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Synthetic Studies on Alotamide A: Construction of *N*-Demethylalotamide A

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Several approaches to the synthesis of cyclodepsipeptide natural product alotamide A are described, eventually affording a very advanced *N*-demethylated analogue of the targeted natural product. The difficulties found in our endeavors on the synthesis of alotamide A have allowed us to gather some valuable information regarding the most convenient synthetic step for each key transformation. The intramolecular Csp^2–Csp^2 Stille cross-coupling and the macrolactam formation were found to be reliable protocols for the final construction of the alotamide A skeleton.

Introduction

With their intricate structures shaped along evolution, natural products continue to be the most prolific source and inspiration for the development of new drugs.[1] Extracts containing secondary metabolites have been used for health benefits and for the treatment of diseases since the existence of human civilization. Furthermore, the development of modern isolation, characterization, and synthetic protocols have allowed the structural identification of the active pharmaceutical ingredient (API) present in the natural source, a deeper understanding of their biological targets, the development of an efficient synthetic route to the metabolite, and the eventual preparation of some synthetic analogues of improved biological profile. Among all sources explored for isolation of natural products, marine organisms have been a very prolific wellspring of secondary metabolites of exciting molecular architecture and biological properties. Up to six drugs have been approved by EMA or FDA for the treatment of different diseases, the structures of which have been the result of appropriate modifications of marine natural products.[2] Furthermore, marine-derived cyclodepsipeptides, a family of cyclic natural products that contain an ester group replacing at least one of the amide bonds within a peptide chain, have been identified as a group of secondary metabolites with very promising biological activities, and several natural products-inspired analogues are undergoing advanced clinical trials (Figure 1).[3]

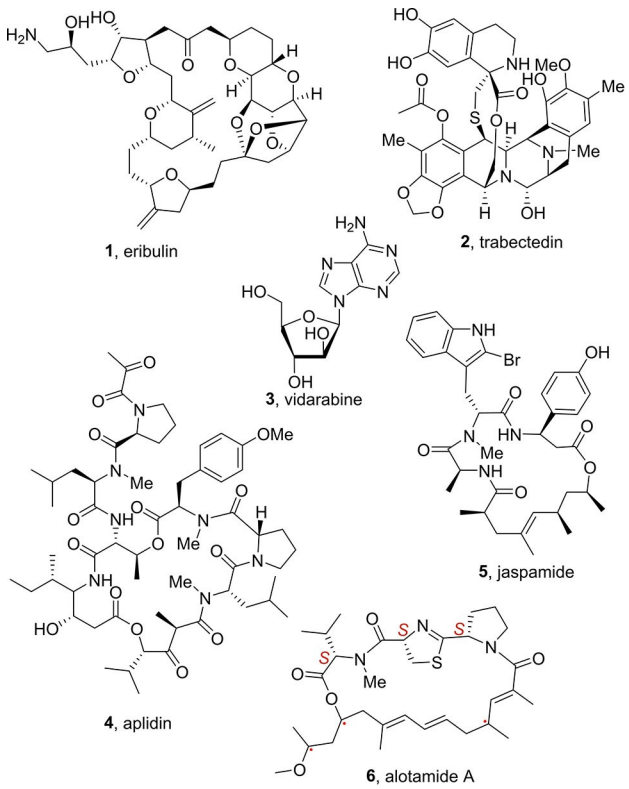

Figure 1. Selection of biologically active marine natural products and derivatives, including a selection of FDA-approved drugs.

Alotamide A (**6**), a secondary metabolite isolated from the marine mat-forming cyanobacterium *Lyngbya bouillonii* in Papua New Guinea,[4] belongs to the previously mentioned family of cyclodepsipeptide natural products. Its structure features a peptidic fragment derived from L-Val, D-Cys, and L-Pro units, the last two forming a thiazoline ring, which is connected to a trienylheptaketide containing three additional stereocenters. Furthermore, alotamide A (**6**) exhibited very interesting biological activity as calcium-influx activator (EC_{50} of 4.18 μM) of murine cerebrocortical neurons, and therefore this natural product holds potential interest as neurotoxin, since calcium overload may induce several diseases, including

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Alzheimer and epilepsy. Unfortunately, due to the scarce amounts of the compound isolated from the natural source (in the microgram scale), its complete structural elucidation was not possible, and the relative and absolute configurations of the three stereocenters of the polyketide fragment remain undefined.

Over the past decade our group has developed an extensive work in the synthesis of biologically active natural products, contributing to the confirmation, and in some cases revision, of the initially proposed structures.[5]

In view of this, a total synthesis of natural product alotamide A (**6**) seemed to us a very attractive, although challenging, enterprise that would eventually afford unambiguous structural determination of the secondary metabolite while rendering enough material for deeper biological characterization, an activity that could be extended to some synthetically advanced intermediates and analogues. Herein, we describe our results on the synthesis of a *N*-demethylated-alotamide A stereoisomer. Up to three different synthetic approaches are described (routes A–C, Figure 2), pitfalls deeply discussed, and more productive steps highlighted, in order to define the most convenient manner to address the challenging preparation of this natural product.

Results and Discussion

Route A

Considering the structural divergence between the northern (**7**) and southern (**8**) fragments comprising alotamide A (**6**), we initially envisaged a convergent approach (namely, esterification-lactamization) that would make use of an esterification reaction for the initial connection of the two independent fragments while the macrocyclization would proceed through the formation of the C(O)-N bond. The upper fragment could be prepared by sequential coupling of properly functionalized amino acids[6] (i.e. L-Val, D-Cys, L-Pro) and eventual thiazoline formation.[7] For the polyketide fragment, we envisioned the diastereoselective alkylation of enolates induced by an external chiral auxiliary[8] and a diastereoselective allylation of aldehyde **14**, derived from enantiopure ethyl 3-hydroxybutanoate (**12**)[9] for the generation of the required stereocenters at C4 and C11, combined with palladium-catalyzed cross-coupling, as well as olefination reactions for the stereoselective construction of the triene fragment.[10]

Due to the previously mentioned lack of information regarding the configuration at C4, C11 and C2′, and in order to explore the suitability of our synthetic proposal, commercially available ethyl (*R*)-3-hydroxybutanoate (**12**) was arbitrarily chosen as starting material, which would allow the generation of up to four, out of eight, possible stereoisomers of fragment **8**.

The methylation of ethyl (*R*)-3-hydroxybutanoate (**12**), using methyl triflate as electrophile and 2,6-di-*tert*-butyl-4-methylpyridine as base[11] rendered methyl ether **13** in 88% yield, which was subsequently reduced to aldehyde **14** in 69% yield with just one equivalent of DIBAL-H at low temperature. Unfortunately, upon treatment of **14** with prop-2-yn-1-ylmagnesium bromide, homopropargylic alcohol **15** was obtained in good yields but as a mixture of diastereomers in a 1:1 ratio.[12] Since separation of the two diastereomers proved challenging at this stage, we decided to continue our synthesis with the diastereomeric mixture, in order to determine the most convenient step for the separation of the two compounds using regular purification techniques. After protection of alcohol **15** as silyl ether **16** (TBSCl, Imidazole, DMF, 87% yield), the terminal alkyne was transformed into the trisubstituted *E*-alkenylsilane **17**, in quantitative yield and regioselective manner, by addition of *in situ* generated lithium bis(phenyldimethylsilyl)cuprate and MeI. Using the methodology previously developed by Kishi[13] and Zakarian,[14] we were able to perform a combined stereoselective iododesilylation and silyl ether cleavage, without isolation of the intermediate, in good yield and complete preservation of the olefin geometry. After deprotection, the diastereomeric mixture of alcohols **18** could be then separated by HPLC and their absolute configuration determined using the methodology described by Riguera and co-workers with meth-

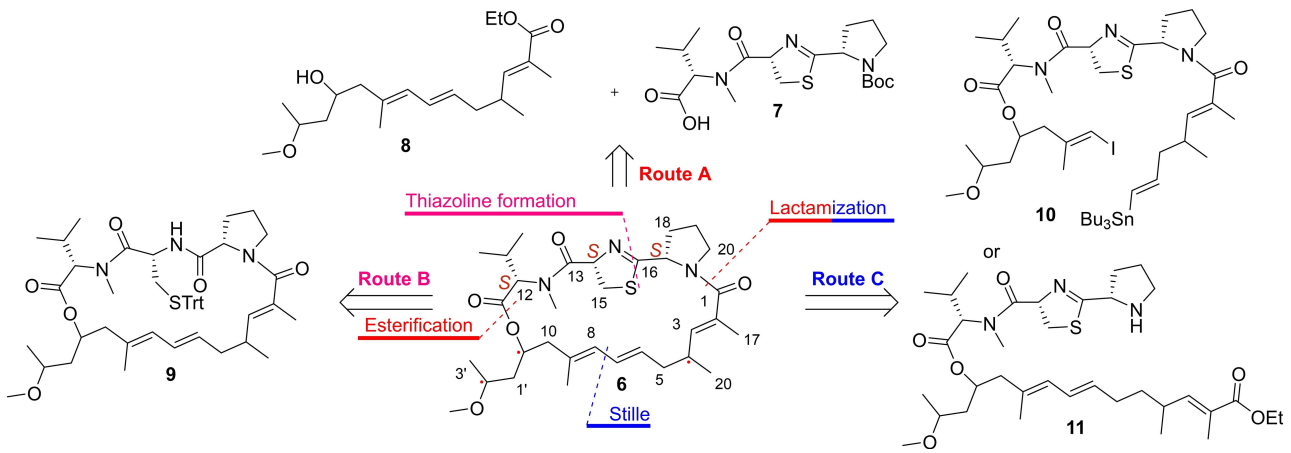
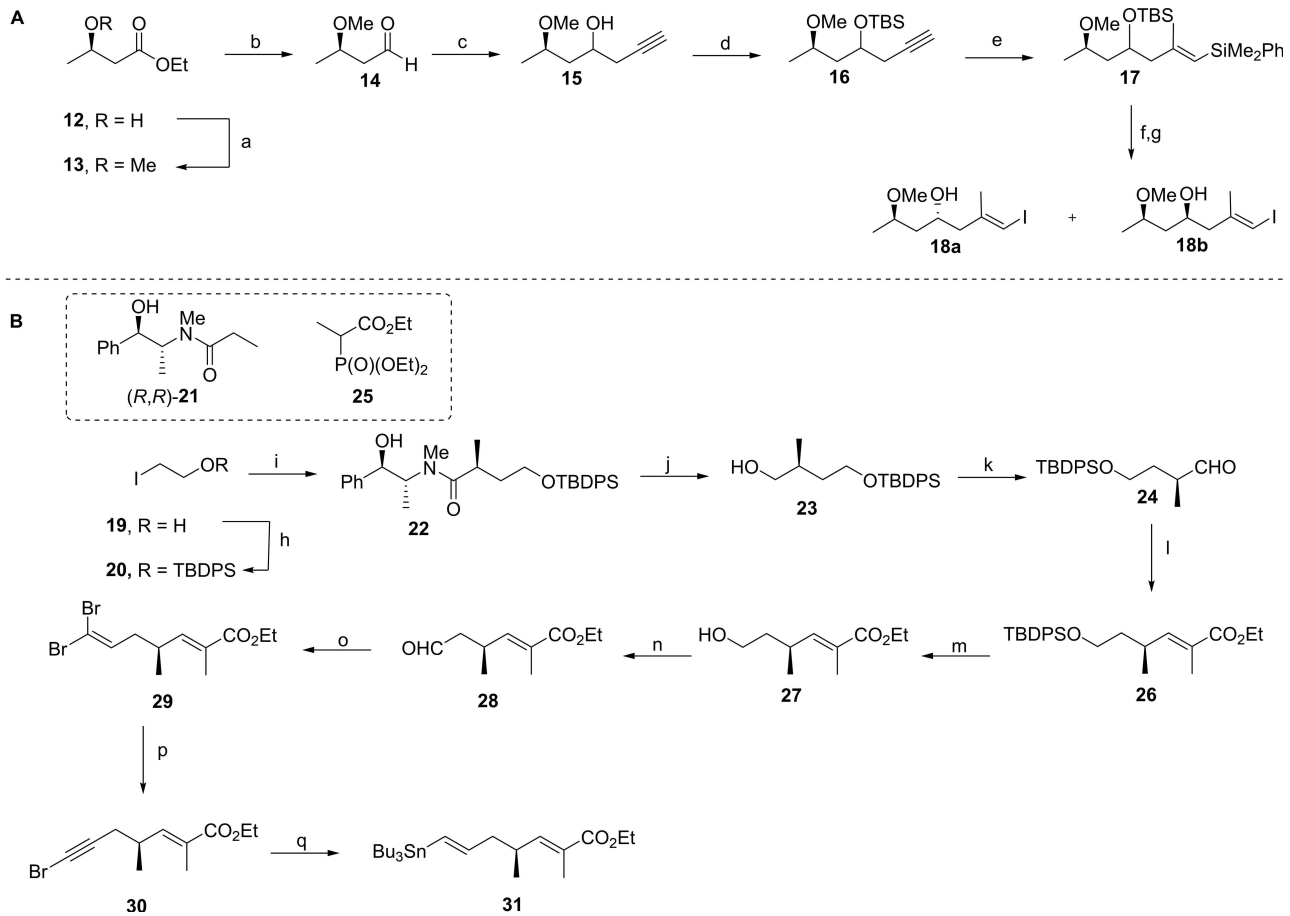


Figure 2. Synthetic pathways, and their key transfomations, explored en route to alotamide A (**6**).

oxypheynylacetic acid esters as auxiliary reagents for the assignment of the absolute configuration of secondary alcohols (Scheme 1A).[15]

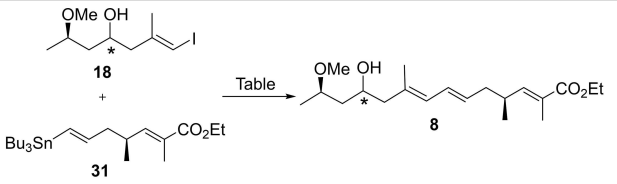
The synthesis of alkenylstannane **31** started with the protection of 2-iodoethanol **19** as silyl ether to render **20** in almost quantitative manner. Then, the compound was subjected to reaction conditions previously developed by Myers and co-workers[8b,16] for the asymmetric alkylation of pseudoephedrine derivative (*R*,*R*)-**21** (LDA, THF, −78 °C), which led to the isolation of **22** in 94% yield, with exquisite diastereoselectivity towards the *S* configuration of the newly created stereocenter. Subsequent reductive elimination of the directing group upon treatment with $BH_3{\cdot}NH_3$, *n*-BuLi and *i*-Pr_2NH in THF, afforded the corresponding alcohol **23** in 85% yield, which was oxidized to **24**, without epimerization of the chiral center at the vicinal position, using the Swern variant ($(COCl)_2$, DMSO, Et_3N, −60 °C) in 90% yield.[17] Aldehyde **24** was subjected to thermodynamically-controlled Horner-Wadsworth-Emmons reaction, previously developed by Davies,[18] with the anion of phosphonate **25** generated using MeMgBr as base in THF at 90 °C to afford stereoselectively (10:1 *E*/*Z* ratio), the α,β-unsaturated ester **26** in good yield (87%). Deprotection of the silyl ether and Swern oxidation of the corresponding alcohol **27** afforded aldehyde **28** in 74% yield over two steps. Then, a three-step sequence initiated with the formation of the geminal alkenyl dibromide **29**, employing PPh_3 and CBr_4, transformation into the corresponding bromoalkyne **30** upon addition of NaHMDS, and finally Pd-promoted regio- and stereoselective addition of Bu_3SnH allowed to generate the alkenylstannane **31** in 45% combined yield (Scheme 1B).[19]

With **18a**/**18b** and **31** in hand, we next performed the Stille cross-coupling to generate the non-conjugated ethyl trienoate diastereomers (4*S*,11*R*,2′*R*)-**8a** (*anti*-1,3-hydroxy methyl ether moiety) and (4*S*,11*S*,2′*R*)-**8b** (*syn*-1,3-hydroxy methyl ether moiety). We initially tested the reaction conditions previously described by Farina and co-workers for the Stille cross-coupling,[20] although no reaction was observed between **18a** and **31** (Table 1, entry 1). Alternatively, under the reaction conditions used by Maier for the synthesis of palmerolide A,[21] the desired product could be isolated, albeit in marginal yield (Table 1, entry 2). To our delight, when the methodology previously developed by Fürstner and co-workers[22] was applied



Scheme 1. Reagents and conditions. a) DTBMP, MeOTf, CH_2Cl_2, 25 °C, 88%; b) DIBAL-H, CH_2Cl_2, −85 °C, 69%; c) Prop-2-yn-1-ylmagnesium bromide, THF, −78 °C, 71%; d) TBSCl, imidazole, DMF, 25 °C, 87%; e) $Me_2PhSiLi$, CuCN, MeI, THF, 0 °C, 98%; f) NIS, 2,6-lutidine, HFIP, 0 °C, 98%; g) TBAF, THF, 0 °C, 80%; h) TBDPSCl, imidazole, DMF, 25 °C, 97%; i) (*R*,*R*)-**21**, LiCl, *n*-BuLi, *i*-Pr_2NH, THF, −78 °C, 94%, >99% dr; j) $BH_3{\cdot}NH_3$, *n*-BuLi, *i*-Pr_2NH, THF, 25 °C, 85%; k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C, 90% for **24**, 90% for **28**; l) **25**, MeMgBr, THF, 90 °C, 87% (10:1 *E*/*Z* ratio); m) TBAF, THF, 25 °C, 82%; n) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 61%; o) NaHMDS, THF, −78 °C, 91%; p) *n*-Bu_3SnH, $Pd_2(dba)_3$, PPh_3, THF, 25 °C, 72%.

