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A convergent approach toward phoslactomycins and leustroducsins

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ABSTRACT

Synthetic studies devoted to the development of a convergent approach toward phoslactomycins and leustroducsins, a family of natural products inhibitors of serine/threonine phosphatase 2A, are reported. A formal synthesis of phoslactomycin B was achieved in which the key steps are a [2,3]-Wittig rearrangement to control the C4 and C5 stereocenters, a diastereoselective addition of an acetylenic Grignard reagent to an α-alkoxy ketone to create the C8 tertiary alcohol, and a relay ring-closing metathesis to construct the α,β-unsaturated δ-lactone. In this approach, all the stereocenters originate, either directly or indirectly, from catalytic enantioselective reductions of acetylenic ketones.

1. Introduction

Phoslactomycins (PLMs) A–F are six antibiotics isolated in 1989 by Seto et al. from the culture broth of a strain of *Streptomyces nigrescens* (SC-273), which were found to be active against resistant phytopathogenic fungi.[1] In the same year, phospholine, a compound which turned out to be identical to PLM B, was isolated from the fermentation broth of *Streptomyces hygroscopicus*. This compound showed strong in vitro cytotoxicity against L1210, P388, and EL-4 tumor cell lines.[2] A few years later, while using a new screening method for colony-stimulating factors (CSFs) inducers, researchers from the Sankyo group identified three active compounds, leustroducsins (LSNs) A–C, isolated from cultures of *Streptomyces platensis* SANK 600191.[3] Finally, LSN H, a synthetic analogue prepared by saponification, was also found to possess thrombopoietic activity.[4] PLMs and LSNs feature a common backbone comprising an α,β-unsaturated δ-lactone (C1–C5), a disubstituted olefin of *E* configuration (C6–C7), a tertiary alcohol at C8 substituted by an aminoethyl side-chain, a phosphorylated secondary alcohol at C9, a secondary hydroxyl group at C11, and a conjugated diene (C12–C15) consisting of two olefins of *Z* configuration (Fig. 1).

Naturally occurring PLMs and LSNs only differ by the nature of the substituent attached to the cyclohexyl ring at C18 (a hydrogen

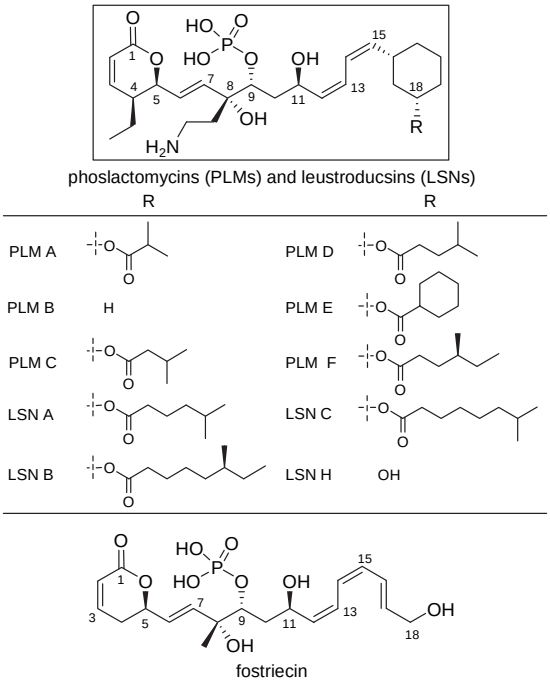

Figure 1. Phoslactomycins, leustroducsins, and fostriecin.

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for PLM B or an acyloxy group for the other members), which does not seem to exert a marked effect on the biological activity. These compounds are also structurally related to the natural product fostriecin from which they differ by the presence of an ethyl group at C4, a 2-aminoethyl side-chain at C8 rather than a simple methyl group and a (*Z*,*Z*)-diene substituted by the cyclohexyl group at C15 instead of a labile (*Z*,*Z*,*E*)-triene subunit (Fig. 1).[5]

Like fostriecin, PLMs and LSNs are potent selective inhibitors of protein phosphatase 2A (PP2A), an enzyme playing important roles in the regulation of cell growth and division, signaling pathways, inhibition of metastasis through activation of natural killer cells, and also in the transcription and regulation of HIV-1.[6] It is therefore not surprising that PLMs and LSNs have elicited considerable interest from the synthetic community. To date, two total syntheses of both PLM B[7,8] and LSN B[9,10] and one total synthesis of PLM A[11] have been reported. Formal syntheses of LSN B[12] and PLM B[13,14] have also been recently disclosed.

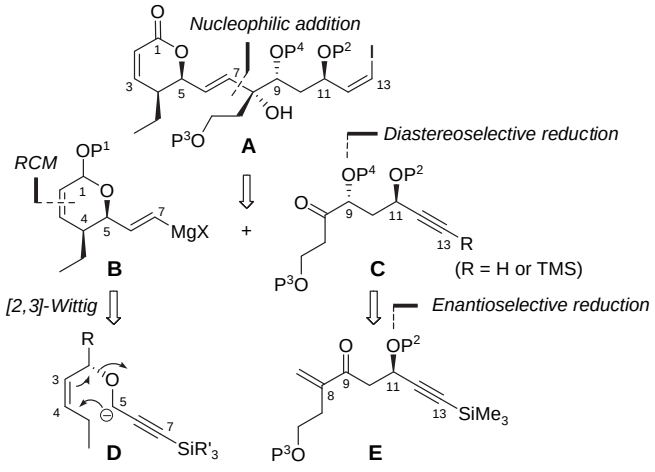
Herein, we report a full account of our studies on the development of convergent approaches toward members of the phoslactomycins/leustroducsins family that have resulted in the formal synthesis of phoslactomycin B.

