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A Ring Closing Metathesis Approach to the Formal Synthesis of (+)-Callyspongiolide

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Abstract

An enantioselective synthesis of macrocyclic core of (+)-callyspongiolide is described, constituting a formal synthesis of this natural product. The synthetic strategy constructs the 14-membered macrocyclic domain *via* Yamaguchi esterification followed by a challenging ring-closing metathesis (RCM) to effect the final formation of the macrolactone.

Introduction

Callyspongia are a genera of sea sponge organisms belonging to the Callyspongiidae family, which are commonly found to inhabit mesophonic reefs across the world's oceans.[1] Over the course of decades, sponges of this genus have provided the scientific community with a plethora of structurally unique and biologically active natural products, including polyketides,[2] polyacetylenes,[3,4] alkaloids,[5–7] terpenoids,[8,9] fatty acids,[10] sterols,[11,12] peroxides,[13] butenolides,[14] and cyclic peptides.[15–17] Many of these metabolites are shown to possess a wide range of biological activities including cytotoxic,[18] anticancer,[2] and antimicrobial and antifouling properties.[19] Amongst this diverse array of isolated natural products however, macrolides were unprecendented in this genus until the discovery of callyspongiolide. Isolated in 2013 by Lai and Proksch *et al.* from an Indonesian marine sponge *Callyspongia sp.*, callyspongiolide is a novel 14-membered macrolide with a unique conjugated yne-diene moiety (C14-C19) terminating with a brominated aromatic moiety.[20] Preliminary *in vitro* studies of callyspongiolide showed potent antiproliferative activities against human Jurkat J16 T and Ramos B lymphocytes with IC_{50} values of 70 nM and 60 nM, respectively. Notably, this cytotoxic activity of callyspongiolide did not diminish on parallel treatment with a caspase inhibitor, QVD-OPh, suggesting a caspase-independent mode of cell death. At the time of isolation, only the relative configuration of the macrocyclic core of this natural product was assigned, with the C21 stereocentre remaining undefined after comprehensive NMR studies (Figure 1.).

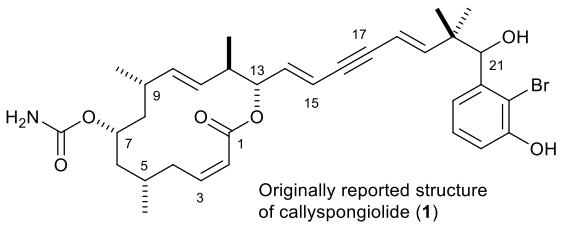

Figure 1. The originally reported structure of callyspongiolide showing relative stereochemistry.

At the onset of our work no syntheses of callyspongiolide had been reported, however in the intervening time the synthesis of callyspongiolide has attracted significant interest. Total syntheses of both C21 epimers (**1a** and **1b**) of the originally proposed callyspongiolide structure by the groups of Xu and Ye[21] and A. Ghosh[22,23] in 2016 enabled optical rotation and NMR comparisons with the published data to establish that structure **1a** in fact represented the unnatural (+)-callyspongiolide, allowing the natural product (-)-callyspongiolide to be assigned the structure **2** with the (*R*) configuration at C21. This structural revision was also confirmed by the successful synthesis of both C21 epimers of **2** by Xu and Ye *et al*[21] and subsequently A. Ghosh *et al.*[23] (Figure 2.).

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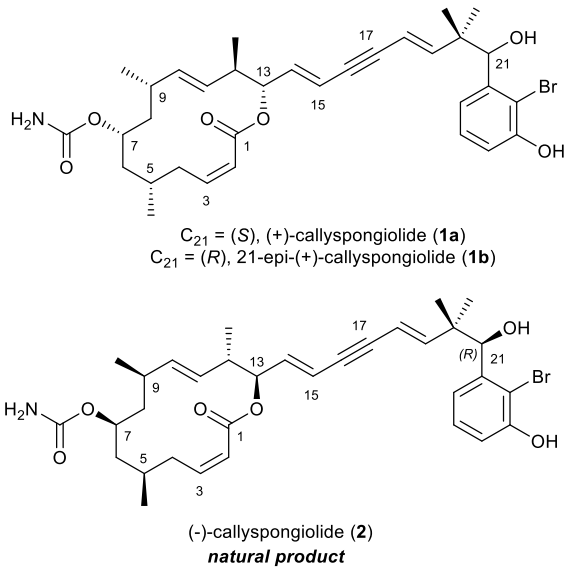

Figure 2. The structural revision of callyspongiolide.

Further total syntheses of (+)-callyspongiolide (**1a**) by Fürstner *et al*[24,25] and the natural enantiomer (-)-callyspongiolide (**2**) by Harran *et al.*[26] and S. Ghosh *et al.*[27] were reported in 2018. Partial syntheses of this natural product have also been reported, with the synthesis of the macrocyclic core of (+)-callyspongiolide (**1a**) by S. Ghosh[28] and the synthesis of the unsaturated side-chain of (-)-callyspongiolide (**2**) by Kotora[29] both reported in 2016, and a further synthesis of C3-C15 fragment of the macrocyclic core of (+)-callyspongiolide (**1a**) published by Mohapatra in 2018[30]. Meanwhile our research group has been working on the synthesis of (+)-callyspongiolide (**1**) (based on the original structural assignment) *via* a RCM approach since prior to any of these publications. While this manuscript was in preparation, Bosch and Amat reported a formal synthesis of (-)-callyspongiolide (**2**) using a low-yielding (16%) RCM to effect formation of the macrocycle[31]. Herein we report the full details of our formal synthesis of (+)-callyspongiolide (**1a**) *via* a RCM strategy, together with our broader investigations into the use of RCM on this molecule, which shed further light onto the low-yielding RCM macrocyclization step also observed in our synthesis.

Results/Discussion

Initial approach: RCM of a diene-yne intermediate

We focused our initial attention on the synthesis of the macrocyclic core of (+)-callyspongiolide (**1a**), with our formal synthesis target identified as di-protected macrocycle **3** based on the total synthesis of this molecule by A. Ghosh *et al.*.[22,23] Our approach to access macrocycle **3** hinged on the key RCM of diene-yne **4** and its subsequent *cis*-reduction. It was envisaged that Yamaguchi esterification of alcohol **5** and acid **6** could be used to synthesise the required macrocyclization precursor, **4** (

Scheme **1.**).

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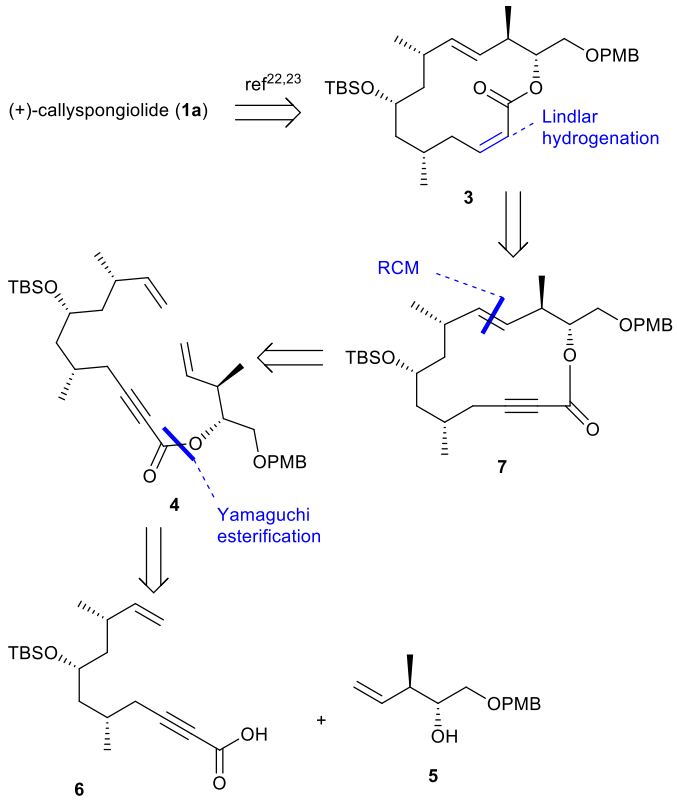
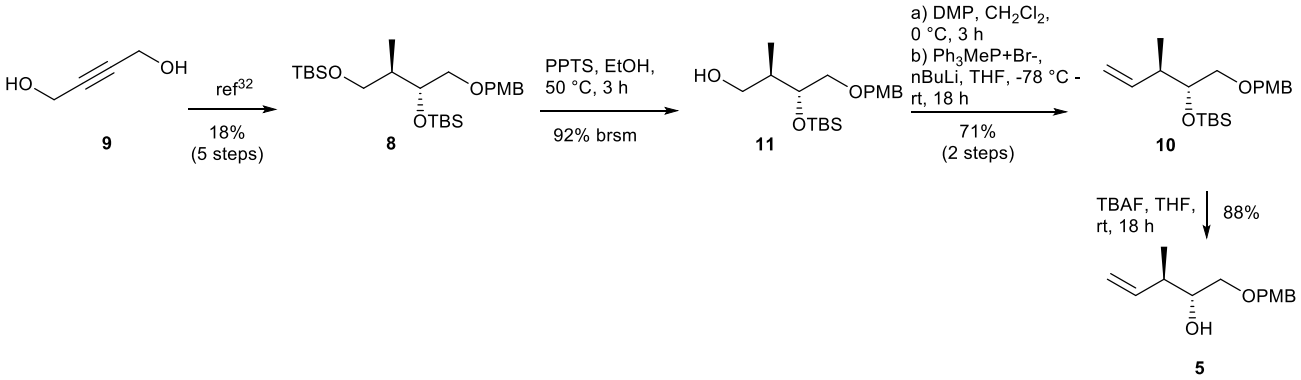


Scheme 1. Our initial synthetic approach to the synthesis of the macrocyclic core of (+)-callyspongiolide (**1**).

Initial attention focused on the synthesis of alcohol coupling partner **5** from bis-*tert*-butyldimethylsilyl (TBS) ether **8**, in turn synthesised from 1,4-butynediol **9** following the method reported by Crimmins and DeBaillie (see SI).[32] The terminal TBS group could be removed selectively in 57% yield (with 38% of **8** recovered) using pyridinium *para*-toluenesulfonate (PPTS). Oxidation to the aldehyde using Dess-Martin Periodinane (DMP), followed by olefination using methyltriphenyl phosphonium bromide gave alkene **10** in 71% yield, before deprotection of the remaining TBS group using *tert*-butylammonium fluoride (TBAF) to afford the desired alcohol coupling partner **5** (Scheme 2).



Scheme 2. Synthesis of alcohol coupling partner **5**.

As the synthesis of acid **6** was predicted to be challenging, it seemed prudent to establish the validity of our overall approach. Accordingly, synthesis of simplified racemic acid **12** and its coupling to alcohol **5** to give model RCM substrate **13** was investigated (Scheme 3.). 5-Hexyn-1-ol **14**, was oxidised to an aldehyde before addition of but-3-en-1-ylmagnesium bromide **15** to afford racemic alcohol **16**. Protection of the alcohol as a TBS ether allowed deprotonation and carbonylation of the alkyne to afford ester **17** in 75% yield. Base-mediated hydrolysis afforded model coupling partner, acid **12**. Yamaguchi esterification conditions were then utilised to couple alcohol **5** with acid **12**, affording model diene-yne **13** in 70% yield.