Table 1. Synthesis of the polyketide fragment **8**.



Entry	18	(*)	Reaction conditions	8	Yield [%]
1	**18a**	(*R*)	Pd_2dba_3, $AsPh_3$, DMF, 25 °C	**8a**	0
2	**18a**	(*R*)	$Pd(CH_3CN)_2Cl_2$, LiCl, Et_3N, DMF, 25 °C	**8a**	< 10
3	**18a**	(*R*)	$Pd(PPh_3)_4$, CuTC, $[Ph_2PO_2][n\text{-}Bu_4N]$, DMF, 25 °C	**8a**	75
4	**18b**	(*S*)	$Pd(PPh_3)_4$, CuTC, $[Ph_2PO_2][n\text{-}Bu_4N]$, DMF, 25 °C	**8b**	59

to our reaction, we were able to obtain **8a** in 75% yield from **18a** and **31**. A similar outcome was observed for the coupling of **18b** and **31**, which led to **8b** in 59% yield (Table 1, entries 3 and 4).

During our investigation, a publication on the synthesis of **8** was released,[23] that used a boron-mediated enantioselective aldol reaction and a Julia-Kocienski olefination as key steps, rendering the desired fragment in 23 steps (longest linear sequence of 14 steps). The authors completed the synthesis of four out of the eight possible diastereomers of the polyketide fragment, in which the *R* configuration of the chiral center at C4 of the natural product was arbitrary set. Then, by comparison of the ^{1}H NMR and ^{13}C NMR spectroscopic data of all synthesized compounds to those of alotamide A (**6**), they proposed a *syn* relative configuration for the 1,3-hydroxyether moiety (C11 and C2′) of the natural product and planned their future work in its total synthesis accordingly.

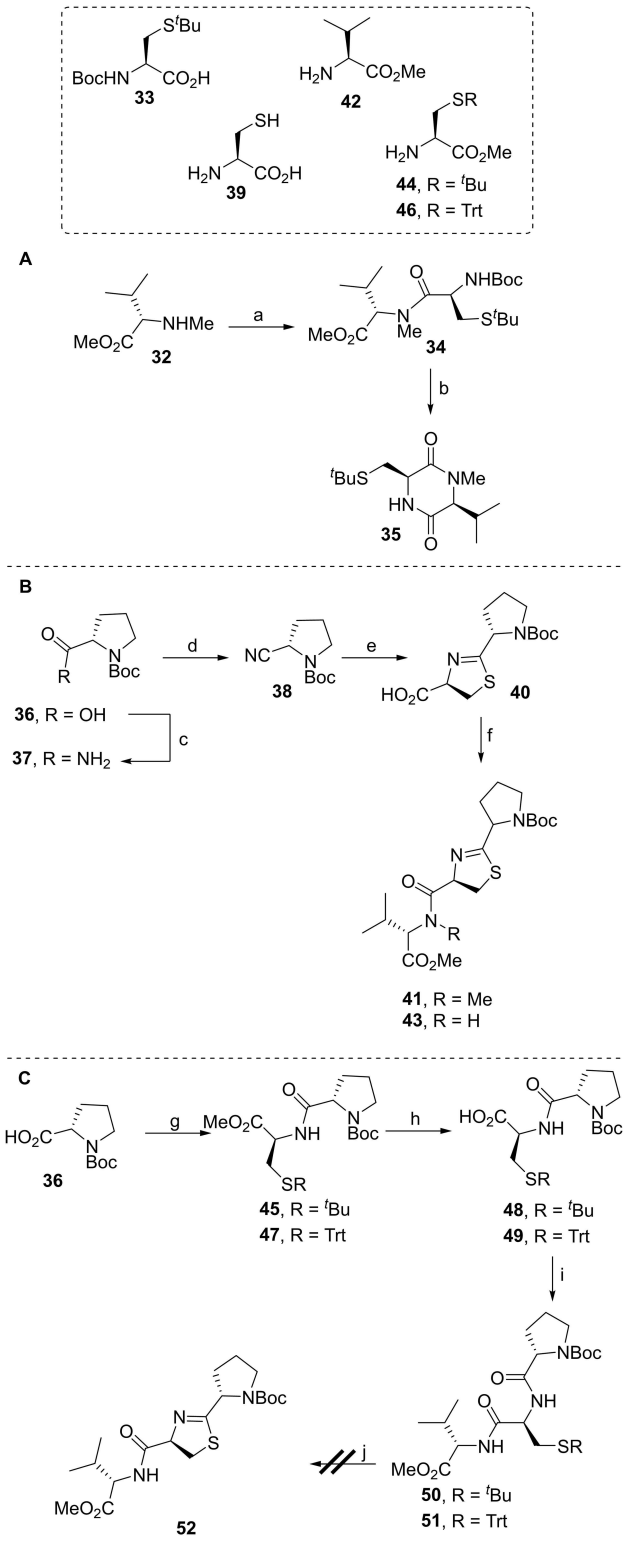
In comparison, our synthetic approach describes the preparation of the heptaketide fragment in a slightly shorter (18 *vs.* 23 steps, 10 *vs.* 14 steps longest linear sequence) and more convergent strategy, that relies on cross-coupling reactions for the stereoselective formation of the diene fragment. Additionally, when we carried out the same ^{1}H and ^{13}C NMR data comparison of alotamide A (**6**) to compounds **8a** (4*S*,11*R*,2′*R*) (*anti*-1,3-hydroxy methyl ether moiety) and **8b** (4*S*,11*S*,2′*R*) (*syn*-1,3-hydroxy methyl ether moiety) we obtained a slightly better fitting for compound **8a** relative to compound **8b**, which is opposite to what was earlier described.[23,24] Although not conclusive comments can arise from it, this finding highlights the difficulty on assigning unknown configuration of natural products based on the preparation of truncated fragments and subsequent NMR data comparison, thus positioning total synthesis of natural products as the only valid methodology for unambiguous structural characterization of secondary metabolites.

For the preparation of the modified peptide fragment **7** (Figure 2), different synthetic routes were explored. Initially, following a C–N peptide bond formation strategy, and using more accessible L-Cys for optimization purposes, we were able to couple *N*-Me-L-Val methyl ester **32** with *N*-Boc-*S*-*t*-Bu-protected L-Cys **33** in 38% yield using HATU and DIPEA as condensation agents. Subsequent TFA-mediated deprotection of the *tert*-butyl carbamate present in **34** did not afford the expected product. Instead, diketopiperazine **35** was isolated (Scheme 2A). An identical reaction outcome was observed when other protecting groups at nitrogen and sulfur atoms (Scheme 2A) were used.[24] Nevertheless, this unsatisfactory side-reaction is a well-documented process, especially with *N*-alkylated amino acids.[25]

An inverted N–C peptide bond formation strategy was then evaluated for the preparation of **7** (Scheme 2B). When *N*-Boc-protected L-proline **36** was treated with Boc_2O and $(NH_4)_2CO_3$ in dioxane,[26] the primary amide **37** was obtained in 99% yield, which was quantitatively transformed into the corresponding nitrile **38** by dehydration promoted by trifluoroacetic anhydride. Subsequently, the condensation of **38** with L-Cys **39** in the presence of DIPEA in EtOH at 90 °C rendered **40** in 85% yield. Unfortunately, any attempt to perform a peptide bond formation reaction of this molecule with *N*-Me-L-Val methyl ester **32** did not generate the expected product **41**, probably due to the well-known lower reactivity for C–N bond generation of *N*-methylated amino acids vs. non-methylated ones,[25b] as experimentally confirmed by the almost quantitative yield (97%) observed for the formation of non-methylated analogue **43**. Disappointingly, peptide **43** was obtained as a mixture of diastereomers, presumably due to the epimerization at the proline stereocenter being adjacent to the thiazoline ring[24] (Scheme2B). An alternative synthetic approach started with the coupling of **36** with either cysteine derivatives **44** or **46**, differing at the protecting group present on the cysteine SH (*t*-Bu or Trt), which rendered the corresponding dipeptides **45** and **47** in 85% and 90% yield, respectively (Scheme 2C). Both compounds were satisfactorily transformed into the corresponding carboxylic acids **48** and **49** in quantitative yield. Surprisingly, only the HATU-promoted amide bond formation reaction between **42** and **49** did work and generated the tripeptide **51** in 64% yield. Unfortunately, all attempts to form the thiazoline ring were unsuccessful.[24]

Route B

Alternatively, arbitrarily chosen vinyl iodide **18a** (*anti* relative configuration) was condensed with *N*-Boc-L-Val **53** in the presence of EDC to render **54** in quantitative yield (Scheme 3). Subsequent deprotection of the carbamate group (TFA, CH_2Cl_2, quantitative yield) followed by coupling with dipeptide **55**, itself synthesized as described for diastereomer **49** (Scheme 2C), promoted by HATU and DIPEA in CH_2Cl_2, rendered **56**, a molecule that already contains all the amino acids present in the natural product, in 60% yield. Subsequently carbamate hydrolysis, followed by amide bond formation reaction with carboxylic acid **57**, prepared by basic hydrolysis of ester **31**,[24] using likewise HATU and DIPEA, generated acyclic structure **58** in 63% combined yield. Eventually, the intramolecular Stille cross-coupling using reaction conditions previously described by Farina and co-workers,[20] using $Pd_2(dba)_3$ and $AsPh_3$ in DMF rendered the desired compound **59** in 47% yield, together with



Scheme 2. Reagents and conditions. a) **33**, HATU, DIPEA, CH_2Cl_2, 16 h, 25 °C, 38%; b) TFA, CH_2Cl_2, 1 h, 25 °C, 73% (two steps); c) Boc_2O, pyridine, $(NH_4)_2CO_3$, dioxane, 25 °C, 99%; d) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 25 °C, 99%; e) **39**, DIPEA, EtOH, 90 °C, 85%; f) (**R** = **Me**), **32**, PyBOP, DIPEA, CH_2Cl_2, 25 °C, NR. (**R** = **H**), **42**, PyBOP, DIPEA, CH_2Cl_2, 25 °C, 97%; g) (**R** = ***t*-Bu**), **44**, HATU, DIPEA, CH_2Cl_2, 25 °C, 85%. (**R** = **Trt**), **46**, HATU, DIPEA, CH_2Cl_2, 25 °C, 90%; h) (**R** = ***t*-Bu**), LiOH·H_2O, THF, H_2O, 25 °C, 99%. (**R** = **Trt**), LiOH·H_2O, THF, H_2O, 25 °C, 99%; i) (**R** = ***t*-Bu**), **42**, HATU, DIPEA, CH_2Cl_2, 25 °C, NR. (**R** = **Trt**), **42**, HATU, DIPEA, CH_2Cl_2, 25 °C, 64%; j) Tf_2O, Ph_3PO, CH_2Cl_2, 15 min, 25 °C, NR. NR: no reaction.

an isomeric secondary product that could be isolated separately, and, despite extensive spectroscopic characterization, its precise structure remains unknown at present. Unfortunately, all attempts to perform the formation of the thiazoline ring, using hypervalent phosphorous reagents under the reaction conditions previously developed by Kelly and co-workers,[27] did not afford the desired product **60**. Alternatively, the Stille cross-coupling reaction of **56** with stannane **31** rendered compound **61** in 85% yield. TMSOTf-mediated deprotection of the *N*-Boc group, followed by basic hydrolysis of the ethyl ester (TMSOK, THF) did not afford the desired compound. Instead, alcohol **8a**, resulting from the selective hydrolysis of the tripeptide-derived ester, was obtained in 65% combined yield as the only reaction product (Scheme 3).

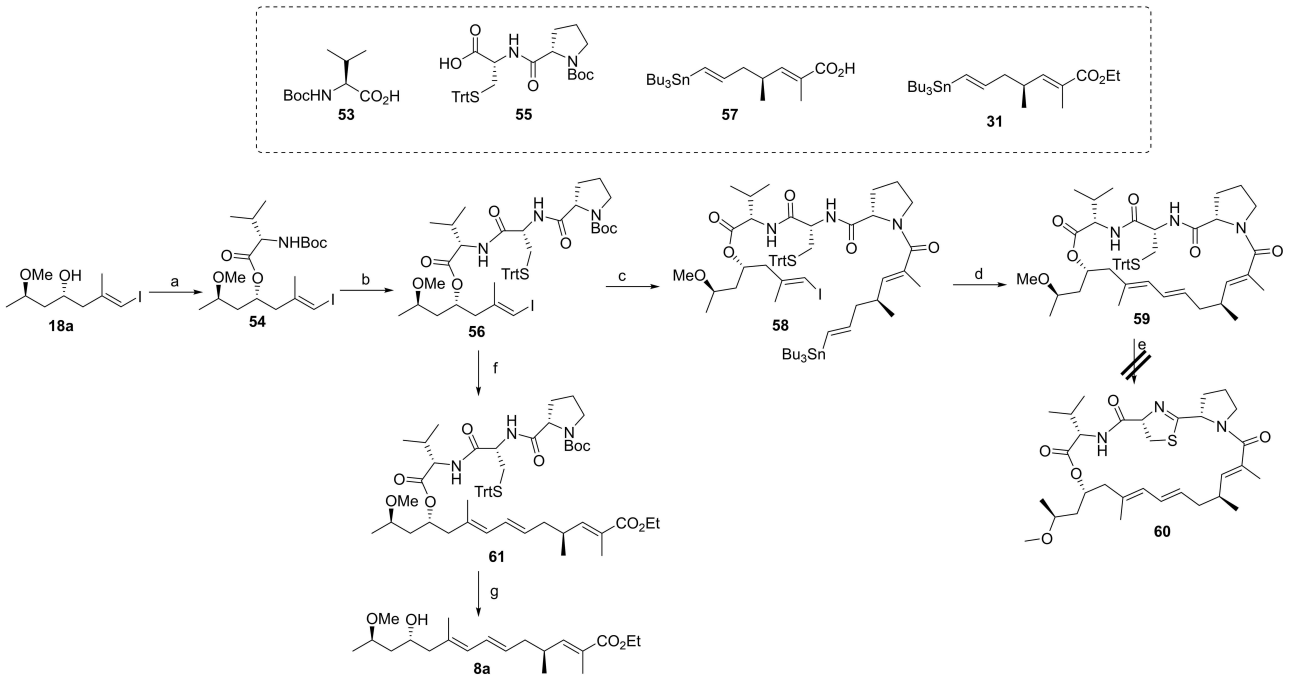
Route C

In view of all the difficulties previously mentioned, we decided to modify the order of connection of the already prepared fragments and to test the convenience of such modification (Scheme 4). For that purpose, **18a** (*anti* relative configuration) was condensed with *N*-Boc-L-Val **53** using EDC in CH_2Cl_2 to afford **54** which, after TFA-promoted deprotection of the carbamate group and coupling with Fmoc-protected dipeptide **67** using HATU and DIPEA, rendered compound **66** in 75% combined yield.

In parallel, coupling of **18a** with *N*-Me-Boc-L-Val **62** under the same conditions afforded ester **63** in 77% yield. TFA-mediated *N*-Boc deprotection of **63** provided the free amine, which was condensed with *N*-Boc-*S*-trityl-Cys **64** (92% combined yield). The same deprotection and amino acid condensation synthetic protocol was repeated to incorporate the required *N*-Fmoc-L-Pro residue **65**, rendering compound **68** in 42% yield over two steps (Scheme 4).

Then, already prepared compounds **66** and **68** were submitted to the methodology previously developed by Kelly and co-workers for the formation of the thiazoline ring.[27] Unexpectedly, the desired heterocycle-containing product was not obtained for the *N*-methylated analogue **68**. Fortunately, the reaction sequence worked nicely for analogue **66**, showing excellent compatibility with all functional groups present in this molecule. Subsequent nitrogen deprotection[28] proceeded without epimerization affording **69** in 49% yield, and coupling with the tin-containing dimethylheptadienoic acid **57** rendered the acyclic intermediate **71** in 63% yield. Final intramolecular Stille cross-coupling reaction, using the methodology previously described by Farina *et al.*[20] led to the isolation of **60** in 49% yield (Scheme 4), as the major product of the reaction, together with an isomer which, despite isolation and extensive characterization, its actual structure remains elusive.

Instead, if iodide **66** was transformed into the corresponding thiazoline and subsequently coupled with stannane **72** having a trimethylsilylmethyl-protected ester, which was obtained from **57** in 62% yield, using the previously described reaction conditions, we were able to isolate **73** as the only product of the reaction which, after carbamate and silyl alkyl



Scheme 3. Reagents and conditions. a) **53**, EDC, CH_2Cl_2, 25 °C, 99%; b) *i.* TFA, CH_2Cl_2, 25 °C, 99%, *ii.* **55**, HATU, DIPEA, CH_2Cl_2, 25 °C, 60%; c) *i.* TMSOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, *ii.* **57**, HATU, DIPEA, CH_2Cl_2, 25 °C, 63% (two steps); d) $Pd_2(dba)_3$, $AsPh_3$, DMF, 25 °C, 47%; e) Tf_2O, Ph_3PO, CH_2Cl_2, 25 °C, NR; f) **31**, $Pd_2(dba)_3$, $AsPh_3$, DMF, 25 °C, 85%; g) *i.* TMSOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, *ii.* TMSOK, THF, 25 °C, 65% (two steps). NR: no reaction.

ester cleavage and, without isolation of intermediates, smoothly converted into macrolactam **60** in 22% combined yield for the three steps as a single product (Scheme 4).