2. Examination of a convergent approach toward the C1–C13 subunit of PLMs and LSNs

2.1. Retrosynthetic analysis

The C1–C13 subunit **A**, common to all PLMs and LSNs, was selected as the target. With the aim of developing a convergent route, an appropriate disconnection appears to be at the C7–C8 bond. In the forward sense, the tertiary alcohol at C8 would be created by nucleophilic addition of an alkenyl Grignard reagent **B**, containing a cyclic mixed acetal as a temporarily masked form of the lactone (with the C4 and C5 stereocenters in place), to an α,γ-dialkoxy ketone **C**. The *syn* relationship between the tertiary hydroxyl group at C8 and the alkoxy group at C9 entails that the nucleophilic addition of the Grignard reagent **B** has to be performed under chelation control.[15] This would be achieved by the appropriate choice of the protecting group of the hydroxyl at C9 (P^4=PMB or MOM) (Scheme 1).

The chelation-controlled addition of vinylic organometallic species to a methyl ketone has been used as a key step in several syntheses of fostriecin (Fig. 1)[16] and it was surprising to see that a similar strategy had never been implemented in a convergent approach toward PLMs and LSNs. Although the chelation-controlled addition of vinylmagnesium bromide to a ketone of type **C** (P^2=TBS, P^3=TBDPS, P^4=PMB) was used by Kobayashi et al. in their total synthesis of PLM B to create the tertiary alcohol at C8, 11 steps were subsequently required to introduce the C4 and C5 stereocenters (Evans aldolization) and create the lactone ring (by Ando olefination and subsequent lactonization).[7] Therefore, the more convergent chelation-controlled addition of a functionalized alkenyl Grignard reagent **B** to a ketone **C** appeared particularly appealing.



Scheme 1. Retrosynthetic analysis of the C1–C13 subunit.

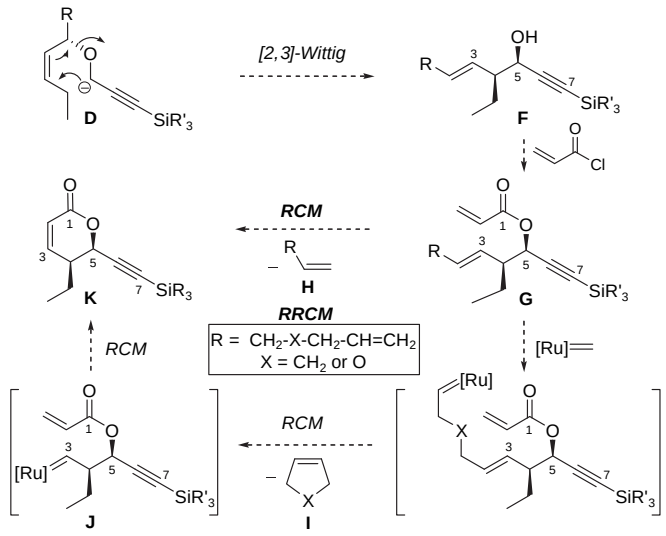
The use of RCM was obvious to create the α,β-unsaturated δ-lactone or its protected cyclic mixed acetal precursor **B** and an original approach relying on the [2,3]-Wittig rearrangement of an allylic and propargylic ether of type **D** was envisaged for the control of the C4 and C5 stereocenters.[17,18] The synthesis of the α,γ-dialkoxy ketone **C** (C8–C13 subunit), which was planned from enone **E**, would involve a diastereoselective reduction to create the C9 stereocenter and an ozonolysis of the methylene unit at C8. The initial C11 stereocenter would, in turn, be introduced by enantioselective reduction of an acetylenic β-ketoester (Scheme 1).

2.2. Synthesis of the C1–C7 subunit

The control of the configuration of the C4 and C5 stereocenters is the key issue in the synthesis of the C1–C7 subunit. Evans aldol condensations[7,9,11] or Brown-type pentenylations[8,12] have been successfully used to achieve this task. However, these reactions imply the use of stoichiometric quantities of chiral auxiliaries or reagents. The ring-opening of an epoxy-alcohol derivative (prepared by Sharpless asymmetric epoxidation) with an alkynylaluminum reagent has also been reported.[10] In another convergent approach, the C4 stereocenter was first established through a lipase promoted resolution of a racemic alcohol by acetylation and a Nozaki/Hiyama/Kishi reaction was used to create the C5 allylic alcohol, though the desired configuration was only attained after an oxidation/stereoselective reduction sequence.[10b]

As a novel approach for the control of C4 and C5, the use of a [2,3]-Wittig rearrangement of an allylic and propargylic ether **D** was considered. The goal was to create the initial asymmetric carbon by a catalytic enantioselective reduction and to subsequently transfer the chirality by the [2,3]-Wittig rearrangement to C4 and C5 in the resulting alcohol **F** while a disubstituted olefin would be created at the same time.[17,18] One critical issue regarding the use of the [2,3]-Wittig rearrangement, combined with subsequent formation of the unsaturated δ-lactone by RCM, was the appropriate selection of the R group in compound **D** and in the future acrylate intermediate **G**. Although the R residue would be expelled in the form of an alkene **H** (RCH=CH_2) during the RCM, having a disubstituted olefin as well as an alkyne in the acrylate **G** may hamper the initial formation of the ruthenium carbene at C3 and hence be detrimental to the success of this step.[19–21] A relay ring-closing metathesis (RRCM) appeared to be an attractive solution to this problem.[22] The presence of an appropriately located terminal olefin in the R group (R=CH_2–X–CH_2CH=CH_2) should result in an initial RCM expelling the relay in the form of a five-membered ring alkene **I** and producing the ruthenium carbene **J** at C3. This should facilitate the second RCM leading to the unsaturated δ-lactone **K** (Scheme 2).

