per million (ppm), are reported relative to the residual proton peak in the deuterated solvent (as specified).

Low resolution electrospray ionisation (ESI) mass spectra were recorded on a Micromass Platform Electrospray mass spectrometer (QMS-quadrupole mass spectrometry) as solutions in specified solvents. Spectra were recorded in positive and negative modes (ESI^+ and ESI^-) as specified. High resolution electrospray mass spectra (HRMS) were recorded on a Bruker BioApex 47e Fourier Transform mass spectrometer (4.7 Tesla magnet) fitted with an analytical electrospray source. The mass spectrometer was calibrated with an internal standard solution of sodium iodide in CH_3OH.

Solvents and Reagents

Dichloromethane (DCM) was supplied by Merck and distilled over CaH_2 prior to use. Diethyl ether (Et_2O), tetrahydrofuran (THF) and toluene ($C_6H_5CH_3$) were supplied by Merck and distilled over potassium prior to use. Ethyl acetate (EtOAc), hexane, methanol (CH_3OH) and triethylamine (Et_3N) were used as supplied by Merck. All reagents were purchased from Sigma-Aldrich and used as received, unless otherwise stated.

((2*R*,3*R*)-3-Hexyloxiran-2-yl)methanol (S1). Compound **S1** was prepared following a modified procedure developed by Sharpless and coworkers.[22] DCM (600 mL) was added to 4 Å molecular sieves (7.00 g) and the mixture was cooled to -20 °C. (-)-DIPT (2.96 g, 12.7 mmol), $Ti(O^iPr)_4$ (3.00 g, 10.5 mmol) and (*E*)-non-2-en-1-ol (15.0 g, 105 mmol) were added sequentially and the resulting mixture was stirred for 0.5 h. ^{t}BuOOH (38.3 mL, 5.50 M in heptane, 211 mmol) was added using a syringe pump over 20 min, the internal temperature never reaching greater than -15 °C. Stirring was continued for 4 h, at ≤-4 °C, at which point the reaction mixture was poured onto an aqueous solution (200 mL) of $FeSO_4$ (33.0 g) and citric acid (11.0 g), and the biphasic mixture was stirred for 2 h. The mixture was separated and the aqueous phase extracted with ether (3x100 mL). The combined organic extract was then stirred with aqueous sodium hydroxide (2 M, 300 mL) at room temperature for 2 h. The phases were again separated and the aqueous phase further extracted with ether (2x100 mL). The

combined organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was recrystallized from hexane to yield **S1** (6.50 g). Two further crops could be obtained through concentration and crystallization (4.50 g) and (3.00 g). Total yield of **S1** as a colorless semi-solid (14.0 g, 84%). $[\alpha]_D^{22}$ +26.0 (*c* 0.94, $CHCl_3$). IR ν_{max} 3279b cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.90 (ddd, *J* = 16.8, 8.8, 3.6 Hz, 1H), 3.61 (ddd, *J* = 16.8, 8.8, 6.0 Hz, 1H), 2.97-2.90 (m, 2H), 1.83 (dd, *J* = 9.6, 2.0 Hz, 1H), 1.60-1.53 (m, 2H), 1.46-1.25 (m, 8H), 0.88 (t, *J* = 9.2 Hz, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$): δ 61.9, 58.6, 56.2, 31.9, 31.7, 29.2, 26.0, 22.7, 14.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_9H_{19}O_2^+$ 159.1380; Found 159.1389.

(3-Hexyloxiran-2-yl)methanol (S2). *m*CPBA (485 mg, 2.81 mmol) was added to a solution of (*E*)-non-2-en-1-ol (200 mg, 1.41 mmol) in DCM (5 mL). After stirring for 3 h, the reaction was quenched with saturated aqueous sodium thiosulfate (5 mL). The product was extracted with Et_2O (2x5 mL) and the combined organic extract was washed with aqueous sodium hydroxide (2 M, 3x5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (1:1, EtOAc:hexane) to afford **S2** (80 mg, 36%) as a colorless solid. All relevant data matches that reported for compound **S1**.

((2*R*,3*R*)-3-Hexyloxiran-2-yl)methyl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S3). (*S*)-Mosher's acid (157 mg, 0.66 mmol), EDCI.HCl (127 mg, 0.66 mmol), and DMAP (7 mg, 0.06 mmol) were added to DCM (2 mL) at room temperature. The epoxide **S1** (100 mg, 0.63 mmol) and triethylamine (0.25 mL, 1.89 mmol) were then added and the mixture stirred for 6 h. The reaction was quenched with aqueous HCl (1 M, 5 mL). The product was extracted with DCM (2x5 mL) and the combined organic extract was washed with aqueous sodium hydroxide (2 M, 3x5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (1:5 → 1:1, EtOAc : hexane) to afford **S3** (89 mg, 38%) as a colorless oil. IR ν_{max} 1755s, 1770s cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.55-7.52 (m, 2H), 7.43-7.40 (m, 3H), 4.53 (dd, *J* = 12.0, 3.6, 1H), 4.23 (dd, *J* = 12.0, 6.4 Hz, 1H), 3.57 (q, *J* = 1.2 Hz, 3H), 3.00-2.97 (m, 1H), 2.83 (td, *J* = 5.6, 2.0 Hz, 1H) 1.57-1.52 (m, 2H), 1.43-1.38 (m, 2H), 1.35-1.25 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.5, 132.2, 129.9, 128.6, 127.4, 121.9 ($q_{C\text{-}F}$, *J* = 290 Hz), 84.7 ($q_{C\text{-}F}$, *J* = 30 Hz) 66.4, 56.9, 56.7, 54.7, 31.8, 31.6, 29.1, 25.9, 22.7, 14.2. ^{19}F-NMR (100 MHz, $CDCl_3$): δ -71.8. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{26}F_3O_4^+$ 375.1778; Found 375.1779. Enantiomeric excess = >95%, assessed by chiral HPLC, Daicel AS column, 10 μL injection, 100% hexane → 1.5% IPA: hexane. t_R major = 9.69 min. Optical purity was also assessed by integration of ^{1}H NMR signals (d.r. = 22:1), and verified by synthesis of compound **S4**, *vide infra*.

(3-Hexyloxiran-2-yl)methyl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S4). Synthesised according to the procedure for **S3** from **S2**. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.55-7.52 (m, 2H), 7.43-7.40 (m, 3H), 4.59-4.51 (m, 1H), 4.25-4.20 (m, 1H), 3.57-3.60 (m, 3H), 3.02-2.97 (m, 1H), 2.86-2.81 (m, 1H), 1.57-1.52 (m, 2H), 1.43-1.38 (m, 2H), 1.35-1.25 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.5, 132.2, 129.9, 128.6, 127.4, 121.9 ($q_{C\text{-}F}$, *J* = 290 Hz), 84.7 ($q_{C\text{-}F}$, *J* = 30 Hz), 66.4, 56.9, 56.7, 54.7, 31.8, 31.6, 29.1, 25.9, 22.7, 14.2. Enantiomeric excess = 0%, assessed by chiral HPLC, Daicel AS column, 10 μL injection, 100% hexane → 1.5% IPA: hexane. t_R = 10.22 min, t_R = 6.68 min.