Despite the myriad of methodologies described for the methylation of peptidic nitrogen atoms,[6a,29] due to the scarcity of compound obtained, only two different reaction conditions, essentially varying the nature of the base (LiHMDS or NaH) and the use of co-solvents (DMPU), could be tested. Unfortunately, all efforts to perform that reaction resulted in either recovery or decomposition of the starting material (Scheme 4).

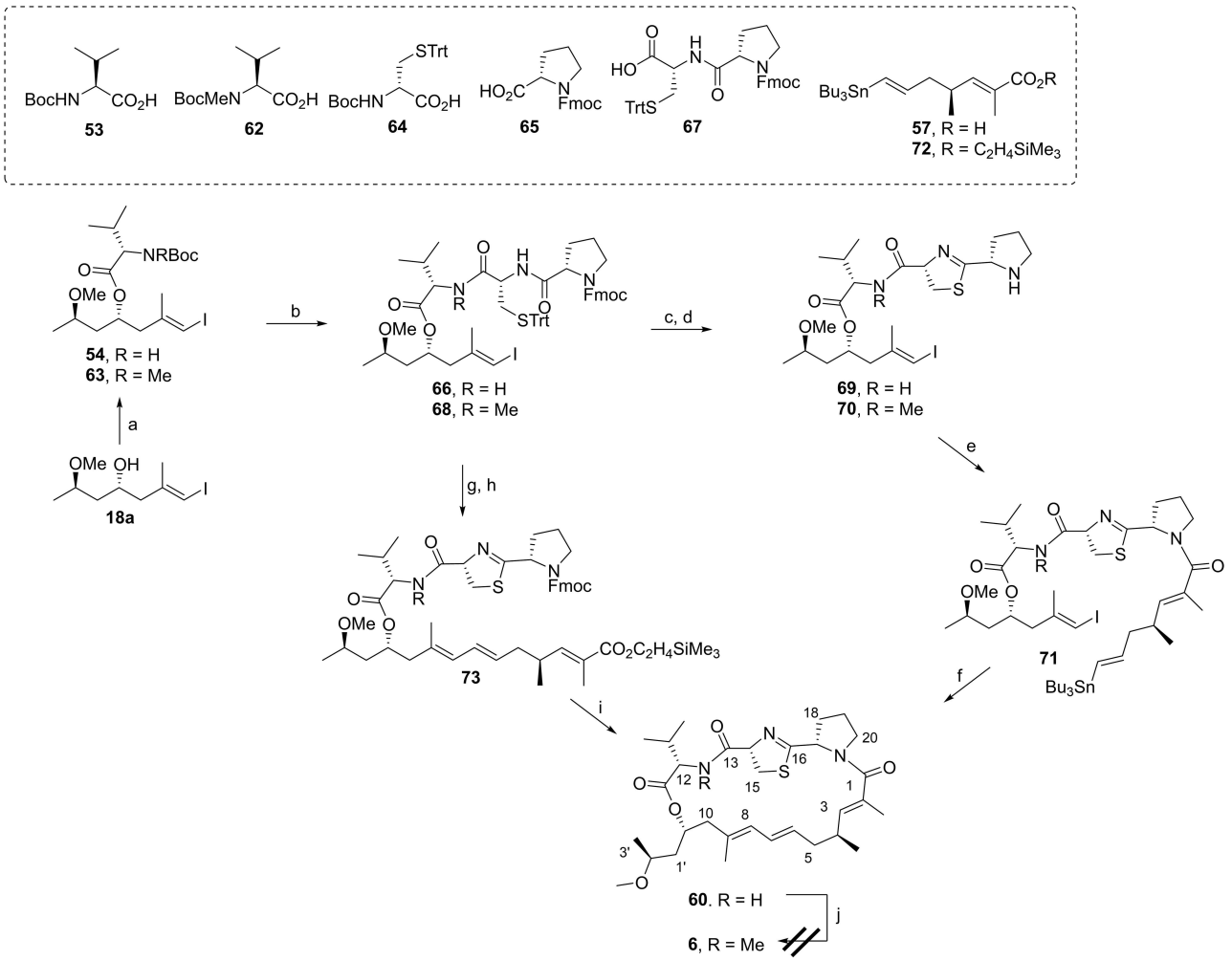
With macrolactam **60** in hand, we performed a ^1H and ^{13}C-NMR data comparison between the non-methylated analogue and natural product alotamide A (**6**).[24] Although no conclusive, we point out that the C3–C6 region showed an unexpected deviation that could hide a difference other than configuration at the C4 stereocenter. The C2=C3 double bond, which was defined as *E* in the isolation paper based on a nOe correlation between C2–$\underline{CH_3}$ and C4–$\underline{CH_3}$, could be missassigned as the isomeric compound bearing a *Z* olefin would presumably show the same correlation due to the high flexibility and conformational freedom present in this macrocycle.

Conclusion

We have developed an extensive work towards the synthesis of natural product alotamide A (**6**) with the preparation of an advanced intermediate **60**. Although not successful at the present stage, our work describes a very efficient protocol for the stereoselective synthesis of the polyketide fragment present in the natural product, while shedding some light on the identification of the most convenient synthetic strategy towards its preparation, namely:

- forming C11-OH ester bond prior to peptide fragment build-up,
- postponing methylation of C13-N in the synthetic sequence,
- using a Fmoc protecting group for the proline nitrogen atom,
- performing thiazoline formation prior to macrocyclization, and
- generating the macrocycle by amide bond formation or Stille cross-coupling reaction.

Furthermore, a comparison of NMR data gathered for several diastereomers of the polyketide fragment highlights the risk of extracting structural conclusions of the 3D arrangement of natural products from isolated small fragments that are embedded in their structure. All gathered data, in combination with modern computational tools for the prediction of NMR chemical shifts of complex molecules,[30] would allow a more rational prediction of the most likely candidate, among all possible diastereomers of alotamide A (**6**). This synergistic approach will be used to re-design our synthetic plan towards the total synthesis of the natural product, which will hopefully unambiguously confirm the absolute configuration of the remaining unknown stereocenters present in the molecule and provide enough material for further biological studies. This work is underway in our laboratories and will be disclosed in due course.



Scheme 4. Reagents and conditions. **1. (R = H)** a) **53**, EDC, CH_2Cl_2, 25 °C, 99%; b) *i.* TFA, CH_2Cl_2, 25 °C, 97%, *ii.* **67**, HATU, DIPEA, CH_2Cl_2, 25 °C, 77%; c) Tf_2O, Ph_3PO, CH_2Cl_2, 15 min, 25 °C, 88%; d) piperidine, CH_3CN, 25 °C, 49%; e) **57**, HATU, DIPEA, CH_2Cl_2, 25 °C, 63%; f) $Pd_2(dba)_3$, $AsPh_3$, DMF, 25 °C, 49%; **2. (R = Me)** a) **62**, EDC, CH_2Cl_2, 25 °C, 77%; b) *i.* TFA, CH_2Cl_2, 25 °C, *ii.* **64**, HATU, DIPEA, CH_2Cl_2, 25 °C, 92% (two steps), *iii.* TFA, CH_2Cl_2, 25 °C; *iv.* **65**, HATU, DIPEA, CH_2Cl_2, 25 °C, 42% (two steps); c) Tf_2O, Ph_3PO, CH_2Cl_2, 15 min, 25 °C, NR; g) Tf_2O, Ph_3PO, CH_2Cl_2, 15 min, 25 °C, 88%. h) **72**, $Pd_2(dba)_3$, $AsPh_3$, DMF, 25 °C, 15%; i) *i.* Piperidine, CH_3CN, 25 °C, 49%, *ii.* TBAF, THF, 25 °C, *iii.* HATU, DIPEA, CH_2Cl_2, 25 °C, 22% (three steps); j) CH_3I, LiHMDS, DMPU, THF, −78 °C or CH_3I, NaH, THF, 0 °C. NR: no reaction.

Experimental Section

General Procedures (see S.I. Section)

Ethyl (*R*)-3-Methoxybutanoate 13

To a cooled (0 °C) solution of ethyl (*R*)-3-hydroxybutanoate **12** (1.54 g, 11.69 mmol) in CH_2Cl_2 (51 mL) were added 2,6-di-*tert*-butyl-4-methylpyridine (12 g, 58.44 mmol) and methyl trifluoromethanesulfonate (6.41 mL, 58.44 mmol). After stirring for 19 h at 25 °C, methyl trifluoromethanesulfonate (3.85 mL, 35.07 mmol) was added and the reaction mixture was further stirred for 8 h. The solvent was evaporated and the residue was purified by flash-column chromatography (silica gel, 97:3 v/v hexane/Et_2O) to afford 1.5 g (88%) of a colorless liquid identified as ethyl (*R*)-3-methoxybutanoate **13**. $[\alpha]^{25}_D$ −3.7 (*c* 1.11, MeOH). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 4.15 (q, *J* = 7.1 Hz, 2H, –O–$\underline{CH_2}$–CH_3), 3.77 (dq, *J* = 7.2, 6.1 Hz, 1H, H_3), 3.33 (s, 3H, $-OCH_3$), 2.57 (dd, *J* = 15.1, 7.2 Hz, 1H, H_{2A}), 2.35 (dd, *J* = 15.1, 5.8 Hz, 1H, H_{2B}), 1.26 (t, *J* = 7.1 Hz, 3H, –O–CH_2–$\underline{CH_3}$), 1.20 (d, *J* = 6.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 171.1 (s), 73.4 (d), 60.0 (t), 56.0 (q), 41.4 (t), 18.9 (q), 13.9 (q) ppm. HRMS (ESI^+): Calcd. for $C_7H_{14}NaO_3$ ([M + Na]$^+$), 169.0835; found, 169.0841. **IR** (NaCl): ν 2978 (m, C–H), 2935 (w, C–H), 1737 (s, C=O), 1177 (s), 1085 (s) cm^{-1}.

(*R*)-3-Methoxybutanal 14

To a cooled (−85 °C) solution of ethyl (*R*)-3-methoxybutanoate **13** (0.85 g, 5.84 mmol) in CH_2Cl_2 (70 mL) was added DIBAL-H (6.42 mL, 1 M in hexane, 6.42 mmol). After stirring for 3 h at −85 °C, a saturated aqueous solution of sodium potassium tartrate was added and the mixture was stirred at 25 °C until a clear solution was obtained. The mixture was extracted with CH_2Cl_2 (3×), the combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 90:10 v/v hexane/Et_2O) to afford 0.41 g (69%) of a colorless liquid identified as (*R*)-3-methoxybutanal **14**. $[\alpha]^{22}_D$ −6.4 (*c* 0.97, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 9.79 (dd, *J* = 2.5, 1.9 Hz, 1H, H_1), 3.90–3.80 (m, 1H, H_3), 3.34 (s, 3H, $-OCH_3$), 2.63 (ddd, *J* = 16.3, 7.2, 2.5 Hz, 1H, H_{2A}), 2.48 (ddd, *J* = 16.3, 5.1, 1.9 Hz, 1H, H_{2B}),

1.23 (d, $J=6.2$ Hz, 3H, CH_3) ppm. ^{13}C NMR (100.62 MHz, CD_2Cl_2): δ 201.9 (s), 72.6 (d), 56.4 (q), 50.8 (t), 19.5 (q) ppm. HRMS (EI^+): Calcd. for $C_5H_{10}O_2$ ($[M+1]^+$), 103.0757; found, 103.0759. IR (NaCl): ν 2973 (s, C–H), 2930 (s, C–H), 1713 (s, C=O), 1084 (s) cm^{-1}.

(4*R*,6*R*)- and (4*S*,6*R*)-6-Methoxyhept-1-yn-4-ol 15

To a suspension of magnesium (1.59 g, 66.55 mmol) and $HgCl_2$ (0.07 g, 0.24 mmol) in Et_2O (14.4 mL) in a three-necked flask, freshly distilled propargyl bromide (0.2 mL, 2.66 mmol) was added. The mixture was stirred until solvent boiling was observed. The reaction was then cooled down to −20 °C and a solution of freshly distilled propargyl bromide (2.80 mL, 37.20 mmol) in Et_2O (14.4 mL) was added over 30 min, and the reaction mixture was stirred for 1 h. The concentration was determined by titration in triplicate with (1*R*,2*S*,5*R*)-(−)-menthol in THF.

To a cooled solution (−78 °C) of (*R*)-3-methoxybutanal **14** (0.92 g, 9.05 mmol) in THF (113 mL) was added the solution of prop-2-yn-1-ylmagnesium bromide obtained above (9.97 mL, 11.76 mmol, 1.18 M in Et_2O). After stirring for 4 h the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with Et_2O (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 90:10 v/v hexane/Et_2O) to afford 0.91 g (71 %) of a yellow oil identified as 6-methoxyhept-1-yn-4-ol **15** as a mixture of diastereomers in a 1:1 ratio. ^1H NMR (400.16 MHz, $CDCl_3$, signals for both diastereomers): δ 4.06 (dtd, $J=$ 9.0, 6.3, 2.9 Hz, 1H, H_6), 4.01–3.92 (m, 1H, H_6), 3.69 (dqd, $J=12.4$, 6.2, 3.4 Hz, 1H, H_4), 3.61 (dqd, $J=9.4$, 6.1, 3.2 Hz, 1H, H_4), 3.35 (s, 3H, $-OCH_3$), 3.34 (s, 3H, $-OCH_3$), 2.47–2.26 (m, 4H, $2H_3$), 2.03 (t, $J=$ 2.6 Hz, 1H, H_1), 2.02 (t, $J=2.7$ Hz, 1H, H_1), 1.87–1.74 (m, 2H, $2H_5$), 1.74–1.58 (m, 2H, $2H_5$), 1.21 (d, $J=6.3$ Hz, 3H, CH_3), 1.19 (d, $J=$ 6.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, signals for both diastereomers): δ 81.1 (s, 2×), 77.9 (d), 74.6 (d), 70.5 (d), 70.3 (d), 70.2 (d), 67.2 (d), 56.2 (q), 55.8 (q), 42.4 (t), 41.5 (t), 27.3 (t), 27.2 (t), 19.1 (q), 18.7 (q) ppm. HRMS (ESI^+): Calcd. for $C_8H_{15}O_2$ ($[M+H]^+$), 143.1067; found, 143.1062. IR (NaCl): ν 3550–3200 (br, O–H), 3297 (m, C≡C–H), 2970 (s, C–H), 2935 (s, C–H), 2118 (w, C≡C), 1085 (s) cm^{-1}.

tert-Butyldimethylsilyl 6-Methoxyhept-1-yn-4-yl ether 16

To a solution of (4*R*,6*R*)- and (4*S*,6*R*)-6-methoxyhept-1-yn-4-ol **15** (0.91 g, 6.4 mmol) and TBSCl (1.26 g, 8.4 mmol) in a CH_2Cl_2–CH_3CN mixture (17 mL, 1:1 v/v), was added imidazole (0.70 g, 10.3 mmol) and the resulting mixture was stirred overnight. The mixture was diluted with CH_2Cl_2 (15 mL), washed with brine (1x), dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 90:10 v/v hexane/EtOAc) to afford 1.44 g (87 %) of a colorless oil identified as *tert*-butyldimethylsilyl 6-methoxyhept-1-yn-4-yl ether **16** as a mixture of diastereomers in a 1:1 ratio. ^1H NMR (400.16 MHz, $CDCl_3$, signals for both diastereomers): δ 4.08–3.98 (m, 1H, H_6), 3.91 (app quint, $J=6.1$ Hz, 1H, H_6), 3.60–3.40 (m, 1H, H_4), 3.45 (app sex, $J=6.3$ Hz, 1H, H_4), 3.30 (s, 6H, 2× $-OCH_3$), 2.43–2.35 (m, 2H, $2H_3$), 2.34–2.26 (m, 2H, $2H_3$), 1.98 (t, $J=2.7$ Hz, 2H, $2H_1$), 1.86 (app dt, $J=13.5$, 6.6 Hz, 1H, H_5), 1.78 (ddd, $J=14.1$, 9.7, 2.7 Hz, 1H, H_5), 1.64 (dt, $J=13.9$, 5.9 Hz, 1H, H_5), 1.55 (ddd, $J=14.1$, 9.5, 2.8 Hz, 1H, H_5), 1.15 (d, $J=6.1$ Hz, 3H, CH_3), 1.14 (d, $J=6.1$ Hz, 3H, CH_3), 0.90 (s, 9H, $-C(CH_3)_3$), 0.89 (s, 9H, $-C(CH_3)_3$), 0.09 (s, 3H, Si–CH_3), 0.08 (s, 6H, Si–CH_3), 0.06 (s, 3H, Si–CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, signals for both diastereomers): δ 81.7 (s), 81.4 (s), 73.9 (d), 72.9 (d), 70.4 (d), 70.2 (d), 68.4 (d), 67.4 (d), 55.9 (q), 55.7 (q), 44.7 (t), 43.4 (t), 28.2 (t), 27.5 (t), 26.0 (q, 3×), 25.9 (q, 3×), 19.4 (q), 19.2 (q), 18.1 (s, 2×), −4.2 (q), −4.3 (q), −4.6 (q), −4.7 (q) ppm. HRMS (ESI^+): Calcd. for $C_{14}H_{29}O_2Si$ ($[M+H]^+$), 257.1931; found, 257.1930. IR (NaCl): ν 3315 (m, C≡C–H), 2954 (s, C–H), 2930 (s, C–H), 2857 (m, C–H), 2121 (w, C≡C), 1473 (m), 1373 (m), 1105 (s), 1028 (s) cm^{-1}.