The preparation of propargylic ethers **D** was first examined. Commercially available hex-5-enoic acid (**1**) or allyloxyacetic acid (**2**)[23] were activated as mixed anhydrides and converted to Weinreb amides **3** (73%) and **4** (81%), respectively.[24,25] Addition of the acetylenic organolithium reagent generated from 1-butyne (*n*-BuLi, THF, −78 °C) to Weinreb amides **3** and **4** provided ketones **5** (97%)

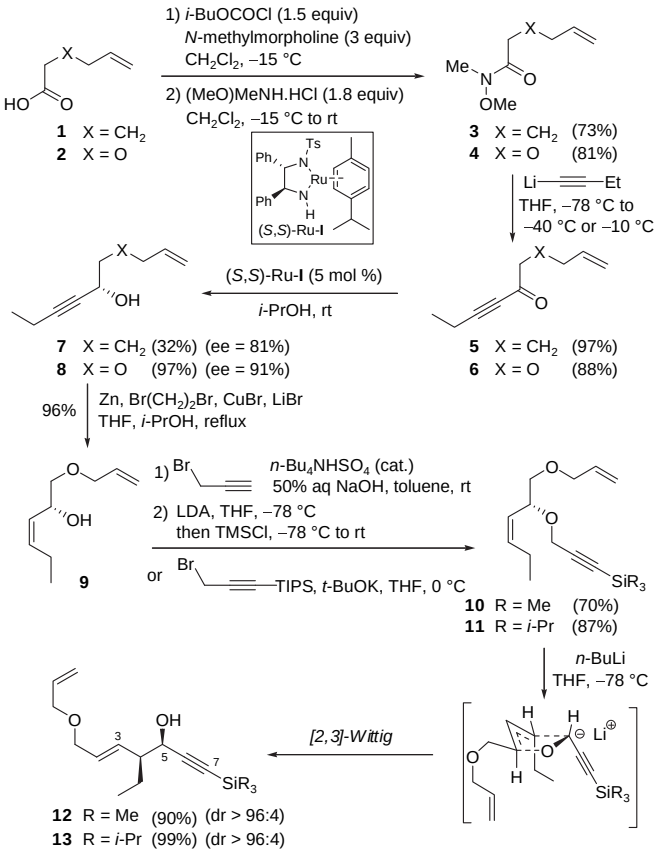


Scheme 2. RCM vs RRCM for the synthesis of the δ-lactone.

and **6** (88%). Enantioselective reduction of these acetylenic ketones was achieved under Noyori's catalytic conditions using the 16-electron catalyst (*S*,*S*)-Ru-**I** (5 mol %) in isopropanol.[26] Surprisingly, the reduction of **5** provided propargylic alcohol **7** in low yield (32%) and modest enantiomeric excess (ee=81%).[27] Better results were obtained with acetylenic ketone **6** possessing an allylic ether linkage, which led to the corresponding propargylic alcohol **8** in very high yield (97%) with an enantiomeric excess of 91%.[27] The synthesis of the C1–C7 subunit of PLMs and LSNs was thus pursued from **8** only. Chemoselective reduction of the alkyne, using an in situ prepared zinc/copper couple in refluxing THF/isopropanol, afforded the *Z*-disubstituted alkene **9** (96%).[28] To prepare the corresponding (trimethylsilyl)propargylic ether, the secondary alcohol was first alkylated with propargyl bromide under phase-transfer catalysis conditions and the terminal alkyne underwent subsequent lithiation (LDA) and silylation with TMSCl to provide compound **10** (70%, two steps from **9**). Propargylic ether **11** was more conveniently prepared in a single step (87%) by alkylation of the secondary alcohol **9** with 3-(triisopropylsilyl)propargyl bromide,[29] owing to the slower cleavage of acetylenic TIPS group (compared to TMS) under alkaline conditions. With the propargylic ethers **10** and **11** in hand, the stage was set to create the C4 and C5 stereocenters by the [2,3]-Wittig rearrangement, which was triggered by treatment with *n*-BuLi (THF, −78 °C). The corresponding propargylic alcohols **12** and **13** were generated as single detectable diastereomers (dr>96:4 by ^{1}H NMR) and were isolated in high yields (90% and 99%, respectively) (Scheme 3).

As anticipated, the stereochemical outcome is in agreement with a five-membered ring transition state of envelope conformation wherein the allylyoxymethyl chain preferentially occupies a pseudo-equatorial position whereas an *exo* orientation is known to be favored for π-donating anionic stabilizing groups such as alkynes.[30,31] The *syn* relative orientation of the ethyl group at C4 and the hydroxyl group at C5 has been confirmed later in the synthesis after construction of the δ-lactone.

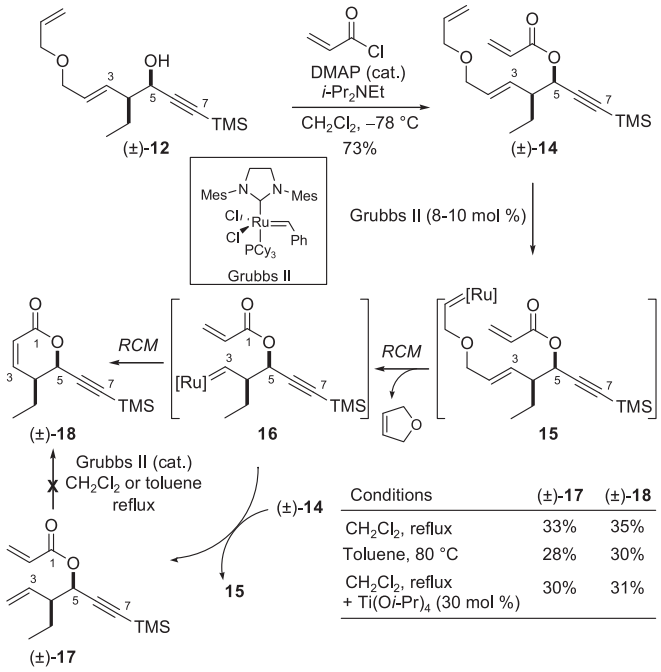
The formation of the unsaturated δ-lactone moiety by RRCM was next investigated and the initial studies were carried out in the racemic series. The trimethylsilyl-substituted propargylic alcohol (±)-**12**, prepared from alcohol (±)-**8**, was acylated with acryloyl chloride. The resulting acrylate (±)-**14** (73%) was then treated with Grubbs II catalyst[32] (8 mol %) in refluxing CH_2Cl_2. Under these conditions, acrylate (±)-**17** and the desired δ-lactone (±)-**18** were formed in nearly identical amounts and were isolated in 33% and 35% yield, respectively. Thus, a first RCM triggered by carbene **15**