With model diene-yne **13** in hand, attention turned to the subsequent RCM step to form macrocycle **19**. A range of solvents, temperatures and catalyst loadings were attempted using Grubbs I and II and Hoveyda-Grubbs II catalyst, with

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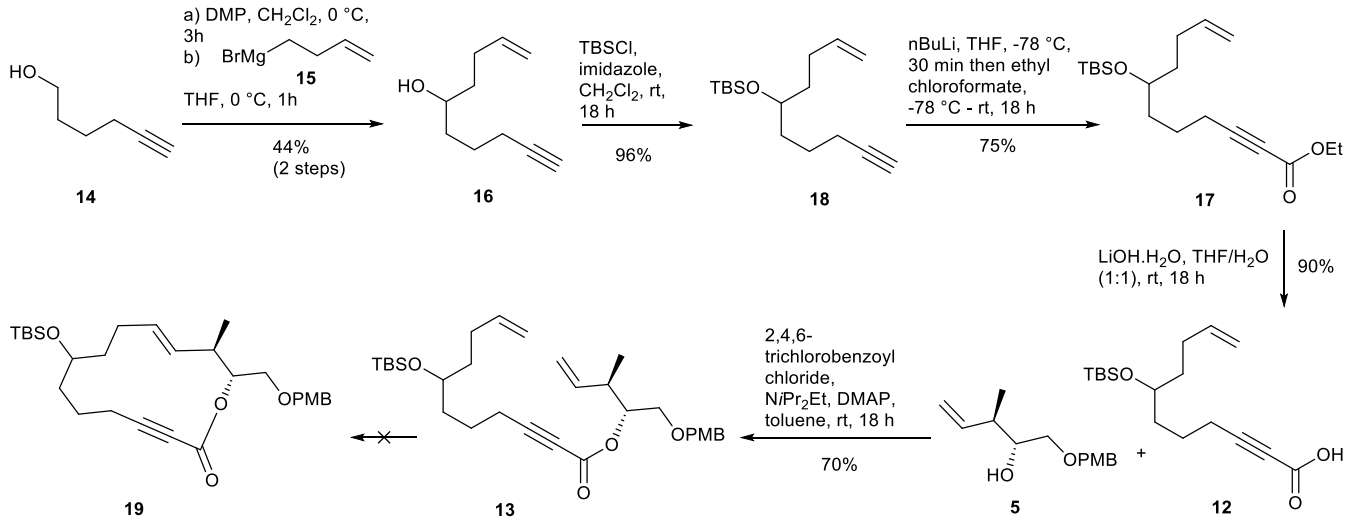
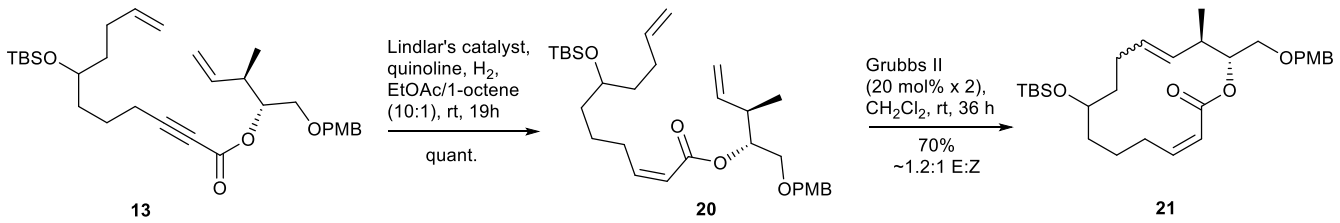
no evidence of the formation of desired product **19** being seen (See SI, Table S1.). When the reaction was carried out in toluene at 120 °C with both Grubbs II and Hoveyda-Grubbs II catalyst (entries 10 and 11, Table S1.), a trace amount of an undesired side product was formed in insufficient quantities to enable isolation and characterisation, otherwise **13** was recovered unchanged.



Scheme 3. Synthesis of model RCM substrate **13**.

It was reasoned that the presence of the conformationally rigid triple bond within the macrocyclic ring system significantly reduced the overall flexibility of diene **13**, thereby preventing the terminal alkenes from coming into close proximity to achieve successful metathesis. To test this hypothesis, the alkyne of **13** was successfuly reduced to the *Z* alkene **20** by hydrogenation over Lindlar catalyst. It was found that triene **20** successfully underwent RCM using Grubbs II catalyst in dichloromethane at room temperature to provide the model macrocycle **21** in 70% yield as a mixture of *E*/*Z* isomers (~1.2:1 ratio) at the newly formed alkene, supporting this as a more promising approach for our proposed synthesis of (+)-callyspongiolide (**1a**) (Scheme 4.).



Scheme 4. Synthesis of model triene **20** and its successful RCM to give model macrocycle **21**.

Revised approach: RCM of a triene intermediate

Given that our model studies had identified that the originally planned macrocyclization of alkyne-containing diene **4** was unlikely to be successful, our synthetic strategy was revised focusing on the RCM of triene **22**, accessed by coupling alcohol **5** with diene acid **23**. It was hoped that the presence of additional chiral methyl groups in **22** would favour formation of the desired *E* product from the RCM macrocyclisation step. It was envisaged that fully elaborated acid **23** could be synthesised by homo-crotylation of the aldehyde derived from protected alcohol **24** (Scheme 5.).

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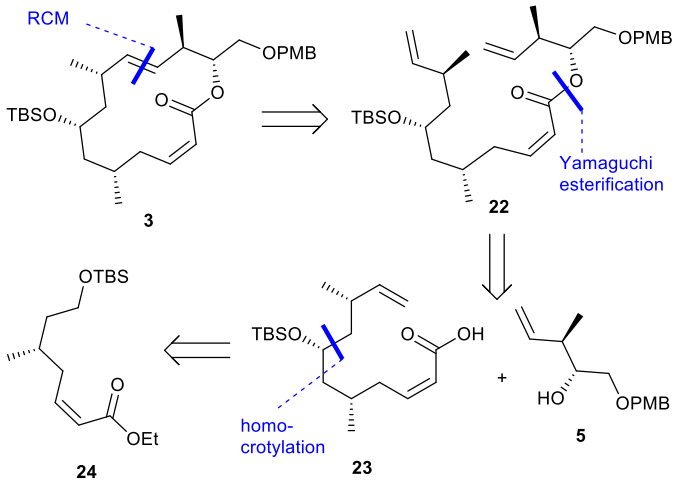
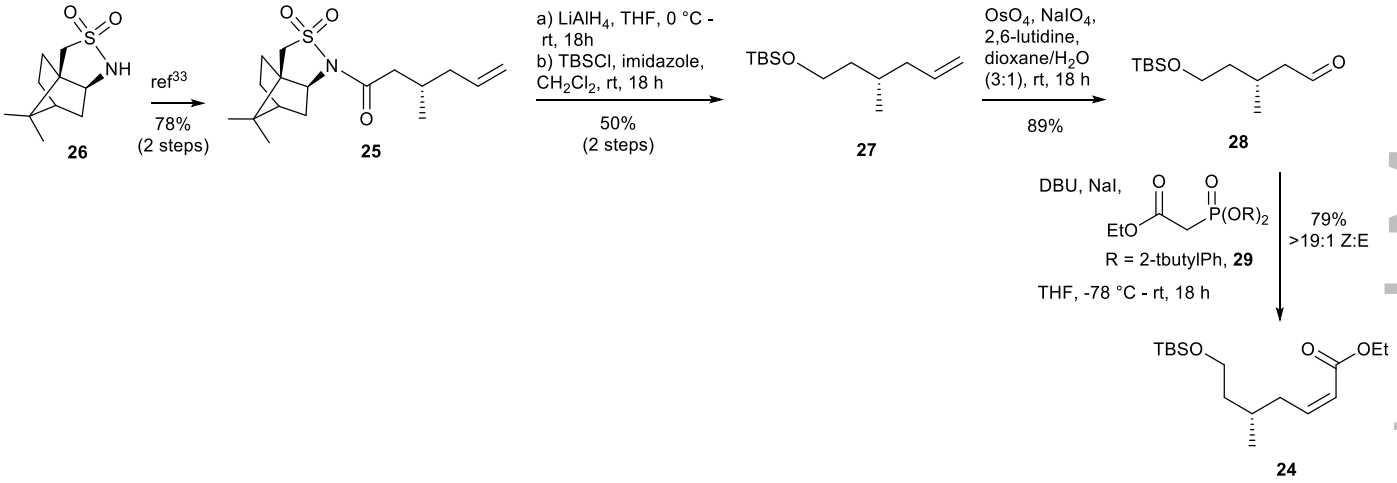


Scheme 5. Revised synthetic approach for the synthesis of formal synthesis intermediate **3**.

Accordingly, attention next focused on the synthesis of ester **24**. Initially this was achieved by adopting a camphorsultam chiral auxiliary approach (Scheme 6.). The chiral auxiliary was removed from alkene **25**, synthesised from (+)-camphorsultam (**26**) according to the procedure of Willis *et al.*[33] (see SI), and the resulting alcohol protected to give TBS ether **27**. Oxidative cleavage of the olefin in **27** afforded aldehyde **28** which was then subjected to a Horner-Wadsworth-Emmons reaction with phosphonate **29**, under *Z*-selective Ando[34,35]-Touchard[36,37] conditions to afford ester **24** in 79% yield with a >19:1 *Z*:*E* ratio.



Scheme 6. Synthesis of ester **24** *via* a chiral auxiliary/Horner-Wadsworth-Emmons approach.

A higher yielding (overall yield 35% versus 29%) reliable approach for the synthesis of ester **24** was subsequently developed from chiral lactone **30** (Scheme 7.), obtained by desymmetrisation of commercially available cyclic anhydride **31** in three steps using the protocol of Yokoshima and Fukuyama[38] (see SI). Dichloro-olefin **32** was synthesised from lactone **30** following literature precedent[39], before reductive elimination using excess lithium metal and protection of the resultant alcohol to give TBS ether **33**. Carbonylation of the alkyne with ethyl chloroformate followed by semi-hydrogenation of the alkyne functionality over Lindlar catalyst afforded ester **24**.