(1*E*,4*R*,6*R*)- and (1*E*,4*S*,6*R*)-*tert*-Butyl-((1-(dimethyl(phenyl) silyl)-6-methoxy-2-methylhept-1-en-4-yl)oxy)dimethylsilane 17

To a cooled (0 °C) suspension of CuCN (21 mg, 0.23 mmol) in THF (0.50 mL) was added $Me_2PhSiLi$ (6 mL, 0.47 mmol). After stirring for 30 min, a solution of (4*R*,6*R*)- and (4*S*,6*R*)-*tert*-butyldimethylsilyl 6-methoxyhept-1-yn-4-yl ether **16** (40 mg, 0.16 mmol) in THF (1.31 mL) was added. After stirring for 1 h, MeI (97 μL, 1.56 mmol) was added and the reaction mixture was stirred for 2.5 h. The mixture was diluted with an aqueous solution of NH_4OH (10 mL), Et_2O (10 mL) and water (10 mL). The mixture was extracted with Et_2O (3×) and the combined organic layers were washed with water (1x) and brine (1x), dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 98:2 v/v hexane/EtOAc) to afford 62 mg (98 %) of a colorless oil identified as (1*E*,4*R*,6*R*)- and (1*E*,4*S*,6*R*)-*tert*-butyl-((1-(dimethyl (phenyl)silyl)-6-methoxy-2-methylhept-1-en-4-yl)oxy)dimethylsilane **17** as a mixture of diastereomers in a 1:1 ratio.^1H NMR (400.16 MHz, C_6D_6, signals for both diastereomers): δ 7.67–7.58 (m, 4H, ArH), 7.29–7.19 (m, 6H, ArH), 5.60 (s, 1H, H_1), 5.58 (s, 1H, H_1), 4.34–4.20 (m, 1H, H_4), 4.15–4.03 (m, 1H, H_4), 3.61–3.46 (m, 1H, H_6), 3.42–3.29 (m, 1H, H_6), 3.15 (s, 3H, O–CH_3), 3.10 (s, 3H, O–CH_3), 2.48 (dd, $J=13.2$, 5.1 Hz, 1H, H_{3A}), 2.39–2.26 (m, 3H, H_{3A} + $2H_{3B}$), 2.00–1.89 (m, 1H, H_{5A}), 1.90–1.78 (m, 1H, H_{5B}), 1.76 (s, 3H, C_2–CH_3), 1.74 (s, 3H, C_2–CH_3), 1.66–1.54 (m, 1H, H_{5A}), 1.53–1.43 (m, 1H, H_{5B}), 1.17 (d, $J=6.0$ Hz, 3H, C–CH_3), 1.07 (dd, $J=6.0$ Hz, 3H, C–CH_3), 1.03 (s, 12H, C–CH_3 + $-C(CH_3)_3$), 1.00 (s, 9H, $-C(CH_3)_3$), 0.45–0.36 (m, 12H, 4× Si–CH_3), 0.15 (s, 3H, Si–CH_3), 0.12 (s, 3H, Si–CH_3), 0.10 (s, 3H, Si–CH_3), 0.08 (s, 3H, Si–CH_3) ppm. ^{13}C NMR (100.62 MHz, C_6D_6, signals for both diastereomers): δ 154.8 (s), 154.6 (s), 140.0 (s), 134.2 (d, 2×), 134.1 (d, 2×), 129.1 (d), 129.0 (d), 128.2 (d, 4×), 124.9 (d, 2×), 74.1 (d), 72.9 (d), 69.0 (d), 68.1 (d), 55.7 (q), 55.4 (q), 52.7 (t), 51.4 (t), 46.2 (t), 46.1 (t), 26.3 (q, 3×), 26.2 (q, 3×), 23.0 (q), 22.9 (q), 19.6 (q), 19.4 (q), 18.4 (q), 18.3 (q), −0.5 (q), −0.6 (q), −0.7 (q), −0.8 (q), −3.8 (q), −4.1 (q), −4.2 (q), −4.3 (q) ppm. HRMS (ESI^+): Calcd. for $C_{23}H_{43}O_2Si_2$ ($[M+H]^+$), 407.2796; found, 407.2794. IR (NaCl): ν 2954 (s, C–H), 2931 (s, C–H), 2899 (m, C–H), 2855 (m, C–H), 1614 (w), 1249 (s), 1112 (s), 854 (s) cm^{-1}.

(1*E*,4*R*,6*R*)- and (1*E*,4*S*,6*R*)-1-Iodo-6-methoxy-2-methylhept-1-en-4-ol 18

To a cooled (0 °C) solution of (1*E*,4*R*,6*R*)- and (1*E*,4*S*,6*R*)-*tert*-butyl-1-{[(dimethyl(phenyl)silyl)-6-methoxy-2-methylhept-1-en-4-yl]oxy} dimethylsilane **17** (0.58 g, 1.43 mmol) in HFIP (14.3 mL) were added 2,6-lutidine (0.11 mL, 0.99 mmol) and NIS (0.39 g, 1.72 mmol). After stirring for 5 min, the reaction mixture was diluted with water (10 mL) and Et_2O (10 mL). The organic layer was washed with an aqueous solution of $Na_2S_2O_3$ (1x), water (1x) and brine (1x), dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 98:2 v/v hexane/EtOAc) to afford 62 mg (98 %) of a colorless oil identified as *tert*-butyl-((1-iodo-6-methoxy-2-methylhept-1-en-4-yl)oxy) dimethylsilane **SI-1** as a mixture of diastereomers in a 1:1 ratio, which was used in the next step without further purification.

General procedure for the deprotection of silyl ethers with TBAF. To a cooled (0 °C) solution of (1*E*,4*R*,6*R*)- and (1*E*,4*S*,6*R*)-*tert*-butyl-((1-iodo-6-methoxy-2-methylhept-1-en-4-yl)oxy)dimethylsilane **SI-1** (77 mg, 0.19 mmol) in THF (3.2 mL) was added TBAF (0.23 mL, 1 M in THF, 0.23 mmol) and the mixture was stirred for 17 h at 25 °C.

The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with Et_2O (3×). The combined organic layers were washed with brine (3×) and dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 90:10 v/v hexane/EtOAc), to afford 44 mg (80%) of a yellow oil identified as a mixture of (1*E*,4*R*,6*R*), and (1*E*,4*S*,6*R*)-1-Iodo-6-methoxy-2-methylhept-1-en-4-ol **18**. The compounds were separated by HPLC (Waters Spherisorb™ 5 μm silica 10 x 250 mm, hexane: 8% EtOAc, 3 mL/min, retention time (r.t.) for (*S*,*R*)-**18b** = 33.9 min and r.t. for (*R*,*R*)-**18a** = 36.7 min).

Data for (1*E*,4*R*,6*R*)-1-iodo-6-methoxy-2-methylhept-1-en-4-ol (*R*,*R*)-**18a**: $[\alpha]^{24}_D$ −8.6 (*c* 0.35, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 5.99 (s, 1H, H_1), 4.05 (app dt, *J* = 8.7, 4.6 Hz, 1H, H_4), 3.76–3.60 (m, 1H, H_6), 3.34 (s, 3H, –OCH_3), 2.81 (br, 1H, OH), 2.39 (app dd, *J* = 13.8, 7.9 Hz, 1H, H_{3A}), 2.33 (app dd, *J* = 5.1, 1.2 Hz, 1H, H_{3B}), 1.88 (s, 3H, C_2–CH_3), 1.61 (ddd, *J* = 14.6, 8.7, 3.6 Hz, 1H, H_{5A}), 1.54 (ddd, *J* = 14.6, 7.3, 3.0 Hz, 1H, H_{5B}), 1.19 (d, *J* = 6.2 Hz, 3H, C–CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 145.3 (s), 77.2 (d), 74.8 (d), 66.3 (d), 56.4 (q), 47.7 (t), 42.3 (t), 24.3 (q), 18.8 (q) ppm. HRMS (ESI$^+$): Calcd. for $C_9H_{18}IO_2$ ([M + H]$^+$), 285.0337; found, 285.0346. IR (NaCl): ν 3500–3100 (br, O–H), 2970 (s, C–H), 2933 (s, C–H), 2822 (s, C–H), 1442 (s), 1085 (s) cm^{-1}.

Data for (1*E*,4*S*,6*R*)-1-iodo-6-methoxy-2-methylhept-1-en-4-ol (*S*,*R*)-**18b**: $[\alpha]^{23}_D$ −30.3 (*c* 0.4, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 5.97 (s, 1H, H_1), 3.95 (app qd, *J* = 7.5, 4.6 Hz, 1H, H_4), 3.80 (br, 1H, OH), 3.66–3.49 (m, 1H, H_6), 3.35 (s, 3H, O–CH_3), 2.39 (app dd, *J* = 13.9, 7.2, Hz, 1H, H_{3A}), 2.27 (app dd, *J* = 13.7, 5.8 Hz, 1H, H_{3B}), 1.88 (s, 3H, C_2–CH_3), 1.58–1.49 (m, 2H, $2H_5$), 1.17 (d, *J* = 6.1 Hz, 3H, C–CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 145.2 (s), 78.2 (d), 77.1 (d), 69.7 (d), 55.9 (q), 47.6 (t), 43.2 (t), 24.4 (q), 19.2 (q) ppm. HRMS (ESI$^+$): Calcd. For $C_9H_{18}IO_2$ ([M + H]$^+$), 285.0337; found, 285.0346. IR (NaCl): δ 3500–3100 (br, O–H), 2970 (s, C–H), 2933 (s, C–H), 2822 (s, C–H), 1442 (s), 1085 (s) cm^{-1}.

tert-Butyldiphenylsilyl 2-Iodoethan-1-yl Ether 20

To a cooled (0 °C) solution of 2-iodoethanol **19** (15.02 g, 87.3 mmol) in DMF (43.6 mL) were sequentially added imidazole (7.73 g, 113.5 mmol) and TBDPSiCl (29.4 mL, 113.5 mmol). After stirring for 2.5 h at 25 °C, the reaction was quenched with a saturated aqueous solution of NaCl and extracted with Et_2O (3×). The combined organic layers were washed with H_2O (3×) and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, hexane) to afford 34.65 g (97%) of a white solid identified as *tert*-butyldiphenylsilyl 2-iodoethan-1-yl ether **20**. m.p.: 42–45 °C (hexane). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.79–7.72 (m, 4H, ArH), 7.54–7.42 (m, 6H, ArH), 3.91 (t, *J* = 6.8 Hz, 2H, $2H_1$), 3.25 (t, *J* = 6.8 Hz, 2H, $2H_2$), 1.12 (s, 9H, –C($\underline{CH_3}$)$_3$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 135.7 (d, 4×), 133.4 (s, 2×), 129.9 (d, 2×), 127.9 (d, 4×), 64.7 (t), 26.9 (q, 3×), 19.4 (s), 6.9 (t) ppm. HRMS (ESI$^+$): Calcd. for $C_{18}H_{23}INaOSi$ ([M + Na]$^+$), 433.0455; found, 433.0451. IR (NaCl): υ 3068 (w, C–H), 3048 (w, C–H), 2956 (m, C–H), 2932 (m, C–H), 2856 (m, C–H), 1219 (s), 1110 (s) cm^{-1}.

Compound 22

To a cooled (0 °C) suspension of anhydrous LiCl (4.16 g, 98.1 mmol) and *N*,*N*-diisopropylamine (6.92 mL, 49 mmol) in THF (43.7 mL) was added *n*-BuLi (28.6 mL, 45.8 mmol, 1.6 M in hexanes) and the mixture was stirred for 15 min at 0 °C and for 20 min at 25 °C. The resulting mixture was cooled down to −78 °C, and a solution of *N*-((2*R*,3*R*)-3-hydroxy-3-phenylpropan-2-yl)-*N*-methylpropionamide (*R*,*R*)-**21** (5.17 g, 22.9 mmol) in THF (76.6 mL). After being stirred for 45 min at −78 °C, for 15 min at 0 °C and for 15 min at 25 °C, the reaction mixture was cooled down to −78 °C, *tert*-butyldiphenylsilyl 2-iodoethan-1-yl ether **20** (6.71 g, 16.35 mmol) was added and the mixture was stirred for 17 h at 0 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (3×). The combined organic layers were washed with brine (3×) and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 70:30 v/v hexane/EtOAc) to afford 7.77 g (94%) of a colorless oil identified as compound **22**. ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.72–7.60 (m, 3H, ArH), 7.45–7.30 (m, 12H, ArH), 4.63 (d, *J* = 7.7 Hz, 1H, $H_{2'}$), 4.44 (bs, 1H, OH), 3.67 (ddd, *J* = 10.6, 6.7, 5.1 Hz, 1H, H_4), 3.60 (ddd, *J* = 10.5, 6.8, 5.0 Hz, 1H, H_4), 3.02 (q, *J* = 6.8 Hz, 1H, $H_{1'}$), 2.90 (s, 3H, N–CH_3), 1.89-1.80 (m, 1H, H_3), 1.59-1.50 (m, 1H, H_3), 1.12 (d, *J* = 6.9 Hz, 3H, $C_{1'}$–CH_3) 1.10–1.00 (m, 12H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 178.8 (s), 142.6 (s), 135.5 (d, 4×), 133.8 (s, 2×), 129.7 (d, 2×), 128.3 (d, 2×), 127.7 (d, 4×), 126.4 (d, 2×), 76.4 (d), 61.5 (t), 57.9 (d), 36.8 (t), 32.6 (d), 27.0 (q), 26.9 (q, 3×), 19.2 (s), 16.9 (q), 14.5 (q) ppm. HRMS (ESI$^+$): Calcd. for $C_{31}H_{42}NO_3Si$ ([M + H]$^+$), 504.29285; found, 504.29181. IR (NaCl): υ 3500–3100 (br, O–H), 3069 (w, C–H), 2960 (m, C–H), 2930 (m, C–H), 2857 (m, C–H), 1617 (s, C=O), 1472 (m), 1427 (m), 1164 (s), 1083 (s), 699 (s) cm^{-1}.

(*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-2-methylbutan-1-ol (*S*)-23

To a cooled (0 °C) solution of *N*,*N*-diisopropylamine (9.14 mL, 64.8 mmol) in THF (44.5 mL) was added *n*-BuLi (38.6 mL, 1.6 M in hexanes, 61.7 mmol) and the mixture was stirred for 10 min at 25 °C. The solution was cooled down to 0 °C and $BH_3{\cdot}NH_3$ complex (2.22 g, 64.8 mmol) was added in small portions. After stirring for 1 h at 25 °C, the mixture was cooled down to 0 °C and a solution of **22** (7.77 g, 15.4 mmol) in THF (44.5 mL) was added carefully. After stirring for 2 h at 25 °C, the mixture was cooled down to 0 °C and a 10% aqueous solution of HCl was added. The mixture was extracted with EtOAc (3×) and the combined organic layers were washed with a 10% aqueous solution of HCl (1×), brine (3×) and dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 90:10 v/v hexane/EtOAc) to afford 4.51 g (85%) of a pale yellow oil identified as (*S*)-[(4-*tert*-butyldiphenylsilyl)oxy]-2-methylbutan-1-ol (*S*)-**23**. $[\alpha]^{23}_D$ −5.7 (*c* 0.97, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.76–7.69 (m, 4H, ArH), 7.49–7.39 (m, 6H, ArH), 3.85–3.70 (m, 2H, $2H_4$), 3.54 (dd, *J* = 10.8, 5.5 Hz, 1H, H_{1A}), 3.49 (dd, *J* = 10.8, 6.4 Hz, 1H, H_{1B}), 2.77 (s, 1H, OH), 1.95–1.83 (m, 1H, H_2), 1.74–1.62 (m, 1H, H_{3A}), 1.57–1.46 (m, 1H, H_{3B}), 1.10 (s, 9H, –C($\underline{CH_3}$)$_3$), 0.93 (d, *J* = 6.8 Hz, 3H, C2–CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 135.6 (d, 4×), 133.5 (s, 2×), 129.8 (d, 2×), 127.8 (d, 4×), 68.3 (t), 62.6 (t), 36.8 (t), 33.9 (d), 26.9 (q, 3×), 19.2 (s), 17.2 (q) ppm. HRMS (ESI$^+$): Calcd. for $C_{21}H_{31}O_2Si$ ([M + H]$^+$), 343.2088; found, 343.2088. IR (NaCl): υ 3500–3100 (br, O–H), 3071 (w, C–H), 2957 (s, C–H), 2930 (s, C–H), 2858 (s, C–H), 1472 (m), 1428 (m), 1112 (s), 702 (s) cm^{-1}.