Scheme 3. Control of C4 and C5 by a [2,3]-Wittig rearrangement.

produces 2,5-dihydrofuran and a new ruthenium carbene **16** that undergoes subsequent RCM leading to lactone (±)-**18**. The rate of this latter step being probably slow, carbene **16** can act as a metathesis initiator itself and competitively react with the starting material (±)-**14** to provide acrylate (±)-**17**, resulting from truncation of the unsaturated relay,[22] and carbene **15**. Performing the reaction under harsher conditions (toluene, 80 °C) or in the presence of Ti(O*i*-Pr)$_4$ as an additive[33] did not significantly affect the results. Indeed, we demonstrated that acrylate (±)-**17** was completely unable to undergo RCM to the unsaturated δ-lactone (±)-18, whatever the conditions, presumably due to the presence of the trimethylsilylalkyne.[19,20] This result highlights the tremendous importance of the RRCM strategy to achieve the formation of the unsaturated δ-lactone (±)-**18** bearing a trimethylsilylethynyl group. The relative configuration of C4 and C5 was confirmed by ^{1}H NMR spectroscopy through the determination of the ^3J coupling constant between H4 and H5 suggesting a *syn* relative orientation ($^3J_{H4\text{-}H5}$=4.9 Hz) (Scheme 4).[34–36]

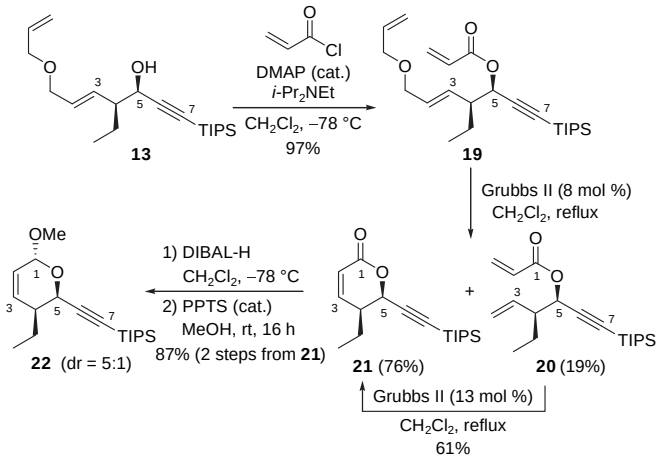
The reactivity of acrylate **19**, synthesized by acylation of the triisopropylsilyl-substituted propargyl alcohol **13** with acryloyl chloride (97%), was next investigated. When acrylate **19** was treated with Grubbs II catalyst (8 mol %) (CH_2Cl_2, reflux), lactone **21** was isolated in 76% yield, whereas acrylate **20** resulting from truncation of the relay was a minor product (19%). The truncated acrylate **20** could undergo RCM to the corresponding unsaturated δ-lactone **21** presumably because the bulky TIPS group sterically shields the alkyne and disfavors its interaction with ruthenium carbenes.[21] It is worth pointing out that the RCM of acrylate **20** required a higher catalyst loading (13 mol %) and provided lactone **21** in lower yield (61%) compared to the RRCM route from acrylate **19**. Once again, the *syn* relationship between H4 and H5 was confirmed by ^{1}H NMR for lactone **21** ($^3J_{H4\text{-}H5}$=5.1 Hz).[34–36] As a vinylic organometallic



Scheme 4. RRCM of acrylate (±)-**14**.

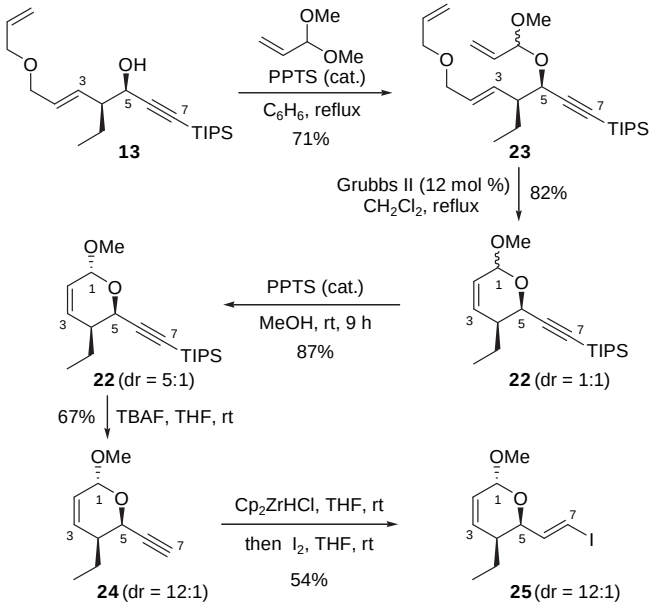
species will have to be generated at C7 later in the synthesis, lactone **21** was temporarily masked as a mixed methyl ketal by reduction with DIBAL-H followed by treatment of the crude lactol with a catalytic amount of PPTS in MeOH. The cyclic methyl acetal **22** was isolated as a 5:1 equilibrium mixture of epimers (87%, two steps from lactone **21**) (Scheme 5).[35–37]