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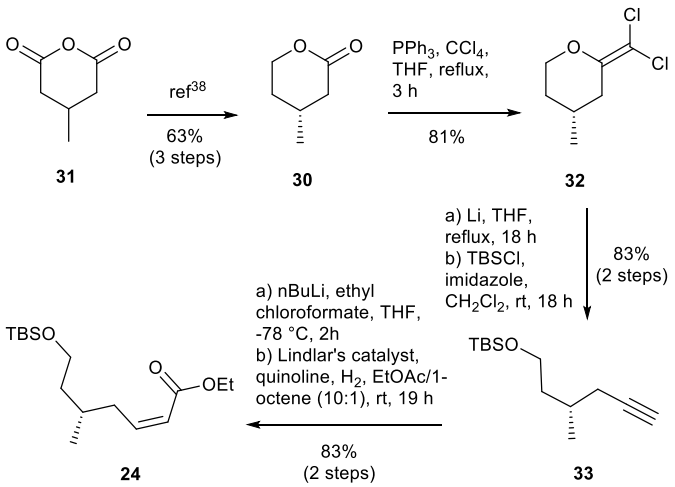
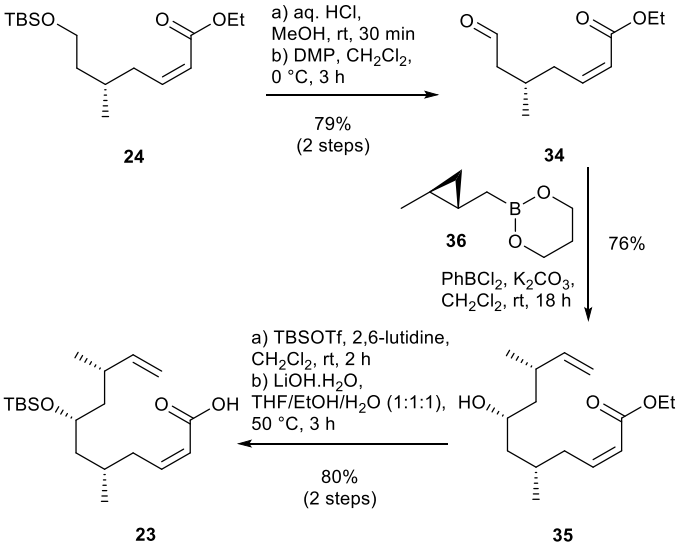


Scheme 7. Synthesis of ester **24** from racemic cyclic anhydride **31**.

To complete the synthesis of acid coupling partner **23** (Scheme 8.), the terminal TBS ether of ester **24** was deprotected and the resultant alcohol oxidised using DMP to give aldehyde **34**. Next Kraus homocrotylation[40–42] was used to install the two additional stereocentres in alcohol **35** in excellent 76% yield with only the desired diastereomer observed. It should be noted that when the same sequence of reactions was attempted on alkyne **33**, the homocrotylation yielded only 6% of the desired product (see SI). TBS protection of the newly formed alcohol functionality followed by base-mediated hydrolysis of the ester afforded the required coupling partner acid **23** in an overall 17% yield (13 steps) from cyclic anhydride **31**.



Scheme 8. Synthesis of fully elaborated coupling partner acid **23.**

With the two coupling partners, acid **23** and alcohol **5**, in hand, attention next turned to their Yamaguchi coupling. Disappointingly, it was found that while this reaction was successful in forming the desired ester linkage in good yield, this was accompanied by significant isomerism of the internal double bond, with only 19% of the desired *cis*-triene **22** being isolated, along with 59% of *trans*-triene **37** (Scheme 9.). In Bosch and Amat's recent formal synthesis of (-)-callyspongiolide (**2**) they too utilised a Yamaguchi coupling to assemble their RCM precursor **38** (see Scheme 10.), obtaining a 1.2:1 mixture of *Z*:*E* isomers in 45% yield. This prompted them to use an alternative Mitsunobu approach to access the desired triene **38** exclusively in 51% yield.[31]

In their total synthesis of (-)-callyspongiolide (**2**), Harran and co-workers demonstrated the facile *E* to *Z* photoisomerization of a macrocycle structurally similar to **39**[26], hence it was hoped that **39** could also be isomerised to the desired formal synthesis target **3**. Accordingly, both **22** and **37** were submitted to the RCM using Grubbs II catalyst. Unfortunately, in both cases the desired macrocycles were only isolated as the minor products (9% **3**/10% **39**), with the major less polar product being cyclooctene **40** (42%/57% respectively for the different substrates), resulting from metathesis taking place with the internal α,β-unsaturated olefin (Scheme 9.). A preliminary ^{1}H NMR experiment indicated that the irradiation of a solution of **39** at 254 nM in deuterated acetone led to the formation of an equilibrium

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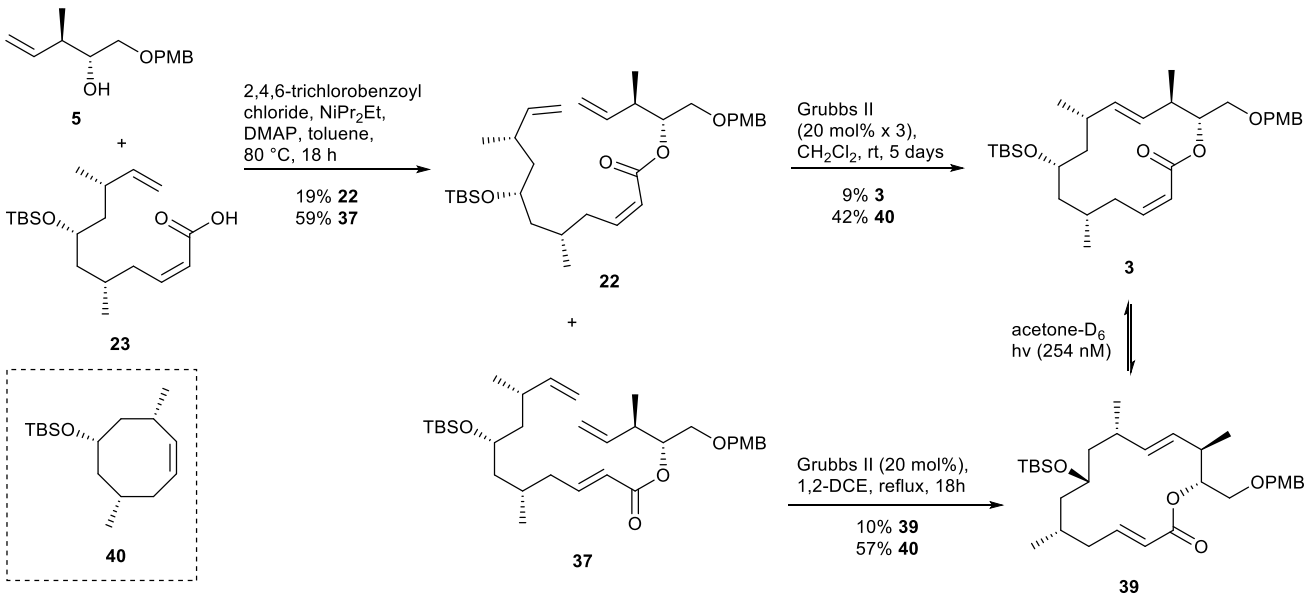
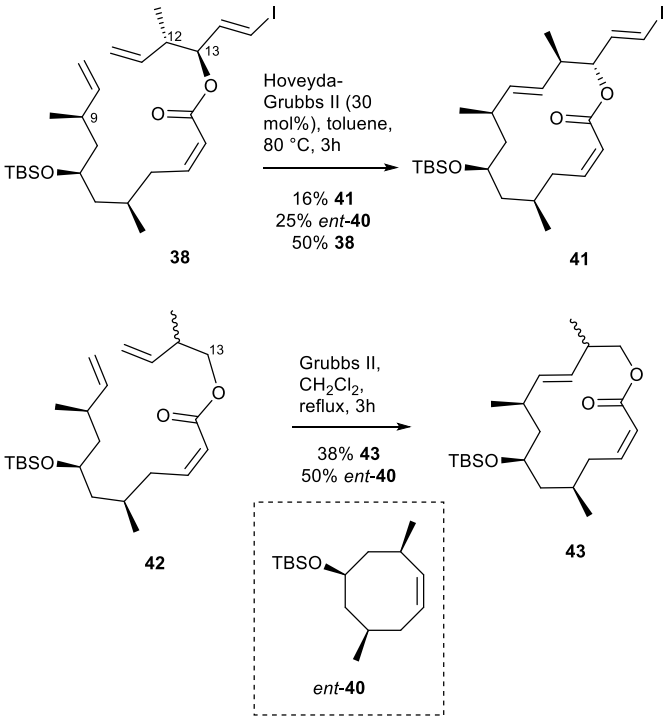
mixture of **3**:**39**, however the limited availability of **39** precluded further investigation and quantification of this photoisomerisation step (see SI).



Scheme 9. Completion of formal synthesis of (+)-callyspongiolide (**1a**).

In their formal synthesis of (-)-callyspongiolide (**2**), Bosch and Amat reported the RCM (using Hoveyda-Grubbs II catalyst) of enantiomeric related compound **38**, which otherwise differs from **22** only in its C13 substitution (Scheme 10.).[31] In this case a similar result to ours was obtained, with *ent*-**40** being the major product (25%) and only 16% of macrocycle **41** formed, with significant quantity of starting material **38** recovered (50%). These authors proposed that either the presence of the C9 or C12 allylic methyl groups or the C13 iodovinyl substituent could account for the observed difficulties in the RCM. They also reported the macrocyclization of model triene **42**, which lacks C13 substitution, but found that while an improved 38% yield of macrocyclic product **43** was obtained, indicating that the C13 substitution may be playing a slight role in the failure of the RCM, the major product was still *ent*-**40** (50%)



Scheme 10. Related RCM's carried out by Bosch and Amat in their recently reported synthesis of (-)-callyspongiolide (**2**).[31]

Combining our findings with those of Bosch and Amat[31] forges a much clearer picture of the utility of RCM reactions in the context of the synthesis of complex macrolides such as callyspongiolide. It was found that model diene-yne **13** was largely unreactive to RCM conditions, thus thwarting this approach. Whilst, relative to model triene **20**, it can be seen that the additional α-chiral methyl groups in **22** and **37** appear to have suppressed the formation of the undesired *Z*

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double bond at the macrocyclization point, this increase in steric hindrance appears to have favoured the addition of the ruthenium to the internal double bond, leading to formation of cyclooctene **40** as the major product in all RCM precursors containing both C9 and C12 allylic methyl groups. Previously, the RCM of two allylic methyl substituted terminal alkenes to form a 14-membered macrocycle had been used successfully (80-93% yield) by three groups in the synthesis of spongidepsin,[43–45] however it should be noted that in these cases there was no competing internal alkene. In model triene **20** where the C5 and C9 methyl groups are not present the competing RCM to form **40** is not observed, presumably because the C10 olefin is now significantly less sterically hindered thereby favouring addition of the ruthenium catalyst to this olefin.