(*R*)-Nonane-1,3-diol (S5). Compound **S5** was prepared following a modified procedure developed by Sharpless and coworkers.[23] Red-Al® (7.13 mL, 22.9 mmol, 65% w/w in toluene) in THF (50 mL) was added dropwise (over 15 min) to a cooled (0 °C) and magnetically stirred solution of epoxide S1 (3.30 g, 20.8 mmol) in THF (100 mL). The mixture was allowed to warm to room temperature and then stirred for 16 h. The reaction was quenched with by careful addition of MeOH (5 mL) at 0 °C. Saturated aqueous Rochelle's salt (200 mL) and DCM (100 mL) were added and the biphasic mixture stirred until a clear solution was obtained (5 h). The product was extracted with DCM (3x50 mL) and the combined organic extract dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (EtOAc) to afford **S5** (3.15 g, 95%) as a colorless oil. Contains ~2% 1,2-diol judged by integration of ^{13}C NMR signals (observable peaks denoted by *). IR ν_{max} 3331b cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.82-3.70 (m, 4H), 3.50 (br s, 1H), 1.70-1.54 (m, 2H), 1.45-1.30 (m, 3H), 1.26-1.21 (m, 7H), 0.84 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 72.3*, 71.7, 66.7*, 61.3, 38.4, 37.8, 33.1*, 31.9, 29.4, 29.3*, 25.6*, 25.6, 22.7, 14.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_9H_{21}O_2^+$ 161.1536; Found 161.1540.

(*R*)-1-Iodononan-3-ol (5). Iodine (1.50 g, 5.93 mmol) in MeCN:Et_2O (1:2, 100 mL) was added dropwise over 3 h to a solution of diol **S5** (1.00 g, 6.24 mmol), imidazole (467 mg, 6.86 mmol) and triphenylphosphine (2.46 g, 9.36 mmol) in MeCN:Et_2O (1:2, 100 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 16 h. The mixture was concentrated under reduced pressure and Et_2O (100 mL) was added. The precipitate was filtered and washed with Et_2O (2x100 mL). The combined organic extract was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (50:1 → 20:1, EtOAc : hexane) to afford **5** (1.31 g, 78%) as a colorless

oil. IR ν_{max} 3353b cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.71 (br s, 1H), 3.33-3.28 (m, 2H), 1.99-1.83 (m, 2H), 1.45-1.41 (m, 4H), 1.38-1.26 (m, 7H), 0.88 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 71.9, 40.9, 37.4, 31.9, 29.4, 25.6, 22.7, 14.2, 3.3. HRMS (ESI-TOF) *m/z*: $[M + H - OH_2]^+$ Calcd for $C_9H_{18}I^+$ 253.0448; Found 253.0448.

(*R*)-*tert*-Butyl((1-iodononan-3-yl)oxy)dimethylsilane (6). A solution of iodide **5** (1.25 g, 4.63 mmol) in DCM (20 mL) was added to a magnetically stirred and cooled (0 °C) mixture of TBSOTf (1.16 mL, 5.09 mmol) and Hünig's base (1.01 mL, 5.78 mmol). The mixture was allowed to warm to room temperature and then stirred for 1 h. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (20 mL). The product was extracted with DCM (3x50 mL) and the combined organic extract was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (hexane) to afford **6** (1.61 g, 91%) as a colorless oil. IR ν_{max} 2928s, 2856m, 1462m, 1254m, 1065m, 833s cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.73-3.68 (m, 1H), 3.26-3.15 (m, 2H), 1.99-1.92 (m, 2H), 1.44-1.41 (m, 2H), 1.32-1.22 (m, 8H), 0.92-0.82 (m, 12H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 72.4, 41.1, 37.1, 32.0, 29.6, 26.0, 25.0, 22.7, 18.2, 14.2, 3.6, -4.1, -4.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{34}IOSi^+$ 385.1418; Found 385.1413.

Allyl 1-((*R*)-3-((*tert*-butyldimethylsilyl)oxy)nonyl)-2-oxocyclohexane-1-carboxylate (8). To a magnetically stirred solution of iodide **6** (8.70 g, 22.6 mmol) and allyl 2-oxocyclohexane-1-carboxylate **7**[20] (3.91, 21.5 mmol) in DMF (50 mL) was added Cs_2CO_3 (14.7 g, 45.2 mmol). The resulting suspension was warmed to 50 °C and then stirred for 16 h. The yellow reaction mixture was quenched by addition of water (100 mL). The product was extracted with Et_2O (3x50 mL) and the combined organic extract was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (hexane → 1:20, EtOAc: hexane) to afford **8** (7.34 g, 78%) as a colorless oil. The β-ketoester **8** was obtained as an inconsequential 1:1 mixture of diastereoisomers, split peaks in the ^{13}C NMR spectrum are arbitrarily assigned with *. IR ν_{max} 1734m, 1717m cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.94-5.84 (m, 1H), 5.32 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.24 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.61-4.58 (m, 2H), 3.61-3.57 (m, 1H), 2.50-2.39 (m, 3H), 1.98-1.91 (m, 2H), 1.63-1.43 (m, 4H), 1.34-1.31 (m, 4H), 1.29-1.21 (m, 8H), 0.90-0.81 (m, 12H), 0.05-0.00 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 207.8, 207.7*, 171.8, 171.8*, 131.7, 119.1, 72.4, 72.3*, 65.7, 60.8, 60.8*, 41.2, 41.1*, 37.1, 36.9*, 36.1, 36.0*, 32.0, 31.4, 31.4*, 30.6, 29.6, 26.0, 25.9*, 25.4, 25.3*, 22.7, 22.6, 18.2, 14.2, 1.1, -4.3, -4.3. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{46}NaO_4Si^+$ 461.3063; Found 461.3054.

2-((*R*)-3-((*tert*-Butyldimethylsilyl)oxy)nonyl)cyclohexan-1-one (S6). $Pd_2(dba)_3$ (22 mg, 0.024 mmol) and dppf (16 mg, 0.029 mmol) in 1,4-dioxane (3 mL) were heated at 60 °C for 0.5 h. The resulting bright orange homogenous solution was then cooled to 13 °C and a solution of β-keto ester **8** (100 mg, 0.235 mmol) and Meldrum's acid (85 mg, 0.589 mmol) in 1,4-dioxane (3 mL) was added *via* a cannula over 2 min. The mixture was stirred at 13 °C for 2 h. The reaction was quenched by addition of hexane (10 mL) and the resulting suspension filtered through a short pad of silica and washed with hexane (2x10 mL). The combined organic extract was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (1:20, EtOAc: hexane) to afford **S6** (62 mg, 74%) as a colorless oil. *R,R*-Diastereoisomer denoted in ^{13}C NMR spectrum by *. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.63 (apparent quintet, *J* = 6.0 Hz, 1H), 2.40-2.35 (m, 1H), 2.30-2.23 (m, 2H), 2.08-2.00 (m, 2H), 1.78-1.60 (m, 4H), 1.42-1.22 (m, 14H), 0.90-0.83 (m, 12H), 0.04 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 213.5, 72.7, 72.5*, 51.1, 51.0*, 42.1, 42.0*, 37.3, 37.0*, 34.7, 34.6*, 34.1, 34.0*, 32.0, 29.7, 29.7*, 28.2, 28.2*, 26.1, 26.1*, 25.6, 25.4, 25.4*, 25.1, 25.0, 24.9*, 22.8, 18.3, 14.2, -4.3.