An alternative approach was also examined for a more direct preparation of the cyclic methyl ketal **22** by RRCM. Propargylic alcohol **13** was engaged in a transacetalisation with acrolein dimethyl acetal to deliver the mixed methyl acetal **23** (1:1 mixture of epimers).[38] RRCM of **23** was initiated with Grubbs II catalyst (12 mol %, CH_2Cl_2, reflux) and provided the cyclic methyl ketal **22** (82%) as a 1:1 mixture of epimers.[39] Thermodynamic equilibration could be achieved by treatment with a catalytic amount of PPTS in MeOH to afford, as previously observed from the preceding route, a 5:1 mixture of epimers (87%). Removal of the TIPS group was accomplished by treatment of **22** with TBAF and the volatile terminal alkyne **24** was isolated in moderate yield (67%) as a 12:1 mixture of



Scheme 5. RRCM of acrylate **19**.

epimers at C1. Subsequent hydrozirconation of **24** with Schwartz's reagent followed by iodinolysis delivered alkenyl iodide **25** (54%). The latter compound, which constitutes the C1–C7 subunit of PLMs and LSNs, was synthesized in 11 steps from α-allyloxyacetic acid (shortest linear route) in 14% overall yield at best (Scheme 6). The synthesis of the C8–C13 subunit was then carried out.

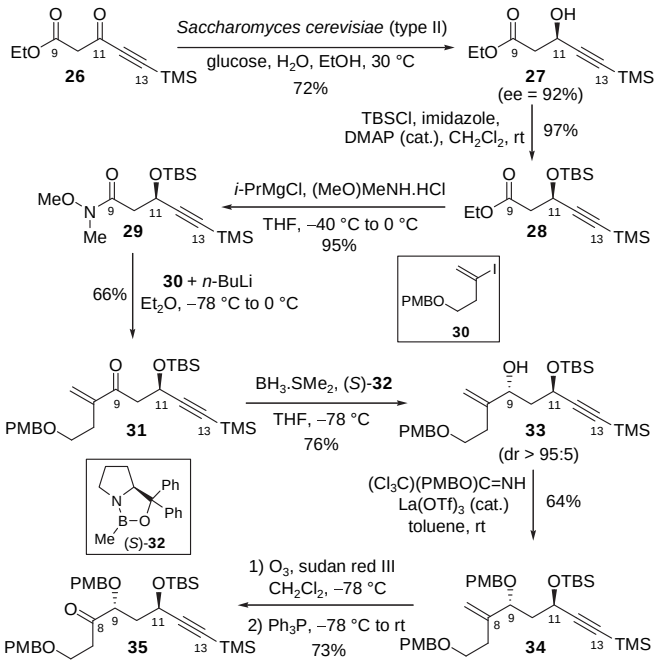


Scheme 6. Synthesis of the C1–C7 subunit.

2.3. Synthesis of the C8–C13 subunit

The preparation of the C8–C13 subunit was achieved from the optically active β-hydroxyester **27**, easily prepared (72% yield, ee=92%) by reduction of the acetylenic β-ketoester **26** using *Saccharomyces Cerevisiae* type II (Baker's yeast).[36] The hydroxyl group was protected as a TBS ether to provide the β-silyloxyester **28** (97%), which was converted to Weinreb amide **29** (95%).[40] Condensation of the organolithium reagent generated from the readily available alkenyl iodide **30**[41] (*n*-BuLi, Et_2O, −78 °C) with Weinreb amide **29** led to enone **31** in 66% yield. The diastereoselective reduction of the carbonyl group was then achieved through a reagent-controlled reduction using $BH_3{\cdot}SMe_2$ in the presence of oxazaborolidine (*S*)-**32**.[42] The resulting allylic alcohol **33** was obtained with high diastereoselectivity (dr>95:5) and was isolated in 76% yield.[43] The hydroxyl group at C9 was protected as a PMB ether using *p*-methoxybenzyl trichloroacetimidate and $La(OTf)_3$ as the catalyst to deliver **34** (64%).[44] The latter compound contains two PMB ethers but it was reasonable to consider that the primary and secondary alcohols resulting from their deprotection could be selectively manipulated. To achieve the oxidative cleavage of the methylene unit at C8, a dihydroxylation/1,2-diol cleavage sequence was initially considered but osmylation was unsuccessful under a variety of conditions.[45] This operation was therefore accomplished by a carefully controlled ozonolysis of **34**,[46] followed by reduction of the ozonide with PPh_3, and the α-alkoxy ketone **35** was obtained in 73% yield. Compound **35**, which corresponds to the C8–C13 subunit of PLMs and LSNs, was thus synthesized in seven steps from β-ketoester **26** (16% overall yield) (Scheme 7).

The coupling of the C1–C7 and C8–C13 subunits was attempted.



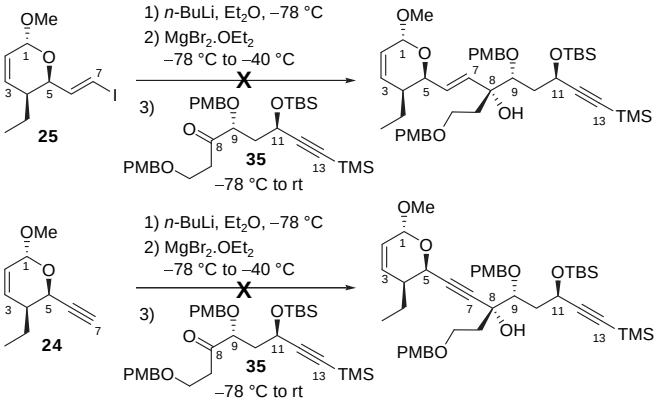
Scheme 7. Synthesis of the C8–C13 subunit.