Conclusions

In summary, we have reported the synthesis of macrocycle **3** in 15 steps from commercially available cyclic anhydride **31**, constituting an enantioselective formal synthesis[22,23] of (+)-callyspongiolide (**1a**), the unnatural isomer of the natural product. Anhydride desymmetrisation and a Kraus homocrotylation successfully established the C5, C7 and C9 stereocentres. Our synthesis hinged on an endgame involving Yamaguchi esterification followed by RCM to form the macrocycle. The C2-C3 double bond of callyspongiolide however proved problematic in both key steps of our approach, with isomerisation being observed during the key esterification reaction, and a competing RCM with this olefin was favoured when attempting RCM construction of the fully assembled macrocycle. Recently, Bosch and Amat reported adoption of a similar approach to the formal synthesis of (-)-callyspongiolide (**2**), in which similar problems were encountered[31]. Through the execution of model studies we have gained insight into the use of an RCM approach to the synthesis of callyspongiolide, establishing that this is limited by the internal (C2-C3) double bond reacting preferentially in the RCM step when the terminal alkenes both have the required α-chiral methyl groups present, whereas in the absence of one of these substitutions the RCM proceeded straightforwardly, albeit lacking any *E*/*Z* selectivity. Additionally, preliminary investigations demonstrated that photoisomerization of C2-C3 *E* double bond in macrocycle **39** resulting from the undesired Yamaguchi product **37**, was possible, indicating that either C2-C3 *Z* or *E* trienes could be used as precursors in the critical macrocyclization step.

Experimental Procedures

General Details

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon. Tetrahydrofuran and diethyl ether were freshly distilled over sodium/benzophenone ketyl. Dichloromethane and methanol were freshly distilled from calcium hydride. Toluene was freshly distilled over sodium. All other reagents were used as received unless otherwise noted.

Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions performed at low temperature were cooled either with an acetone/dry ice bath to reach −78 °C or an ice/water bath to reach 0 °C. Reactions were monitored by thin-layer chromatography (TLC) carried out on E. Merck silica gel plates using UV light as visualizing agent and an ethanolic solution of vanillin and potassium permanganate and heat as developing agents. Kieselgel S 63-100 μm (Riedel-de-Hahn) silica gel was used for flash chromatography.

Unless stated, NMR spectra were recorded at room temperature in $CDCl_3$ solution on either a Bruker DRX300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or using a Bruker DRX400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane ($\delta = 0$) and were measured relative to the solvent in which the sample was analysed. Coupling constants, *J*, are reported in hertz (Hz). Multiplicities are reported as "s" (singlet), "br s" (broad singlet), "d" (doublet), "br d" (broad doublet), "dd" (doublet of doublets), "ddd" (doublet of doublets of doublets), "t" (triplet), "dt" (doublet of triplets), "q" (quartet) and "m" (multiplets). Optical rotations ($[\alpha]_D$) are given in 10^{-1} deg cm^2 g^{-1} and were measured with an Autopol® IV automatic polarimeter, using the sodium-D line (589 nm), with the concentration measured in grams per 100 mL. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a diamond ATR sampling accessory. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. High-resolution mass spectra (HRMS) were obtained using a VG70SE spectrometer or on a micrOTOF-Q II mass spectrometer.

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Synthesis of alcohol coupling partner 5

(2*R*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-2-methylbutan-1-ol (**11**)

To a stirred solution of **8** (0.60 g, 1.28 mmol) in EtOH (13.0 mL) at rt was added PPTS (32.0 mg, 127 μmol). The reaction mixture was stirred at 50 °C for 3 h and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 4:1) afforded the *title compound* **11** (0.26 g, 57%) as a colourless oil with recovered **8** (0.23 g, 38%) also isolated as a colourless oil.

R_f 0.36 (petroleum ether/EtOAc, 4:1); $[\alpha]_D^{20}$ +10.0 (*c* 0.10, CH_2Cl_2); IR ν_{max}/cm^{-1} 3383, 2956, 2931, 2859, 1613, 1514, 1464, 1249, 1100, 1035, 836, 777, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.45 (ABq, $\Delta\nu_{AB}$ = 8.5 Hz, J_{AB} = 11.5 Hz, 2H), 3.89–3.83 (m, 1H), 3.81 (s, 3H), 3.72 (td, J = 11.2, 3.9 Hz, 1H), 3.59–3.42 (m, 3H), 2.84–2.81 (m, 1H), 1.91–1.86 (m, 1H), 1.01 (d, J = 7.1 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 130.1, 129.5, 114.0, 75.9, 73.3, 72.7, 65.0, 55.4, 37.9, 26.0, 18.2, 14.5, −4.2, −4.9; HRMS (ESI$^+$) $[M + Na]^+$ *m*/*z*: calcd. for $C_{19}H_{34}NaO_4Si^+$ 377.2119, found: 377.2110.

tert-Butyl(((2*R*,3*R*)-1-((4-methoxybenzyl)oxy)-3-methylpent-4-en-2-yl)oxy)dimethylsilane (**10**)

To a stirred solution of **11** (200 mg, 564 μmol) in CH_2Cl_2 (10.0 mL) at 0 °C was added DMP (360 mg, 849 μmol) and the reaction mixture was stirred at 0 °C for 3 h. The reaction was then quenched with sat. aq. $Na_2S_2O_3$ (5.00 mL) and sat. aq. $NaHCO_3$ (5.00 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2 × 5.00 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dissolved in petroleum ether (5.00 mL) and the precipitate that formed was filtered. The filtrate was concentrated *in vacuo* to afford the crude aldehyde which was used directly in the next step without further purification.

In a separate flask, to a stirred solution of methyltriphenylphosphonium bromide (300 mg, 840 μmol) in THF (5.00 mL) at −78 °C was added *n*BuLi (710 μL, 1.2 M in cyclohexane, 852 μmol) dropwise. The reaction mixture was warmed to 0 °C and stirred for 30 min then recooled to −78 °C. The crude aldehyde from above was dissolved in THF (5.00 mL) and added dropwise at −78 °C and the reaction mixture was stirred for 18 h warming to rt. The reaction was quenched with sat. aq. NH_4Cl (10.0 mL) and the separated aqueous layer was extracted with EtOAc (2 × 5.00 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 9:1) afforded *title compound* **10** (140 mg, 71% over 2 steps) as a colourless oil.

R_f 0.78 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{25}$ +4.7 (*c* 0.43, $CHCl_3$); IR ν_{max}/cm^{-1} 2957, 2930, 2857, 1514, 1463, 1248, 1097, 1038, 835, 776, 666; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.85–5.76 (m, 1H), 5.02–4.96 (m, 2H), 4.41 (ABq, $\Delta\nu_{AB}$ = 10.6 Hz, J_{AB} = 11.5 Hz, 2H), 3.81 (s, 3H), 3.72 (dt, J = 8.6, 3.3 Hz, 1H), 3.34 (ABX, $\Delta\nu_{AB}$ = 17.0 Hz, J_{AB} = 9.5 Hz, J_{AX} = 5.9 Hz, J_{BX} = 5.8 Hz, 2H), 2.44–2.36 (m, 1H), 1.02 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 140.3, 130.8, 129.4, 114.9, 113.8, 74.9, 73.13, 73.09, 55.4, 41.7, 26.1, 18.4, 17.1, −4.0, −4.7; HRMS (ESI$^+$) $[M + Na]^+$ *m*/*z*: calcd. for $C_{20}H_{34}NaO_3Si^+$ 373.2158, found: 373.2169.

(2*R*,3*R*)-1-((4-Methoxybenzyl)oxy)-3-methylpent-4-en-2-ol (**5**)

To a stirred solution of **10** (120 mg, 342 μmol) in THF (1.50 mL) at rt was added TBAF (680 μL, 1 M in THF, 680 μmol). The reaction mixture was stirred at rt for 18 h and quenched with H_2O (1.00 mL). The separated aqueous layer was extracted with EtOAc (2 × 2.00 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 4:1) afforded *title compound* **5** (71.0 mg, 88%) as a colourless oil.

R_f 0.48 (petroleum ether/EtOAc, 4:1); $[\alpha]_D^{25}$ +6.0 (*c* 0.10, $CHCl_3$); IR ν_{max}/cm^{-1} 3446, 2961, 2931, 2862, 1612, 1513, 1247, 1091, 1035, 916, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.87–5.78 (m, 1H), 5.10–5.05 (m, 2H), 4.48 (s, 2H), 3.81 (s, 3H), 3.68–3.63 (m, 1H), 3.45 (ABX, $\Delta\nu_{AB}$ = 50.6 Hz, J_{AB} = 9.6 Hz,

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J_{AX} = 7.6 Hz, J_{BX} = 3.2 Hz, 2H), 2.39–2.30 (m, 1H), 2.25 (d, J = 3.1 Hz, 1H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 140.3, 130.3, 129.5, 115.7, 114.0, 73.7, 73.2, 72.4, 55.4, 41.0, 16.3; HRMS (ESI$^+$) $[M + Na]^+$ m/z: calcd. for $C_{14}H_{20}NaO_3^+$ 259.1305, found: 259.1313.

Synthesis of model macrocycle 21

Dec-1-en-9-yn-5-ol (**16**)

To a stirred solution of 5-hexyn-1-ol **14** (200 mg, 2.04 mmol) in CH_2Cl_2 (20.0 mL) at 0 °C was added DMP (1.30 g, 3.06 mmol). The reaction mixture stirred at 0 °C for 3 h then quenched with sat. aq. $Na_2S_2O_3$ (20.0 mL) and sat. aq. $NaHCO_3$ (10.0 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2 × 10.0 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was passed through a short plug of silica, washed with pentane/Et_2O (1:2), and concentrated *in vacuo* to afford volatile aldehyde which was used directly in the next step.

To a stirred solution of the crude aldehyde in THF (20.0 mL) at 0 °C was added but-3-en-1-ylmagnesium bromide (**15**) (3.12 mL, 0.65 M in THF, 2.02 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 h then quenched with sat. aq. NH_4Cl (20.0 mL). The separated aqueous layer was extracted with EtOAc (2 ×10.0 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc, 4:1) afforded *title compound* **16** (272 mg, 44% over 2 steps) as a colourless oil.

R_f 0.53 (petroleum ether/EtOAc, 4:1); IR ν_{max}/cm^{-1} 3304, 2937, 2867, 1970, 1641, 1435, 1266, 1088, 996, 912, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90–5.79 (m, 1H), 5.09–4.96 (m, 2H), 3.70–3.63 (m, 1H), 2.25–2.09 (m, 4H), 1.96 (t, J = 2.6 Hz, 1H), 1.75–1.49 (m, 6H), 1.37 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 115.0, 84.5, 71.2, 68.7, 36.7, 36.5, 30.2, 24.7, 18.5.

5-((*tert*-Butyldimethylsilyl)oxy)-dec-1-en-9-yn (**18**)

To a stirred solution of **16** (100 mg, 657 µmol) in CH_2Cl_2 (1.00 mL) at rt was added TBSCl (200 mg, 1.33 mmol) and imidazole (135 mg, 1.98 mmol) and the reaction mixture stirred at rt for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (3.00 mL) and the separated aqueous layer was extracted with CH_2Cl_2 (2 × 3.00 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc, 9:1) afforded *title compound* **18** (168 mg, 96%) as a colourless oil.

R_f 0.94 (petroleum ether/EtOAc, 9:1); IR ν_{max}/cm^{-1} 3314, 2953, 2931, 2858, 2026, 1473, 1361, 1255, 1088, 911, 835, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87–5.77 (m, 1H), 5.04–4.92 (m, 2H), 3.73–3.67 (m, 1H), 2.21–2.16 (m, 2H), 2.14–2.03 (m, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.61–1.50 (m, 6H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 114.4, 84.7, 71.4, 68.5, 36.4, 36.1, 29.7, 26.1, 24.3, 18.7, 18.3, −4.26, −4.28.