(*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-2-methylbutanal (*S*)-24

General procedure for the Swern oxidation. To a cooled (−60 °C) solution of $(COCl)_2$ (0.701 mL, 8.2 mmol) in CH_2Cl_2 (23.35 mL) was added DMSO (0.995 mL, 14 mmol). After stirring for 5 min at −60 °C, a solution of (*S*)-4-[(*tert*-butyldiphenylsilyl)oxy]-2-methylbutan-1-ol (*S*)-**23** (2 g, 5.84 mmol) in CH_2Cl_2 (12.97 mL) was added and the mixture was stirred for 15 min at −60 °C before Et_3N (5.36 mL, 38.53 mmol) was added. After stirring for 30 min at −60 °C, the reaction was allowed to reach 25 °C and then poured into H_2O. The mixture was extracted with CH_2Cl_2 (3×) and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 90:10 v/v hexane/EtOAc) to afford 1.8 g (90%) of a colorless oil identified as (*S*)-4-

[(*tert*-butyldiphenylsilyl)oxy]-2-methylbutanal (*S*)-**24**. $[\alpha]^{23}_{D}$ −14.5 (*c* 1, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 9.73 (d, *J* = 1.6 Hz, 1H, H_1), 7.75–7.62 (m, 4H, ArH), 7.48–7.34 (m, 6H, ArH), 3.81–3.63 (m, 2H, $2H_4$), 2.67–2.51 (m, 1H, H_2), 2.05–1.97 (m, 1H, H_{3A}), 1.69–1.58 (m, 1H, H_{3B}), 1.13 (d, *J* = 7.1 Hz, 3H, C2–CH_3), 1.11 (s, 9H, –C($\underline{CH_3}$)$_3$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 204.8 (d), 135.6 (d, 4×), 133.5 (s, 2×), 129.8 (d, 2×), 127.8 (d, 4×), 61.2 (t), 43.6 (d), 33.5 (t), 26.9 (q, 3×), 19.2 (s), 13.2 (q) ppm. HRMS (ESI$^+$): Calcd. for $C_{21}H_{29}O_2Si$ ([M + H]$^+$), 341.1931; found, 341.1930. IR (NaCl): υ 3071 (w, C–H), 2959 (m, C–H), 2931 (m, C–H), 2858 (m, C–H), 1727 (s, C=O), 1428 (m), 1111 (s) cm^{-1}.

Ethyl (2*E*,4*S*)- and (2*Z*,4*S*)-6-[(*tert*-Butyldiphenylsilyl) oxy]-2,4-dimethylhex-2-enoate (*S*,*E*)-26

To a cooled (0 °C) solution of ethyl 2-(diethoxyphosphoryl) propanoate **25** (3.62 g, 15.12 mmol) in THF (128 mL) was added methylmagnesium bromide (5.06 mL, 3 M in Et_2O, 15.2 mmol). After stirring for 30 min at 25 °C, the mixture was cooled down to 0 °C and a solution of (*S*)-4-[(*tert*-butyldiphenylsilyl)oxy]-2-methylbutanal (*S*)-**24** (3.44 g, 10.1 mmol) in THF (64 mL) was added. The resulting mixture was stirred for 17 h at 90 °C and, after cooling down to 25 °C, a saturated aqueous solution of NH_4Cl was added. The mixture was extracted with Et_2O (3×) and the combined organic layers were washed with brine (3×) and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, from 97:3 to 90:10 v/v hexane/EtOAc) to afford 0.35 g (8%) of a colorless oil identified as ethyl (2*Z*,4*S*)-6-[(*tert*-butyldiphenylsilyl)oxy]-2,4-dimethylhex-2-enoate (*S*,*Z*)-**26** and 3.41 g (79%) of a colorless oil identified as ethyl (2*E*,4*S*)-6-[(*tert*-butyldiphenylsilyl)oxy]-2,4-dimethylhex-2-enoate (*S*,*E*)-**26**.

Data for ethyl (2E,4S)-6-[(tert-butyldiphenylsilyl)oxy]-2,4-dimethylhex-2-enoate (*S*,*E*)-**26***:* $[\alpha]^{24}_{D}$ +16.8 (*c* 1.1, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.73–7.58 (m, 4H, ArH), 7.49–7.31 (m, 6H, ArH), 6.56 (d, *J* = 10.1 Hz, 1H, H_3), 4.20 (q, *J* = 7.1 Hz, 2H, OC$\underline{H_2}$CH$_3$), 3.72–3.55 (m, 2H, $2H_6$), 2.86–2.70 (m, 1H, H_4), 1.88 (s, 3H, C2–CH_3), 1.69–1.57 (m, 1H, H_{5A}), 1.57–1.47 (m, 1H, H_{5B}), 1.31 (t, *J* = 7.1 Hz, 3H, OCH$_2$C$\underline{H_3}$), 1.07 (s, 9H, –C($\underline{CH_3}$)$_3$), 1.02 (d, *J* = 6.6 Hz, 3H, C4–$\underline{CH_3}$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.5 (s), 147.6 (d), 135.6 (d, 2×), 135.5 (d, 2×), 134.0 (s), 133.9 (s) 129.7 (d, 2×), 127.7 (d, 4×), 126.8 (s), 61.8 (t), 60.5 (t), 39.5 (t), 29.7 (d), 26.9 (q. 3×), 20.0 (q), 19.3 (s), 14.4 (q), 12.6 (q) ppm. HRMS (ESI$^+$): Calcd. for $C_{26}H_{36}NaO_3Si$ ([M + Na]$^+$), 447.2326; found, 447.2320. IR (NaCl): υ 2958 (m, C–H), 2923 (m, C–H), 2860 (w, C–H), 1711 (s, C=O), 1468 (m), 1266 (m), 1108 (s), 704 (s) cm^{-1}.

Data for ethyl (2Z,4S)-6-[(tert-butyldiphenylsilyl)oxy]-2,4-dimethylhex-2-enoate (*S*,*Z*)-**26***:* $[\alpha]^{23}_{D}$ −8.2 (*c* 1.08, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.71–7.59 (m, 4H, ArH), 7.47–7.32 (m, 6H, ArH), 5.62 (d, *J* = 9.9 Hz, 1H, H_3), 4.14 (q, *J* = 7.1 Hz, 2H, –OC$\underline{H_2}$CH$_3$), 3.72–3.54 (m, 2H, $2H_6$), 3.31–3.16 (m, 1H, H_4), 1.84 (s, 3H, C2–CH_3), 1.68–1.57 (m, 1H, H_{5A}), 1.57- 1.47 (m, 1H, H_{5B}), 1.24 (t, *J* = 7.1 Hz, 3H, –OCH$_2$C$\underline{H_3}$), 1.03 (s, 9H, –C($\underline{CH_3}$)$_3$), 0.97 (d, *J* = 6.7 Hz, 3H, C4–$\underline{CH_3}$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.0 (s), 148.0 (d), 135.6 (d, ×x), 134.0 (s, 2×), 129.6 (d, 2×), 127.6 (d, 4×) 126.1 (s), 62.3 (t), 60.0 (t), 40.2 (t), 30.5 (d), 26.9 (q, 3×), 20.8 (q), 20.7 (q), 19.2 (s), 14.3 (q) ppm. HRMS (ESI$^+$): Calcd. for $C_{26}H_{36}NaO_3Si$ ([M + Na]$^+$), 447.2326; found, 447.2322. IR (NaCl): υ 2958 (m, C–H), 2930 (m, C–H), 2858 (w, C–H), 1715 (s, C=O), 1428 (m), 1111 (s), 702 (s) cm^{-1}.

Ethyl (2*E*,4*S*)-6-Hydroxy-2,4-dimethylhex-2-enoate 27

Folllowing the general procedure for the deprotection of silyl ethers with TBAF, the reaction of ethyl (2*E*,4*S*)-6-[(*tert*-butyldiphenylsilyl) oxy]-2,4-dimethylhex-2-enoate (*S*,*E*)-**26** (2.19 g, 5.15 mmol) with TBAF (15.5 mL, 1 M in THF, 15.5 mmol) in THF (121 mL) for 4 h at 25 °C afforded, after purification by flash-column chromatography (silica gel, from 85:15 to 70:30 v/v hexane/EtOAc), 0.79 g (82%) of a colorless oil identified as ethyl (2*E*,4*S*)-6-hydroxy-2,4-dimethylhex-2-enoate **27**. $[\alpha]^{24}_{D}$ +28.3 (*c* 0.43, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 6.53 (d, *J* = 10.1 Hz, 1H, H_3), 4.18 (q, *J* = 7.1 Hz, 2H, –OC$\underline{H_2}$CH$_3$), 3.70–3.60 (m, 1H, H_6), 3.60–3.52 (m, 1H, H_6), 2.77–2.63 (m, 1H, H_4), 1.85 (s, 3H, C2–CH_3), 1.74–1.63 (m, 1H, H_5), 1.63–1.52 (m, 1H, H_5), 1.30 (t, *J* = 7.1 Hz, 3H, –OCH$_2$C$\underline{H_3}$), 1.04 (d, *J* = 6.7 Hz, 3H, C4–CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.5 (s), 147.2 (d), 126.8 (s), 60.5 (t), 60.4 (t), 39.3 (t), 29.7 (d), 19.9 (q), 14.2 (q), 12.4 (q) ppm. HRMS (EI$^+$): Calcd. for $C_{10}H_{18}O_3$ ([M + H]$^+$), 186.1256; found, 186.1264. IR (NaCl): υ 3550–3100 (br, O–H), 2960 (m, C–H), 2931 (m, C–H), 2872 (w, C–H), 1710 (s, C=O), 1267 (m) cm^{-1}.

Ethyl (2*E*,4*S*)-2,4-Dimethyl-6-oxohex-2-enoate (*S*,*E*)-28

Following the general procedure for the Swern oxidation, the reaction of ethyl (2*E*,4*S*)-6-hydroxy-2,4-dimethylhex-2-enoate **27** (0.73 g, 3.93 mmol) with $(COCl)_2$ (0.48 mL, 5.5 mmol), DMSO (0.67 mL, 9.4 mmol) and Et_3N (3.6 mL, 25.9 mmol) in CH_2Cl_2 (13.3 mL) afforded, after purification by flash-column chromatography (silica gel, 95:5 v/v hexane/EtOAc), 0.65 g (90%) of a colorless oil identified as ethyl (2*E*,4*S*)-2,4-dimethyl-6-oxohex-2-enoate (*S*,*E*)-**28**. $[\alpha]^{26}_{D}$ +32.5 (*c* 1, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 9.72 (t, *J* = 1.6 Hz, 1H, H_6), 6.53 (dq, *J* = 10.1, 1.3 Hz, 1H, H_3), 4.18 (q, *J* = 7.1 Hz, 2H, –OC$\underline{H_2}$CH$_3$), 3.17–3.04 (m, 1H, H_4), 2.49–2.47 (m, 2H, $2H_5$), 1.89 (d, *J* = 1.2 Hz, 3H, C2–CH_3), 1.29 (t, *J* = 7.1 Hz, 3H, –OCH$_2$C$\underline{H_3}$), 1.09 (d, *J* = 6.7 Hz, 3H, C4–CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 200.6 (d), 167.7 (s), 144.5 (d), 127.2 (s), 60.3 (t), 49.8 (t), 27.7 (d), 19.6 (q), 14.0 (q), 12.3 (q) ppm. HRMS (EI$^+$): Calcd. for $C_{10}H_{16}O_3$ ([M + H]$^+$), 184.1099; found, 184.1090. IR (NaCl): υ 2971 (m, C–H), 2742 (w, C–H), 1711 (s, C=O), 1455 (w), 1255 (m) cm^{-1}.

Ethyl (2*E*,4*S*)-7,7-Dibromo-2,4-dimethylhepta-2,6-dienoate 29

To a cooled (0 °C) solution of triphenylphosphine (0.57 g, 2.17 mmol) and CBr_4 (0.36 g, 1.09 mmol) in CH_2Cl_2 (16 mL) was added ethyl (2*E*,4*S*)-2,4-dimethyl-6-oxohex-2-enoate (*S*,*E*)-**28** (0.1 g, 0.54 mmol). After stirring for 40 min at 0 °C, the mixture was quenched with water and extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 80:20 v/v hexane/Et_2O) to afford 0.112 g (61%) of a colorless liquid identified as ethyl (2*E*,4*S*)-7,7-dibromo-2,4-dimethylhepta-2,6-dienoate **29**. $[\alpha]^{20}_{D}$ +23.4 (*c* 0.9, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 6.54 (dq, *J* = 10.0, 1.5 Hz, 1H, H_3), 6.34 (dd, *J* = 7.7, 6.9 Hz, 1H, H_6), 4.20 (q, *J* = 7.1 Hz, 2H, –OC$\underline{H_2}$CH$_3$), 2.77–2.56 (m, 1H, H_4), 2.31–2.00 (m, 2H, $2H_5$), 1.85 (d, *J* = 1.5 Hz, 3H, C2–CH_3), 1.31 (t, *J* = 7.1 Hz, 3H, –OCH$_2$C$\underline{H_3}$), 1.06 (d, *J* = 6.7 Hz, 3H, C4–CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.3 (s), 145.4 (d), 136.3 (d), 127.8 (s), 90.3 (s), 60.8 (t), 39.7 (t), 32.6 (d), 19.8 (q), 14.4 (q), 12.7 (q) ppm. HRMS (ESI$^+$): Calcd. for $C_{11}H_{17}{}^{79}Br_2O_2$ ([M + H]$^+$), 338.9590; found, 338.9588. IR (NaCl): υ 2965 (m, C–H), 2928 (m, C–H), 1709 (s, C=O), 1260 (m) cm^{-1}.

Ethyl (2*E*,4*S*)-7-Bromo-2,4-dimethylhept-2-en-6-ynoate (*S*,*E*)-30

To a cooled (−78 °C) solution of ethyl (2*E*,4*S*)-7,7-dibromo-2,4-dimethylhepta-2,6-dienoate **29** (0.09 g, 0.27 mmol) in THF (2.7 mL) was added NaHMDS (0.32 mL, 1 M in THF, 0.32 mmol). After stirring for 2 h at −78 °C a saturated aqueous solution of NH_4Cl was added, the mixture was extracted with Et_2O (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel,

80:20 v/v hexane/Et_2O) to afford 0.64 g (91%) of a colorless liquid identified as ethyl (2*E*,4*S*)-7-bromo-2,4-dimethylhept-2-en-6-ynoate (*S*,*E*)-**30**. $[\alpha]^{20}_D$ +7.7 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 6.55 (dd, *J* = 9.9, 1.5 Hz, 1H, H_3), 4.19 (q, *J* = 7.1 Hz, 2H, –OC$\underline{H_2}$CH$_3$), 2.80–2.50 (m, 1H, H_4), 2.27–2.21 (m, 2H, $2H_5$), 1.86 (d, *J* = 1.5 Hz, 3H, C2–CH_3), 1.30 (t, *J* = 7.1 Hz, 3H, –OCH$_2$C$\underline{H_3}$), 1.11 (d, *J* = 6.7 Hz, 3H, C4–CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.2 (s), 144.8 (d), 127.9 (s), 78.1 (s), 60.7 (t), 39.4 (s), 32.7 (d), 26.7 (t), 19.4 (q), 14.4 (q), 12.7 (q) ppm. HRMS (ESI$^+$): Calcd. for $C_{11}H_{16}{}^{79}BrO_2$ ([M + H]$^+$), 259.0328; found, 259.0327. IR (NaCl): υ 2963 (m, C–H), 2929 (m, C–H), 2216 (w, C≡H), 1710 (s, C=O), 1276 (m) cm^{-1}.

Ethyl (2*E*,4*S*,6*E*)-2,4-Dimethyl-7-(tributylstannyl) hepta-2,6-dienoate (*S*)-31

To a solution of ethyl (2*E*,4*S*)-7-bromo-2,4-dimethylhept-2-en-6-ynoate (*S*,*E*)-**30** (0.06 g, 0.25 mmol) in THF (1.2 mL) triphenylphosphine (3 mg, 0.01 mmol), $Pd_2(dba)_3$ (0.001 mL, 0.001 mmol) and Bu_3SnH (0.16 mL, 0.55 mmol) were added. After stirring for 1.5 h at 25 °C the solvent was evaporated and the residue was purified by flash-column chromatography (C18 silica gel, CH_3CN) to afford 0.084 g (72%) of a colorless liquid identified as ethyl (2*E*,4*S*,6*E*)-2,4-dimethyl-7-(tributylstannyl)hepta-2,6-dienoate (*S*)-**31**. $[\alpha]^{20}_D$ +32.3 (*c* 0.8, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 6.56 (dq, *J* = 10.1, 1.5 Hz, 1H, H_3), 6.07–5.69 (m, 2H, $H_6 + H_7$), 4.18 (q, *J* = 7.1 Hz, 2H, –OC$\underline{H_2}$CH$_3$), 2.65–2.50 (m, 1H, H_4), 2.25–2.10 (m, 2H, $2H_5$), 1.83 (d, *J* = 1.5 Hz, 3H, C2–CH_3), 1.54–1.40 (m, 6H, –Sn–$\underline{CH_2}$–CH_2–CH_2–CH_3), 1.38–1.21 (m, 9H, –OCH$_2$C$\underline{H_3}$ + –Sn–CH_2–$\underline{CH_2}$–CH_2–CH_3), 1.01 (d, *J* = 6.7 Hz, 3H, C4–CH_3), 0.88 (t, *J* = 7.3 Hz, 9H, –Sn–CH_2–CH_2–CH_2–$\underline{CH_3}$), 0.92–0.82 (m, 6H, –Sn–CH_2–CH_2–$\underline{CH_2}$–CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.5 (s), 147.4 (d), 146.7 (d), 130.1 (d), 126.4 (s), 60.5 (t), 45.0 (t), 33.5 (d), 29.2 (t, 3×, $^2J_{C-Sn}$ = 20.6 Hz), 27.3 (t, 3×, $^3J_{C-Sn}$ = 52.3 Hz), 19.6 (q), 14.4 (q), 13.8 (q, 3×), 12.7 (q), 9.5 (t, 3×, $^1J_{C-^{119}Sn}$ = 342 Hz, $^1J_{C-^{117}Sn}$ = 327 Hz) ppm. HRMS (ESI$^+$): Calcd. for $C_{23}H_{45}O_2{}^{119}Sn$ ([M + H]$^+$), 473.2440; found, 473.2438. IR (NaCl): υ 2957 (s, C–H), 2926 (s, C–H), 1712 (s, C=O) cm^{-1}.

