Total Synthesis and Structural Reassignment of Laingolide A

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Abstract: The asymmetric total synthesis of four diastereomers of laingolide A was achieved, which led to the unambiguous assignment of the stereochemistry of the natural product. The salient features of the convergent, fully stereocontrolled approach were a copper-catalysed stereospecific Kumada-type coupling, a Julia-Kocienski olefination and an RCM/alkene migration sequence to access the desired macrocyclic enamide.

Keywords: total synthesis; structural reassignment; laingolide A

1. Introduction

The modern structure determination of unknown natural products remains a challenging problem, especially when a small quantity of the natural compound is available, limiting the full possibility of the modern spectroscopic methods. For this reason, total synthesis has played a major role in the structure elucidation and revision of complex natural products for a long time. In the absence of a firm structural assignment, a combination of the stereochemical logic of the synthesis and spectroscopic comparison could be employed as tools to establish the correct structure of natural products [1–4]. Previous work in our group led to the reassignment of the configuration of a number of marine natural products [5–11]. These results encouraged us to embark upon the synthesis of other natural products with unknown configurations. We describe herein the determination of the complete relative and absolute stereochemistries of (+)-laingolide A and the total synthesis of this material.

Laingolide A (1), along with madangolide (2), was isolated in 1999 from the marine cyanobacterium Lyngbya bouillonii collected in Papua New Guinea [12]. The very same blue-green algae also produced laingolide (3) (Scheme 1), which was disclosed as the first member of the novel macrolide family [13]. Additionally, another chlorinated analogue, laingolide B (4), was isolated in 2010 by Luesch and co-workers from the same species of bacteria collected in Apra Harbor, Guam [14]. The planar structures of the laingolides were established using a combination of detailed 1D and 2D NMR analysis. However, these macrolides underwent degradation over time, which hampered progress towards complete assignments of their absolute stereochemistry. In 2010, Gerwick and co-workers reported the isolation of palmyrolide A (5), a structurally closely related 15-member macrolide from a cyanobacterial assemblage comprised of Leptolyngbya and Oscillatoria species collected at Palmyra Atoll, south of Hawaii [6]. One of the absolute configurations present in palmyrolide A was correctly assigned upon its initial isolation [15], and the absolute configurations of the remaining stereocentres were later established via total syntheses [16–24]. The structurally intriguing laingolides have attracted considerable attention from the synthetic community [25–27]. In 2018, Dai and co-workers reported the first total synthesis of laingolide B and unambiguously assigned the absolute configuration as depicted in structure 4 [27]. Laingolide A (1) was isolated from the bacteria collected in a different location and eleven years before the isolation of laingolide B (4). Laingolide A contains...
an extra undefined stereogenic centre located at C-(7), whose absolute structure remained elusive. Furthermore, laingolide A (1) bears a close resemblance to palmyrolide A (5); specifically, these two macrolides contain a tert-butyl carbinol and a methyl group beta to the tert-butyl substituted stereocenter.

![Scheme 1. Structures of laingolide A (1), madangolide (2), laingolide (3), laingolide B (4) and palmyrolide A (5).](image)

It would be interesting to find out whether the absolute configurations of laingolide A (1) were likely the same based on the possible similar biogenesis to palmyrolide A (5). Through the completion of the synthesis of four diastereomers, we shall be able to provide conclusive evidence for the absolute and relative stereochemistry of laingolide A (1) [28].

Structurally, laingolide A features a 15-member macrocyclic core, which is composed of a sterically encumbered ester derived from a tert-butyl carbinol, a trans-N-methyl enamide subunit and two chiral methyl appendages. At the outset of this synthetic venture, our primary objective was to rapidly access four diastereomers (Scheme 2) and thus conclusively establish the absolute configuration of laingolide A. With this in mind, we opted for a modular and flexible approach as we pondered its retrosynthetic analysis (Supplementary Materials) (Scheme 2) [29–36]. We envisioned that the four diastereomers of laingolide A could be constructed from fragments 6, 7, 8 and ent-8 via three key transformations, as illustrated in Scheme 2. This highly convergent strategy relied on a ring-closing metathesis (RCM) at C-12 and C-13 to deliver the macrocycle and olefin migration to forge the enamido moiety at the final stage [19,22,27]. Both copper-catalysed Kumada-type coupling [37] of cyclic sulfate esters and Julia-Kocienski olefination [38–40] were then employed to construct the RCM precursor.
Scheme 2. Retrosynthetic analysis of laingolide A and its diastereomers (1a–d).

2. Results

The synthesis towards the chiral aldehydes (Scheme 3) commenced with the known chiral 1,3-hydroxy ketone 9 [23], which was prepared via List’s proline-catalysed aldolisation between acetone and pivalaldehyde [41]. A three-step sequence [23] was employed to elaborate 1,3-hydroxy ketone 9 into cyclic sulfate ester 6 involving (1) the syn reduction of ketone 9 with DIBAL-H, (2) conversion of the syn-diol into the corresponding sulfite with thionyl chloride and (3) oxidation of the cyclic sulfite with NaIO₄ in the presence of catalytic amounts of RuCl₃. Nucleophilic ring-opening of the cyclic sulfate 6 using a mixed organometallic reagent derived from allylmagnesium chloride and stoichiometric quantities of copper(I) iodide has already been reported [42]. Recently, a catalytic version of this reaction, also termed C(sp³)-C(sp³) Kumada-type coupling of cyclic sulfate esters was reported [37]. We opted to incorporate this catalytic reaction into our synthesis. Thus, treatment of cyclic sulfate 6 and 10 mol% of cuprous iodide in THF with allylmagnesium bromide at −20 °C followed by hydrolysis of the corresponding intermediate gave rise to the corresponding alcohol with a 75% yield with a >95:5 diastereomeric ratio (dr), as determined using ¹H NMR spectroscopy. This reaction occurred at the least-hindered site, with the complete inversion of the configuration at that centre. Protection of the resulting alcohol with TBSOTf (tert-butyldimethylsilyl trifluoromethanesulfonate) and triethylamine afforded TBS ether 10 with a 96% yield. Hydroboration of 10 with 9-borabicyclo[3.3.1]nonane (9-BBN) and oxidation of the resulting organoborane (NaHCO₃, H₂O₂) furnished alcohol 11 with an 89% yield, which in turn was subjected to oxidation with TEMPO, NaOCl and NaBr [43] to provide aldehyde 12 with an 85% yield. In parallel, the hydroxyl-
directed antireduction of hydroxy ketone 9 with the Evans–Carreira protocol [44] proceeded smoothly to furnish the desired 1,3-anti diol with a diastereomeric ratio of 5:1 (determined by $^1$H NMR of the crude reaction mixture). These diastereomers were separated using flash chromatography and the major one was used in subsequent reactions. The anti-substituted cyclic sulfate 7 was prepared with a 60% yield over three steps using the same procedure as described for 6. The elaboration of the substituted cyclic sulfate 7 into aldehyde 15 was accomplished in a way similar to that described for the preparation of aldehyde 12.

![Scheme 3. Synthesis of aldehydes 12 and 15.](image)

With a reliable route to useful quantities of the required aldehydes 12 and 15 in hand, our efforts turned to the divergent total synthesis of laingolide A (Scheme 4). This required the combination of aldehydes 12 and 15 separately with BT-sulfones 8 and then with ent-8 [45] (Scheme 4a). Under the optimum conditions investigated, each aldehyde (12 or 15) underwent condensation with 1.2 molar equivalent of sulfone (8 or ent-8) treated with 1.2 molar equivalent of NaHMDS in toluene at $-78^\circ$C to afford the corresponding alkene as a mixture of geometrical isomers ($Z:E \approx 3–7:1$) in high yield. Next, each of the resultant internal alkenes (16, 20, 24, 28) was separately subjected to palladium-chloride-mediated hydrogenation in ethanol with the concomitant removal of the TBS ethers that furnish the corresponding diol (17, 21, 25, 29) [46]. The primary alcohol of the above diol was selectively oxidised with TEMPO in the presence of bis-acetoxyiodobenzene (BAIB) [47] and the resulting carboxylic acid was then coupled with the N-methylallylamine by utilising EDCI-HOAt and DMAP as a base to provide the corresponding amide (18, 22, 26, 30). For the conversion to the required diene (19, 23, 27, 31), each amide alcohol was separately acylated with acryloyl chloride in the presence of triethylamine and DMAP. The four diastereomeric dienes (19, 23, 27, 31) were separately subjected to ring-closing metathesis using the second-generation Grubbs catalyst (G-II) to afford the corresponding unsaturated macrolactone as isomeric mixtures, which were subsequently treated with RuH(PPh$_3$)$_3$(CO)Cl in refluxing toluene [48] to furnish the desired enamides 1a–d with good yields. The comparison of the spectral data of 1a–d with the reported spectra of laingolide A was informative. Compound 1a, featuring a C(7)-R methyl beta to the C(9)-R-tert-butyl-substituted stereocenter, the same as that of natural palmyrolide A (5), did
not match the literature values reported for the laingolide A. This suggested that the biogenesis of the laingolide A and palmyrolide A might follow different pathways or that C7 is epimerized at some stage of the biosynthesis of laingolide A (or of palmyrolide A). It was clear from comparing the $^{13}$C NMR data (Scheme 4b) that diastereomer 1c represented the correct structure of natural laingolide A. The absolute stereochemical assignment of laingolide A was thus assigned as 2S,7S,9R, as shown in 1c (Scheme 4).