Ethyl 7-((*tert*-butyldimethylsilyl)oxy)undec-10-en-2-ynoate (**17**)

To a stirred solution of **18** (0.11 g, 413 µmol) in THF (5.00 mL) at −78 °C was added *n*BuLi (490 µL, 1.0 M in cyclohexane, 490 µmol). The reaction mixture stirred at −78 °C for 30 min, then ethyl chloroformate (78.0 µL, 819 µmol) was added dropwise. The reaction mixture was stirred for 18 h warming to rt then quenched with sat. aq. NH_4Cl (5.00 mL). The separated aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 9:1) afforded *title compound* **17** (105 mg, 75%) as a colourless oil.

R_f 0.73 (petroleum ether/EtOAc, 9:1); IR ν_{max}/cm^{-1} 2931, 2858, 2237, 1713, 1473, 1366, 1248, 1075, 835, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86–5.76 (m, 1H), 5.04–4.93 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.73–3.67 (m, 1H), 2.34 (t, J = 6.8 Hz, 2H), 2.15–2.00 (m, 2H), 1.68–1.49 (m, 6H), 1.30 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100

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MHz, $CDCl_3$) δ 154.0, 138.9, 114.6, 89.3, 73.5, 71.2, 61.9, 36.3, 36.1, 29.7, 26.0, 23.3, 19.0, 18.2, 14.2, −4.3; HRMS (ESI^+) $[M + Na]^+$ *m/z*: calcd. for $C_{19}H_{34}NaO_3Si^+$ 361.2169, found: 361.2177.

7-((tert-Butyldimethylsilyl)oxy)undec-10-en-2-ynoic acid (**12**)

To a stirred solution of **17** (70.0 mg, 207 μmol) in THF/H_2O (2.00 mL, 1:1 v/v) at rt was added $LiOH·H_2O$ (87.0 mg, 2.07 mmol). The reaction mixture was stirred at rt for 18 h then quenched with sat. aq. NH_4Cl (5.00 mL). The separated aqueous layer was extracted with EtOAc (3 × 3.00 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (EtOAc/CH_3CO_2H, 100:1) afforded *title compound* **12** (58.0 mg, 90%) as a colourless oil.

R_f 0.76 (EtOAc/CH_3CO_2H, 100:1); IR ν_{max}/cm^{-1} 2930, 2857, 2238, 1687, 1255, 1085, 1054, 1005, 910, 835, 774; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86–5.75 (m, 1H), 5.04–4.93 (m, 2H), 3.73–3.68 (m, 1H), 2.37 (t, *J* = 6.8 Hz, 2H), 2.12–2.03 (m, 2H), 1.69–1.50 (m, 6H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 138.8, 114.6, 92.4, 72.8, 71.2, 36.3, 36.0, 29.7, 26.0, 23.2, 19.1, 18.2, −4.3; HRMS (ESI^+) $[M + Na]^+$ *m/z*: calcd. for $C_{17}H_{30}NaO_3Si^+$ 333.1856, found: 333.1855.

(2*R*,3*R*)-1-((4-Methoxybenzyl)oxy)-3-methylpent-4-en-2-yl 7-((*tert*-butyldimethylsilyl)oxy)undec-10-en-2-ynoate (**13**)

To a stirred solution of **12** (30.0 mg, 96.6 μmol) in toluene (5.00 mL) at rt was added 2,4,6-trichlorobenzoyl chloride (16.0 μL, 102 μmol) followed by N*i*Pr_2Et (74.0 μL, 0.425 μmol) and DMAP (5.00 mg, 40.9 μmol). The reaction mixture was stirred at rt for 5 min, then a solution of **5** (20.0 mg, 84.6 μmol) in toluene (1.00 mL) was added. The reaction mixture was stirred at rt for 18 h then quenched with sat. aq. $NaHCO_3$ (5.00 mL). The separated aqueous layer was extracted with EtOAc (3 × 3.00 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 9:1) afforded *title compound* **13** (31.5 mg, 70%) as a colourless oil. Diastereomeric ratio could not be determined from NMR.

R_f 0.69 (petroleum ether/EtOAc, 9:1); IR ν_{max}/cm^{-1} 2930, 2859, 2342, 1719, 1642, 1515, 1455, 1243, 1037, 837, 763, ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.86–5.69 (m, 2H), 5.10–4.92 (m, 5H), 4.45 (ABq, $\Delta\nu_{AB}$ = 20.9 Hz, J_{AB} = 11.7 Hz, 2H), 3.80 (s, 3H), 3.73–3.67 (m, 1H), 3.51 (ABX, $\Delta\nu_{AB}$ = 7.7 Hz, J_{AB} = 10.7 Hz, J_{AX} = 5.9 Hz, J_{BX} = 4.6 Hz, 2H), 2.63–2.54 (m, 1H), 2.34 (t, *J* = 6.8 Hz, 2H), 2.11–2.04 (m, 2H), 1.67–1.49 (m, 6H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 153.7, 138.9, 138.8, 130.2, 129.4, 116.2, 114.6, 113.9, 89.8, 76.9, 73.5, 72.9, 71.2, 69.1, 55.4, 39.1, 36.3, 36.1, 29.7, 26.0, 23.3, 19.1, 18.2, 16.4, −4.25, −4.29; HRMS (ESI^+) $[M + Na]^+$ *m/z*: calcd. for $C_{31}H_{48}NaO_5Si^+$ 551.3163, found: 551.3157.

(2*R*,3*R*)-1-((4-Methoxybenzyl)oxy)-3-methylpent-4-en-2-yl (*Z*)-7-((*tert*-butyldimethylsilyl)oxy)undeca-2,10-dienoate (**20**)

A stirred solution of **13** (10.0 mg, 18.9 μmol), quinoline (20.0 μL, 169 μmol) and Lindlar catalyst (2.00 mg, 20% w/w) in degassed EtOAc/1-octene (4.40 mL, 10:1 v/v) at rt was bubbled through with H_2 for 1 h. The reaction was then stirred under H_2 balloon at rt for 18 h. The reaction mixture was filtered through a pad of celite®, washed with EtOAc and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 9:1) afforded *title compound* **20** (10.0 mg, quant.) as a colourless oil. Diastereomeric ratio could not be determined from NMR.

R_f 0.72 (petroleum ether/EtOAc, 9:1); IR ν_{max}/cm^{-1} 2958, 2924, 2854, 1727, 1458, 1377, 1259, 1079, 1023, 798, 739; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.20 (dt, *J* = 11.5, 7.4 Hz, 1H), 5.86–5.69 (m, 3H), 5.08–4.92 (m, 5H), 4.45 (ABq, $\Delta\nu_{AB}$ = 25.4 Hz, J_{AB} = 11.7 Hz, 2H), 3.80 (s, 3H), 3.70–3.65 (m, 1H), 3.51 (ABX, $\Delta\nu_{AB}$ = 9.6 Hz, J_{AB} = 10.5 Hz, J_{AX} = 5.7 Hz, J_{BX} = 4.7 Hz, 2H), 2.67–2.56 (m, 3H), 2.12–1.99 (m, 2H), 1.55–1.42 (m, 6H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 159.3, 150.7, 139.4, 139.1, 130.4, 129.4, 120.0, 115.8, 114.4, 113.9, 74.7, 72.9, 71.6, 69.4, 55.4, 39.1, 36.7, 36.4, 29.7, 29.3, 26.1, 24.9, 18.3, 16.5, −4.2, −4.3; HRMS (ESI^+) $[M + Na]^+$ *m/z*: calcd. for $C_{31}H_{50}NaO_5Si^+$ 553.3320, found: 553.3312.

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(3*Z*,13*R*,14*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-14-(((4-methoxybenzyl)oxy)methyl)-13-methyloxacyclotetradeca-3,11-dien-2-one (**21**)

To a stirred solution of **20** (10.0 mg, 18.8 μmol) in CH_2Cl_2 (30.0 mL) at rt was added a solution of Grubbs Catalyst™ 2nd Generation (3.30 mg, 3.89 μmol) in CH_2Cl_2 (1.00 mL). The reaction mixture was stirred at rt for 18 h then a second portion of Grubbs Catalyst™ 2nd Generation (3.30 mg, 3.89 μmol) in CH_2Cl_2 (1.00 mL) was added. The reaction mixture was stirred at rt for a further 18 h then filtered through a pad of Celite® eluting with CH_2Cl_2, and the filtrate concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 18:1) afforded *title compound* **21** (6.60 mg, 70%) as a yellow oil in a 1.2:1 mixture of isomers.

R_f 0.65 (petroleum ether/EtOAc, 9:1); IR ν_{max}/cm^{-1} 2929, 2857, 2339, 1718, 1642, 1514, 1463, 1249, 1171, 1036, 834, 774, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.24 (m, 2H), 6.872 (d, *J* = 8.7 Hz, 2H), 6.869 (d, *J* = 8.7 Hz, 2H), 6.16 (dt, *J* = 11.6, 8.4 Hz, 1H), 6.07 (ddd, *J* = 11.6, 10.2, 6.2 Hz, 1H), 5.88–5.85 (m, 1H), 5.78 (dt, *J* = 11.6, 1.2 Hz, 1H), 5.43–5.23 (m, 2H), 5.12–5.07 (m, 1H), 4.99–4.94 (m, 1H), 4.57–4.40 (m, 2H), 3.80 (s, 3H), 3.72–3.62 (m, 1H), 3.61–3.56 (m, 2H), 3.21–3.11 (m, 1H), 2.65–2.47 (m, 2H), 2.31–2.22 (m, 1H), 2.07–2.00 (m, 2H), 1.75–1.23 (m, 6H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.883 (s, 9H), 0.879 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.031 (s, 3H), 0.029 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 166.3, 159.4, 149.0, 148.1, 132.1, 131.5, 131.3, 130.3, 129.44, 129.42, 121.7, 121.0, 113.94, 113.92, 75.7, 75.5, 73.0, 70.4, 69.8, 69.6, 68.0, 55.4, 38.3, 38.1, 36.7, 36.1, 35.4, 33.9, 29.3, 27.9, 27.5, 27.3, 27.1, 26.11, 26.07, 24.2, 23.3, 22.8, 18.3, 18.2, 17.8, 17.2, −3.8, −3.87, −3.94, −4.0; HRMS (ESI$^+$) $[M + Na]^+$ *m*/*z*: calcd. for $C_{29}H_{46}NaO_5Si^+$ 525.3007, found: 525.2995.