2.4. Coupling attempts between the C1–C7 and C8–C13 subunits

The alkenyl iodide **25** was subjected to lithium/iodine exchange (*n*-BuLi, Et_2O, −78 °C) and the generated alkenyllithium was transmetallated with $MgBr_2{\cdot}OEt_2$ (−78 to −40 °C). Unfortunately, no addition of the resulting vinylic Grignard reagent to the α-alkoxy ketone **35** took place, even upon warming to rt. Attempts to add the acetylenic Grignard reagent generated from alkyne **24** (*n*-BuLi, Et_2O, −78 °C then $MgBr_2{\cdot}OEt_2$, −78 to −40 °C) to ketone **35** were also unsuccessful (Scheme 8).

In some of these unsuccessful experiments, we noticed that the recovered ketone **35** had undergone partial epimerization at C9 suggesting that enolization presumably took place as a side-reaction. The apparent lack of reactivity of ketone **35** toward Grignard reagents seemed to compromise the development of a convergent approach toward PLMs and LSNs based on the formation of the C7–C8 bond.

At this point of our studies, we decided to modify the structures of the partners involved in the planned coupling reaction that would lead to the tertiary alcohol at C8 and a convergent approach toward the C1–C11 subunit of PLMs and LSNs was devised.

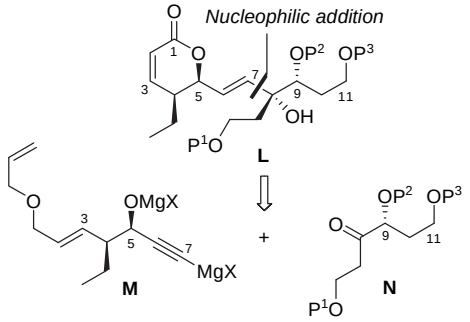


Scheme 8. Coupling attempts between C1–C7 and C8–C13 subunits.

3. Convergent approach toward the C1–C11 subunit of PLMs and LSNs. Formal synthesis of PLM BRetrosynthetic analysis

3.1. Retrosynthetic analysis

In this revised convergent approach, the C1–C11 subunit of PLMs and LSNs **L** was selected as the new target and the formation of the C7–C8 bond was envisaged by nucleophilic addition of the acetylenic Grignard reagent **M** to an α-alkoxy ketone **N**. This simplification was aimed at reducing the number of steps involved in the preparation of the two subunits prior to the evaluation of the feasibility of the coupling but the organometallic reagent **M** still incorporates the C4 and C5 stereocenters (Scheme 9).



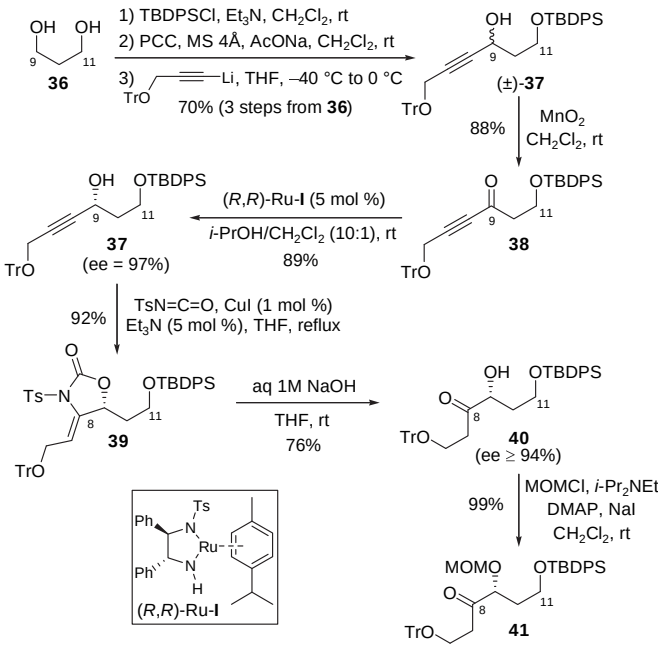
Scheme 9. Retrosynthetic analysis of the C1–C11 subunit.

In the previous approach, alkynylsilanes **12** or **13** that are suitable precursors of the Grignard reagent **M** have already been prepared. The preparation of the α-alkoxy ketone **N** (C8–C11 subunit) was therefore required and we sought to develop a catalytic enantioselective route to this compound.

3.2. Synthesis of the C8–C11 subunit

The synthesis of the C8–C11 subunit began with the monoprotection of propane-1,3-diol (**36**) as a TBDPS ether followed by oxidation of the second hydroxyl group with PCC.[47] The resulting aldehyde was treated with the acetylenic organolithium generated from propargyl trityl ether[48] to afford the racemic propargylic alcohol (±)-**37** (70%, three steps from **36**). Oxidation of (±)-**37** with MnO_2 provided the acetylenic ketone **38** (88%), which underwent enantioselective reduction catalyzed by (*R*,*R*)-Ru-**I**[26] in an *i*-PrOH/CH_2Cl_2 (10:1) mixture. The use of CH_2Cl_2 as a co-solvent was necessary to ensure solubilization of the starting material and the enantiomerically enriched propargylic alcohol **37** (ee=97%) was isolated in high yield (89%).[27] Conversion of this propargylic alcohol **37** into the α-hydroxyketone **40** formally requires the regioselective hydration of the disubstituted alkyne. However, in the presence of a metal catalyst or a Brønsted acid, a Meyer/Schuster rearrangement would take place leading to the regioisomeric enone.[49] To formally achieve hydration of **37** with the desired regioselectivity, a cyclofunctionalization process could be used whereby an appropriate nucleophile (generated from the hydroxyl group) would add across the triple bond through a 5-*exo* dig process. Thus, alcohol **37** was treated with tosyl isocyanate in the presence of a catalytic amount of CuI and Et_3N (THF, reflux) and the 4-alkylidene-oxazolidin-2-one **39** was obtained in high yield (92%).[50,51] It is worth noting that an alkoxymethyl substituent on the alkyne was perfectly tolerated.[50] Compound **39** contains an enamide moiety, which was seen as a suitable precursor for the corresponding ketone at C8 but its hydrolysis had to be achieved under carefully