Scheme 4. (a) Total synthesis of laingolide A and its diastereomers (1a–d); (b) comparison of the $^{13}$C NMR data of the synthetic compounds (1a–d) with the naturally occurring laingolide A.
3. Materials and Methods
3.1. General Information

All reactions were conducted in flame-dried or oven-dried glassware under an atmosphere of dry nitrogen or argon. Oxygen and/or moisture-sensitive solids and liquids were transferred appropriately. The concentration of solutions in vacuo was accomplished using a rotary evaporator fitted with a water aspirator. Residual solvents were removed under a high vacuum (0.1–0.2 mm Hg). All reaction solvents were purified before use: tetrahydrofuran (THF) was distilled from Na/benzophenone. Toluene was distilled over molten sodium metal. Dichloromethane (DCM), 1,2-dichloroethane (DCE) and trimethylamine (Et$_3$N) were distilled from CaH$_2$. Methanol (MeOH) was distilled from Mg/I$_2$. The reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Flash column chromatography was performed using the indicated solvents on E. Qingdao silica gel 60 (230–400 mesh ASTM). Reactions were monitored using thin-layer chromatography (TLC), which was carried out using pre-coated sheets (Qingdao silica gel 60-F250, 0.2 mm, Tsingtao, China). Compounds were visualised with UV light, iodine and ceric ammonium molybdate stain or phosphomolybdic acid in EtOH. The $^1$H NMR spectra were recorded on Bruker Avance 300 MHz, Avance 400 MHz or Avance 500 MHz spectrometers (Karlsruhe, Germany). Chemical shifts were reported in parts per million (ppm), relative to either a tetramethylsilane (TMS) internal standard or the signals due to the solvent (Supplementary Materials). The following abbreviations are used to describe the spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quadruplets, ddd = doublet of doublet of doublets; other combinations are derived from those listed above. Coupling constants (J) are reported in hertz (Hz) for corresponding solutions, and chemical shifts are reported as parts per million (ppm) relative to residual CHCl$_3$ δH (7.26 ppm). $^{13}$C Nuclear magnetic resonance spectra were recorded using a 75 MHz, 100 MHz or 125 MHz spectrometer (Karlsruhe, Germany) for corresponding solutions, and chemical shifts are reported as parts per million (ppm) relative to residual CDCl$_3$ δC (77.16 ppm) (Supplementary Materials). High-resolution mass spectra were measured on an ABI Q-star Elite (Beijing, China). Optical rotations were recorded on a Rudolph AutoPol-I polarimeter (Shanghai, China) at 589 nm with a 50 mm cell. Data are reported as follows: specific rotation ($\alpha$ (c (g/100 mL), solvent)).

3.2. General Experimental Procedures
3.2.1. Synthesis of (3R,5R)-2,2,5-trimethyloct-7-en-3-ol (S11)

To a solution of cyclic sulfate 6 (620 mg, 2.98 mmol, 1.0 eq.) and CuI (57 mg, 0.3 mmol, 0.1 eq.) in dry THF (1 mL) at −20 °C, allylmagnesium bromide (1.0 M in THF, 14.9 mL, 14.9 mmol, 5.0 eq.) was added under an argon atmosphere. The purple-colored reaction mixture was allowed to stir at −20 °C for 7 h before it was allowed to warm to room temperature and then become concentrated in vacuo. The solid residue was redissolved in Et$_2$O (30 mL) and treated with 20% aqueous H$_2$SO$_4$ (10 mL) solution. The contents of the flask were then stirred vigorously for another 12 h before the phases were separated. The aqueous layer was extracted with Et$_2$O (3 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 20:1) to afford alcohol S11 (380 mg, 75%) as a colorless oil. TLC: R$_f$ = 0.6 (hexanes/EtOAc = 10:1), iodine and PMA stain. $\Delta\theta$$_{23}$ = +36.0 (c 1.00, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 5.86–5.67 (m, 1H), 5.14–4.91 (m, 2H), 3.29 (dd, $J$ = 10.3, 1.6 Hz, 1H), 2.30–2.13 (m, 1H), 1.92–1.82 (m, 1H), 1.81–1.72 (m, 1H), 1.53 (s, 1H), 1.46–1.34 (m, 1H), 1.18 (ddd, $J$ = 14.3, 10.3, 4.1 Hz, 1H), 0.93 (d, $J$ = 6.7 Hz, 3H), 0.87 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 137.2, 116.1, 77.7, 39.9, 38.6, 35.1, 29.9, 25.7, 21.0; HRMS (ESI) calculated for C$_{11}$H$_{22}$ONa$^+$ [M + Na$^+$] 193.1563, found 193.1565.
3.2.2. Synthesis of tert-butylidimethyl(3R,5R)-2,2,5-trimethylct-7-en-3-yl)oxy)silane (10)

To a solution of alcohol S11 (2.8 g, 16.5 mmol, 1.0 eq.) in dry DCM (30 mL, 0.55 M), Et3N (33 mmol, 4.6 mL, 2.0 eq.) and TBSOTf (21.5 mmol, 4.9 mL, 1.3 eq.) were added at 0 °C. The reaction mixture was allowed to stir at 0 °C for 2 h before it was diluted with DCM (20 mL) and quenched with a saturated aqueous solution of NH4Cl (30 mL). The aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 20:1) to afford with EtOAc (3 × 25 mL) and anhydrous AcOH (15 mL) at 100 °C. The reaction mixture was stirred at room temperature for 8 h before a saturated aqueous solution of NaHCO3 (10 mL) and 30% H2O2 (2 mL) were added sequentially at 0 °C and stirred for another 12 h at room temperature. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 10:1) to afford alcohol 11 (473 mg, 89%) as a colorless oil. TLC: RF = 0.95 (hexanes), iodine and PMA stain. 1H NMR (500 MHz, CDCl3) δ 7.4 (c 0.02, CHCl3); 13C NMR (100 MHz, CDCl3) δ 173.3, 116.1, 78.6, 41.0, 40.5, 36.0, 29.8, 26.6, 20.9, 18.7, –3.2, –3.6; HRMS (ESI) calculated for C17H36O3SiNa+[M + Na]+ 325.2428, found 325.2425.

3.2.3. Synthesis of (4R,6R)-6-((tert-butyldimethylsilyl)oxy)-4,7,7-trimethyloctan-1-ol (11)

To a solution of alkene 10 (0.5 g, 1.7 mmol, 1.0 eq.) in dry THF (3 mL, 0.17 M), 9-BBN (0.5 M in THF, 3.52 mmol, 7.0 mL, 2.0 eq.) was added at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature for 8 h before a saturated aqueous solution of NaHCO3 (10 mL) and 30% H2O2 (2 mL) were added sequentially at 0 °C and stirred for another 12 h at room temperature. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 10:1) to afford alcohol 11 (473 mg, 89%) as a colorless oil. TLC: RF = 0.95 (hexanes/EtOAc = 1:1), PMA stain. 1H NMR (500 MHz, CDCl3) δ 3.63 (td, J = 6.6, 1.5 Hz, 2H), 3.30 (dd, J = 7.3, 2.9 Hz, 1H), 1.73–1.58 (m, 1H), 1.59–1.53 (m, 1H), 1.52–1.36 (m, 4H), 1.19 (dd, J = 14.2, 7.3, 4.4 Hz, 1H), 1.06–0.94 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.04 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 78.5, 63.7, 41.7, 35.9, 32.2, 30.3, 29.9, 26.5, 26.3, 20.9, 18.6, –3.3, –3.7; HRMS (ESI) calculated for C17H36O3SiNa+[M + Na]+ 325.2533, found 325.2528.