Synthesis of acid coupling partner 23

(*S*)-3-Methylhex-5-en-1-ol (**44**)

To a stirred suspension of $LiAlH_4$ (350 mg, 9.22 mmol) in THF (30.0 mL) at 0 °C was added a solution of **25** (1.50 g, 4.61 mmol) in THF (10.0 mL) dropwise. The reaction mixture was stirred for 18 h warming to rt. The reaction mixture was diluted with Et_2O (15.0 mL) and cooled to 0 °C then carefully quenched with H_2O (350 μL) followed by addition of 2M NaOH (700 μL) and H_2O (1.00 mL). The reaction mixture was warmed to rt and stirred for 15 min then was added anhydrous $MgSO_4$ and stirred for a further 15 min. The reaction mixture was filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 4:1) afforded *title compound* **44** (310 mg, 59%) as a colourless oil.

R_f 0.39 (petroleum ether/EtOAc, 4:1); $[\alpha]_D^{22}$ +37.0 (*c* 0.10, $CHCl_3$); IR ν_{max}/cm^{-1} 3077, 2957, 2928, 1641, 1539, 1458, 1378, 1135, 1057, 994, 967, 909, 837; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83–5.73 (m, 1H), 5.04–4.98 (m, 2H), 3.74–3.64 (m, 2H), 2.12–1.90 (m, 2H), 1.74–1.59 (m, 2H), 1.44–1.35 (m, 1H), 1.28 (brs, 1H), 0.91 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 116.0, 61.1, 41.4, 39.4, 29.5, 19.5; Analytical data was in agreement with that reported in the literature.[46]

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-methylhex-5-ene (**27**)

To a stirred solution of **44** (300 mg, 2.63 mmol) in CH_2Cl_2 (6.50 mL) at rt was added imidazole (540 mg, 7.93 mmol) and TBSCl (790 mg, 5.24 mmol). The reaction mixture was stirred at rt for 18 h then quenched with H_2O (10.0 mL). The separated aqueous layer was extracted with EtOAc (3 × 10.0 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 9:1) afforded *title compound* **27** (510 mg, 85%) as a colourless oil.

R_f 0.91 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{22}$ +21.0 (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83–5.73 (m, 1H), 5.03–4.97 (m, 2H), 3.70–3.60 (m, 2H), 2.11–1.87 (m, 2H), 1.70–1.54 (m, 2H), 1.38–1.29 (m, 1H), 0.89 (s, 9H), 0.87 (d, *J* = 5.2 Hz, 3H), 0.05 (s, 6H); Analytical data was in agreement with that reported in the literature.[46]

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(*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-methylpentanal (**28**)

To a stirred solution of **27** (500 mg, 2.19 mmol) in dioxane/H_2O (20.0 mL, 3:1 v/v) at rt was added OsO_4 (560 µL, 2.0% w/v in *t*-BuOH, 44.1 µmol) followed by 2,6-lutidine (1.00 mL, 8.63 mmol) and $NaIO_4$ (1.87 g, 8.75 mmol). The reaction mixture was stirred at rt for 18 h then quenched with sat. aq. $Na_2S_2O_3$ (10.0 mL) and the mixture was stirred at rt for a further 1 h. The mixture was extracted with CH_2Cl_2 (3 × 20.0 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 9:1) afforded *title compound* **28** (451 mg, 89%) as a yellow oil.

R_f 0.58 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{25}$ −6.2 (*c* 0.50, $CHCl_3$); IR ν_{max}/cm^{-1} 2957, 2930, 2858, 1727, 1472, 1463, 1388, 1361, 1254, 1093, 834, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, *J* = 2.2 Hz, 1H), 3.69–3.63 (m, 2H), 2.49–2.42 (m, 1H), 2.29–2.21 (m, 2H), 1.60–1.42 (m, 2H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 60.9, 51.1, 39.7, 26.1, 25.3, 20.2, 18.4, −5.2; HRMS (ESI$^+$) [M + Na]$^+$ *m*/*z*: calcd. for $C_{12}H_{26}NaO_2Si^+$ 253.1594, found: 253.1598.

(*S*,*Z*)-Ethyl 7-(*tert*-butyldimethylsilyloxy)-5-methylhept-2-enoate (**24**)

From 28:

To a stirred solution of **29** (600 mg, 1.39 mmol) in THF (20.0 mL) at 0 °C was added DBU (230 µL, 1.53 mmol) and NaI (230 mg, 1.53 mmol). The reaction mixture was stirred at 0 °C for 10 min then cooled to −78 °C. A solution of **28** (320 mg, 1.39 mmol) in THF (2.00 mL) was added dropwise at −78 °C and the reaction mixture was stirred for 18 h warming to rt. The reaction was quenched with sat. aq. NH_4Cl (10.0 mL) and the separated aqueous layer was extracted with EtOAc (3 × 10.0 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 9:1) afforded *title compound* **24** (330 mg, 79%) as a yellow oil in a >19:1 *Z*/*E* ratio of stereoisomers.

From 45:

A stirred solution of **45** (100 mg, 335 µmol), quinoline (350 µL, 2.96 mmol) and Lindlar catalyst (20.0 mg, 20% w/w) in degassed EtOAc/1-octene (22.0 mL, 10:1 v/v) at rt was bubbled through with H_2 for 1 h. The reaction was then stirred under H_2 balloon at rt for 18 h. The reaction mixture was filtered through a pad of celite®, washed with EtOAc and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 9:1) afforded *title compound* **24** (100 mg, quant.) as a yellow oil.

R_f 0.77 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{25}$ +4.5 (*c* 0.40, $CHCl_3$); IR ν_{max}/cm^{-1} 2957, 2930, 2859, 1721, 1254, 1176, 1092, 1037, 834, 775; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (dt, *J* = 11.6, 7.5 Hz, 1H), 5.81 (dt, *J* = 11.6, 1.7 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.70–3.60 (m, 2H), 2.64–2.57 (m, 2H), 1.80–1.72 (m, 1H), 1.64–1.34 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 149.4, 120.6, 61.3, 59.9, 39.7, 36.2, 30.1, 26.1, 19.7, 18.5, 14.4, −5.1, −5.2; HRMS (ESI$^+$) [M + Na]$^+$ *m*/*z*: calcd. for $C_{16}H_{32}NaO_3Si^+$ 323.2013, found: 323.2019.

(*R*)-2-(Dichloromethylene)-4-methyltetrahydro-2H-pyran (**32**)

To a stirred solution of **30** (250 mg, 2.19 mmol) in THF (20.0 mL) was added triphenylphosphine (2.30 g, 8.77 mmol) followed by CCl_4 (5.00 mL, 51.6 mmol). The reaction mixture was heated under reflux for 3 h. The reaction was cooled to rt then quenched with H_2O (20.0 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2 × 15.0 mL) and the combined organic extracts were washed with $NaHCO_3$ (15.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was diluted with pentane (15.0 mL) and the resulting precipitate was filtered and washed with pentane (5.00 mL). Purification by column chromatography (petroleum ether/Et_2O, 19:1) afforded *title compound* **32** (322 mg, 81%) as a yellow oil.

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R_f 0.95 (petroleum ether/Et_2O, 9:1); $[\alpha]_D^{22}$ −161.1 (*c* 0.36, $CHCl_3$), (lit.[39] *ent*-32 $[\alpha]_D^{23}$ +128.0 (*c* 1.00, $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (ddd, *J* = 11.0, 4.6, 2.8 Hz, 1H), 3.73 (dt, *J* = 16.9, 2.8 Hz, 1H), 2.84–2.76 (m, 1H), 1.81–1.69 (m, 3H), 1.50–1.40 (m, 1H), 1.03 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 104.1, 69.5, 34.0, 32.9, 28.6, 21.8; HRMS (ESI^+) $[M + Na]^+$ *m/z*: calcd. for $C_7H_{10}Cl_2NaO^+$ 203.0001, found: 203.0012. Analytical data was in agreement with that reported in the literature for *ent*-32.[39]

(*S*)-3-Methylhex-5-yn-1-ol (**46**)

To a stirred solution of **32** (1.00 g, 5.52 mmol) in THF (40.0 mL) at rt was added lithium metal (~2 g, ~50 eqv.). The reaction mixture was heated under reflux for 18 h then cooled to rt and excess lithium was removed. The reaction mixture was diluted with Et_2O (20.0 mL) and washed with H_2O (20.0 mL) and the separated aqueous layer extracted with Et_2O (2 × 10.0 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/Et_2O, 1:1) afforded *title compound* **46** (530 mg, 86%) as a colourless oil.

R_f 0.31 (petroleum ether/Et_2O, 1:1); $[\alpha]_D^{22}$ −5.0 (*c* 0.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.77–3.67 (m, 2H), 2.24–2.12 (m, 2H), 1.98 (t, *J* = 2.7 Hz, 1H), 1.93–1.82 (m, 1H), 1.77–1.46 (m, 2H), 1.03 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.1, 69.6, 61.0, 38.7, 29.2, 25.9, 19.6. Analytical data was in agreement with that reported in the literature.[47]

(*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-methylhex-5-yne (**33**)

To a stirred solution of **46** (500 mg, 4.46 mmol) in CH_2Cl_2 (40.0 mL) at rt was added imidazole (900 mg, 6.51 mmol) and TBSCl (1.34 g, 8.89 mmol). The reaction mixture was stirred at rt for 18 h then quenched with H_2O (20.0 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2 × 20.0 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 18:1) afforded *title compound* **33** (965 mg, 96%) as a colourless oil.

R_f 0.84 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{23}$ −3.0 (*c* 0.45, $CHCl_3$); IR ν_{max}/cm^{-1} 3315, 2957, 2930, 2859, 1255, 1091, 834, 774, 661; ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (dt, *J* = 6.5, 1.6 Hz, 2H), 2.16 (ABXY, $\Delta\nu_{AB}$ = 34.0 Hz, J_{AB} = 16.7 Hz, J_{AX} = 6.8 Hz, J_{BX} = 5.6 Hz, J_{AY} = 2.7 Hz, J_{BY} = 2.6 Hz, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.90–1.79 (m, 1H), 1.70–1.38 (m, 2H), 1.01 (t, *J* = 6.7 Hz), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.3, 69.3, 61.2, 38.8, 29.2, 26.1, 25.9, 19.5, 18.5, −5.2; HRMS (ESI^+) $[M + Na]^+$ *m/z*: calcd. for $C_{13}H_{26}NaOSi^+$ 249.1645, found: 249.1638.

Ethyl (*S*)-7-((*tert*-butyldimethylsilyl)oxy)-5-methylhept-2-ynoate (**45**)

To a stirred solution of **33** (40.0 mg, 177 µmol) in THF (2.00 mL) at −78 °C was added *n*BuLi (160 µL, 1.3 M in cyclohexane, 208 µmol) dropwise. The reaction mixture was stirred at −78 °C for 20 min then was added ethyl chloroformate (35.0 µL, 368 µmol) dropwise. The reaction was stirred at −78 °C for 2 h then quenched with sat. aq. NH_4Cl (5.00 mL) and warmed to rt. The separated aqueous layer was extracted with EtOAc (2 × 5.00 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 9:1) afforded *title compound* **45** (44.0 mg, 83%) as a colourless oil.