(*S*)-2-((*R*)-3-((*tert*-Butyldimethylsilyl)oxy)nonyl)cyclohexan-1-one (9). Compound **9** was prepared following a modified procedure developed by Stoltz and coworkers.[13] The reaction was carried out in triplicate, d.r. 8:1, judged by integration of ^{13}C NMR signals, verified by synthesis of compound **S6**, *vide infra*. $Pd_2(dba)_3$ (104 mg, 0.140 mmol) and (*S*)-^{t}BuPHOX (110 mg, 0.284 mmol) in 1,4-dioxane (30 mL) were heated at 60 °C for 0.5 h. The resulting bright orange homogenous solution was then cooled to 13 °C and a solution of β-keto ester **8** (1.00 g, 2.28 mmol) and Meldrum's acid (821 mg, 5.70 mmol) in 1,4-dioxane (30 mL) was added *via* cannula over 2 min. The mixture was stirred at 13 °C for 2 h. The reaction was quenched by addition of hexane (100 mL) and the resulting suspension filtered through a short pad of silica and washed with hexane (2x100 mL). The combined organic extract was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (1:20, EtOAc: hexane) to afford **9** (663 mg, 82%) as a colorless oil. Minor *R,R*-diastereoisomer denoted in the ^{13}C NMR spectrum by *.IR ν_{max} 1711s cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.63 (apparent quintet, *J* = 6.0 Hz, 1H), 2.40-2.35 (m, 1H), 2.30-2.23 (m, 2H), 2.08-2.00 (m, 2H), 1.78-1.60 (m, 4H), 1.42-1.22 (m, 14H), 0.90-0.83 (m, 12H), 0.04 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 213.5, 72.7, 72.5*, 51.2, 51.1*, 42.1, 42.0*, 37.3, 37.0*, 34.6*, 34.1, 34.0*, 32.0, 31.7*, 27.9, 28.2, 26.1, 25.8, 25.6, 25.4, 22.8, 18.3, 14.2, 14.3, -4.3, -4.3. HRMS (ESI-TOF) *m/z*:

$[M + H]^+$ Calcd for $C_{21}H_{43}O_2Si^+$ 355.3027; Found 355.3027.

***tert*-Butyldimethyl(((*R*)-1-((*S*)-2-methylenecyclohexyl)nonan-3-yl)oxy)silane (S7).** ^{n}Butyllithium (4.40 mL, 7.04 mmol, 1.60 M hexane) was added to a stirred and cooled (0 °C) solution of methyltriphenylphosphonium bromide (4.20 g, 11.7 mmol) in Et_2O (60 mL). After 0.5 h, the resulting yellow solution was cooled to -25 °C and a solution of ketone **9** (2.00 g, 5.64 mmol) in Et_2O (10 mL) was added over 2 min. The mixture was then warmed to room temperature and left to stir for 16 h. The reaction mixture was filtered through a short pad of celite® and the filter cake washed with Et_2O (2x100 mL). The combined organic extract was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (1:100, EtOAc: hexane) to afford **S7** (1.71 g, 86%) as a colorless oil. IR ν_{max} 833s, 772m cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.65 (br s, 1H), 4.56 (br s, 1H), 3.63 (apparent quintet, *J* = 7.2 Hz, 1H), 2.23-2.17 (m, 1H), 2.03-1.96 (m, 2H), 1.66-1.51 (m, 3H), 1.47-1.35 (m, 5H), 1.31-1.01 (m, 12H), 0.97-0.83 (m, 12H), 0.01 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 153.3, 105.6, 72.8, 43.6, 37.4, 35.1, 35.0, 34.1, 32.1, 29.7, 29.0, 28.0, 26.1, 25.5, 24.5, 22.8, 18.3, 14.2, 1.2, -4.2, -4.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{45}OSi^+$ 353.3234; Found 353.3223.

(*R*)-1-((*S*)-2-Methylenecyclohexyl)nonan-3-ol (10). TBAF (10.0 mL, 10.0 mmol, 1.0 M THF) was added to a stirred and cooled (0 °C) solution of olefin **S7** (1.70 g, 4.83 mmol) in THF (2 mL). After 0.5 h, the resulting yellow solution was warmed to room temperature and stirred for 16 h. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride (50 mL). The product was extracted with DCM (3x50 mL), the combined organic extract was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (1:50, EtOAc: hexane) to afford *R,S*-**10** (800 mg, 78%) as a colorless oil. IR ν_{max} 2927s cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.66 (br s, 1H), 4.57 (br s, 1H), 3.61-3.57 (m, 1H), 2.25-2.18 (m, 1H), 2.03-1.96 (m, 2H), 1.66-1.38 (m, 10H), 1.30-1.21 (m, 11H), 0.86 (t, *J* = 8.0 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 153.0, 105.8, 72.5, 43.5, 37.7, 35.6, 34.8, 34.0, 32.0, 29.5, 29.0, 28.2, 25.8, 24.3, 22.8, 14.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{31}O^+$ 239.2369; Found 239.2370.

(*R*)-1-((*S*)-2-Methylenecyclohexyl)nonan-3-yl benzoate ((-)-fasicularin precursor) (11). Benzoyl chloride (0.21 mL, 1.84 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **10** (400 mg, 1.68 mmol) and pyridine (0.20 mL, 2.51 mmol) in DCM (2.5 mL). After 0.5 h, the resulting solution was warmed to room temperature and stirred for 16 h. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride (50 mL). The product was extracted with DCM (3x50 mL) and the combined organic extract was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (1:100, EtOAc: hexane) to afford **11** (540 mg, 94%) as a colorless oil. IR ν_{max} 1715s cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.06-8.03 (m, 2H), 7.47-7.41 (m, 1H), 7.44-7.41 (m, 2H), 5.13 (apparent quintet, *J* = 8.4 Hz, 1H), 4.65 (br s, 1H), 4.56 (br s, 1H), 2.20-2.16 (m, 1H), 2.02-1.97 (m, 2H), 1.76-160 (m, 7H), 1.43-1.21 (m, 13H), 0.86 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.5, 152.7, 132.8, 131.1, 129.7, 128.4, 106.0, 75.6, 43.3, 34.8, 34.4, 34.0, 32.4, 31.9, 29.4, 28.9, 27.8, 25.5, 24.3, 22.7, 14.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{35}O_2^+$ 343.2632; Found 343.2635.

(*S*)-1-((*S*)-2-Methylenecyclohexyl)nonan-3-yl benzoate 12 ((-)-lepadiformine A precursor). Diethyl azodicarboxylate (0.751 mL, 4.79 mmol) was added to a solution of PPh_3 (1.26 g, 4.79 mmol) in THF (30 mL) at 0 °C. The reaction was stirred for 0.5 h before (*R*)-1-((*S*)-2-Methylenecyclohexyl)nonan-3-ol **10** (760 mg, 3.19 mmol) was added by syringe. After stirring for a further 0.5 h, benzoic acid (585 mg, 4.79 mmol) was added. The mixture was warmed to room temperature and stirred for 4 h. The reaction was quenched with H_2O (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Diastereoselectivity of the crude product was assessed by integration of the ^{13}C signal at 75.4 ppm as 5:1; only the major signals are described below. The crude residue was purified by column chromatography (1:100, EtOAc:hexane) to afford *S,S*-**12** (830 mg, 88%) as a colorless oil. IR ν_{max} 1714s cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.01-7.98 (m, 2H), 7.49-7.45 (m, 1H), 7.39-7.26 (m, 2H), 5.10 (apparent quintet, *J* = 8.4 Hz, 1H), 4.60 (br s, 1H), 4.52 (br s, 1H), 2.27-2.11 (m, 1H), 1.98-1.94 (m, 2H), 1.71-.41 (m, 7H), 1.41-1.21 (m, 13H), 0.80 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.4, 152.4, 132.7, 131.0, 129.6, 128.4, 106.0, 75.4, 43.2, 34.7, 34.4, 34.1, 32.2, 31.8, 29.3, 28.9, 27.7, 25.4, 24.2, 22.7, 14.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{35}O_2^+$ 343.2632; Found 343.2639.