3.2.4. Synthesis of (4R,6R)-6-((tert-butyldimethylsilyl)oxy)-4,7,7-trimethyloctan-1-ol (12)

To a solution of alcohol 11 (1.0 g, 3.3 mmol, 1.0 eq.) and TEMPO (51 mg, 0.33 mmol, 0.1 eq.) in DCM (30 mL), a solution of NaBr (2.0 g, 19.8 mmol, 6.0 eq.) and NaHCO3 (1.7 g, 19.8 mmol, 6.0 eq.) were added in water (50 mL), followed by NaClO (1 M, 3.3 mL, 1.0 eq.) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 10 min and then quenched with a saturated aqueous solution of Na2S2O3 (3 mL) and extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 20:1) to afford aldehyde 12 (842 mg, 85%) as a colorless oil. TLC: RF = 0.6 (hexanes/EtOAc = 10:1), PMA stain. 1H NMR (500 MHz, CDCl3) δ 9.78 (t, J = 1.8 Hz, 1H), 3.30 (dd, J = 7.3, 2.9 Hz, 1H), 2.58–2.44 (m, 1H), 2.40–2.29 (m, 1H), 1.90–1.71 (m, 1H), 1.65–1.53 (m, 1H), 1.44 (dd, J = 14.3, 9.0, 2.8 Hz, 1H), 1.34–1.25 (m, 1H), 1.22 (dd, J = 14.3, 7.1, 4.3 Hz, 1H), 0.90 (d, J = 6.7 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 202.7, 78.4, 41.6, 41.5, 36.0, 29.7, 28.0, 26.5, 26.3, 20.7, 18.6, –3.3, –3.7; HRMS (ESI) calculated for C17H38O2SiNa+[M + Na]+ 323.2377, found 323.2367.

3.2.5. Synthesis of (4R,6S)-4-(tert-butyl)-6-methyl-1,3,2-dioxathiane 2,2-dioxide (7)

To a solution of Me4NHB(OAc)3 (13.7 g, 52.1 mmol, 5.0 eq.) in anhydrous CH3CN (25 mL) and anhydrous AcOH (15 mL) at −40 °C, a solution of 9 [23] (1.5 g, 10.4 mmol,
1.0 eq.) was added in anhydrous CH$_2$CN (15 mL). The reaction mixture was stirred at –40°C for 12 h, allowed to warm to ambient temperature, poured into a saturated aqueous solution of Na$_2$CO$_3$ (80 mL) and then extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 10:1–5:1) to afford diol S13 (1.1 g, 71%) as a white solid. [43] $^1$H NMR analysis revealed the presence of a 5:1 ratio of anti/syn.

To a solution of anti-diol S13 (3.15 g, 21.5 mmol, 1.0 eq.) in dry DCM (200 mL, 0.22 M), pyridine (17.3 mL, 215.0 mmol, 10.0 eq.) and SOCl$_2$ (7.9 mL, 108.0 mmol, 5.0 eq.) were added sequentially at 0°C. The reaction mixture was allowed to stir at 0°C for 45 min before it was quenched by the addition of water (50 mL) and then extracted with DCM (3 × 100 mL). The combined organic layers were washed with saturated aqueous KH$_2$SO$_4$ solution (50 mL), followed by saturated aqueous NaHCO$_3$ solution (60 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude sulfite, which was used in the next step without further purification. To a solution of the crude sulfite in a mixture of H$_2$O/MeCN/CCl$_4$ (200 mL:200 mL:100 mL), RuCl$_3$·nH$_2$O (562 mg, 2.15 mmol, 0.1 eq.) and NaIO$_4$ (6.9 g, 32.3 mmol, 1.5 eq.) were added. The biphasic reaction mixture was vigorously stirred at room temperature for 2 h before it was diluted with Et$_2$O (60 mL) and quenched with a saturated aqueous solution of NaHCO$_3$ (100 mL). The aqueous layer was extracted with Et$_2$O (3 × 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 17.3 mL, 215.0 mmol, 10.0 eq.) and SOCl$_2$ (100 mL). The combined organic layers were washed with saturated aqueous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 10:1–5:1) to afford anti-cyclic sulfate 7 (3.76 g, 84% for two steps) as an amorphous white solid. The spectral data are in accordance with those reported in literature for its enantiomer [23]. TLC: $R_f$ = 0.5 (hexanes/ EtOAc = 4:1), PMA stain. $\alpha_D^{23} = +24.9$ (c 0.01, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) δ 4.94 (ddq, $J = 6.7, 6.1, 4.4$ Hz, 1H), 4.59 (dd, $J = 11.4, 3.6$ Hz, 1H), 2.30 (ddd, $J = 14.2, 4.4, 3.6$ Hz, 1H), 1.69−1.50 (m, 1H), 0.89 (d, $J = 6.8$ Hz, 3H), 1.00 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 88.1, 81.6, 76.1, 34.3, 30.0, 25.2, 19.7. HRMS (ESI) calculated for C$_8$H$_{16}$SO$_4$Na$^+$ [M + Na]$^+$ 231.0662, found 231.0661.

3.2.6. Synthesis of (3R,5S)-2,2,5-trimethyloct-7-en-3-ol (S12)

The product S12 was synthesised according to the procedures for the synthesis of S11 from 7 (620 mg, 2.98 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 20:1) to afford S12 (370 mg, 73%) as a colorless oil. TLC: $R_f$ = 0.6 (hexanes/EtOAc = 10:1), iodine and PMA stain. $\alpha_D^{25} = -24.9$ (c 0.01, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.78 (ddt, $J = 17.4, 10.4, 7.1$ Hz, 1H), 5.13−4.81 (m, 2H), 3.28 (dd, $J = 10.6, 1.8$ Hz, 1H), 2.21–1.85 (m, 2H), 1.75 (dt, $J = 13.6, 6.7, 3.3$ Hz, 1H), 1.35 (dd, $J = 13.9, 10.6, 3.2$ Hz, 1H), 1.18 (ddd, $J = 14.0, 10.6, 1.8$ Hz, 1H), 0.89 (d, $J = 6.5$ Hz, 3H), 0.87 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 137.6, 115.9, 77.4, 42.8, 38.5, 35.0, 29.7, 25.8, 18.9. HRMS (ESI) calculated for C$_{13}$H$_{22}$ONa$^+$ [M + Na]$^+$ 193.1563, found 193.1562.

3.2.7. Synthesis of tert-butyldimethyl(((3R,5S)-2,2,5-trimethyloct-7-en-3-yl)oxy)silane (13)

The product 13 was synthesised according to the procedures for the synthesis of 10 from S12 (2.9 g, 17.14 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes) to afford 13 (4.67 g, 96%) as a colorless oil. TLC: $R_f$ = 0.95 (hexanes), iodine and PMA stain. $\alpha_D^{27} = +11.1$ (c 0.01, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.98–5.61 (m, 1H), 5.19−4.90 (m, 2H), 3.30 (ddd, $J = 8.5, 1.8$ Hz, 1H), 2.12–1.97 (m, 1H), 1.96–1.84 (m, 1H), 1.75–1.62 (m, 1H), 1.38 (ddd, $J = 14.1, 8.5, 2.9$ Hz, 1H), 1.19 (ddd, $J = 14.0, 10.9, 8.0$ Hz, 1H), 0.89 (s, 8H), 0.84 (d, $J = 6.5$ Hz, 3H), 0.84 (s, 9H), 0.04 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 137.7, 115.7, 78.6, 43.1, 40.6, 35.8, 29.6, 26.6, 26.4, 19.2, 18.7, −3.2, −3.5. HRMS (ESI) calculated for C$_{17}$H$_{36}$OSi Na$^+$ [M + Na]$^+$ 307.2428, found 307.2423.
3.2.8. Synthesis of \((4S,6R)-6-(\text{tert-butyldimethylsilyl})oxy\)-4,7,7-trimethyloctan-1-ol (14)

The product 14 was synthesised according to the procedures for the synthesis of 11 from 13 (2.58 g, 9.08 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 10:1) to afford alcohol 14 (2.33 g, 85%) as a colorless oil. TLC: \(R_f = 0.5\) (hexanes/EtOAc = 4:1), PMA stain. \(\delta_{29}^{13}C = +11.1\) (c 0.01, CHCl₃). \(^1H\) NMR (400 MHz, CDCl₃) \(\delta = 3.62\) (td, \(J = 6.8, 1.1\) Hz, 2H), 3.29 (dd, \(J = 8.6, 1.7\) Hz, 1H), 1.65–1.48 (m, 4H), 1.36 (ddd, \(J = 14.0, 8.6, 2.8\) Hz, 1H), 1.25 (ddd, \(J = 7.3, 6.2, 2.5\) Hz, 1H), 1.25–1.12 (m, 2H), 0.89 (s, 9H), 0.84 (d, \(J = 7.3\) Hz, 3H), 0.83 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). \(^{13}C\) NMR (100 MHz, CDCl₃) \(\delta = 78.6, 63.5, 41.0, 35.7, 34.7, 30.5, 29.3, 26.6, 26.4, 19.4, 18.7, -3.1, -3.5\). HRMS (ESI) calculated for \(C_{17}H_{38}O_2SiNa^+\) [M + Na]⁺ 325.2533, found 325.2534.