R_f 0.68 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{22}$ −8.3 (*c* 0.60, $CHCl_3$); IR ν_{max}/cm^{-1} 3311, 2958, 2932, 2859, 2233, 1711, 1473, 1251, 1095, 836, 775; ^1H NMR (400 MHz, $CDCl_3$) δ 4.21 (q, *J* = 7.1 Hz, 2H), 3.70–3.61 (m, 2H), 2.31 (ABX, $\Delta\nu_{AB}$ = 40.9 Hz, J_{AB} = 17.1 Hz, J_{AX} = 7.0 Hz, J_{BX} = 5.6 Hz, 2H), 2.00–1.89 (m, 1H), 1.68–1.60 (m, 1H), 1.49–1.41 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 88.3, 74.4, 61.9, 61.0, 38.8, 29.1, 26.12, 26.08, 19.7, 18.4, 14.2, −5.2; HRMS (ESI^+) $[M + Na]^+$ *m/z*: calcd. for $C_{16}H_{30}NaO_3Si^+$ 321.1856, found: 321.1859.

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Ethyl (*S*,*Z*)-7-hydroxy-5-methylhept-2-enoate (**47**)

To a stirred solution of **24** (40.0 mg, 133 μmol) in MeOH (1.30 mL) at rt was added aq. HCl (10.0 μL, 1 M). The reaction micture was stirred at rt for 30 min then quenched with sat. aq. NH_4Cl (5.00 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3 × 1.50 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 1:4) afforded *title compound* **47** (23.5 mg, 95%) as a pale yellow oil.

R_f 0.56 (petroleum ether/Et_2O, 1:4); $[\alpha]_D^{23}$ −33.3 (*c* 0.55, $CHCl_3$); IR ν_{max}/cm^{-1} 3309, 2959, 2928, 1718, 1642, 1464,1416, 1380, 1176, 1034, 806; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (dt, *J* = 11.6, 7.7 Hz, 1H), 5.82 (dt, *J* = 11.5, 1.6 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.78–3.64 (m, 2H), 2.78–2.70 (m, 1H), 2.48–2.40 (m, 1H), 1.84–1.74 (m, 1H), 1.62–1.44 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 149.4, 120.7, 60.9, 60.0, 39.6, 35.7, 30.2, 19.9, 14.4; HRMS (ESI$^+$) $[M + Na]^+$ *m*/*z*: calcd. for $C_{10}H_{18}NaO_3^+$ 209.1148, found: 209.1164.

Ethyl (*S*,*Z*)-5-methyl-7-oxohept-2-enoate (**34**)

To a stirred solution of **47** (50.0 mg, 268 μmol) in CH_2Cl_2 (5.00 mL) at 0 °C was added DMP (170 mg, 401 μmol). The reaction mixture was stirred at 0 °C for 3 h then quenched with sat. aq. $Na_2S_2O_3$ (5.00 mL) and sat. aq. $NaHCO_3$ (5.00 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2 × 5.00 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 2:1) afforded *title compound* **34** (41.0 mg, 83%) as a yellow oil.

R_f 0.48 (petroleum ether/Et_2O, 2:1); $[\alpha]_D^{23}$ −24.6 (*c* 0.13, $CHCl_3$); IR ν_{max}/cm^{-1} 2961, 2919, 2851, 1717, 1633, 1462, 1380, 1260, 1176, 1034, 807; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.9 Hz, 1H), 6.20 (dt, *J* = 11.6, 7.7 Hz, 1H), 5.85 (dt, *J* = 11.6, 1.7 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.75–2.58 (m, 2H), 2.49–2.43 (m, 1H), 2.34–2.21 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 166.4, 147.5, 121.6, 60.1, 50.6, 35.7, 28.5, 20.1, 14.4; HRMS (ESI$^+$) $[M + Na]^+$ *m*/*z*: calcd. for $C_{10}H_{16}NaO_3^+$ 207.0992, found: 207.0988.

Ethyl (5*S*,7*S*,9*S*,*Z*)-7-hydroxy-5,9-dimethylundeca-2,10-dienoate (**35**)

To a stirred solution of **36** (75.0 mg, 487 μmol) in CH_2Cl_2 (3.00 mL) at rt was added $PhBCl_2$ (35.0 μL, 270 μmol) followed by K_2CO_3 (135 mg, 977 μmol) and the reaction mixture was stirred for 5 min. Then **34** (30.0 mg, 163 μmol) dissolved in CH_2Cl_2 (1.50 mL) was then added at rt and the reaction mixture stirred for 18 h. The reaction was quenched with 2 M NaOH (5.00 mL) and the separated aqueous layer was extracted with EtOAc (2 × 5.00 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/Et_2O, 1:1) afforded *title compound* **35** (31.5 mg, 76%) as a yellow oil.

R_f 0.67 (petroleum ether/Et_2O, 1:1); $[\alpha]_D^{23}$ −22.5 (*c* 0.08, $CHCl_3$); IR ν_{max}/cm^{-1} 3384, 2957, 2925, 1721, 1641, 1378, 1177, 1035, 911, 906; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (dt, *J* = 11.5, 7.8 Hz, 1H), 5.82 (ddd, *J* = 11.5, 1.7, 1.3 Hz, 1H), 5.68 (ddd, *J* = 17.2, 10.2, 8.1 Hz, 1H), 5.03 (ddd, *J* = 17.2, 1.9, 1.0 Hz, 1H), 4.95 (ddd, *J* = 10.2, 1.9, 0.7 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.83–3.77 (m, 1H), 2.86–2.79 (m, 1H), 2.48–2.38 (m, 1H), 2.34–2.26 (m, 1H), 1.89–1.79 (m, 1H), 1.46–1.30 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 149.8, 144.4, 120.7, 113.5, 67.3, 60.1, 45.5, 44.7, 35.1, 34.9, 30.6, 21.3, 20.7, 14.4; HRMS (ESI$^+$) $[M + Na]^+$ *m*/*z*: calcd. for $C_{15}H_{26}NaO_3^+$ 277.1774, found: 277.1778.

Ethyl (5*S*,7*S*,9*S*,*Z*)-7-((*tert*-butyldimethylsilyl)oxy)-5,9-dimethylundeca-2,10-dienoate (**48**)

To a stirred solution of **35** (30.0 mg, 118 μmol) in CH_2Cl_2 (1.00 mL) at rt was added 2,6-lutidine (27.0 μL, 233 μmol) followed by TBSOTf (40.0 μL, 174 μmol) and the reaction mixture was stirred at rt for 2 h. The reaction was quenched with H_2O (5.00 mL) and the separated aqueous layer was extracted with CH_2Cl_2 (2 × 5.00 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/Et_2O, 9:1) afforded *title compound* **48** (39.5 mg, 91%) as a yellow oil.

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R_f 0.90 (petroleum ether/Et_2O, 9:1); $[\alpha]_D^{23}$ +17.0 (*c* 0.10, $CHCl_3$); IR ν_{max}/cm^{-1} 2957, 2926, 2854, 2358, 2312, 1722, 1633, 1257, 1177, 1038, 911,835, 806, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (ddd, *J* = 11.6, 7.9, 7.1 Hz, 1H), 5.81 (dt, *J* = 11.6, 1.8 Hz, 1H), 5.68 (ddd, *J* = 17.3, 10.3, 7.5 Hz, 1H), 4.99–4.91 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.78–3.71 (m, 1H), 2.67–2.53 (m, 2H), 2.36–2.23 (m, 1H), 1.73–1.62 (m, 1H), 1.49–1.31 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 149.1, 144.7, 120.8, 112.9, 68.9, 59.9, 45.2, 44.6, 36.4, 34.2, 30.0, 26.1, 21.3, 20.1, 18.2, 14.4, −3.8, −4.0; HRMS (ESI$^+$) $[M + Na]^+$ *m*/*z*: calcd. for $C_{21}H_{40}NaO_3Si^+$ 391.2639, found: 391.2649.

(5*S*,7*S*,9*S*,*Z*)-7-((*tert*-Butyldimethylsilyl)oxy)-5,9-dimethylundeca-2,10-dienoic acid (**23**)

To a stirred solution of **48** (38.0 mg, 103 μmol) in THF/EtOH/H_2O (1.50 mL, 1:1:1 v/v) at rt was added $LiOH·H_2O$ (43.0 mg, 1.02 mmol). The reaction mixture was stirred at 50 °C for 3 h. The reaction was then cooled to rt and quenched with sat. aq. NH_4Cl (10.00 mL). The reaction mixture was extracted with EtOAc (3 × 5.00 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/Et_2O, 1:1) afforded *title compound* **23** (31.0 mg, 88%) as a yellow oil.

R_f 0.77 (petroleum ether/Et_2O, 1:1); $[\alpha]_D^{23}$ +22.0 (*c* 0.05, $CHCl_3$); IR ν_{max}/cm^{-1} 2956, 2927, 2856, 2344, 2310, 1695, 1640, 1462, 1250, 1053, 912, 835,775; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (dt, *J* = 11.7, 7.5 Hz, 1H), 5.85 (d, *J* = 11.6 Hz, 1H), 5.68 (ddd, *J* = 17.3, 10.3, 7.6 Hz, 1H), 5.00–4.91 (m, 2H), 3.79–3.73 (m, 1H), 2.64–2.59 (m, 2H), 2.37–2.24 (m, 1H), 1.75–1.66 (m, 1H), 1.49–1.31 (m, 2H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 152.0, 144.7, 120.0, 112.9, 68.9, 45.2, 44.6, 36.5, 34.2, 30.0, 26.1, 21.3, 20.1, 18.2, −3.8, −4.0; HRMS (ESI$^+$) $[M + Na]^+$ *m*/*z*: calcd. for $C_{19}H_{36}NaO_3Si^+$ 363.2326, found: 363.2326.

(2*R*,3*R*)-1-((4-Methoxybenzyl)oxy)-3-methylpent-4-en-2-yl (5*S*,7*S*,9*S*,*Z*)-7-((*tert*-butyldimethylsilyl)oxy)-5,9-dimethylundeca-2,10-dienoate (**22**) and (2*R*,3*R*)-1-((4-methoxybenzyl)oxy)-3-methylpent-4-en-2-yl (5*S*,7*S*,9*S*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-5,9-dimethylundeca-2,10-dienoate (**37**)

To a stirred solution of **23** (30.0 mg, 88.1 μmol) in toluene (1.00 mL) at rt was added 2,4,6-trichlorobenzoyl chloride (15.0 μL, 95.9 μmol) followed by N*i*Pr_2Et (70.0 μL, 402 μmol) and DMAP (5.50 mg, 49.0 μmol). The reaction mixture was stirred at rt for 5 min, then a solution of **5** (20.0 mg, 84.6 μmol) in toluene (0.50 mL) was added. The reaction mixture was stirred at 80 °C for 18 h then cooled to rt. The reaction was quenched with sat. aq. $NaHCO_3$ (5.00 mL) and the separated aqueous layer was extracted with EtOAc (3 × 3.00 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 19:1) afforded *desired compound* **22** (9.00 mg, 19%) as a colourless oil and *E isomer* **37** (28.0 mg, 59%) as a colourless oil.