Synthesis of prenyl cross-partner (15)

Methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enoate (S8). Potassium carbonate (4.81 g, 34.9 mmol) was added to a stirred solution of *N*-Boc-allylglycine (2.50 g, 11.6 mmol) in DMF (50 mL) at room temperature. Iodomethane (2.17 mL, 34.9 mmol) was then added to the resulting suspension and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with Et_2O (50 mL) and washed with water (2 x 50 mL), 10% aqueous $CuSO_4$ (50 mL) and brine (50 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was further purified by silica column

chromatography (EtOAc: hexane, 1:4) to give **S8** as a colourless oil (2.55 g, 96%).[24] IR ν_{max} 3369w, 2979w, 1701s cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.73-5.63 (m, 1H), 5.14-5.10 (m, 2H), 5.03 (d, *J* = 6.0 Hz, 1H), 4.36 (dt, *J* = 6.4, 6.0 Hz, 1H), 3.72 (s, 3H), 2.55-2.42 (m, 2H), 1.42 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.5, 155.2, 132.4, 118.9, 79.7, 52.9, 52.1, 36.7, 28.2.

***tert*-Butyl (*S*)-(1-hydroxypent-4-en-2-yl)carbamate (13).** A solution of ester **S8** (2.00 g, 8.73 mmol) in THF (90 mL) was added to a two-neck RBF equipped with a stir-bar and an efficient reflux condenser. Sodium borohydride (663 mg, 17.5 mmol) was added to the stirred solution at room temperature and the resulting suspension was heated to 70 °C. Methanol (10 mL) was added dropwise to the heated suspension *via* a syringe and the resulting mixture was heated to reflux for 3 h. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. Diethyl ether was added to the residue and the resulting suspension was filtered. The filtrate was concentrated under reduced pressure and the residue purified by silica column chromatography (EtOAc: hexane, 1:1) to afford **13** as a colourless oil (1.44 g, 82%). IR ν_{max} 3355m, 2979m, 2933m, 1683s cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.81-5.70 (m, 1H), 5.11-5.05 (m, 2H), 4.85 (br s, 1H), 3.65-3.53 (m, 3H), 3.15 (br s, 1H), 2.32-2.17 (m, 2H), 1.41 (9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.4, 134.4, 117.8, 79.6, 64.6, 52.1, 36.0, 28.4. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_5H_{12}NO^+$ 102.0913; Found 102.0907.

***tert*-Butyl (*S*)-(1-(benzyloxy)pent-4-en-2-yl)carbamate (S9).** A solution of alcohol **13** (1.40 g, 6.96 mmol) in DMF (100 mL) was added to a flame-dried Schlenk flask equipped with an efficient stir-bar. The solution was cooled to -20 °C in an ice bath containing 50% $CaCl_2$. Sodium hydride (351 mg, 14.6 mmol) was added in small portions to the solution and the mixture was stirred for 1 h at -20 °C. Benzyl bromide (0.827 mL, 6.96 mmol) was then added dropwise *via* syringe and the resulting mixture was allowed to warm to room temperature. After complete consumption of the alcohol, the reaction was quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extract was washed with water (2 x 50 mL), 10% aqueous $CuSO_4$ (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (EtOAc: hexane, 1:3) to give **S9** as a colourless oil (1.52 g, 75%). IR ν_{max} 1696s cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.82-5.72 (m, 1H), 5.11-5.04 (m, 2H), 4.75 (br s, 1H), 4.53 (ABq, *J* = 16.8, 12.0 Hz, 2H), 3.82 (br m, 1H), 3.55-3.45 (m, 2H), 2.44-2.28 (m, 2H), 1.46 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.6, 138.3, 134.7, 128.5, 127.8, 127.7, 117.8, 79.4, 73.4, 71.3, 50.1, 36.6, 28.6. HRMS (ESI-TOF) *m/z*: $[[M - Boc + H]^+$ Calcd for $C_{12}H_{18}NO^+$ 192.1383; Found 192.1378.

(*S*)-*N*-(1-(Benzyloxy)pent-4-en-2-yl)-4-methylbenzenesulfonamide (14). Trifluoroacetic acid (5.0 mL) was added to a solution of ether **S9** (1.00 g, 3.43 mmol) in DCM (5.0 mL). The resulting mixture was stirred for 2 h at room temperature. The solution was then concentrated under reduced pressure. Residual TFA was co-evaporated with several portions of DCM. The residue was then dissolved in fresh DCM (50 mL) and cooled to 0 °C. Triethylamine (1.20 mL, 8.58 mmol) and *p*-TsCl (719 mg, 3.77 mmol) were then added to the solution and the mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was washed with water (2 x 50 mL), 10% aqueous $CuSO_4$ (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (EtOAc: hexane, 1:3) to give **14** as a colourless solid (900 mg, 76%), m.p. 50.7-51.3 °C. IR ν_{max} 3307m cm^{-1}. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.8 Hz, 2H), 7.34-7.29 (m, 3H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.23 (d, *J* = 6.6 Hz, 2H), 5.62-5.55 (m, 1H), 5.05 (d, *J* = 7.8 Hz, 1H), 5.02-4.99 (m, 2H), 4.37 (s, 2H), 3.44-3.39 (m, 2H), 3.29-3.26 (m, 1H), 2.40 (s, 3H), 2.33-2.26 (m, 2H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 143.2, 137.9, 137.8, 133.6, 129.6, 128.4, 127.8, 127.6, 127.1, 118.5, 73.1, 70.7, 53.0, 36.7, 21.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{24}NO_3S^+$ 346.1471; Found 346.1470.

(*S*)-*N*-(1-(Benzyloxy)-5-methylhex-4-en-2-yl)-4-methylbenzenesulfonamide (15). A solution of tosylate **14** (900 mg, 2.61 mmol) in DCM (10 mL) was added to a flame-dried pressure tube under a nitrogen atmosphere. The solution was frozen with liquid nitrogen and HGII (81.7 mg, 0.130 mmol) was added under a flow of nitrogen. Isobutylene (5 mL) was condensed into the reaction mixture and the vessel was sealed, warmed to room temperature and then lowered into an oil bath preheated to 40 °C. The reaction was stirred for 16 h at 40 °C, cooled to room temperature and the excess isobutylene carefully vented from the vessel. The remaining solution was quenched with ethyl vinyl ether (1 mL) and concentrated under reduced pressure. The residue was purified by silica column chromatography (EtOAc: hexane, 3:1) to afford **15** (810 g, 83%) as a viscous oil which solidified on standing, m.p. 56.8-58.1 °C. IR ν_{max} 3311m cm^{-1}. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.75 (dt, *J* = 7.8, 1.2 Hz, 2H), 7.32 (tt, *J* = 7.2, 1.2 Hz, 2H), 7.30-7.27 (m, 1H), 7.24 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 5.06 (d, *J* = 7.8 Hz, 1H), 4.88 (tt, *J* = 7.2, 1.2 Hz, 1H), 4.38 (s, 2H), 3.41 (ABX, *J* = 9.0, 4.2 Hz, 1H), 3.37-3.32 (m, 1H), 3.29 (ABX, *J* = 9.0, 4.8 Hz, 1H), 2.39 (s, 3H), 2.29-2.17 (m, 2H), 1.60 (s, 3H), 1.53 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 143.1, 137.9, 137.9, 135.1, 129.5, 128.3, 127.6, 127.6, 127.1, 119.2, 73.1, 70.9, 53.6, 30.8,

25.7, 21.5, 17.8. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{28}NO_3S^+$ 374.1784; Found 374.1782.