3.2.9. Synthesis of \((4S,6R)-6-(\text{tert-butyldimethylsilyl})oxy\)-4,7,7-trimethyloctanol (15)

The product 15 was synthesised according to the procedures for the synthesis of 12 from 14 (2.0 g, 6.6 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 20:1) to afford aldehyde 15 (1.68 g, 85%) as a colorless oil. TLC: \(R_f = 0.6\) (hexanes/EtOAc = 10:1), PMA stain. \(\delta_{29}^{13}C = +12.7\) (c 0.01, CHCl₃). \(^1H\) NMR (400 MHz, CDCl₃) \(\delta = 9.76\) (t, \(J = 1.8\) Hz, 1H), 3.29 (dd, \(J = 8.6, 1.7\) Hz, 1H), 2.51–2.30 (m, 2H), 1.68–1.43 (m, 3H), 1.35 (ddd, \(J = 13.9, 8.6, 2.5\) Hz, 1H), 1.20 (ddd, \(J = 14.0, 10.4, 1.8\) Hz, 1H), 0.88 (s, 9H), 0.85 (d, \(J = 6.1\) Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). \(^{13}C\) NMR (100 MHz, CDCl₃) \(\delta = 202.9, 78.4, 41.9, 40.7, 35.7, 30.5, 29.2, 26.5, 26.4, 19.2, 18.7, -3.2, -3.5\). HRMS (ESI) calculated for \(C_{17}H_{38}O_2SiNa^+\) [M + Na]⁺ 323.2377, found 323.2376.

3.2.10. Synthesis of \((6S,11R,13R,13)-\text{(tert-buty1)-2,2,3,6,11,15,15,16,16-decymethyl-4,14-dioxa-3,15-disilaheptadec-7-ene} (16)

To a cooled (−78 °C) stirring solution of sulfone 8 [44] (200 mg, 0.52 mmol, 1.2 eq.) in dry toluene (4 mL, 0.1 M), NaHMDS (2 M in THF; 0.26 mL, 0.52 mmol, 1.2 eq.) was added dropwise for 1 h, followed by a solution of aldehyde 12 (130 mg, 0.43 mmol, 1.0 eq.) in dry toluene (2 mL, 0.22 M). The reaction mixture was stirred at −78 °C for 3 h and then quenched with a saturated aqueous solution of NH₄Cl (10 mL). The layers were separated and the aqueous layer was extracted with MTBE (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 100:1) to afford olefin 16 (149 mg, 74%) as a colorless oil. TLC: \(R_f = 0.5\) (hexanes/EtOAc = 80:1), iodine and PMA stain. \(\delta_{29}^{13}C = +15.8\) (c 0.01, CHCl₃). \(^1H\) NMR (400 MHz, CDCl₃ as a mixture of \(Z/E = 3:1\)) \(\delta = 5.53–5.27\) (m) and 5.14 (ddt, \(J = 11.0, 9.5, 1.6\) Hz, 2H), 3.47 (ddd, \(J = 9.7, 6.0, 4.9\) Hz, 1H), 3.35 (ddd, \(J = 9.8, 7.3, 5.3\) Hz, 1H), 3.30 (dd, \(J = 7.1, 2.9\) Hz, 1H), 2.69–2.54 (m) and 2.33–2.21 (m), 2.21–2.08 (m, 1H), 2.12–1.98 (m, 1H), 2.02–1.86 (m, 1H), 1.64–1.51 (m, 1H), 1.52–1.37 (m, 2H), 1.42–1.12 (m, 1H), 1.09–0.97 (m, 1H), 0.97 (d, \(J = 6.8\) Hz) and 0.96 (d, \(J = 6.7\) Hz), 3H), 0.92 (d, \(J = 6.6\) Hz, 3H), 0.90 (m, 18H), 0.85 (s, 9H), 0.89 (m, 12H). \(^{13}C\) NMR (100 MHz, CDCl₃) \(\delta = 132.8, 132.6, 130.5, 130.4, 78.7, 78.6, 68.5, 68.2, 41.9, 41.8, 39.5, 36.7, 36.3, 36.0, 35.0, 30.2, 30.0, 29.7, 26.5, 25.6, 26.4, 26.2, 25.1, 20.9, 20.8, 18.7, 18.6, 17.7, 16.9, -3.2, -3.7, -5.1, -5.1. HRMS (ESI) calculated for \(C_{27}H_{54}O_2Si_2Na^+\) [M + Na]⁺ 493.3869, found 493.3869.

3.2.11. Synthesis of \((2S,7R,9R)-2,7,10,10\text{-tetramethylundecane-1,9-diol} (17)

To a solution of alkene 16 (149 mg, 0.317 mmol, 1.0 eq.) in anaerobic MeOH (10 mL, 0.03 M), PdCl₂ (17 mg, 0.095 mmol, 0.3 eq.) was added under an argon atmosphere. The reaction flask was evacuated and purged with H₂ three times and then the reaction was stirred at ambient temperature under a hydrogen atmosphere for 10 h. The reaction flask was then evacuated and purged with nitrogen three times. The catalyst was removed via filtration through Celite. The filter cake was rinsed thoroughly with MeOH and the filtrate...
was concentrated in vacuo to provide the crude product. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 3:1) to afford diol 17 (39 mg, 50%) as a colorless oil. TLC: Rf = 0.3 (hexanes/EtOAc = 3:1), PMA stain.

\alpha_D^{19} = +26.0 (c 0.01, CHCl_3). \H NMR (500 MHz, CDCl_3) \delta 3.48 (dd, J = 10.5, 5.8 Hz, 1H), 3.42 (dd, J = 10.5, 6.3 Hz, 1H), 3.28 (dd, J = 10.2, 1.8 Hz, 1H), 1.65–1.57 (m, 3H), 1.45–1.39 (m, 2H), 1.38–1.33 (m, 3H), 1.25–1.19 (m, 3H), 1.18–1.14 (m, 1H), 1.11–1.05 (m, 1H), 1.03–0.99 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H) 0.87 (s, 9H). 13C NMR (125 MHz, CDCl_3) \delta 77.7, 68.4, 39.4, 35.9, 35.4, 35.1, 33.2, 29.9, 27.4, 27.1, 25.8, 21.2, 16.8. HRMS (ESI) calculated for C_{15}H_{32}O_2Na^+ [M + Na]^+ 267.2295, found 267.2293.

3.2.12. Synthesis of (2S,7R,9R)-9-hydroxy-2,7,10,10-tetramethylundecanoic acid (S14)

To a solution of diol 17 (53 mg, 0.217 mmol, 1.0 eq.) in DCM (3 mL, 0.07 M), TEMPO (7 mg, 0.043 mmol, 0.2 eq.), H_2O (0.2 mL, 11.0 mmol, 50 eq.) and Ph_3OAc (175 mg, 0.54 mmol, 2.5 eq.) were sequentially added and stirred at room temperature for 20 h before it was quenched with saturated aqueous solution of Na_2SO_3 (3 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 10:1–5:1) to afford the corresponding acid S14 (51 mg, 90%) as a colorless oil. TLC: Rf = 0.4 (hexanes/EtOAc = 3:1), PMA stain. \alpha_D^{22} = +20.6 (c 0.01, CHCl_3).

\H NMR (400 MHz, CDCl_3) \delta 3.29 (dd, J = 10.3, 1.8 Hz, 1H), 2.52–2.36 (m, 1H), 1.77–1.64 (m, 1H), 1.67–1.57 (m, 1H), 1.49–1.37 (m, 2H), 1.40–1.27 (m, 4H), 1.25–1.13 (m, 2H), 1.16 (d, J = 7.0 Hz, 3H), 1.08–0.95 (m, 1H), 0.91 (d, J = 6.7 Hz, 3H), 0.87 (s, 9H). 13C NMR (100 MHz, CDCl_3) \delta 182.7, 77.8, 39.5, 39.3, 35.2, 35.0, 33.6, 29.8, 27.5, 26.7, 25.7, 21.1, 17.1. HRMS (ESI) calculated for C_{15}H_{30}O_2Na^+ [M + Na]^+ 281.2087, found 281.2091.