Characterisation of 22:

R_f 0.66 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{23}$ +18.0 (*c* 0.10, $CHCl_3$); IR ν_{max}/cm^{-1} 2957, 2927, 2856, 1722, 1641, 1514, 1463, 1416, 1376, 1249, 1172, 1101, 1039, 913, 805, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.20 (ddd, *J* = 11.6, 6.8, 8.0 Hz, 1H), 5.84 (dt, *J* = 11.6, 1.8 Hz, 1H), 5.78–5.63 (m, 2H), 5.07–4.91 (m, 3H), 4.45 (ABq, $\Delta\nu_{AB}$ = 25.0 Hz, J_{AB} = 11.7 Hz, 2H), 3.80 (s, 3H), 3.78–3.71 (m, 1H), 3.51 (ABX, $\Delta\nu_{AB}$ = 10.0 Hz, J_{AB} = 10.5 Hz, J_{AX} = 5.7 Hz, J_{BX} = 4.7 Hz, 2H), 2.69–2.51 (m, 3H), 2.37–2.26 (m, 1H), 1.72–1.62 (m, 1H), 1.49–1.28 (m, 4H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.90–0.87 (m, 12H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 159.4, 149.4, 144.7, 139.4, 130.4, 129.4, 120.8, 115.8, 113.9, 112.9, 74.8, 72.9, 69.3, 68.9, 55.4, 45.3, 44.6, 39.1, 36.5, 34.2, 30.0, 26.1, 21.3, 20.0, 18.2, 16.5, −3.8, −4.0; HRMS (ESI$^+$) $[M + Na]^+$ *m*/*z*: calcd. for $C_{33}H_{54}NaO_5Si^+$ 581.3633, found: 581.3626.

Characterisation of 37:

R_f 0.59 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{23}$ +4.0 (*c* 0.10, $CHCl_3$); IR ν_{max}/cm^{-1} 2957, 2929, 2857, 1722, 1654, 1614, 1514, 1463, 1361, 1249, 1172, 1102, 1039, 913, 835, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.97–

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6.88 (m, 1H), 6.86 (d, J = 8.7 Hz, 2H), 5.83 (dt, J = 15.6, 1.4 Hz, 1H), 5.78–5.63 (m, 2H), 5.08–4.92 (m, 5H), 4.45 (ABq, $\Delta\nu_{AB}$ = 27.5 Hz, J_{AB} = 11.7 Hz, 2H), 3.80 (s, 3H), 3.78–3.71 (m, 1H), 3.52 (ABX, $\Delta\nu_{AB}$ = 10.5 Hz, J_{AB} = 10.5 Hz, J_{AX} = 5.7 Hz, J_{BX} = 4.6 Hz, 2H), 2.65–2.56 (m, 1H), 2.34–2.22 (m, 2H), 2.05–1.96 (m, 1H), 1.77–1.68 (m, 1H), 1.46–1.28 (m, 4H), 1.01 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.90–0.88 (m, 12H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 159.4, 148.2, 144.7, 139.4, 130.4, 129.4, 122.8, 115.8, 113.9, 112.9, 75.1, 72.9, 69.3, 68.9, 55.4, 45.2, 44.6, 40.1, 39.2, 34.3, 29.2, 26.1, 21.3, 20.2, 18.2, 16.5, −3.8, −4.0; HRMS (ESI$^+$) $[M + Na]^+$ m/z: calcd. for $C_{33}H_{54}NaO_5Si^+$ 581.3633, found: 581.3620.

(3*Z*,6*S*,8*S*,10*S*,11*E*,13*R*,14*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-14-(((4-methoxybenzyl)oxy)methyl)-6,10,13-trimethyloxacyclotetradeca-3,11-dien-2-one (**3**) and (1*S*,3*S*,7*S*,*Z*)-1-((*tert*-butyldimethylsilyl)oxy)-3,7-dimethylcyclooct-4-ene (**40**)

To a stirred solution of **22** (8.00 mg, 14.3 µmol) in CH_2Cl_2 (30.0 mL) at rt was added a solution of Grubbs Catalyst™ 2nd Generation (2.50 mg, 2.94 µmol) in CH_2Cl_2 (1.00 mL). The reaction mixture was stirred at rt for 18 h then a second solution of Grubbs Catalyst™ 2nd Generation (2.50 mg, 2.94 µmol) in CH_2Cl_2 (1.00 mL) was added. The reaction mixture was stirred at rt for another 24 h then a final solution of Grubbs Catalyst™ 2nd Generation (1.20 mg, 1.41 µmol) in CH_2Cl_2 (1.00 mL) was added. The reaction mixture was then stirred at rt for a further 3 d, then filtered through a pad of Celite® eluting with CH_2Cl_2, and the filtrate concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 18:1) afforded *desired product* **3** (0.70 mg, 9%) as a colourless residue and *side product* **40** (1.60 mg, 42%) as a colourless oil.

Characterisation of 3:

R_f 0.60 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{23}$ +25.0 (*c* 0.04, $CHCl_3$), (lit.[22] $[\alpha]_D^{20}$ +40.6 (*c* 0.87, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.24 (m, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.21 (dt, J = 12.2, 3.7 Hz, 1H), 5.92 (dd, J = 11.7, 2.3 Hz, 1H), 5.16 (dd, J = 15.1, 9.3 Hz, 1H), 5.02 (dd, J = 15.1, 9.2 Hz, 1H), 4.94 (ddd, J = 10.3, 4.5, 2.6 Hz, 1H), 4.48 (ABq, $\Delta\nu_{AB}$ = 62.7 Hz, J_{AB} = 9.5 Hz, 2H), 3.80 (s, 3H), 3.68 (dt, J = 20.1, 4.5 Hz, 1H), 3.56 (ABX, $\Delta\nu_{AB}$ = 12.9 Hz, J_{AB} = 8.8 Hz, J_{AX} = 3.8 Hz, J_{BX} = 2.1 Hz, 2H), 3.48 (t, J = 9.9 Hz, 1H), 2.43–2.38 (m, 1H), 2.24–2.17 (m, 1H), 2.08–2.01 (m, 1H), 1.95–1.90 (m, 1H), 1.00 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.89–0.87 (m, 12H), 0.13 (s, 3H), 0.09 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 145.9, 137.6, 132.0, 130.3, 129.5, 122.2, 113.9, 74.6, 73.0, 69.7, 68.6, 55.4, 47.8, 44.9, 39.5, 34.7, 31.2, 27.6, 26.2, 22.8, 20.2, 18.5, 17.4, −3.0, −3.3; HRMS (ESI$^+$) $[M + Na]^+$ m/z: calcd. for $C_{31}H_{50}NaO_5Si^+$ 553.3320, found: 553.3322. Analytical data was in agreement with that reported in the literature.[22]

Characterisation of 40:

R_f 0.95 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{23}$ +14.3 (*c* 0.30, $CHCl_3$); IR ν_{max}/cm^{-1} 2955, 2927, 2857, 1461, 1376, 1257, 1085, 1044, 835, 807, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49–5.38 (m, 2H), 3.67–3.61 (m, 1H), 2.54–2.38 (m, 2H), 1.94–1.86 (m, 1H), 1.83–1.78 (m, 1H), 1.71–1.55 (m, 3H), 1.45–1.36 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.87 (d, J = 6.8 Hz, 3H), 0.055 (s, 3H), 0.053 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 124.5, 73.5, 49.0, 45.1, 31.4, 31.0, 29.0, 26.1, 23.5, 21.4, 18.4, −4.6; HRMS (ESI$^+$) $[M + Na]^+$ m/z: calcd. for $C_{16}H_{32}NaOSi^+$ 291.2115, found: 291.2102. Analytical data was in agreement with that reported in the literature for *ent*-**40**.[31]

(3*E*,6*S*,8*S*,10*S*,11*E*,13*R*,14*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-14-(((4-methoxybenzyl)oxy)methyl)-6,10,13-trimethyloxacyclotetradeca-3,11-dien-2-one (**39**) and (1*S*,3*S*,7*S*,*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethylcyclooct-4-ene (**40**)

To a stirred solution of **37** (17.0 mg, 30.4 µmol) in 1,2-dichloroethane (50.0 mL) at rt was added a solution of Grubbs Catalyst™ 2nd Generation (5.20 mg, 6.13 µmol) in CH_2Cl_2 (1.00 mL). The reaction mixture was then stirred under reflux for 18 h. The reaction mixture was cooled to rt then filtered through a pad of Celite® eluting with CH_2Cl_2, and the filtrate concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 18:1) afforded *desired compound* **39** (1.60 mg, 10%) as a colourless residue and *side product* **40** (4.60 mg, 57%) as a colourless oil.

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Characterisation of 39:

R_f 0.52 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{23}$ +37.5 (*c* 0.05, $CHCl_3$); IR ν_{max}/cm^{-1} 2959, 2921, 2851, 2372, 1717, 1607, 1513, 1461, 1378, 1259, 1169, 1092, 1019, 796; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.24 (m, 2H), 7.06–6.99 (m, 1H), 6.87 (d, J = 8.7 Hz, 2H), 5.79 (d, J = 15.6 Hz, 1H), 5.15–5.06 (m, 2H), 4.73 (ddd, J = 10.5, 3.8, 2.5 Hz, 1H), 4.48 (ABq, $\Delta\nu_{AB}$ = 75.5 Hz, J_{AB} = 9.5 Hz, 2H), 3.80 (s, 3H), 3.64 (ABX, $\Delta\nu_{AB}$ = 18.3 Hz, J_{AB} = 9.0 Hz, J_{AX} = 3.1 Hz, J_{BX} = 2.0 Hz, 2H), 3.59–3.52 (m, 1H), 2.65–2.56 (m, 1H), 2.37–2.30 (m, 1H), 2.19–2.13 (m, 1H), 1.88–1.80 (m, 1H), 0.95 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.89–0.86 (m, 12H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 159.4, 149.8, 138.7, 131.6, 130.3, 129.5, 122.2, 113.9, 76.0, 73.0, 71.5, 69.0, 55.4, 48.0, 42.3, 39.4, 35.1, 30.6, 26.2, 26.1, 24.5, 23.2, 18.5, 17.7, −3.1; HRMS (ESI^+) $[M + Na]^+$ *m/z*: calcd. for $C_{31}H_{50}NaO_5Si^+$ 553.3320, found: 553.3317.

Analytical data for **40** was in agreement with that reported above.

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Keywords: callyspongiolide • homocrotylation • natural product • ring closing metathesis • Yamaguchi esterification

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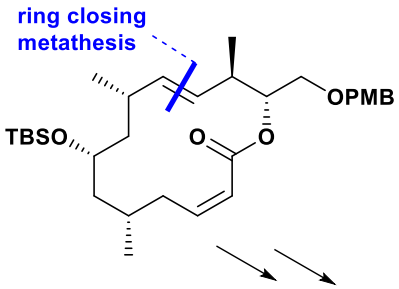

(+)-callyspongiolide

An enantioselective synthesis of macrocyclic core of (+)-callyspongiolide is described, constituting a formal synthesis of this natural product. The synthetic strategy constructs the 14-membered macrocyclic domain *via* Yamaguchi esterification followed by a challenging ring-closing metathesis to effect the final formation of the macrolactone.

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