controlled conditions to avoid racemization.[52,53] In order to reduce the concentration of the base in the organic solvent, hydrolysis of **39** was achieved in THF as the solvent in the presence of a 1 M aqueous solution of NaOH. The α-hydroxyketone **40** was isolated in 76% yield with an acceptable optical purity (ee≥94%).[27] The hydroxyl group has to be protected in the form of an ether that would allow the nucleophilic addition to the adjacent carbonyl group to proceed under chelation control. Attempts to protect the alcohol at C9 as a PMB ether were unsuccessful under a variety of different conditions. A MOM ether could not be introduced under standard conditions (MOMCl, *i*-Pr_2NEt, CH_2Cl_2) but the reaction proceeded in almost quantitative yield (99%) in the presence of DMAP and NaI to afford α-alkoxy ketone **41**.[54] This latter compound (C8–C11 subunit) was thus synthesized in eight steps from propane-1,3-diol (38% overall yield) (Scheme 10).

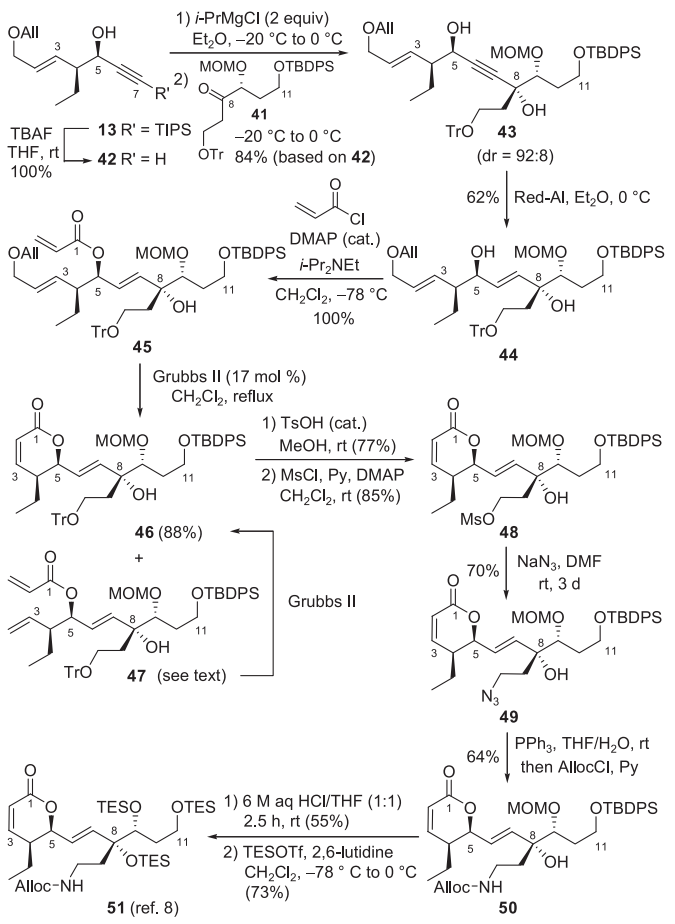


Scheme 10. Preparation of the C8–C11 subunit.

The key coupling reaction with an acetylenic Grignard reagent corresponding to the C3–C7 subunit was then tested.

3.3. Synthesis of the C1–C11 subunit of PLMs and LSNs. Formal synthesis of PLM B

The previously prepared propargylic alcohol **13** was desilylated to afford the terminal alkyne **42** in quantitative yield. This compound was treated with *i*-PrMgCl (2 equiv, Et_2O, −20 to 0 °C) and the resulting acetylenic Grignard reagent was condensed with ketone **41**. In this reaction, an excess of the alkyne partner **42** was conveniently used (3.5 equiv) to ensure complete consumption of **41**. Indeed, the use of an alkynyl rather than an alkenyl organometallic species has a significant advantage since the terminal alkyne precursor of the former can be recovered and recycled after protonation (adventitious or work-up), whereas the alkenyl halide precursor cannot. Under these conditions, we were pleased to see that the desired tertiary alcohol **43** was obtained as a 92:8 mixture of diastereomers and isolated in good yield (84%). It was reasonable to assume that the stereochemical outcome was the result of a Cram-chelate control exerted by the OMOM ether at C9.[15] Hydroalumination of the alkyne with Red-Al delivered the allylic diol **44** (62%)[55] and subsequent selective acylation of the secondary allylic alcohol at C5 with acryloyl chloride delivered acrylate **45** in quantitative yield (Scheme 11).



Scheme 11. Synthesis of the C1–C11 subunit of PLMs and LSNs. Formal synthesis of PLM B.

The formation of the unsaturated δ-lactone moiety has been previously achieved by classical RCM either with the C8–C9 protected 1,2-diol in place[12] or with a conjugated diene (C6–C9).[8] Acrylate **45** was initially treated with Grubbs II catalyst (5 mol %, CH_2Cl_2, reflux). After 2 h, the starting material was completely consumed and a mixture of lactone **46** and acrylate **47**, resulting from truncation of the unsaturated relay, was obtained in a 75:25 ratio. These two compounds were isolated in 65% and 13% yield, respectively. The use of a higher catalyst loading (17 mol %, successive additions every 2 h) and a longer reaction time (reflux, 20 h) allowed the transformation of acrylate **45** into the desired lactone **46** as the sole product, which was isolated in 88% yield. These results indicate that the RRCM of acrylate **45** to lactone **46** is a fast reaction since the latter compound is already obtained as the major product after only 2 h and using 5 mol % catalyst. By contrast, the RCM of acrylate **47** is a slower process, which requires a higher catalyst loading (12 mol % to convert the initially formed 75:25 mixture of **46**:**47** to **46** exclusively within 12 h).