3.2.13. Synthesis of (2S,7R,9R)-N-allyl-9-hydroxy-2,7,10,10-pentamethylundecanamide (18)

To a solution of acid S14 (39 mg, 0.15 mmol, 1.0 eq.) and N-allylmethylamine (29 \muL, 0.30 mmol, 2.0 eq.) in dry DCM (2 mL, 0.08 M), HOAt (41 mg, 0.30 mmol, 2.0 eq.), DMAP (56 mg, 0.46 mmol, 3.0 eq.) and EDCI (58 mg, 0.30 mmol, 2.0 eq.) were sequentially added at 0 °C. The reaction mixture was allowed to stir at room temperature for 12 h, quenched with saturated aqueous solution of NaHCO_3 (5 mL) and extracted with DCM (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 10:1) to afford the amide 18 (32 mg, 68%) as a colorless oil. TLC: Rf = 0.4 (hexanes/EtOAc = 2:1), iodine and PMA stain.

\alpha_D^{22} = +26.0 (c 0.01, CHCl_3). \H NMR (400 MHz, CDCl_3) \delta 5.82–5.66 (m, 1H), 5.24–5.04 (m, 2H), 4.07–3.94 (m, 1H), 3.94–3.90 (m, 1H), 3.34–3.20 (m, 1H), 2.97 and 2.91 (s, 3H), 2.74–2.52 (m, 1H), 1.87 (s, 1H), 1.78–1.66 (m, 1H), 1.65–1.55 (m, 1H), 1.51–1.40 (m, 1H), 1.36–1.32 (m, 1H), 1.32–1.29 (m, 1H), 1.29–1.26 (m, 1H), 1.26–1.21 (m, 2H), 1.21–1.19 (m, 1H), 1.18–1.12 (m, 1H), 1.09 and 1.08 (d, J = 6.7 Hz), 3H), 1.04–0.92 (m, 1H), 0.89 and 0.89 (d, J = 6.7 Hz), 3H), 0.87 (s, 9H). 13C NMR (100 MHz, CDCl_3) as a 1:1 mixture of two major conformers) \delta 177.3 and 176.6, 133.4, 138.2, 133.1, 117.0 and 116.6, 77.4, 52.2 and 50.3, 39.5 and 39.5, 36.0 and 35.8, 35.1 and 35.0, 34.9 and 34.8, 34.4, 34.1 and 34.0, 29.5 and 29.5, 27.7 and 27.7, 26.8 and 26.8, 25.8 and 25.8, 21.2 and 21.2, 18.4 and 17.8. HRMS (ESI) calculated for C_{39}H_{77}NO_2Na^+ [M + Na]^+ 334.2717, found 334.2717.

3.2.14. Synthesis of (3R,5R,10S)-11-(allyl(methyl)amino)-2,2,5,10-tetramethyl-11-oxoundecan-3-yl acrylate (19)

To a solution of alcohol 18 (32 mg, 0.1 mmol, 1.0 eq.) in dry DCM (2 mL, 0.05 M), Et_3N (69 \muL, 0.5 mmol, 5.0 eq.), DMAP (2.4 mg, 0.02 mmol, 0.2 eq.) and acryloyl chloride (24 \muL, 0.3 mmol, 3.0 eq.) were sequentially added at 0 °C. The reaction mixture was allowed to stir at room temperature for 12 h, quenched with water (1 mL) and extracted...
with DCM (3 × 3 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 5:1) to afford ester 19 (33 mg, 90%) as a colorless oil. TLC: Rf = 0.4 (hexanes/EtOAc = 3:1), iodine and PMA stain. δH = +23.6 (c 0.01, CHCl3). 1H NMR (400 MHz, CDCl3 as a 1:1 mixture of two major conformers) δ 6.37 (dd, J = 17.3, 1.6 Hz, 1H), 6.11 (dd, J = 17.3, 10.4 Hz, 1H), 5.80 (dd, J = 10.4, 1.6 Hz, 1H), 5.80–5.66 (m, 1H), 5.26–5.04 (m, 2H), 4.88 (ddd, J = 7.9, 4.3, 1.1 Hz, 1H), 4.06–3.95 (m, 1H), 3.98–3.89 (m, 1H), (2.97 and 2.92 (s, 3H)), 2.75–2.52 (m, 1H), 1.71–1.58 (m, 1H), 1.51–1.36 (m, 3H), 1.37–1.23 (m, 3H), 1.27–1.10 (m, 3H), (1.09 and 1.08 (d, J = 6.5 Hz, 3H)), 1.06–0.94 (m, 1H), 0.88 (s, 9H), (0.85 and 0.84 (d, J = 6.5 Hz, 3H)). 13C NMR (100 MHz, CDCl3 as a 1:1 mixture of two major conformers) δ 177.4 and 176.7, 166.2, 133.5 and 133.2, 130.3, 129.1, 117.0 and 116.6, 79.2, 52.2 and 50.2, 37.3, 35.7, 35.7, 35.0, 34.8 and 34.7, 34.4 and 34.0, 29.8, 28.1 and 28.1, 27.0 and 27.0, 26.0, 20.9, 18.24 and 17.6. HRMS (ESI) calculated for C22H35NO3Na+ [M + Na]+ 388.2822, found 388.2822.

3.2.15. Synthesis of (2S,7R,9R)-laingolide A (1a)

To a solution of diene 19 (33 mg, 0.009 mmol, 1.0 eq.) in DCE (90 mL, 0.001 M) at room temperature, second-generation Grubbs catalyst (G-II) (7.6 mg, 0.009 mmol, 0.1 eq.) was added. The reaction mixture was heated at 80 °C for 24 h and then a second portion of G-II (7.6 mg, 0.009 mmol, 0.1 eq.) was added. The reaction mixture was kept at 80 °C, stirred for another 24 h and then concentrated under reduced pressure. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 5:1) to afford an inseparable mixture of the desired product S15 and a minor unidentified byproduct as a white solid.

To a solution of the above mixture of S15 and a minor unidentified byproduct in degassed dry toluene (1 mL) under argon, a solution of RuH(PPh3)2(CO)Cl (8.6 mg, 0.009 mmol, 0.1 eq.) was added. The reaction mixture was heated to reflux for 24 h, cooled to room temperature, then concentrated under reduced pressure to provide the crude product. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 5:1) to afford (2S,7R,9R)-laingolide A (1a) (13.6 mg, 45% for two steps) as a white solid. TLC: Rf = 0.6 (hexanes/EtOAc = 2:1), UV and PMA stain. δH = +301 (c 0.01, MeOH). 1H NMR (400 MHz, CDCl3) δ 6.76 (d, J = 13.8 Hz, 1H), 5.21 (ddd, J = 13.8, 9.4, 6.0 Hz, 1H), 4.94 (ddd, J = 11.1, 2.5 Hz, 1H), 3.17–3.08 (m, 1H), 3.11 (s, 3H), 2.98 (ddd, J = 16.0, 9.5, 0.8 Hz, 1H), 2.86–2.72 (m, 1H), 1.80–1.63 (m, 2H), 1.59–1.52 (m, 1H), 1.46–1.40 (m, 1H), 1.40–1.33 (m, 2H), 1.32–1.27 (m, 2H), 1.25–1.17 (m, 2H), 1.15 (d, J = 6.5 Hz, 3H), 0.96–0.91 (m, 1H), 0.89 (d, J = 6.8 Hz, 3H), 0.88 (s, 9H). 13C NMR (100 MHz, CDCl3) δ 176.3, 173.3, 133.4, 104.2, 77.9, 37.7, 37.1, 35.7, 35.4, 34.3, 34.2, 31.3, 30.5, 27.6, 27.4, 26.7, 20.1, 17.2. HRMS (ESI) calculated for C22H35NO3Na+[M + Na]+ 360.2509, found 360.2510.