Ethyl (2*E*,4*S*,6*E*,8*E*,11*R*,2′*R*)-11-Hydroxy-2′-methoxy-2,4,9-trimethyltetradeca-2,6,8-trienoate 8a

General procedure for the Stille cross-coupling reaction. To a round-bottomed flask containing $(Ph_2PO_2)(NBu_4)$ (34 mg, 0.074 mmol) was added a solution of stannane **31** (19 mg, 0.067 mmol) and iodide **18a** (41 mg, 0.087 mmol) in DMF (0.4 mL). CuTC (14 mg, 0.074 mmol) and $Pd(PPh_3)_4$ (7.7 mg, 0.007 mmol) were subsequently added and the resulting mixture was stirred for 1 h at 25 °C. After completion was judged by tlc analysis, the temperature was cooled down to 0 °C and water was slowly added. The aqueous phase was extracted with EtOAc (3×) and the combined organic layers were washed with H_2O (3×), dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by flash-column chromatography (silica gel, 0% to 40% hexane/EtOAc gradient in 20 min) to afford 17 mg (75%) of a colorless oil identified as ethyl (2*E*,4*S*,6*E*,8*E*,11*R*,2′*R*)-11-hydroxy-2′-methoxy-2,4,9-trimethyltetradeca-2,6,8-trienoate **8a**. $[\alpha]^{22}_D$ −1.14 (*c* 0.85, $CHCl_3$). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 6.55 (dq, *J* = 10.0, 1.5 Hz, 1H, H_3), 6.23 (dd, *J* = 15.0, 10.8 Hz, 1H, H_7), 5.83 (d, *J* = 10.8 Hz, 1H, H_8), 5.51 (dt, *J* = 14.8, 7.3 Hz, 1H, H_6), 4.18 (q, *J* = 7.1 Hz, 2H, O–$\underline{CH_2}$CH$_3$), 4.05–3.95 (m, 1H, H_{11}), 3.65 (dq, *J* = 12.3, 6.1 Hz, 1H, H_{13}), 3.34 (s, 3H, O–CH_3), 2.65–2.60 (m, 1H, OH), 2.56 (dq, *J* = 10.0, 6.8 Hz, 1H, H_4), 2.18–2.09 (m, 4H, $2H_5 + 2H_{10}$), 1.82 (d, *J* = 1.5 Hz, 3H, C_2–CH_3), 1.75 (s, 3H, C_9–CH_3), 1.60–1.53 (m, 2H, $2H_{12}$), 1.29 (t, *J* = 7.1 Hz, 3H, O–$CH_2\underline{CH_3}$), 1.17 (d, *J* = 6.2 Hz, 3H, C_{13}–CH_3), 1.01 (d, *J* = 6.6 Hz, 3H, C_4–CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 168.5 (s, C=O), 147.2 (d, C_3), 133.6 (s, C_2 or C_9), 130.4 (d, C_6), 128.2 (d, C_7), 127.6 (d, C_8), 126.8 (s, C_9 or C_2), 74.7 (d, C_{13}), 66.4 (d, C_{11}), 60.6 (t, O–$\underline{CH_2}$CH$_3$), 56.3 (q, O–CH_3), 48.4 (t, C_{10}), 42.9 (t, C_{12}), 40.0 (t, C_5), 33.9 (d, C_4), 19.7 (q, C_4–$\underline{CH_3}$), 19.0 (q, C_{14}), 16.9 (q, C_9–$\underline{CH_3}$), 14.4 (q, O–$CH_2\underline{CH_3}$), 12.7 (q, C_2–$\underline{CH_3}$). HRMS (ESI$^+$): Calcd. for $C_{20}H_{35}O_4$ ([M + H]$^+$), 339.2530; found, 339.2527. IR (NaCl): ν 3600–3200 (br, O–H), 2966 (s, C–H), 2928 (s, C–H), 2827 (m, C–H), 1708 (s, C=O), 1647 (m), 1449 (m), 1373 (m), 1265 (s), 1088 (s), 749 (m) cm^{-1}.

Ethyl (2*E*,4*S*,6*E*,8*E*,11*S*,2′*R*)-11-Hydroxy-2′-methoxy-2,4,9-trimethyltetradeca-2,6,8-trienoate 8b

Following the general procedure previously described for the Stille coupling, the reaction of stannane **31** (29 mg, 0.067 mmol), iodide **18b** (63 mg, 0.087 mmol), $(Ph_2PO_2)(NBu_4)$ (52 mg, 0.074 mmol), CuTC (21 mg, 0.074 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.007 mmol) in DMF (0.6 mL) afforded, after purification by flash-column chromatography (silica gel, 0% to 40% hexane/EtOAc gradient in 20 min), 7 mg (59%) of a colorless oil identified as (2*E*,4*S*,6*E*,8*E*,11*S*,2′*R*)-11-hydroxy-2′-methoxy-2,4,9-trimethyltetradeca-2,6,8-trienoate **8b**. $[\alpha]^{23}_D$ −1.8 (*c* 0.35, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.59 (dd, *J* = 9.9, 1.5 Hz, 1H, H_3), 6.26 (dd, *J* = 15.0, 10.8 Hz, 1H, H_7), 5.86 (d, *J* = 10.8 Hz, 1H, H_8), 5.54 (dt, *J* = 14.8, 7.3 Hz, 1H, H_6), 4.21 (q, *J* = 7.1 Hz, 2H, O–$\underline{CH_2}$CH$_3$), 3.96 (q, *J* = 8.7 Hz, 1H, H_{11}), 3.62–3.54 (br s, 1H, OH), 3.37 (s, 3H, O–CH_3), 2.58 (dq, *J* = 9.6, 6.9 Hz, 1H, H_{11}), 2.25 (dd, *J* = 13.5, 7.2 Hz, 1H, H_{12}), 2.14 (dq, *J* = 13.4, 6.5, 6.0 Hz, 3H, $2H_5 + H_{10}$), 1.85 (s, 3H, C_2–CH_3), 1.79 (s, 3H, C_9–CH_3), 1.59–1.56 (m, 2H, $2H_{12}$), 1.32 (t, *J* = 7.1 Hz, 3H, O–$CH_2\underline{CH_3}$), 1.19 (d, *J* = 6.0 Hz, 3H, C_{13}–CH_3), 1.04 (d, *J* = 6.7 Hz, 3H, C_4–CH_3) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.6 (s, C=O), 147.23 (d, C_3), 133.7 (s, C_2 or C_9), 130.3 (d, C_6), 128.3 (d, C_7), 127.5 (d, C_8), 126.8 (s, C_9 or C_2), 78.0 (d, C_{13}), 69.8 (d, C_{11}), 60.6 (t, O–$\underline{CH_2}$CH$_3$), 55.9 (q, O–CH_3), 48.3 (t, C_{10}), 43.4 (t, C_{12}), 40.1 (t, C_5), 33.9 (d, C_4), 19.7 (q, C_4–$\underline{CH_3}$), 19.3 (q, C_{14}–$\underline{CH_3}$), 17.1 (q, C_9–$\underline{CH_3}$), 14.5 (q, O–$CH_2\underline{CH_3}$), 12.7 (q, C_2–$\underline{CH_3}$) ppm. HRMS (ESI$^+$): Calcd. for $C_{20}H_{35}O_4$ ([M + H]$^+$), 339.2530; found, 339.2527. IR (NaCl): ν 3600–3200 (br, O–H), 2968 (s, C–H), 2927 (s, C–H), 1709 (s, C=O), 1648 (m), 1450 (m), 1373 (m), 1264 (s), 1087 (s), 750 (s) cm^{-1}.

(1*E*,4*R*,6*R*)-(1-Iodo-6-methoxy-2-methylhept-1-en-4-yl)-(*tert*-butoxycarbonyl)-L-valinate (*S*,*R*,*R*)-54

General procedure for the EDC-mediated peptide coupling. To a solution of (1*E*,4*R*,6*R*)-1-iodo-6-methoxy-2-methylhept-1-en-4-ol (*R*,*R*)-**18a** (0.47 g, 1.65 mmol) in $CHCl_3$ (6.58 mL) EDC hydrochloride (0.38 g, 1.97 mmol) and DMAP (0.69 g, 5.59 mmol) were added, followed by *N*-Boc-*L*–Val **53** (0.42 g, 1.97 mmol) and the reaction mixture was stirred at 25 °C for 23 h. The solvent was removed under reduced pressure and the residue was purified by flash-column chromatography (silica gel, 98:2 hexane/EtOAc) to afford 0.79 g (99%) of a yellow oil identified as (1*E*,4*R*,6*R*)-(1-iodo-6-methoxy-2-methylhept-1-en-4-yl)-(*tert*-butoxycarbonyl)-L-valinate (*S*,*R*,*R*)-**54**. $[\alpha]^{21}_D$ −12.5 (*c* 1.45, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 5.97 (br s, 1H, $H_{1'}$), 5.45–5.25 (m, 1H, $H_{4'}$), 4.95 (d, *J* = 9.5 Hz, 1H, NH), 4.23–4.06 (m, 1H, H_2), 3.42–3.27 (m, 1H, $H_{6'}$), 3.25 (s, 3H, –OCH_3), 2.51 (dd, *J* = 14.0, 8.5 Hz, 1H, $H_{3'A}$), 2.35 (dd, *J* = 14.3, 3.9 Hz, 1H, $H_{3'B}$), 2.09 (ddt, *J* = 9.4, 6.9, 4.6 Hz, 1H, –$\underline{CH}(CH_3)_2$), 1.85 (s, 3H, C2′–CH_3), 1.59 (dd, *J* = 7.1, 5.3 Hz, 2H, $2H_{5'}$), 1.43 (s, 9H, –$C(CH_3)_3$), 1.11 (d, *J* = 6.1 Hz, 3H, C–CH_3), 0.96 (d, *J* = 6.9 Hz, 3H, –CH($\underline{CH_3}$)$_2$), 0.86 (d, *J* = 6.9 Hz, 3H, –CH($\underline{CH_3}$)$_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 172.2 (s), 155.9 (s), 143.9 (s), 79.8 (s), 78.2 (d), 72.9 (d), 69.6 (d), 58.8 (d), 56.4 (q), 45.1 (t), 42.3 (t), 31.0 (d), 28.4 (q, 3×), 23.8 (q), 19.6 (q), 19.3 (q), 17.5 (q) ppm. HRMS (ESI$^+$): Calcd. for $C_{19}H_{35}INO_5$ ([M + H]$^+$), 484.1554; found, 484.1552. IR (NaCl): ν 3500–3200 (br,

N–H), 2971 (s, C–H), 2932 (s, C–H), 1716 (s, C=O), 1503 (s), 1367 (s), 1159 (s) cm^{-1}.

Compound 56

To a solution of **54** (200 mg, 0.24 mmol) in CH_2Cl_2 (1.3 mL), TFA (1.3 mL) was added and the resulting solution was stirred at room temperature for 3 h. The solvent was removed and the residue was used in the next step without further purification.

General procedure for the HATU-mediated peptide coupling. To a solution of *N*-((*tert*-butoxycarbonyl)-L-prolyl)-*S*-trityl-D-cysteine **55** (0.179 g, 0.32 mmol), HATU (0.122 g, 0.32 mmol) and DIPEA (0.145 mL, 0.83 mmol) in CH_2Cl_2 (2.8 mL), a solution of the previously prepared amine (0.094 g, 0.24 mmol) in CH_2Cl_2 (1 mL) was added and the resulting mixture was stirred for 23 h at 25 °C. The mixture was diluted with CH_2Cl_2, washed with H_2O (3×), dried (Na_2SO_4) and the solvent was removed. The residue was purified by flash-column chromatography (silica gel, from 75:25 to 40:60 v/v hexane/EtOAc), to afford 136 mg (60%) of a colorless foam identified as **56** as a mixture of rotamers. m.p. 49–52 °C (EtOAc). $[\alpha]^{21}_D$ −15.1 (*c* 0.56, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.7 Hz, 6H, ArH), 7.30 (t, *J* = 7.8 Hz, 6H, ArH), 7.23 (d, *J* = 7.2 Hz, 3H, ArH), 6.91–6.76 (m, 1H, NH), 6.46 (s, 1H, NH), 5.96 (s, 1H, $H_{1'''}$), 5.15–5.05 (m, 1H, $H_{4'''}$), 4.35 (dd, *J* = 8.6, 5.0 Hz, 1H, $H_{2'}$), 4.22–4.15 (m, 2H, $H_2 + H_{2''}$), 3.52–3.40 (m, 1H, H_{5A}), 3.33 (q, *J* = 6.2 Hz, 1H, $H_{6'''}$), 3.27 (s, 3H, –OCH_3), 3.30–3.22 (m, 1H, H_{5B}), 2.82–2.53 (m, 2H, $2H_3$ or $2H_4$), 2.55–2.34 (m, 2H, $2H_{3'''}$), 2.21–2.00 (m, 3H, $2H_{3'}$ + –$\underline{CH}(CH_3)_2$), 1.84 (s, H, C2'''–CH_3 + $H_{5'''B}$), 1.60–1.49 (m, 1H, $H_{5'''A}$), 1.49–1.20 (m, 11H, –$C(\underline{CH_2})_3$ + $2H_3$ or $2H_4$), 1.13 (d, *J* = 6.1 Hz, 3H, C7'''–CH_3), 0.91 (d, *J* = 6.8 Hz, 3H, –$CH(\underline{CH_2})_2$)), 0.85 (d, *J* = 6.8 Hz, 3H, –$CH(\underline{CH_2})_2$)) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 172.7 (s), 170.8 (s), 169.7 (s), 154.9 (s), 144.4 (s, 3×), 143.6 (s), 129.6 (d, 6×), 128.1 (d, 6×), 126.9 (d, 3×), 80.4 (s), 78.6 (d), 73.7 (d), 70.3 (d), 67.1 (s), 60.5 (d), 57.7 (d), 55.9 (q), 52.2 (d), 47.3 (t), 44.5 (t), 40.2 (t), 33.3 (t), 30.9 (d), 29.2 (t), 28.4 (q, 3×), 24.7 (t), 24.1 (q), 19.3 (q), 18.9 (q), 17.9 (q) ppm. HRMS (ESI^+): Calcd. for $C_{46}H_{61}IN_3O_7S$ ($[M+H]^+$), 926.3269; found, 926.3257. IR (NaCl): ν 3306 (w, N–H), 2969 (m, C–H), 1734 (m, C=O), 1670 (s, C=O), 1509 (m) cm^{-1}.

Compound 58

General procedure for TMSOTf-induced deprotection of Boc-protected amines. To a solution of compound **56** (0.057 g, 0.062 mmol) in CH_2Cl_2 (0.123 mL), 2,6-lutidine (0.014 mL, 0.123 mmol) and TMSOTf (0.017 mL, 0.092 mmol) were sequentially added and the resulting mixture was stirred for 1 h. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with H_2O (1×) and brine (1×), dried (Na_2SO_4) and the solvent was removed. The residue was used in the next step without further purification.