General Procedure for Sterically Hindered Cross-Metathesis. Prenyl substrate (1.00 equiv.) and methylene substrate (2.00 equiv.) were dried by co-evaporation with toluene (3x2 mL) in a pressure tube. HGII (25 mol%) was added, followed by toluene (0.50 M) and the mixture placed under partial vacuum. The resulting green mixture was heated at 120 °C for 48 h. After cooling, the solvents were removed under reduced pressure, ethyl vinyl ether (1 x reaction volume) and EtOAc (1 x reaction volume) were added and the mixture was stirred at room temperature for 1 h. The solvents were then removed under reduced pressure and the residue purified by column chromatography (1:20 → 1:10 → 1:5, EtOAc: hexane).

Total Synthesis of (-)-Fasicularin (2).

(*R*)-1-((*S*,*E*)-2-((*S*)-4-(Benzyloxy)-3-((4-methylphenyl)sulfonamido)butylidene)cyclohexyl)nonan-3-yl benzoate (16). Synthesised according to general procedure for sterically hindered cross-metathesis: Table 1, Entry 7: Prenyl substrate **15** = 1.64 mmol, yield of **16** (756 mg, 70%), pale yellow oil. IR ν_{max} 3284b, 1711s cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.04-8.02 (m, 2H), 7.71-7.69 (m, 2H), 7.56-7.52 (m, 1H), 7.45-7.41 (m, 2H), 7.34-7.28 (m, 3H), 7.24-7.19 (m, 5H), 5.12-5.04 (m, 1H), 4.84 (t, *J* = 7.2 Hz, 1H), 4.726 (d, *J* = 7.2 Hz, 1H), 4.32 (br s, 2H), 3.37-3.34 (m, 1H), 3.33-3.26 (m, 1H), 3.26-3.22 (m, 1H), 2.40 (s, 3H), 2.25-2.22 (m, 2H), 2.00-1.95 (m, 2H), 1.94-1.87 (m, 1H), 1.62-1.44 (m, 7H), 1.31-1.14 (m, 12H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.5, 145.6, 143.2, 138.1, 137.9, 132.8, 130.9, 129.7, 129.6, 128.5, 128.4, 127.8, 127.7, 127.2, 115.7, 75.3, 73.3, 70.6, 53.9, 44.7, 34.3, 33.6, 32.5, 31.8, 30.1, 29.4, 28.2, 27.5, 26.4, 25.5, 23.4, 22.7, 21.6, 14.2. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{40}H_{53}NNaO_5S^+$ 682.3537; Found 682.3540.

(*R*)-1-((2*S*,5*S*,6*S*)-2-((Benzyloxy)methyl)-1-tosyl-1-azaspiro[4.5]decan-6-yl)nonan-3-yl benzoate (18). Freshly distilled TFA (2.0 mL) was added to a solution of olefin **16** (400 mg, 0.607 mmol) in $CDCl_3$ (2.0 mL). The reaction vessel was sealed and the mixture stirred at room temperature for 48 h. The solution was then concentrated under reduced pressure and the residue purified by silica column chromatography (EtOAc: hexane, 1:4) to give **18** as a colourless oil (268 mg, 67%). IR ν_{max} 3255w, 1714s cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.35-7.26 (m, 7H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.13 (apparent quintet, *J* = 6.0 Hz, 1H), 4.43 (ABq, *J* = 24.4 & 6.0 Hz, 2H), 3.91-3.86 (m, 1H), 3.69-3.66 (m, 1H), 3.32 (t, *J* = 9.6 Hz, 1H), 2.39 (s, 3H), 2.28 (t, *J* = 9.6 Hz, 1H), 2.11 (t, *J* = 9.6 Hz, 1H), 1.86-1.26 (m, 23H), 0.86 (t, *J* = 6.4 Hz, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 166.5, 142.8, 139.5, 138.4, 132.8, 131.2, 129.7, 129.5, 128.52, 128.50, 128.4, 127.9, 127.7, 75.9, 75.6, 73.4, 71.8, 59.9, 45.1, 34.6, 34.3, 32.8, 31.9, 30.1, 29.5, 26.5, 25.7, 25.6, 25.5, 25.4, 25.0, 22.8, 21.6, 14.2. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{40}H_{53}NNaO_5S^+$ 682.3537; Found 682.3532.

(*R*)-1-((2*S*,5*S*,6*S*)-2-((Benzyloxy)methyl)-1-azaspiro[4.5]decan-6-yl)nonan-3-ol (20). Sodium amalgam (104 mg, 4.55 mmol, 10% w/w) added to the spirocycle **18** (300 mg, 0.455 mmol) in methanol (10 mL). After heating at reflux for 16 h, the mixture was cooled and filtered and washed (2x10 mL) through glass filter paper. The methanol was removed under reduced pressure and the residue was purified by column chromatography ($CHCl_3$ → 200:9:1, $CHCl_3$:MeOH:NH_3) to afford **20** (150 mg, 82%) as a colorless oil. $[\alpha]_D^{22}$ -37.3 (*c* 1.20, $CHCl_3$, lit.[9k] $[\alpha]_D^{20}$-38.4°, $CHCl_3$). IR ν_{max} 3385b, 2925s, 2855m cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30-1.20 (m, 5H), 4.49 (ABq, *J* = 12.0 Hz, 1H), 4.41 (ABq, *J* = 12.0 Hz, 1H), 4.25-3.80 (br s, 2H), 3.67-3.65 (m, 1H), 3.51 (ABX, *J* = 9.2, 4.0 Hz, 1H), 3.42-3.37 (m, 1H), 3.37-3.42 (m, 1H), 1.78-1.74 (m, 1H), 1.70-1.54 (m, 8H), 1.44-1.15 (m, 16H), 1.02-0.91 (m, 2H), 0.82 (t, *J* = 6.4 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.4, 128.4, 127.6, 127.6, 73.1, 71.5, 68.6, 67.0, 59.3, 45.1, 40.1, 37.8, 34.8, 32.0, 30.9, 29.7, 29.2, 28.7, 26.2, 26.1, 25.7, 24.6, 22.7, 14.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{44}NO_2^+$ 402.3367; Found 402.3365.

(3*S*,5,7a*S*,11a*S*)-3-((Benzyloxy)methyl)-5-hexyldecahydro-1H-pyrrolo[2,1-j]quinoline (22). Compound **22** was prepared following a modified procedure developed by the Kibayashi/Zhao group and coworkers.[9k,9i] The amino alcohol **20** (20 mg, 0.05 mmol), PPh_3 (40 mg, 0.15 mmol), DMAP (2.0 mg, 0.02 mol) and NEt_3 (0.02 mL, 0.15 mmol) were dissolved in DCM (2 mL) at 0 °C. CBr_4 (50 mg, 0.15 mmol) was added in one portion and the solution was warmed to room temperature and stirred for 16 h. The reaction mixture was quenched by addition of saturated aqueous sodium bicarbonate (5 mL). The product was then extracted with DCM (3x5 mL). The combined organic extract was dried (K_2CO_3), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography ($CHCl_3$ → 200:9:1, $CHCl_3$:MeOH:NH_3) to afford **22** (16 mg, 84%) as a colorless oil. IR ν_{max} 2925s, 2857m cm^{-1}. ^{1}H-NMR (400 MHz, 5% KOH d_4-MeOD): δ 7.35-7.25 (m, 5H), 4.53 (ABq, *J* = 14.8, 12.4 Hz, 1H), 4.49 (ABq, *J* = 14.8, 12.4 Hz, 1H), 3.61 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.38 (dd, *J* = 9.2, 7.6 Hz, 1H), 3.14 (apparent quintet, *J* = 8.0 Hz, 1H), 2.12-2.16 (m, 1H), 2.13-2.09 (m, 1H), 1.89-1.83 (m, 1H), 1.83-1.78 (m, 1H), 1.74-1.64 (m, 4H), 1.62-1.54 (m, 3H), 1.48-1.37 (m, 2H), 1.34-1.09 (m, 17H), 0.89 (t, *J* = 4.0 Hz, 3H). ^{13}C-NMR (100 MHz, 5% KOH d_4-MeOD): δ 139.9, 129.3, 128.7, 128.6, 78.0, 74.0, 69.7, 66.5, 64.4, 45.2, 38.6, 37.5, 33.0, 32.8, 32.5, 30.7, 27.8,

27.7, 27.4, 25.2, 24.5, 23.7, 22.7, 14.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{42}NO^+$ 384.3266; Found 384.3265.