3.2.16. Synthesis of (6R,11R,13R,Z)-13-(tert-butyl)-2,2,3,3,6,11,15,15,16,16-decamethyl-4,14-dioxa-3,15-disilaheptadec-7-ene (20)

Product 20 was synthesised according to the procedures for the synthesis of 16 from 12 (910 mg, 3.0 mmol, 1.0 eq.) and sulfone ent-8 (1.4 g, 3.6 mmol, 1.2 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 100:1) to afford 20 (998 mg, 70%) as a colorless oil. TLC: Rf = 0.6 (hexanes/EtOAc = 80:1), iodine and PMA stain. δH = +1.10 (c 0.01, CHCl3). 1H NMR (400 MHz, CDCl3 as a mixture of Z/E = 3:1) δ 5.50–5.26 (m and 5.14 (ddd, J = 10.9, 9.4, 1.5 Hz) 2H), 3.55–3.42 (m, 1H), 3.41–3.31 (m, 1H), 3.34–3.27 (m, 1H), (2.78–2.54 (m and 2.37–2.20 (m, 1H), 2.22–2.03 (m, 1H), 2.07–1.94 (m, 1H), 1.69–1.51 (m, 1H), 1.51–1.37 (m, 2H), 1.26–1.13 (m, 1H), 1.10–0.98 (m, 1H), (0.96 (d, J = 6.7 Hz) and 0.96 (d, J = 6.7 Hz), 3H), 0.95–0.86 (m, 21H), 0.88–0.83 (m, 9H), 0.07–0.03 (m, 12H). 13C NMR (100 MHz, CDCl3) δ 132.8, 132.6, 130.5,
130.4, 78.7, 78.6, 68.5, 68.2, 41.9, 39.5, 36.7, 36.4, 36.0, 36.0, 35.0, 30.3, 30.0, 29.8, 26.6, 26.4, 26.2, 26.2, 25.7, 20.9, 18.7, 18.7, 18.6, 18.5, 17.7, 16.9, −3.2, −3.2, −3.7, −5.1, −5.1. HRMS (ESI) calculated for C_{27}H_{38}O_{2}Si_{2}Na^+ [M + Na]^+ 493.3869, found 493.3866.

3.2.17. Synthesis of (2R,7R,9R)-2,7,10,10-tetramethylundecane-1,9-diol (21)

Product 21 was synthesised according to the procedures for the synthesis of 17 from 20 (250 mg, 0.53 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 3:1) to afford 21 (59.5 mg, 46%) as a colorless oil. TLC: R_f = 0.3 (hexanes/EtOAc = 3:1), PMA stain. δ_{D}^{1}H NMR (500 MHz, CDCl_{3}) δ 3.47 (dd, J = 10.4, 5.9 Hz, 1H), 3.39 (dd, J = 10.5, 6.5 Hz, 1H), 3.26 (dd, J = 10.3, 1.8 Hz, 1H), 1.80 (s, 2H), 1.72–1.51 (m, 2H), 1.47–1.35 (m, 2H), 1.37–1.21 (m, 5H), 1.21–1.06 (m, 2H), 1.01 (dd, J = 18.2, 9.5, 3.4 Hz, 1H), 0.91 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H), 0.86 (s, 9H). 13C NMR (125 MHz, CDCl_{3}) δ 77.7, 68.4, 39.5, 35.8, 35.5, 35.0, 33.2, 30.0, 27.2, 27.1, 25.8, 21.1, 16.6. HRMS (ESI) calculated for C_{15}H_{32}O_{2}Na^+ [M + Na]^+ 267.2295, found 267.2293.

3.2.18. Synthesis of (2R,7R,9R)-9-hydroxy-2,7,10,10-tetramethylundecanoic acid (S16)

Product S16 was synthesised according to the procedures for the synthesis of S14 from 21 (258 mg, 1.06 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 10:1–5:1) to afford S16 (246 mg, 90%) as a colorless oil. TLC: R_f = 0.4 (hexanes/EtOAc = 3:1), PMA stain. δ_{D}^{1}H NMR (400 MHz, CDCl_{3}) δ 3.28 (dd, J = 10.3, 1.8 Hz, 1H), 2.53–2.32 (m, 1H), 1.82–1.56 (m, 2H), 1.49–1.37 (m, 2H), 1.39–1.17 (m, 5H), 1.21–1.13 (m, 1H), 1.16 (d, J = 6.9 Hz, 3H), 1.09–0.95 (m, 1H), 0.91 (d, J = 6.7 Hz, 3H), 0.87 (s, 9H). 13C NMR (100 MHz, CDCl_{3}) δ 182.8, 77.9, 39.5, 39.3, 35.4, 35.0, 33.7, 30.0, 27.6, 26.8, 25.8, 21.1, 16.9. HRMS (ESI) calculated for C_{15}H_{30}O_{3}Na^+ [M + Na]^+ 281.2087, found 281.2088.

3.2.19. Synthesis of (2R,7R,9R)-N-allyl-9-hydroxy-N,2,7,10,10-pentamethylundecanamide (22)

Product 22 was synthesised according to the procedures for the synthesis of 18 from S16 (105 mg, 0.4 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 3:1) to afford 22 (83.4 mg, 67%) as a colorless oil. TLC: R_f = 0.4 (hexanes/EtOAc = 2:1), iodine and PMA stain. δ_{D}^{1}H NMR (400 MHz, CDCl_{3}) δ 3.18 (dd, J = +27.7 (c 0.01, CHCl_{3}). δ_{D}^{1}H NMR (400 MHz, CDCl_{3}) δ 0.01, CHCl_{3}). 1H NMR (400 MHz, CDCl_{3}) δ 6.40–5.59 (m, 1H), 5.26–4.94 (m, 2H), 4.14–3.94 (m, 1H), 3.97–3.88 (m, 1H), 3.26 (dd, J = 10.2, 1.7 Hz, 1H), 2.97 and 2.92 (s, 3H), 2.79–2.48 (m, 1H), 1.80–1.55 (m, 3H), 1.44–1.28 (m, 3H), 1.29–1.25 (m, 1H), 1.24 (s, 1H), 1.22–1.12 (m, 3H), 1.00–0.95 (m, 1H), 0.91 and 0.90 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H). 13C NMR (100 MHz, CDCl_{3}) δ 177.3 and 176.7, 133.4 and 133.2, 117.0 and 116.6, 77.7, 52.1 and 50.2, 39.4, 35.9 and 35.7, 35.6, 35.0, 34.8 and 34.5, 34.2 and 34.0, 30.1 and 30.1, 28.1 and 28.1, 27.1 and 27.0, 25.8 and 25.8, 21.2, 18.2 and 17.6. HRMS (ESI) calculated for C_{19}H_{39}NO_{2}Na^+ [M + Na]^+ 334.2717, found 334.2718.

3.2.20. Synthesis of (3R,5R,10R)-11-(allyl(methylamino)-2,2,5,10-tetramethylundecan-3-yl acrylate (23)

Product 23 was synthesised according to the procedures for the synthesis of 19 from 22 (63 mg, 0.2 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 5:1) to afford 23 (64.3 mg, 88%) as a colorless oil. TLC: R_f = 0.4 (hexanes/EtOAc = 3:1), iodine and PMA stain. δ_{D}^{1}H NMR (400 MHz, CDCl_{3}) δ 6.67 (dd, J = 17.3, 1.6 Hz, 1H), 6.11 (dd, J = 17.3, 10.4 Hz, 1H), 5.80 (dd, J = 10.4, 1.6 Hz, 1H), 5.79–5.66 (m, 1H), 5.27–5.04 (m, 2H), 4.94–4.82 (m, 1H), 4.06–3.95 (m, 1H), 3.97–3.84 (m, 1H), 2.97 and 2.91 (s, 3H), 2.76–2.52 (m, 1H), 1.71–1.58 (m, 1H), 1.41 (dd, J = 7.2, 5.6, 1.9 Hz, 2H), 1.39–1.26 (m, 1H), 1.27–1.16 (m, 5H), 1.10 and 1.08 (d, J = 6.7 Hz, 1H), 1.06–0.95 (m, 9H), 0.88 (s, 9H), 0.85 and 0.84 (d, J = 6.5 Hz, 3H). 13C NMR (100 MHz, CDCl_{3} as a 1:1 mixture

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of two major conformers) \( \delta 177.4 \) and 176.7, 166.3, 133.5 and 133.2, 130.3, 129.1, 117.0 and 116.6, 79.2, 52.2 and 50.2, 37.2, 35.9 and 35.7, 35.5 and 35.0, 34.8 and 34.6, 34.3, 33.9, 29.7 and 29.7, 28.0 and 28.0, 26.8 and 26.8, 26.0, 20.9, 18.2 and 17.6. HRMS (ESI) calculated for \( \text{C}_{22} \text{H}_{35} \text{NO}_3 \text{Na}^+ \) [M + Na\(^+\)] found 388.2822, found 388.2822.

3.2.21. Synthesis of (2R,7R,9R)-laingolide A (1b)

Product S17 was synthesised according to the procedures for the synthesis of S15 from 23 (10.3 mg, 0.027 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 100:1) to afford an inseparable mixture of the desired product S17 and a minor unidentified byproduct (9 mg) as a white solid.