Following the general procedure for peptide coupling, the reaction of (2*E*,4*S*,6*E*)-2,4-dimethyl-7-(tributylstannyl)hepta-2,6-dienoic acid **57** (33 mg, 0.074 mmol), the previously prepared intermediate (50.8 mg, 0.062 mmol), HATU (30 mg, 0.08 mmol), and DIPEA (0.027 mL, 0.160 mmol) in CH_2Cl_2 (0.44 mL) afforded, after purification by flash-column chromatography (Combiflash™ C18 silica gel, from 95:5 to 45:65 v/v CH_3CN/CH_2Cl_2), 48.6 mg (63%) of a colorless oil identified as compound **58** as a mixture of rotamers. $[\alpha]^{24}_D$ +2.2 (*c* 0.37, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.8 Hz, 6H, ArH), 7.36 (t, *J* = 7.5 Hz, 6H, ArH), 7.29 (d, *J* = 7.4 Hz, 3H, ArH), 6.99 (d, *J* = 8.4 Hz, 1H, NH), 6.12–5.86 (m, 3H, $H_{1'''} + H_1 + H_2$), 5.57 (d, *J* = 6.1 Hz, 1H, H_5), 5.26–5.06 (m, 1H, $H_{4'''}$), 4.42–4.28 (m, 2H, $H_{2'}$ or $H_{2''}$ or $H_{2'''}$), 4.28–4.12 (m, 1H, $H_{2'}$ or $H_{2''}$ or $H_{2'''}$), 3.70–3.50 (m, 2H, $2H_{5'}$), 3.38 (dt, *J* = 11.3, 5.7 Hz, 1H, $H_{6'''}$), 3.27 (s, 3H, OCH_3), 3.04–2.81 (m, 1H, H_4), 2.74–2.39 (m, 4H, $2H_{3'''} + 2H_3$), 2.32–1.98 (m, 7H, $H_{3'''} + 2H_{4'} + 2H_{3'} + 2H_{4''}$), 1.97–1.88 (1H. $H_{5'''}$), 1.88 (s, 3H, C2''''–CH_3), 1.84 (s, 3H, C_6–CH_3), 1.69–1.44 (m, 7H, $H_{5'''}$ + –Sn–$\underline{CH_2}$–CH_2–CH_2–CH_3), 1.45–1.26 (m, 6H, –Sn–CH_2–$\underline{CH_2}$–CH_2–CH_3), 1.13 (d, *J* = 6.2 Hz, 3H, $C_{7'''}$–CH_3), 1.09–0.75 (m, 24H, –Sn–CH_2–CH_2–CH_2–$\underline{CH_2}$ + –Sn–CH_2–CH_2–$\underline{CH_2}$–CH_3 + 2×–$CH(\underline{CH_2})_2$ + C_4–CH_3) ppm. ^{13}C NMR (100.62 MHz, CD_2Cl_2): δ 172.1 (s), 171.6 (s), 170.8 (s), 169.3 (s), 147.0 (d), 144.6 (s, 3×), 143.8 (s), 139.2 (d), 130.0 (s), 129.6 (d, 6×), 129.5 (d), 128.0 (d, 6×), 126.8 (d, 3×), 78.1 (d), 73.5 (d), 69.8 (d), 66.9 (s), 60.1 (d), 57.7 (d), 55.6 (q), 52.3 (d), 50.3 (t), 45.4 (t), 44.1 (t), 40.7 (t), 33.0 (t), 32.8 (d), 30.6 (d), 29.1 (t, 3×), 27.9 (t), 27.3 (t, 3×), 25.5 (t), 23.5 (q), 19.7 (q), 19.3 (q), 18.8 (q), 17.7 (q), 13.7 (q), 13.5 (q, 3×), 9.35 (t, 3×) ppm. HRMS (ESI^+): Calcd. for $C_{62}H_{91}IN_3O_6SSn$ ($[M+H]^+$), 1252.4703; found, 1252.4695. IR (NaCl): ν 3312 (m, N–H), 2957 (m, C–H), 2925 (s, C–H), 1735 (m, C=O), 1668 (m, C=O), 1603 (m) cm^{-1}.

Compound 59

To a solution of $Pd_2dba_3{\cdot}CHCl_3$ (0.042 g, 0.04 mmol) and $AsPh_3$ (0.049 g, 0.161 mmol) in DMF (99.7 mL), a solution of compound **58** (0.125 g, 0.1 mmol) and DIPEA (0.36 mL, 2.12 mmol) in DMF (99.7 mL) were added and the mixture was stirred for 14.5 h. The solvent was removed, and the residue was purified by flash-column chromatography (CombiflashTM, silica gel, from 85:15 to 0:100 v/v hexane/EtOAc) to afford 35 mg (47%) of a yellow oil identified as a mixture of compound **59** together with a secondary product **iso-59** that were separated by HPLC. **Compound 59**: $[\alpha]^{23}_D$ −14.5 (*c* 0.3, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.3 Hz, 3H, ArH), 7.36–7.27 (m, 7H, ArH + N_2H), 7.26–7.19 (m, 6H, ArH), 6.63 (d, *J* = 8.4 Hz, 1H, N_1H), 6.08 (dd, *J* = 15.0, 10.9 Hz, 1H, H_{23}), 5.75 (d, *J* = 10.8 Hz, 1H, H_{24}), 5.69–5.57 (m, 1H, H_{22}), 5.46 (d, *J* = 9.8 Hz, 1H, H_{18}), 5.29–5.19 (m, 1H, H_{28}), 4.77 (d, *J* = 7.7 Hz, 1H, H_{11}), 4.41 (dd, *J* = 8.5, 3.6 Hz, 1H, H_2), 3.93–3.83 (m, 1H, H_8), 3.47–3.37 (m, 2H, H_{14A}), 3.35 (app q, *J* = 6.2 Hz, 1H, H_{30}), 3.31 (s, 3H, OCH_3), 3.38–3.28 (m, 1H, H_{14B}), 2.76–2.66 (m, 1H, H_{19}), 2.62 (d, *J* = 6.9 Hz, 2H, H_9), 2.58–2.46 (m, 2H, H_{13}), 2.33–2.11 (m, 1H, H_3), 2.33–2.11 (m, 2H, H_{21}), 2.33–2.11 (m, 2H, H_{27}), 2.10–1.87 (m, 2H, H_{12}), 2.10–1.87 (m, 1H, H_{29A}), 1.84 (s, 3H, C17–CH_3), 1.71 (s, 3H C26–CH_3), 1.60–1.50 (m, 1H, H_{29B}), 1.18 (d, *J* = 5.7 Hz, 3H, C_{31}–CH_3), 1.05 (d, *J* = 6.8 Hz, 3H, C20–CH_3), 0.90 (d, *J* = 6.8 Hz, 3H, C5–CH_3), 0.84 (d, *J* = 6.9 Hz, 3H, C4–CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 174.1 (s), 171.7 (s), 170.9 (s), 169.9 (s), 144.6 (3×, s), 137.9 (d), 132.3 (s), 129.8 (6×, d), 129.8 (s), 129.1 (d), 128.7 (d), 128.1 (6×, d), 127.2 (d), 126.9 (3×, d), 73.7 (d), 70.9 (d), 67.2 (s), 58.9 (d), 56.7 (d), 56.0 (q), 52.4 (d), 48.9 (t), 32.2 (t), 31.5 (d), 26.5 (t), 24.5 (t), 45.5 (t), 42.2 (t), 39.8 (t), 31.6 (d), 19.4 (q), 19.1 (q), 18.9 (q), 17.4 (q), 16.8 (q), 13.7 (q) ppm. HRMS (ESI^+): Calcd. for $C_{50}H_{64}N_3O_6S$ ($[M+Na]^+$), 834.4510; found, 834.4514. IR (NaCl): ν 3299 (m, NH), 2966 (m, C–H), 2926 (m, C–H), 1734 (s, C=O), 1667 (s, C=O), 1510 (m) cm^{-1}.

Compound 66

To a solution of (1*E*,4*R*,6*R*)-(1-iodo-6-methoxy-2-methylhept-1-en-4-yl)-(*tert*-butoxycarbonyl)-L-valinate (*S*,*R*,*R*)-**54** (0.21 g, 0.40 mmol) in CH_2Cl_2 (5.1 mL), TFA (5.1 mL) was added and the reaction mixture was stirred for 2 h at 25 °C. The solvent was evaporated and the residue was diluted with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated to afford 0.16 g (97%) of a yellow oil, which was used in the next step without further purification.

Following the general procedure for the peptide coupling, a solution of previously prepared amine (0.16 g, 0.4 mmol), *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-prolyl)-*S*-trityl-D-Cys **67** (0.34 g,

0.5 mmol), HATU (0.189 g, 0.5 mmol) and DIPEA (0.241 mL, 1.41 mmol) in CH_2Cl_2 (3.2 mL), afforded after purification by flash-column chromatography (silica gel, gradient from 80:20 to 25:75 v/v hexane/EtOAc), 0.33 g (77%) of a colorless foam identified as compound **66**. $[\alpha]^{21}_D$ −22.5 (*c* 0.64, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$, 323 K): δ 7.78 (d, *J* = 7.4 Hz, 2H, ArH), 7.58 (d, *J* = 7.0 Hz, 2H, ArH), 7.49–7.37 (m, 9H, ArH), 7.36–7.15 (m, 10H, ArH), 5.98 (s, 1H, $H_{1'''}$), 5.39–5.20 (m, 1H, $H_{4'''}$), 4.44–4.34 (m, 3H, $H_{2''}$ + $2H_{1'''}$), 4.32–4.14 (m, 3H, H_2 + $H_{2'}$ + $H_{2'''}$), 3.66–3.57 (m, 1H, H_{5A}), 3.57–3.48 (m, 1H, H_{5B}), 3.37–3.24 (m, 1H, $H_{6'''}$), 3.20 (s, 3H, –OCH_3), 2.91–2.60 (m, 2H, $2H_{3'}$), 2.51 (dd, *J* = 14.0, 7.9 Hz, 1H, $H_{3'''A}$), 2.35 (dd, *J* = 14.0, 5.0 Hz, 1H, $H_{3'''B}$), 2.28–2.18 (m, 1H, H_{3A}), 2.18–2.02 (m, 3H, H_{3B} + H_{4A} + $H_{3''}$), 1.98–1.86 (m, 1H, H_{4B}), 1.84 (s, 3H, C2'''–CH_3), 1.65–1.53 (m, 2H, $2H_{5'''}$), 1.09 (d, *J* = 5.4 Hz, 3H, C7'''–CH_3), 0.93 (d, *J* = 6.6 Hz, 3H, –CH($\underline{CH_3}$)$_2$), 0.86 (d, *J* = 6.6 Hz, 3H, –CH($\underline{CH_3}$)$_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 323 K): δ 172.0 (s), 170.7 (s), 169.6 (s), 155.4 (s), 144.3 (s, 2×), 143.8 (s), 143.6 (s, 2×), 141.2 (s, 3×), 129.4 (d, 6×), 127.9 (d, 6×), 127.6 (d, 2×), 127.0 (d), 126.9 (d), 126.7 (d, 3×), 125.0 (d, 2×), 119.8 (d, 2×), 78.0 (d), 72.8 (d), 69.7 (d), 67.7 (t), 67.0 (s), 60.8 (d), 57.6 (d), 56.0 (q), 52.2 (d), 47.2 (d), 47.1 (t), 44.8 (t), 41.9 (t), 33.2 (t), 30.6 (d), 29.1 (t), 24.6 (t), 23.7 (q), 19.2 (q), 19.1 (q), 17.6 (q) ppm. HRMS (ESI$^+$): Calcd. for $C_{56}H_{63}IN_3O_7S$ ([M + H]$^+$), 1048.3426; found, 1048.3405. IR (NaCl): ν 3314 (w, N–H), 2967 (m, C–H), 1735 (m, C=O), 1675 (s, C=O), 1512 (m) cm^{-1}.

(4*R*,6*R*,*E*)-1-Iodo-6-methoxy-2-methylhept-1-en-4-yl ((4*S*)-2-(Pyrrolidin-2-yl)-4,5-dihydrothiazole-4-carbonyl)-D-valinate 69

Tf_2O (0.141 mL, 0.859 mmol) was added to a cooled (0 °C) solution of Ph_3PO (0.488 g, 1.72 mmol) in CH_2Cl_2 (3.82 mL), After stirring for 10 min, a solution of **66** (0.30 g, 2.86 mmol) in CH_2Cl_2 (2.82 mL) was added and the mixture was stirred for 15 min at 0 °C. To a cooled (0 °C) saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with EtOAc (3×). The combined organic layers were washed with brine (3×), dried (Na_2SO_4) and the solvent was removed. The residue was purified by flash-colum chromatography (Combiflash™, CN silica gel gold, gradient from 100:0 to 70:30 hexane/EtOAc) to afford 0.185 g of a white solid that was used immediately. To a solution of the compound obtained above (0.185 g, 0.235 mmol) in CH_3CN (3.4 mL), piperidine (0.093 mL, 0.939 mmol) was added and the reaction mixture was stirred for 2 h The solvent was removed, the residue was purified by flash-column chromatography (CombiFlash™, C18 silica gel, gradient from 50:50 to 0:100 v/v H_2O/CH_3CN) to afford 64.9 mg (49%) of a yellowish oil identified as (4*R*,6*R*,*E*)-1-iodo-6-methoxy-2-methylhept-1-en-4-yl ((4*S*)-2-(pyrrolidin-2-yl)-4,5-dihydrothiazole-4-carbonyl)-D-valinate **69**. $[\alpha]^{25}_D$ −88.5 (*c* 0.15, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.09 (d, *J* = 9.0 Hz, 1H, NH), 5.96 (s, 1H, $H_{1'''}$), 5.36 −5.28 (m, 1H, $H_{4'''}$), 5.07 (app t, *J* = 9.9 Hz, 1H, $H_{2'}$), 4.47 (dd, *J* = 9.0, 4.5 Hz, 1H, $H_{2''}$), 4.12–4.07 (m, 1H, H_2), 3.55–3.39 (m, 2H, $2H_{3'}$), 3.32–3.24 (m, 1H, $H_{6'''}$), 3.22 (s, 3H, –OCH_3), 3.11–3.03 (m, 1H, H_{5A}), 3.03–2.95 (m, 1H, H_{5B}), 2.51 (dd, *J* = 14.0, 8.4 Hz, 1H, $H_{3'''A}$), 2.35 (dd, *J* = 13.8, 4.7 Hz, 1H, $H_{3'''B}$), 2.22 −2.11 (m, 2H, $H_{3''}$ + H_{3A}), 1.98–1.86 (m, 2H, H_{3B} + H_{4A}), 1.84 (s, 3H, C2'''–CH_3), 1.83–1.71 (m, 1H, H_{4B}), 1.64–1.57 (m, 2H, $2H_{5'''}$), 1.10 (d, *J* = 6.1 Hz, 3H, C7'''–CH_3), 0.98 (d, *J* = 6.9 Hz, 3H, –CH($\underline{CH_3}$)$_2$), 0.91 (d, *J* = 6.9 Hz, 3H, –CH($\underline{CH_3}$)$_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.5 (s), 171.7 (s), 171.1 (s), 143.8 (s), 79.0 (d), 78.3 (d), 73.0 (d), 69.8 (d), 60.3 (d), 57.2 (d), 56.4 (q), 47.2 (t), 45.1 (t), 42.2 (t), 34.7 (t), 32.1 (t), 31.2 (d), 25.8 (t), 23.8 (q), 19.6 (q), 19.2 (q), 17.7 (q) ppm. HRMS (ESI$^+$): Calcd. for $C_{22}H_{37}IN_3O_4S$ ([M + H]$^+$), 566.1544; found, 566.1526. IR (NaCl): ν 3385 (w, N–H), 2965 (m, C–H), 2927 (m, C–H), 1736 (m, C=O), 1680 (s, C=O), 1511 (s), 1197 (m), 1147 (m) cm^{-1}.

(2*E*,4*S*,6*E*)-2,4-Dimethyl-7-(tributylstannyl)hepta-2,6-dienoic Acid (*S*)-57

To a solution of ethyl (2*E*,4*S*,6*E*)-2,4-dimethyl-7-(tributylstannyl) hepta-2,6-dienoate (*S*)-**28** (0.07 g, 0.14 mmol) in ^{i}PrOH/H_2O (4.0 mL, 1.2/1 v:v), LiOH·H_2O (0.06 g, 1.44 mmol) was added. After stirring for 20 h at 50 °C a saturated aqueous solution of NH_4Cl was added, the mixture was extracted with EtOAc (3×), the organic layers were dried (Na_2SO_4) and the solvent was evaporated to afford 0.058 g (91%) of a yellow oil which was identified as (2*E*,4*S*,6*E*)-2,4-dimethyl-7-(tributylstannyl)hepta-2,6-dienoic acid (*S*)-**57**. $[\alpha]^{22}_D$ +18.1 (*c* 0.3, CH_2Cl_2). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 6.69 (d, *J* = 10.0 Hz, 1H, H_3), 6.10–5.64 (m, 2H, H_6 + H_7), 2.70–2.50 (m, 1H, H_4), 2.26–2.12 (m, 2H, $2H_5$), 1.84 (d, *J* = 1.4 Hz, 3H, C2–CH_3), 1.56–1.39 (m, 6H, -Sn–$\underline{CH_2}$–CH_2–CH_2–CH_3), 1.39–1.22 (m, 6H, -Sn–CH_2–$\underline{CH_2}$–CH_2–CH_3), 1.02 (d, *J* = 6.6 Hz, 3H, C4–CH_3), 0.88 (t, *J* = 7.3 Hz, 9H, –Sn–CH_2–CH_2–CH_2–$\underline{CH_3}$), 0.92–0.82 (m, 6H, –Sn–CH_2–CH_2–$\underline{CH_2}$–CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 174.1 (s), 149.9 (d), 146.7 (d), 130.3 (d), 126.1 (s), 45.0 (t), 33.7 (d), 29.3 (t, 3×, $^2J_{C\text{-}Sn}$ = 20.6 Hz), 27.4 (t, 3×, $^3J_{C\text{-}Sn}$ = 53.4 Hz), 19.5 (q), 13.8 (q, 3×), 12.5 (q), 9. 5 (t, 3×, $^1J_{C\text{-}^{119}Sn}$ = 342 Hz, $^1J_{C\text{-}^{117}Sn}$ = 327 Hz) ppm. HRMS (ESI$^+$): Calcd. for $C_{21}H_{40}NaO_2{}^{119}Sn$ ([M + Na]$^+$), 466.5324; found, 466.5331. IR (NaCl): υ 3500–3000 (br, O–H), 2925 (s, C–H), 2852 (s, C–H), 1648 (w, C=O), 1383 (m) cm^{-1}.