((3*S*,5*S*,7a*S*,11a*S*)-5-Hexyldecahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3-yl)methanol (23). Compound **23** was prepared following a modified procedure developed by Kibayashi group and coworkers.[9k] Tricyclic amine **22** (10 mg, 26.1 μmol) and $Pd(OH)_2$ (10 mg, 1:1 w/w) were added to MeOH (5 mL) at room temperature. Hydrogen was introduced through three purge/refill cycles using a three way stopcock, partial vacuum and a balloon. The reaction mixture was stirred at room temperature for 16 h, at which point the mixture was filtered and washed (2x2 mL) through glass filter paper with methanol. The solvent was removed under reduced pressure to afford **23** (6.0 mg, 80%) as a colorless oil that required no further purification. IR ν_{max} 3396b cm^{-1}. ^{1}H-NMR (400 MHz, 5% KOH d_4-MeOD): δ 3.67 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.42 (dd, *J* = 10.4, 8.8 Hz, 1H), 3.06-3.03 (m, 1H), 2.21-2.20 (m, 1H,), 2.10 (dt, *J* = 12.4, 8.4 Hz, 1H), 1.89 (ABX, 12.0, 3.2 Hz, 1H), 1.83 (ABX, 12.0, 7.6 Hz, 1H), 1.72-1.66 (m, 4H), 1.62-1.55 (m 3H), 1.50-1.43 (m, 2H), 1.34-1.12 (m, 16H), 0.90 (t, *J* = 6.4 Hz, 3H). ^{13}C-NMR (100 MHz, 5% KOH d_4-MeOD): δ 69.4, 69.1, 68.5, 64.1, 45.2, 38.9, 37.6, 33.1, 32.5, 32.4, 30.7, 27.9, 27.4, 27.2, 27.2, 25.4, 24.5, 23.7, 14.4. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{36}NO^+$ 294.2791; Found 294.2788.

(-)-Fasicularin (2). Compound **2** was prepared following a modified procedure developed by Kibayashi and coworkers.[9k] DEAD (16.0 μL, 0.102 mmol), triphenylphosphine (18.0 mg, 0.102 mmol) and ammonium thiocyanate (10.0 mg, 0.128 mmol) were added to DCM (1 mL) and stirred at room temperature for 0.5 h. Tricyclic amino alcohol **23** (15.0 mg, 0.05 mmol) in DCM (1 mL) was added and the solution stirred at room temperature for 16 h. The reaction mixture was quenched by addition of saturated aqueous sodium bicarbonate (2 mL). The product was then extracted with DCM (3x2 mL). The combined organic extract was dried (K_2CO_3), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (20:1, hexane: EtOAc) to afford **2** (7.0 mg, 41%) as a colorless oil. $[\alpha]_D^{22}$ -4.0 (*c* 0.10, MeOH, lit[9k] $[\alpha]_D^{21}$ -4.4° (*c* 0.47, MeOH). IR ν_{max} 2924s, 2857m, 2361m, 2156m, 1464m cm^{-1}. ^{1}H-NMR (400 MHz, d_5-pyridine): δ 3.58-3.52 (m, 1H), 3.38 (dd, *J* = 14.4, 12.0 Hz, 1H), 3.28 (ddd, *J* = 14.4, 4.4, 2.0 Hz, 1H), 2.91 (ddt, *J* = 12.0, 6.0, 3.1 Hz, 1H), 2.52 (d, *J* = 12.0 Hz, 1H), 1.97-1.91 (m, 1H), 1.86 (dd, *J* = 12.0, 4.4 Hz, 1H), 1.83-1.74 (m, 1H), 1.89-1.83 (m, 1H), 1.83-1.78 (m, 1H), 1.58-0.96 (m, 21H), 0.84 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, d_5-pyridine): δ 111.6, 56.3, 52.3, 46.5, 46.1, 40.2, 34.3, 34.1, 32.3, 32.1, 30.2, 29.5, 27.7, 27.2, 26.3, 24.0, 22.9, 22.7, 19.3, 14.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{35}N_2S^+$ 335.2515; Found 335.2514.

Total Synthesis of (-)-lepadiformine A (1)

(*S*)-1-((*S*,*E*)-2-((*S*)-4-(Benzyloxy)-3-((4-methylphenyl)sulfonamido)butylidene)cyclohexyl)nonan-3-yl benzoate (17). Synthesised according to general procedure for sterically hindered cross-metathesis: Table 1, Entry 6: Prenyl substrate **15** = 0.58 mmol, yield of **17** = 67% (255 mg), pale yellow oil as a mixture of *E*/*Z* isomers. IR ν_{max} 3284b, 1713s cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.06-7.02 (m, 2H), 7.73-7.71 (m, 2H), 7.55-7.52 (m, 1H), 7.45-7.41 (m, 2H), 7.30-7.29 (m, 3H), 7.26-7.219 (m, 5H), 5.10-5.08 (m, 1H), 4.93-4.84 (m, 2H), 4.39-4.32 (m, 2H), 3.37-3.32 (m, H3), 2.40 (br s, 3H), 2.27-2.10 (m, 2H), 2.00-1.92 (m, 3H), 1.67-1.48 (m, 9H), 1.33-1.27 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.7, 145.9, 145.8*, 143.5, 143.4*, 138.4, 138.3*, 138.2, 138.1*, 133.0, 131.1, 129.9, 128.7, 128.7, 127.0, 127.9, 127.9, 127.4, 119.5, 115.8, 115.7*, 75.5, 73.5, 70.8, 70.8*, 54.1, 53.9*, 44.8, 44.8*, 34.5, 34.4*, 34.2, 33.9*, 32.1, 31.2, 30.3, 30.1*, 29.6, 28.5, 28.5*, 26.1, 25.7, 23.7, 23.6*, 22.9, 21.8, 14.4. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{40}H_{53}NNaO_5S^+$ 682.3537; Found 682.3538.