(2R,7R,9R)-laingolide A (1b) was synthesised according to the procedures for the synthesis of (2S,7S,9R)-laingolide A (1a) from the above mixture of S17 and a minor unidentified byproduct. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 3:1) to afford product 24 (235 mg, 0.5 mmol, 1.0 eq). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 100:1) to afford 24 (831 mg, 68%) as a colorless oil. TLC: \( R_f \) 0.6 (hexanes/EtOAc = 2:1), UV and PMA stain.

Product 24 was synthesised according to the procedures for the synthesis of 16 from 15 (780 mg, 2.6 mmol, 1.0 eq.) and sulfone 8 (1.2 g, 3.1 mmol, 1.2 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 100:1) to afford 24 (831 mg, 68%) as a colorless oil. TLC: \( R_f \) 0.6 (hexanes/EtOAc = 80:1), iodine and PMA stain.

Product 24 was synthesised according to the procedures for the synthesis of 17 from 24 (235 mg, 0.5 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 3:1) to afford 25 (55 mg, 45%) as a colorless oil. TLC: \( R_f \) 0.3 (hexanes/EtOAc = 3:1), PMA stain.

Product 25 was synthesised according to the procedures for the synthesis of 17 from 24 (235 mg, 0.5 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 3:1) to afford 25 (55 mg, 45%) as a colorless oil. TLC: \( R_f \) 0.3 (hexanes/EtOAc = 3:1), PMA stain.
3.2.24. Synthesis of (2S,7S,9R)-9-hydroxy-2,7,10,10-tetramethylundecanoic acid (S18)

Product S18 was synthesised according to the procedures for the synthesis of S14 from 25 (50 mg, 0.21 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 10:1–5:1) to afford S18 (47.8 mg, 91%) as a colorless oil. TLC: Rf = 0.4 (hexanes/EtOAc = 3:1), PMA stain. δD = +13.8 (c 0.01, CHCl3).

1H NMR (500 MHz, CDCl3) δ 3.29 (dd, J = 10.6, 1.7 Hz, 1H), 2.52–2.35 (m, 1H), 1.72–1.64 (m, 1H), 1.64–1.56 (m, 1H), 1.47–1.39 (m, 1H), 1.35–1.28 (m, 5H), 1.26–1.23 (m, 1H), 1.23–1.10 (m, 2H), 1.16 (d, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.86 (d, J = 6.6 Hz, 3H). 13C NMR (125 MHz, CDCl3) δ 182.6, 77.6, 39.5, 38.9, 38.3, 34.9, 33.7, 29.5, 27.4, 27.0, 25.8, 19.1, 17.0. HRMS (ESI) calculated for C15H30O3Na+ [M + Na]+ 281.2087, found 281.2087.

3.2.25. Synthesis of (2S,7S,9R)-N-allyl-9-hydroxy-N,2,7,10,10-pentamethylundecanamide (26)

Product 26 was synthesised according to the procedures for the synthesis of 18 from S18 (47.8 mg, 0.182 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 3:1) to afford an inseparable mixture of the desired product (28 mg, 91%) as a white solid. TLC: Rf = 0.4 (hexanes/EtOAc = 3:1), iodine and PMA stain.

1H NMR (500 MHz, CDCl3) δ 3.29 (dd, J = 10.5 Hz, 1H), 2.96 and 2.90 (s, 3H), 2.73–2.51 (m, 1H), 1.74–1.62 (m, 1H), 1.61–1.55 (m, 1H), 1.40–1.27 (m, 3H), 1.27–1.18 (m, 5H), 1.17–1.10 (m, 2H), 1.09 and 1.07 (d, J = 6.9 Hz, 3H), 0.86 (s, 9H). 13C NMR (125 MHz, CDCl3) δ 177.3 and 176.6, 133.4 and 133.2, 117.0 and 116.6, 77.3, 52.1 and 50.2, 39.0, 38.4 and 35.9, 34.9 and 34.8, 34.5 and 34.2, 33.9, 29.7, 28.0 and 27.9, 27.3, 25.8, 19.0, 18.2 and 17.6. HRMS (ESI) calculated for C19H37NO2Na+ [M + Na]+ 334.2717, found 334.2721.

3.2.26. Synthesis of (3R,5S,10S)-11-(allyl(methyl)amino)-2,2,5,10-tetramethyl-11-oxoundecan-3-yl acrylate (27)

Product 27 was synthesised according to the procedures for the synthesis of 19 from 26 (116 mg, 0.372 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 3:1) to afford 27 (115 mg, 85%) as a colorless oil. TLC: Rf = 0.4 (hexanes/EtOAc = 3:1), iodine and PMA stain. δD = +8.8 (c 0.01, CHCl3).

1H NMR (400 MHz, CDCl3) δ 3.19 (m, 1H), 3.12–3.03 (m, 1H), 2.52–2.35 (m, 1H), 1.72–1.64 (m, 1H), 1.58–1.52 (m, 1H), 1.36–1.29 (m, 1H), 1.27–1.12 (m, 8H), 1.08 and 1.06 (d, J = 6.5 Hz, 3H), 0.86 (s, 12H). 13C NMR (100 MHz, CDCl3) δ 172.2 and 176.6, 166.3, 133.4 and 133.1, 130.4, 129.0, 117 and 116.6, 79.0, 52.1 and 50.2, 38.1 and 37.1, 35.9 and 35.7, 34.8 and 34.8, 34.5, 34.2, 33.9, 29.5, 27.9 and 27.9, 27.2, 26.1, 19.3, 18.2 and 17.6. HRMS (ESI) calculated for C23H39NO3Na+ [M + Na]+ 388.2822, found 388.2824.

3.2.27. Synthesis of (2S,7S,9R)-laingolide A (1c)

Product S19 was synthesised according to the procedures for the synthesis of S15 from 27 (28 mg, 0.077 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 5:1) to afford an inseparable mixture of the desired product S19 and a minor unidentified byproduct (20 mg) as a white solid.

(2S,7S,9R)-laingolide A (1c) was synthesised according to the procedures for the synthesis of (2S,7,9R)-laingolide A (1a) from the above mixture of S19 and a minor unidentified byproduct. Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 5:1) to afford (2S,7S,9R)-laingolide A (1c) (13 mg, 50% for two steps) as a white solid. TLC: Rf = 0.6 (hexanes/EtOAc = 2:1), UV and PMA stain. δD = +145.6 (c 0.01, CHCl3). 1H NMR (500 MHz, CDCl3) δ 7.02 (dd, J = 6.5 Hz, 3H), 2.96 and 2.90 (s, 3H), 2.72–2.46 (m, 1H), 1.74–1.11 (m, 1H), 1.58–1.52 (m, 1H), 1.36–1.29 (m, 1H), 1.27–1.12 (m, 8H), 1.08 and 1.06 (d, J = 6.5 Hz, 3H), 0.86 (s, 12H).
1.16 (d, J = 1.64–1.57 (m, 1H), 1.60–1.52 (m, 1H), 1.47–1.34 (m, 1H), 1.35–1.27 (m, 1H), 1.30–1.17 (m, 4H), 0.97 (d, J = 6.8 Hz) and 0.95 (d, J = 6.7 Hz), 3H), 0.85–0.82 (m, 12H), 0.04 (m, 12H). 13C NMR (100 MHz, CDCl3) δ 132.5, 130.5, 78.6, 68.2, 41.1, 39.0, 35.8, 35.0, 29.3, 26.6, 26.4, 26.1, 25.4, 19.2, 18.7, 18.5, 17.7, –3.1, –3.5, –5.1, –5.1. HRMS (ESI) calculated for C27H36O2Na+ [M + Na]+ 493.3869, found 493.3866.

3.2.29. Synthesis of (2R,7S,9R)-2,7,10,10-tetramethylundecane-1,9-diol (29)

Product 29 was synthesised according to the procedures for the synthesis of 17 from 28 (250 mg, 0.53 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 3:1) to afford 29 (60.8 mg, 47%) as a colorless oil. TLC: Rf = 0.3 (hexanes/EtOAc = 3:1), PMA stain. αD00 = +8.4 (c 0.01, CHCl3). 1H NMR (500 MHz, CDCl3) δ 1.25 (d, J = 10.6, 5.8, 1.7 Hz, 1H), 1.35 (d, J = 10.5, 6.5, 1.9 Hz, 1H), 2.14–2.10 (m, 2H), 1.30–1.19 (m, 5H), 0.87 (d, J = 6.7 Hz, 3H), 0.85–0.82 (m, 12H). 13C NMR (100 MHz, CDCl3) δ 77.3, 68.2, 39.0, 38.4, 34.9, 33.2, 29.6, 27.4, 27.3, 25.8, 19.0, 16.7. HRMS (ESI) calculated for C15H32O2Na+ [M + Na]+ 267.2295, found 267.2295.