Compound 71

Following the general procedure for peptide coupling, the reaction of (2*E*,4*S*,6*E*)-2,4-dimethyl-7-(tributylstannyl)hepta-2,6-dienoic acid **57** (29.8 mg, 0.067 mmol), (4*R*,6*R*,*E*)-1-iodo-6-methoxy-2-methylhept-1-en-4-yl ((4*S*)-2-(pyrrolidin-2-yl)-4,5-dihydrothiazole-4-carbonyl)-D-valinate **69** (31.7 mg, 0.056 mmol), HATU (27.7 mg, 0.073 mmol) and DIPEA (0.025 mL, 0.15 mmol) in CH_2Cl_2 (0.84 mL) for 17 h at 25 °C afforded, after purification by flash-column chromatography (Combiflash™ C18 silica gel, gradient from 100:0 to 90:10 v/v CH_3CN/CH_2Cl_2), 48.6 mg (63%) of a colorless oil identified as **71**. $[\alpha]^{20}_D$ −17.7 (*c* 0.73, CH_2Cl_2). ^{1}H NMR (400.16 MHz, CD_2Cl_2): δ 7.09 (d, *J* = 8.7 Hz, 1H, NH), 6.08–5.84 (m, 3H, $H_{1'''}$ + H_1 + H_2), 5.56 (d, *J* = 9.7 Hz, 1H, H_5), 5.31–5.22 (m, 1H, $H_{4'''}$), 5.11 (t, *J* = 8.4 Hz, 1H, $H_{2''}$), 4.85 (t, *J* = 7.0 Hz, 1H, $H_{2'}$), 4.41–4.33 (m, 1H, $H_{2'''}$), 3.66–3.48 (m, 4H, $2H_{5'}$ + $2H_{3''}$), 3.32 (app q, *J* = 6.0 Hz, 1H, $H_{6'''}$), 3.21 (s, 3H, OCH_3), 2.68–2.57 (m, 1H, H_4), 2.52 (dd, *J* = 14.0, 8.0 Hz, 1H, $H_{3'''A}$), 2.36 (dd, *J* = 14.1, 5.3 Hz, 1H„ $H_{3'''B}$), 2.31–2.09 (m, 4H, $2H_3$ + $H_{3'A}$ + $H_{3'''}$), 2.09–1.85 (m, 3H, $H_{3'A}$ + $2H_4$), 1.85 (s, 3H, C2''''–CH_3), 1.81 (s, 3H, C_6–CH_3), 1.62–1.54 (m, 2H, $H_{5'''}$), 1.56–1.43 (m, 6H, –Sn–$\underline{CH_2}$–CH_2–CH_2–CH_3), 1.38–1.21 (m, 6H, -Sn–CH_2–$\underline{CH_2}$–CH_2–CH_3), 1.09 (d, *J* = 6.1 Hz, 3H, $C_{7'''}$–CH_3), 1.04–0.80 (m, 24H, -Sn–CH_2–CH_2–CH_2–$\underline{CH_3}$ + -Sn–CH_2–CH_2–$\underline{CH_2}$–CH_3 + 2× –CH($\underline{CH_3}$)$_2$ + C_4–CH_3) ppm. ^{13}C NMR (100.62 MHz, CD_2Cl_2): δ 178.5 (s), 172.7 (s), 171.8 (s), 171.5 (s), 147.8 (d), 144.6 (s), 139.4 (d), 131.1 (s), 130.4 (d), 79.4 (d), 78.4 (d), 73.3 (d), 70.1 (d), 59.6 (d), 58.2 (d), 56.5 (q), 50.8 (t), 45.7 (t), 45.4 (t), 42.4 (t), 36.1 (t), 33.3 (d), 31.7 (t), 31.2 (d), 29.8 (t, $^2J_{C\text{-}Sn}$ = 19.9 Hz, 3×), 27.9 (t, $^3J_{C\text{-}Sn}$ = 53.8 Hz, 3×), 26.0 (t), 24.2 (q), 20.2 (q), 19.8 (q), 19.5 (q), 18.3 (q), 14.1 (q), 14.0 (q, 3×), 9.9 (t, $^1J_{C\text{-}^{119}Sn}$ = 343.0 Hz, $^1J_{C\text{-}^{117}Sn}$ = 327.5 Hz, 3×) ppm. HRMS (ESI$^+$): Calcd. for $C_{43}H_{75}IN_3O_5SSn$ ([M + H]$^+$), 992.3496; found, 992.3482. IR (NaCl): ν 3309 (m, N–H), 2958 (m, C–H), 2925 (s, C–H), 1736 (m, C=O), 1675 (m, C=O), 1619 (m) cm^{-1}.

N-demethylalotamide A 60

To a solution of Pd_2dba_3·$CHCl_3$ (12.5 mg, 0.012 mmol) and $AsPh_3$ (15.3 mg, 0.048 mmol) in DMF (28.8 mL), a solution of **71** (30.0 mg, 0.03 mmol) in DMF (3 mL) was added and the mixture was stirred for 15 h at 25 °C. The solvent was removed, and the residue was purified by flash-column chromatography (Combiflash™, CN silica

gel gold, gradient from 95:5 to 70:30 v/v CH_3CN/H_2O) to afford 8.5 mg of a mixture of **60** and **iso-60** in a 1:0.6 ratio that were separated by HPLC. Data for **60**: $[\alpha]^{24}_D$ −241.6 (*c* 0.28, CH_2Cl_2).^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.12 (d, *J* = 10.1 Hz, 1H, NH), 6.20 (dd, *J* = 15.0, 10.9 Hz, 1H, H_{23}), 5.79 (d, *J* = 8.8 Hz, 1H, H_{18}), 5.66 (d, *J* = 10.9 Hz, 1H, H_{24}), 5.42–5.34 (m, 1H, H_{28}), 5.34–5.26 (m, 1H, H_{22}), 5.14 (dd, *J* = 10.2, 6.2 Hz, 1H, H_8), 4.82 (t, *J* = 7.4 Hz, 1H, H_{11}), 4.69 (dd, *J* = 10.1, 3.5 Hz, 1H, H_2), 3.73–3.54 (m, 3H, $2H_9 + H_{14A}$), 3.54–3.45 (m, 1H, H_{14B}), 3.36–3.28 (m, 1H, H_{30}), 3.28 (s, 3H, OCH_3), 2.54–2.41 (m, 1H, H_{19}), 2.41–2.29 (m, 3H, $H_3 + H_{12A} + H_{21A}$), 2.29–2.07 (m, 2H, $2H_{27}$), 2.07–1.85 (m, 4H, $H_{12B} + H_{13} + H_{21B}$), 1.85 (s, 3H, C17–$CH_3$), 1.81 (s, 3H, C26–$CH_3$), 1.66–1.60 (m, 2H, $2H_{29}$), 1.14 (d, *J* = 6.1 Hz, 3H, C31–CH_3), 1.02 (d, *J* = 6.7 Hz, 3H, C20–CH_3), 0.96 (d, *J* = 6.8 Hz, 3H, C5–CH_3), 0.72 (d, *J* = 6.9 Hz, 3H, C4–CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 176.7 (s), 171.8 (s), 171.7 (s), 169.7 (s), 141.6 (d), 133.5 (s), 131.3 (s), 130.0 (d), 129.0 (d), 127.0 (d), 78.5 (d), 73.6 (d), 70.0 (d), 59.3 (d), 56.7 (d), 56.6 (q), 48.4 (t), 46.5 (t), 43.3 (t), 41.7 (t), 37.4 (t), 32.3 (d), 30.8 (2×, d + t), 25.7 (t), 20.9 (q), 20.4 (q), 19.4 (q), 18.2 (q), 17.2 (q), 14.2 (q) ppm. HRMS (ESI^+): Calcd. for $C_{31}H_{48}N_3O_5S$ ($[M+H]^+$), 574.3309; found, 574.3303. IR (NaCl): ν 3302 (m, NH), 2959 (m, C–H), 2923 (m, C–H), 1740 (s, C=O), 1668 (s, C=O), 1621 (m), 1525 (m), 1415 (m) cm^{-1}.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] a) D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2020**, *83*, 770–803; b) A. R. Carroll, B. R. Copp, R. A. Davis, R. A. Keyzers, M. R. Prinsep, *Nat. Prod. Rep.* **2020**, *37*, 175–223.
[2] a) K.-H. Altmann *Chim. Int. J. Chem.* **2017**, *71*, 646–652; b) C. Jiménez, *ACS Med. Chem. Lett.* **2018**, *9*, 959–961; c) E. Patridge, P. Gareiss, M. S. Kinch, D. Hoyer *Drug Discovery Today* **2016**, *21*, 204–207.
[3] a) G.-M. Suarez-Jimenez, A. Burgos-Hernandez, J.-M. Ezquerra-Brauer, *Mar. Drugs* **2012**, *10*, 963–986; b) M. Pelay-Gimeno, J. Tulla-Puche, F. Albericio *Mar. Drugs* **2013**, *11*, 1693–1717; c) S. Sivanathan, J. Scherkenbeck *Molecules* **2014**, *19*, 12368–12420; d) M. Rangel, C. Santana, A. Pinheiro, L. Anjos, T. Barth, O. Pires Júnior, W. Fontes, M. S. Castro *Curr. Protein Pept. Sci.* **2017**, *18*, 72–91.
[4] I. E. Soria-Mercado, A. Pereira, Z. Cao, T. F. Murray, W. H. Gerwick *Org. Lett.* **2009**, *11*, 4704–4707.
[5] a) S. Sarceda, J. A. Souto, D. Otero, A. R. de Lera, M. Domínguez, R. Álvarez *Tetrahedron* **2019**, *75*, 130604–130616; b) L. Guillade, F. Sarno, H. Tarhonskaya, A. Nebbioso, S. Álvarez, A. Kawamura, C. J. Schofield, L. Altucci, A. R. de Lera *ChemMedChem* **2018**, *13*, 1949–1956; c) I. Alonso, R. Álvarez, A. R. de Lera *Eur. J. Org. Chem.* **2017**, 4948–4954; d) S. Gallego, P. Lorenzo, R. Álvarez, A. R. de Lera *Tetrahedron Lett.* **2017**, *58*, 210–212; e) P. Lorenzo, R. Álvarez, A. R. de Lera *Eur. J. Org. Chem.* **2014**, 2557–2564; f) P. Lorenzo, R. Álvarez, A. R. de Lera *J. Nat. Prod.* **2014**, *77*, 421–423; g) C. Pérez-Balado, A. R. de Lera *Org. Biomol. Chem.* **2010**, *8*, 5179–5186; h) J. A. Souto, E. Vaz, I. Lepore, A. C. Poeppler, G. Franci, R. Álvarez, L. Altucci, A. R. de Lera *J. Med. Chem.* **2010**, *53*, 4654–4667; i) J. García, R. Pereira, A. R. de Lera *Tetrahedron Lett.* **2009**, *50*, 5028–5030; j) C. Pérez-Balado, P. Rodríguez-Graña, A. R. de Lera, *Chem. A Eur. J.* **2009**, *15*, 9928–9937.
[6] a) A. Isidro-Llobet, M. Álvarez, F. Albericio *Chem. Rev.* **2009**, *109*, 2455–2504; b) A. El-Faham, F. Albericio *Chem. Rev.* **2011**, *111*, 6557–6602.
[7] A. C. Gaumont, M. Gulea, J. Levillain *Chem. Rev.* **2009**, *109*, 1371–1401.
[8] a) D. A. Evans, M. D. Ennis, D. J. Mathre *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739; b) A. G. Myers, B. H. Yang, H. Chen, J. L. Gleason *J. Am. Chem. Soc.* **1994**, *116*, 9361–9362.
[9] N. V. Bac, Y. Langlois *Tetrahedron Lett.* **1988**, *29*, 2819–2822.
[10] a) K. C. Nicolaou, P. G. Bulger, D. Sarlah *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489; *Angew. Chem.* **2005**, *117*, 4516–4563; b) *Modern Carbonyl Olefination*, Wiley-VCH Verlag GmbH (Ed. T. Takeda), **2004**.
[11] P. J. Stang, M. Hanack, L. R. Subramanian *Synthesis* **1982**, 85–126.
[12] R. Quach, D. P. Furkert, M. A. Brimble *J. Org. Chem.* **2016**, *81*, 8343–8350.
[13] D. P. Stamos, A. G. Taylor, Y. Kishi *Tetrahedron Lett.* **1996**, *37*, 8647–8650.
[14] E. A. Ilardi, C. E. Stivala, A. Zakarian *Org. Lett.* **2008**, *10*, 1727–1730.
[15] a) J. M. Seco, E. Quiñoá, R. Riguera *Chem. Rev.* **2004**, *104*, 17–118; b) J. M. Seco, E. Quiñoá, R. Riguera *Chem. Rev.* **2012**, *112*, 4603–4641.
[16] a) A. G. Myers, P. Schnider, S. Kwon, D. W. Kung *J. Org. Chem.* **1999**, *64*, 3322–3327; b) D. A. Kummer, W. J. Chain, M. R. Morales, O. Quiroga, A. G. Myers *J. Am. Chem. Soc.* **2008**, *130*, 13231–13233.
[17] J. Ma, H. W. Cheon, Y. Kishi *Org. Lett.* **2007**, *9*, 319–322.
[18] T. D. W. Claridge, S. G. Davies, J. A. Lee, R. L. Nicholson, P. M. Roberts, A. J. Russell, A. D. Smith, S. M. Toms *Org. Lett.* **2008**, *10*, 5437–5440.
[19] C. D. J. Boden, G. Pattenden, T. Ye *J. Chem. Soc. Perkin Trans. 1* **1996**, 2417–2419.
[20] V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
[21] J. Jägel, M. E. Maier *Synthesis* **2009**, 2881–2892.
[22] A. Fürstner, J. A. Funel, M. Tremblay, L. C. Bouchez, C. Nevado, M. Waser, J. Ackerstaff, C. C. Stimson, *Chem. Commun.* **2008**, 2873–2875.
[23] H. Shi, Y. Xie, P. Hu, Z. Guo, Y. Lu, Y. Gao, C. Huang, *Mar. Drugs* **2018**, *16*, 414–433.
[24] See Supporting Information (S. I.) for further details.
[25] a) J. Chatterjee, C. Gilon, A. Hoffman, H. Kessler *Acc. Chem. Res.* **2008**, *41*, 1331–1342; b) N. Bayó-Puxan, J. Tulla-Puche, F. Albericio *Eur. J. Org. Chem.* **2009**, 2957–2974.
[26] J. Wagger, U. Grošelj, A. Meden, J. Svete, B. Stanovnik *Tetrahedron* **2008**, *64*, 2801–2815.
[27] S. L. You, H. Razavi, J. W. Kelly *Angew. Chem. Int. Ed.* **2003**, *42, 83–85; Angew. Chem.* **2003**, 115, 87–89; *Angew. Chem.* **2003**, *115*, 87–89.
[28] S. A. Thomson, J. A. Josey, R. Cadilla, M. D. Gaul, C. F. Hassman, M. J. Luzzio, A. J. Pipe, K. L. Reed, D. J. Ricca, R. W. Wiethe, S. A. Noble *Tetrahedron* **1995**, *51*, 6179–6194.
[29] L. Aurelio, R. T. C. Brownlee, A. B. Hughes *Chem. Rev.* **2004**, *104*, 5823–5846.
[30] a) C. F. Tormena, G. V. J. da Silva, *Chem. Phys. Lett.* **2004**, *398*, 466–470; b) D. J. Giesen, N. Zumbulyadis *Phys. Chem. Chem. Phys.* **2002**, *4*, 5498–5507; c) A. Wu, Y. Zhang, X. Xu, Y. Yan *J. Comput. Chem.* **2007**, *28*, 2431–2442; d) G. Barone, L. Gomez-Paloma, D. Duca, A. Silvestri, R. Riccio, G. Bifulco *Chem. Eur. J.* **2002**, *8*, 3233–3239; e) G. Barone, D. Duca, A. Silvestri, L. Gomez-Paloma, R. Riccio, G Bifulco *Chem. Eur. J.* **2002**, *8*, 3240–3245; f) K. Ermanis, K. E. B. Parkes, T. Agback, J. M. Goodman *Org. Biomol. Chem.* **2016**, *14*, 3943–3949; g) S. G. Smith, J. M. Goodman *J. Am. Chem. Soc.* **2010**, *132*, 12946–12959; h) D. A. Forsyth, A. B. Sebag *J. Am. Chem. Soc.* **1997**, *119*, 9483–9494; i) A. Bagno, F. Rastrelli, G. Saielli *Chem. Eur. J.* **2006**, *12*, 5514–5525; j) A. M. Sarotti, S. C. Pellegrinet *J. Org. Chem.* **2009**, *74*, 7254–7260; k) N. Grimblat, A. M. Sarotti *Chem. Eur. J.* **2016**, *22*, 12246–12261.

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