(*S*)-1-((2*S*,5*S*,6*S*)-2-((Benzyloxy)methyl)-1-tosyl-1-azaspiro[4.5]decan-6-yl)nonan-3-yl benzoate (19). Freshly distilled TFA (2.5 mL) was added to a solution of olefin **17** (255 mg, 0.607 mmol) in $CDCl_3$ (2.5 mL). The reaction vessel was sealed and the mixture stirred at room temperature for 16 h. The solution was then concentrated under reduced pressure and the residue purified by silica column chromatography (EtOAc: hexane, 1:4) to give **19** as a colourless oil (181 mg, 71%). IR ν_{max} 3308w, 1632s cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.06-7.98 (m, 2H), 7.75-7.70 (m, 2H), 7.57-7.53 (m, 1H), 7.45-7.42 (m, 2H), 7.32-7.26 (m, 6H), 7.21 (br d, *J* = 8.0 Hz, 2H), 4.88 (apparent quintet, *J* = 6.4 Hz, 1H), 4.14 (br s, 2H), 3.85-3.82 (m, 1H), 3.64 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.35 (t, *J* = 9.6 Hz, 1H), 2.50 (dt, *J* = 12.0, 2.8 Hz, 1H), 2.37 (s, 3H), 2.28 (br t, *J* = 12.0 Hz, 1H), 2.06 (app quartet, *J* = 7.6 Hz, 1H), 1.91-1.88 (m, 1H), 1.84-1.78 (m, 1H), 1.72-1.61 (m, 7H), 1.40-1.16 (m, 14H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.5, 142.9, 139.9, 138.5, 132.8, 131.1, 129.7, 128.82, 128.82, 128.7, 128.5, 127.6, 127.3, 75.6, 75.5, 73.3, 71.8, 60.8, 42.6, 42.5, 33.9, 32.4, 31.9, 31.7, 30.2, 29.4, 27.6, 26.9, 25.6, 25.2, 24.9, 22.7, 21.6, 14.2. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{40}H_{53}NNaO_5S^+$ 682.3537; Found 682.3534.

(*S*)-1-((2*S*,5*S*,6*S*)-2-((Benzyloxy)methyl)-1-azaspiro[4.5]decan-6-yl)nonan-3-ol (21). Sodium amalgam (126 mg, 5.49 mmol, 10% w/w) added to the spirocycle **19** (181 mg, 0.274 mmol) in methanol (10

mL). After heating at reflux for 4 h, the mixture was cooled and filtered and washed (2x10 mL) through glass filter paper. The methanol was removed under reduced pressure and the residue was purified by column chromatography ($CHCl_3$ → 200:9:1, $CHCl_3$:MeOH:NH_3) to afford **21** (85 mg, 77%) as a colorless oil. $[\alpha]_D^{22}$ -30.2 (c 0.96, MeOH, lit.[9k] $[\alpha]_D^{26}$ -33.2° (*c* 0.98, MeOH)). IR ν_{max} 3402b, 2924m cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35-7.26 (m, 5H), 4.54 (ABq, *J* = 12.0 Hz, 1H), 4.48 (ABq, *J* = 12.0 Hz, 1H), 3.62-3.58 (m, 1H), 3.56 (ABX, *J* = 12.0, 4.8 Hz, 1H), 3.46 (ABX, *J* = 12.0, 4.6 Hz, 1H), 3.46-3.18 (m, 1H), 2.82 (br s, 2H), 1.87-1.81 (m, 1H), 1.72-1.57 (m, 8H), 1.51-1.37 (m, 5H), 1.32-1.83 (m, 11H), 1.10-1.01 (m, 1H), 099-0.81 (m 1H), 0.87 (t, *J* = 6.4 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.4, 128.5, 128.1, 127.7, 73.7, 73.3, 71.9, 67.2, 59.6, 48.1, 40.0, 37.0, 36.2, 32.0, 30.5, 29.9, 29.8, 29.5, 28.7, 27.8, 25.9, 25.3, 22.8, 14.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{44}NO_2^+$ 402.3367; Found 402.3361.

(3*S*,5*R*,7a*S*,11a*S*)-3-((Benzyloxy)methyl)-5-hexyldecahydro-1*H*-pyrrolo[2,1-*j*]quinoline (24). Compound **24** was prepared following a modified procedure developed by Kibayashi/Zhao group and coworkers.[9k,9i] The amino alcohol **21** (20 mg, 0.05 mmol), PPh_3 (65 mg, 0.25 mmol), DMAP (2.0 mg, 0.02 mol) and NEt_3 (70.0 μL, 0.500 mmol) were dissolved in DCM (2 mL) at 0 °C. CBr_4 (83 mg, 0.25 mmol) was added in one portion and the solution was warmed to room temperature and stirred for 16 h. The reaction mixture was quenched by addition of saturated aqueous sodium bicarbonate (5 mL). The product was then extracted with DCM (3x5 mL). The combined organic extract was dried (K_2CO_3), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography ($CHCl_3$ → 200:9:1, $CHCl_3$:MeOH:NH_3) to afford **24** (15 mg, 78%) as a colorless oil. $[\alpha]_D^{27}$ -22.3 (*c* 0.81, MeOH, lit.[9k] -22.0 (*c* 0.71, MeOH)). IR ν_{max} 2927s, 2859m, 1467m, 1116m cm^{-1}. ^{1}H-NMR (400 MHz, 5% KOH d_4-MeOD): δ 7.32-7.24 (m, 5H), 4.52 (ABq, *J* = 24.4, 12.4 Hz, 1H), 4.45 (ABq, *J* = 24.4, 12.4 Hz, 1H), 3.51 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.28-3.25 (m, 1H), 3.11 (app triplet, *J* = 8.8 Hz, 1H), 3.00 (br t, *J* = 7.6 Hz, 1H), 2.03-2.00 (m, 1H), 1.72-1.66 (m, 6H), 1.59-1.41 (m, 6H), 1.28-1.16 (m, 14H), 1.10-1.02 (m, 2H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, 5% KOH d_4-MeOD): δ 139.5, 129.0, 128.4, 128.2, 77.7, 73.6, 68.9, 58.4, 54.9, 41.3, 38.6, 34.7, 32.6, 31.7, 30.3, 29.7, 28.5, 28.3, 27.1, 25.0, 24.7, 22.3, 22.8, 14.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{42}NO^+$ 384.3266; Found 384.3264.

(-)-Lepadiformine A 1. Compound **1** was prepared following a procedure developed by Kibayashi group and coworkers.[9k] Tricyclic amine **24** (10 mg, 26.1 μmol) and $Pd(OH)_2$ (10 mg, 1:1 w/w) were added to MeOH (2 mL) at room temperature. Hydrogen was introduced through three purge/refill cycles using a three way stopcock, partial vacuum and a balloon. The reaction mixture was stirred at room temperature for 16 h, at which point the mixture was filtered and washed with MeOH (2x2 mL) through glass filter paper. The solvent was removed under reduced pressure and the residue was purified by column chromatography ($CHCl_3$ → 200:9:1, $CHCl_3$:MeOH:NH_3) to afford crude **1** (1.8 mg, 24%) as a colorless oil.[21] $[\alpha]_D^{22}$ -5.2 (*c* 0.08, MeOH, lit.[9k] $[\alpha]_D^{28}$ -15.0 (*c* 0.37, MeOH)). IR ν_{max} 3676b, 2459b, 2211m, 1465m, 1120s, 973 s cm^{-1}. ^{1}H-NMR (400 MHz, 5% KOH d_4-MeOD): δ 2.19 (app triplet, *J* = 7.6 Hz, 2H), 2.04 (br q, *J* = 4.8 Hz, 3H), 1.62-1.46 (m, 8H), 1.60-1.24 (m, 18H), 1.09 (dq, *J* = 12.5, 3.2 Hz, 1H), 0.90 (t, *J* = 6.4 Hz, 3H). ^{13}C-NMR (100 MHz, 5% KOH d_4-MeOD): δ 69.2, 67.6, 60.5, 55.2, 41.7, 38.8, 39.1, 34.9, 33.2, 31.5, 30.1, 30.4, 29.2, 27.1, 26.7, 25.0, 24.6, 23.0, 14.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{36}NO^+$ 294.2791; Found 294.2796.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C{1H} NMR spectra of compounds **S1**, **S3-9**, **1**, **2**, **5**, **6**, **8-24**. This material is available free of charge on the ACS Publications website.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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REFERENCES

[1] Cossy, J.; Arseniyadis, S.; Meyer C. Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts; Wiley-VCH Verlag GmbH & Co.; **2010**.