3.2.30. Synthesis of (2R,7S,9R)-9-hydroxy-2,7,10,10-tetramethylundecanoic acid (S20)

Product S20 was synthesised according to the procedures for the synthesis of S14 from S19 (112 mg, 0.46 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 10:1–5:1) to afford S20 (108 mg, 91%) as a colorless oil. TLC: Rf = 0.4 (hexanes/EtOAc = 3:1), PMA stain. αD00 = +8.4 (c 0.01, CHCl3). 1H NMR (500 MHz, CDCl3) δ 3.29 (dd, J = 10.6, 1.7 Hz, 1H), 2.51–2.37 (m, 1H), 1.78–1.57 (m, 2H), 1.46–1.38 (m, 1H), 1.36–1.28 (m, 5H), 1.28–1.23 (m, 1H), 1.22–1.18 (m, 1H), 1.16 (d, J = 6.9 Hz, 3H), 1.16–1.13 (m, 1H), 0.88 (s, 9H), 0.86 (d, J = 6.5 Hz, 3H). 13C NMR (125 MHz, CDCl3) δ 182.7, 77.6, 39.5, 39.0, 38.2, 34.9, 33.7, 29.6, 27.5, 20.5, 25.8, 19.0, 17.1. HRMS (ESI) calculated for C15H32O2Na+ [M + Na]+ 281.2087, found 281.2087.

3.2.31. Synthesis of (2R,7S,9R)-N-allyl-9-hydroxy-N,2,7,10,10-pentamethylundecanamide (30)

Product 30 was synthesised according to the procedures for the synthesis of 18 from S20 (116 mg, 0.45 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 3:1) to afford 30 (105 mg, 75%) as a colorless oil. TLC: Rf = 0.4 (hexanes/EtOAc = 2:1), iodine and PMA stain. αD00 = +2.8 (c 0.01, CHCl3). 1H NMR (400 MHz, CDCl3) as a 1:1 mixture of two major conformers δ 5.97–5.56 (m, 1H), 5.30–5.00 (m, 2H), 4.04–3.92 (m, 1H), 3.93 (dt, J = 4.9, 1.8 Hz, 1H), 3.27 (dt,
$J = 10.3, 1.4$ Hz, 1H), $2.97$ and $2.92$ (s, 3H)), $2.79$–$2.43$ (m, 1H), $1.79$–$1.53$ (m, 3H), $1.38$–$1.23$ (m, 6H), $1.21$–$1.13$ (m, 3H), $1.10$ and $1.08$ (d, $J = 6.8$ Hz, 3H)), $0.87$ (s, 9H), $0.85$ (d, $J = 6.5$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) as a 1:1 mixture of two major conformers $\delta$ $177.3$ and $176.6$, $133.4$ and $133.2$, $117.0$ and $116.6$, $77.4$, $52.2$ and $50.2$, $39.1$, $38.4$ and $38.3$, $35.9$ and $35.7$, $34.9$ and $34.8$, $34.5$ and $34.3$, $33.9$, $29.6$, $27.9$ and $27.9$, $27.3$, $25.8$, $19.0$, $18.3$ and $17.7$. HRMS (ESI) calculated for C$_{19}$H$_{37}$NO$_3$Na$^+$ [M + Na]$^+$ 334.2717, found 334.2716.

3.2.32. Synthesis of (3R,5S,10R)-11-(allyl(methyl)amino)-2,2,5,10-tetramethyl-11-oxoundecan-3-yl acrylate (31)

Product 31 was synthesised according to the procedures for the synthesis of 19 from 30 (88 mg, 0.28 mmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 5:1) to afford 31 (88 mg, 86%) as a colorless oil. TLC: $R_f = 0.4$ (hexanes/EtOAc = 3:1), iodine and PMA stain. $\alpha_D^{27} = +12.1$ ($c$ 0.01, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) as a 1:1 mixture of two major conformers $\delta$ $6.38$ (dd, $J = 17.3$, $1.6$ Hz, 1H), $6.12$ (dd, $J = 17.3$, $10.4$ Hz, 1H), $5.80$ (dd, $J = 10.3$, $1.6$ Hz, 1H), $5.78$–$5.66$ (m, 1H), $5.33$–$5.04$ (m, 2H), $4.90$ (dd, $J = 11.0$, $1.2$ Hz, 1H), $4.16$–$3.94$ (m, 1H), $3.92$ (dt, $J = 4.9$, $1.8$ Hz, 1H), $2.96$ and $2.91$ (s, 3H)), $2.72$–$2.49$ (m, 1H), $1.92$–$1.46$ (m, 3H), $1.29$–$1.15$ (m, 8H), $1.09$ and $1.08$ (d, $J = 6.8$ Hz, 3H)), $0.88$ (s, 12H). $^{13}$C NMR (100 MHz, CDCl$_3$) as a 1:1 mixture of two major conformers $\delta$ $177.3$ and $176.6$, $166.4$, $133.4$ and $133.2$, $130.4$, $129.0$, $117.0$ and $116.6$, $79.0$, $52.1$ and $50.2$, $38.2$, $37.1$, $35.9$ and $35.7$, $34.9$ and $34.8$, $34.5$ and $34.3$, $33.9$, $29.5$, $28.0$ and $27.9$, $27.2$, $26.1$, $19.2$, $18.2$ and $17.6$. HRMS (ESI) calculated for C$_{22}$H$_{39}$NO$_3$Na$^+$ [M + Na]$^+$, found 388.2822, found 388.2821.

3.2.33. Synthesis of (2R,7S,9R)-laingolide A (1d)

Product 21 was synthesised according to the procedures for the synthesis of S15 from 31 (30.9 mg, 85 pmol, 1.0 eq.). Purification of the crude product was performed using flash chromatography on silica gel (hexanes/EtOAc = 5:1) to afford S15 (30.9 mg, 86%) as a white solid. TLC: $R_f = 0.4$ (hexanes/EtOAc = 3:1), iodine and PMA stain. $\alpha_D^{27} = -55.3$ ($c$ 0.01, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ $6.74$ (d, $J = 13.9$ Hz, 1H), $5.21$ (dd, $J = 13.9$, $8.6$, $6.3$ Hz, 1H), $4.86$ (dd, $J = 10.9$, $1.3$ Hz, 1H), $3.20$ (ddd, $J = 16.5$, $6.3$, $1.4$ Hz, 1H), $3.11$ (s, 3H), $3.07$ (ddd, $J = 16.5$, $8.7$, $1.0$ Hz, 1H), $2.68$ (dqd, $J = 12.9$, $6.6$, $4.4$ Hz, 1H), $1.63$–$1.50$ (m, 1H), $1.49$–$1.33$ (m, 3H), $1.29$–$1.25$ (m, 1H), $1.25$–$1.23$ (m, 2H), $1.22$–$1.16$ (m, 2H), $1.14$ (d, $J = 6.4$ Hz, 4H), $1.14$–$1.05$ (m, 1H), $0.88$ (s, 9H), $0.85$ (d, $J = 5.8$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ $176.6$, $171.9$, $132.6$, $106.8$, $80.5$, $38.7$, $37.5$, $36.2$, $35.6$, $35.0$, $33.7$, $32.2$, $26.9$, $26.6$, $25.3$, $24.9$, $18.9$, $16.6$. HRMS (ESI) calculated for C$_{20}$H$_{35}$NO$_3$Na$^+$ [M + Na]$^+$, found 360.2509, found 360.2513.

4. Conclusions

In summary, we have unambiguously established the relative and absolute configuration of laingolide A through the total synthesis of four diastereomers of the natural product. The key features of the convergent and fully stereocontrolled route included a copper-catalysed stereospecific Kumada-type coupling, a Julia-Kocienski olefination and an RCM/alkene migration sequence to access the desired macrocyclic enamide.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/md19050247/s1: initial approaches via the cross-metathesis and $^1$H- and $^{13}$C-NMR charts of all the compounds.
Author Contributions: F.W., Y.G. and T.Y. conceived and designed this research; F.W. and T.Z. prepared the compounds and collected their spectral data; F.W., J.Y. and Y.G. analysed the experimental data; Y.G. and T.Y. prepared the manuscript. All authors have read and agreed to the published version of the manuscript.

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