[2] Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed*., **2006**, *45*, 6086-6101

[3] Grubbs, R. H.; Handbook of Metathesis, Three Volume Set; Wiley-VCH Verlag GmbH & Co.; **2003**.

[4] There are examples where CM is used in the construction of advanced intermediates in the context of total synthesis, such as; (a) the homodimerisation of complex olefins: Smith, III, A. B.; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc*., **2001**, *123*, 5925-5937. (b) Prenylation of advanced intermediates: Qi, J.; Porco, Jr., J. A. *J. Am. Chem. Soc*., **2007**, *129*, 12682-12683. (c) Construction of unhindered olefins, often with an excess of a non-precious substrate:

Yamamoto, T.; Hasegawa, H.; Hakogi, T.; Katsumura, S. *Org. Lett*., **2006**, *8*, 5569-5572.

[5] Wang, Z. J.; Jackson, W. R.; Robinson, A. J. *Org. Lett*., **2013**, *15*, 3006-3009.

[6] Wang, Z.J.; Spiccia, N. D.; Gartshore, C. J.; Illesinghe, J.; Jackson, W.R.; Robinson, A. J. *Synthesis*, **2013**, *45*, 3118-3124.

[7] (a) Biard, J.-F.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boufek, K. *Tetrahedron Lett.* **1994**, *35*, 2691–2694. (b) Sauviat, M.-P.; Vercauteren, J.; Grimaud, N.; Jugé, M.; Nabil, M.; Petit, J.-Y.; Biard, J.-F. *J. Nat. Prod*. **2006**, *69*, 558-562.

[8] For review articles see: (a) Weinreb, S. M. *Acc. Chem. Res*., **2003**, *36*, 59-65. (b) Kibayashi, C.; Aoyagi, S.; Abe, H. *Bull. Chem. Soc. Jpn*., **2003**, *76*, 2059-2074. (c) Kibayashi, C. *Chem. Pharm. Bull*., **2005**, *53*, 1375-1386. (d) Schär, P.; Cren, S.; Renaud, P. *Chimia*, **2006**, *60*, 131-141. (e) Weinreb, S. M. *Chem. Rev*., **2006**, *106*, 2531-2549.

[9] For selected syntheses of the lepadiformines see: (a) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem*., **1999**, *64*, 686-687 (b) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem*., **1999**, *64*, 4865-4873. (c) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc*., **2000**, 122, 4583-4592. (d) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem*., **2002**, 67, 4337-4345. (e) Meyer A.M.; Katz, C. E.; Li, S.-W.; Vander Velde, D.; Aubé, J. *Org. Lett*., **2010**, *12*, 1244-1247. (f) Bagley, M. C.; Oppolzer, W. *Tetrahedron: Asymmetry* **2000**, *11*, 2625-2633. (g) Swidorski, J. J.; Wang, J.; Hsung, R. P. *Org. Lett*., **2006**, *8*, 777-780. (h) Schär, P.; Renaud, P. *Org. Lett.,* **2006**, 8, 1569-1571 (i) Mei, S.-L.; Zhao, G. *Eur. J. Org. Chem*., **2010**, 1660-1668. (j) Weidner, K.; Giroult, A.; Panchaud, P.; Renaud, P. *J. Am. Chem. Soc*., **2010**, *132*, 17511-17515. (k) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc*., **2005**, *127*, 1473-1480. (l) Liu, J.; Hsung, R. P.; Peters, S. D. *Org. Lett*., **2004**, *6*, 3989-3992. (m) Greshock, J. T.; Funk, R. L. *Org. Lett.*, **2001**, *3*, 3511-3514. (n) Jinkyung, I; Seokwoo, L.; Yongseok, L.; Kim, S. *Chem. Eur. J*., **2014**, *20*, 17433-17442. (o) Nishikawa, K.; Kikuchi, S.; Ezaki, S.; Koyama, T.; Nokubo, H.; Kodama, T.; Tachi, Y.; Morimoto, T. *Org. Lett*., **2015**, *17*, 5772–5775. (p) Tabor, M. G.; Shenvi, R. A., *Org. Lett*., **2015**, *17*, 5776–5779. (q) Kaga, A.; Tnay, A. L.; Chiba, S. *Org. Lett.*,**2016**, *18*, 3506-3508. (r) Lee, S.; Bae, M; In, J. H.; Lim, H.; Kim, *Org. Lett.,* **2017**, 19, 254–25.

[10] For selected syntheses of fasicularin see: (a) Fenster, M. D. B.; Dake, G. R. *Org. Lett*., **2003**, *5*, 4313-4316. (b) Wardrop, D. J.; Zhang, W.; Landrie, C. L. *Tetrahedron Lett.,* **2004**, *45*, 4229-4231. (c) Maengm J.-H.; Funk, R. L.; *Org. Lett*., **2002**, *4*, 331-333. Also see references: 9(b)(c)(f)(j)(k)(n).

[11] Made in three steps from commercially available trans-2-nonen-1-ol.

[12] When unprotected iodoalcohol **5** was used in place of the protected alcohol **6**, immediate cyclisation occurred delivering a lactol that proved unreactive in the subsequent palladium catalysed enantionselective protonation.

[13] Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz. B. M. *Org. Lett*., **2008**, *10*, 1039-1042.

[14] Diastereoisomers **9** were inseparable and indistinguishable by H nmr spectroscopy; reverse and normal phase chromatography were also investigated but failed to give effective resolution, hence ^{13}C nmr spectroscopy was used to estimate diastereomeric ratio. A 1:1 epimeric mixture (i.e. **S6**) was prepared to facilitate this analysis. Separation was achieved by column chromatography after deprotection as alcohol **10**.

[15] Diastereoisomers **12** were indistinguishable by H nmr spectroscopy hence ^{13}C nmr spectroscopy was used to estimate diastereomeric ratio.

[16] Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H.; *Org. Lett.,* **2002**, *4*, 1939-1942.

[17] Minor isomerisation (<1%) of **11** was noted after each pass.

[18] Haskins, C. M.; Knight, D. W. *Chem. Commun*., **2002**, 2724-2725.

[19] Examples of this process used in synthesis: (a) Schlummer, B.; Hartwig, J. F. *Org. Lett*. **2002**, *4*, 1471-1474. (b) Leger, P. R.; Murphy, R. A.; Pushkarskaya, E.; Sarpong, R. *Chem. Eur. J*., **2015**, *21*, 4377-4383. (c) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc*., **2005**, *127*, 14542-14543.

[20.] M. R. Krout, J. T. Mohr, B. M. Stoltz, *Org. Synth.* **2009**, *86*, 181-193.

[21.] NMR spectra acquired in $CDCl_3$ were unresolved and suggested the existence of multiple conformations in solution. Resolved spectra could be obtained in 5% KOH *d4*-MeOD but this prevented comparison to literature cited values.

[22] Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1987**, *109*, 5765-5780.

[23] Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem*., **1982**, *47*, 1378-1380.

[24.] Robinson, A. J.; van Lierop, B. J., Patent US20120225811, **2011**.