The trityl group was cleaved by acid-catalyzed methanolysis and the resulting primary alcohol (77%) was converted into the corresponding mesylate **48** (85%). Nucleophilic substitution with NaN_3 (DMF, 70 °C) led to azide **49** in 10% yield only since extensive decomposition was observed. However, under milder conditions (DMF, rt, 3 days), azide **49** could be obtained in 70% yield. Staudinger reduction of **49** followed by in situ acylation of the primary amine with allyl chloroformate provided allyl carbamate

50 (64%), which corresponds to the targeted C1–C11 subunit of PLMs and LSNs. In order to check the stereochemical assignments made previously, the MOM and TBDPS ethers in compound **50** were cleaved by brief hydrolysis under acidic conditions [6 M aq HCl/THF (1:1), rt, 55%] and all hydroxyl groups of the resulting triol were silylated with TESOTf to provide the protected triol **51** (73%). The spectroscopic data of **51** matched with those previously reported for this key intermediate in the total synthesis of PLM B reported by Hatakeyama et al.,[8] thereby accounting for a formal synthesis of this natural product (Scheme 11).

In conclusion, we have achieved a formal convergent and catalytic asymmetric synthesis of phoslactomycin B. The diastereoselective addition of an alkynyl Grignard reagent to an α-alkoxy ketone was involved as a key step to create the C8 tertiary alcohol. The lactone was constructed by a RRCM whereas a [2,3]-Wittig rearrangement was used to control C4 and C5. A copper-catalyzed cyclofunctionalization allowed to elaborate an α-hydroxyketone from a propargylic alcohol. Notably, all the stereocenters originate, either directly or indirectly, from catalytic enantioselective reductions of acetylenic ketones.

4. Experimental section

4.1. General

Infrared (IR) spectra were recorded on a Bruker Tensor 27 (IR-FT), wavenumbers are indicated in cm^{-1}. Optical rotations were measured using a Perkin Elmer 343 plarimeter at 25 °C. ^1H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) and data are reported as follows: chemical shift in parts per million from tetramethylsilane as an internal standard, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet or overlap of non-equivalent resonances), integration. ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 or 100 MHz and data are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$, δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s=quaternary C, d=CH, t=CH_2, q=CH_3). Mass spectra with electronic impact (MS-EI) were recorded from a Hewlett/Packard tandem 5890A GC (12 m capillary column)—5971 MS (70 eV). THF and diethyl ether were distilled from sodium/benzophenone. CH_2Cl_2, CH_3CN, toluene, Et_3N, *i*-Pr_2NH, *i*-Pr_2NEt, pyridine, 2,6-lutidine, *i*-PrOH, and TMSCl were distilled from CaH_2. Other reagents were obtained from commercial suppliers and used as received. TLC was performed on silica gel plates and visualized either with a UV lamp (254 nm), or by using solutions of *p*-anisaldehyde/H_2SO_4/AcOH in EtOH or $KMnO_4/K_2CO_3$ in water followed by heating. Flash chromatography was performed on silica gel (230–400 mesh).

4.2. Examination of a convergent approach toward the C1–C13 subunit of PLMs and LSNs

4.2.1. Synthesis of the C3–C7 subunit.

*4.2.1.1. N-methoxy-N-methyhex-5-enamide (**3**).* To a solution of hex-5-enoic acid (**1**) (5.2 mL, 44 mmol) in CH_2Cl_2 (70 mL) at −15 °C were added *N*-methyl-morpholine (14.4 mL, 131 mmol, 3 equiv) and isobutyl chloroformate (8.5 mL, 66 mmol, 1.5 equiv). After 1.5 h at −15 °C, *N*,*O*-dimethylhydroxylamine hydrochloride (7.69 g, 78.8 mmol, 1.8 equiv) was added in one portion. After 15 min at 0 °C and 16 h at rt, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, the layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 80/20 to 40/60) to afford 4.81 g (73%) of Weinreb amide **3**[25] as a colorless oil; IR 1661, 1414, 1384, 1177, 1118, 994, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J*=17.1, 10.3, 6.6 Hz, 1H), 5.04 (dq, *J*=17.1, 1.5 Hz, 1H), 4.98 (dq, *J*=10.3, 1.5 Hz, 1H), 3.68 (s, 3H), 3.18 (s, 3H), 2.43 (t, *J*=7.5 Hz, 2H), 2.15–2.08 (m, 2H), 1.75 (apparent quintuplet, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5 (s), 138.1 (d), 115.0 (t), 61.2 (q), 33.3 (t), 32.2 (q), 31.1 (t), 23.7 (t); HRMS: M+Na^+, found 180.0991. $C_8H_{15}O_2NNa$ requires 180.0995.

*4.2.1.2. 2-Allyloxy-N-methoxy-N-methyl-acetamide (**4**).* To a solution of allyloxyacetic acid (**2**)[23] (3.55 g, 30.6 mmol) in CH_2Cl_2 (55 mL) at −15 °C were added *N*-methyl-morpholine (10.1 mL, 91.8 mmol, 3 equiv) and isobutyl chloroformate (6.0 mL, 46 mmol, 1.5 equiv). After 1.5 h at −15 °C, *N*,*O*-dimethylhydroxylamine hydrochloride (5.37 g, 55.1 mmol, 1.8 equiv) was added in one portion. After 15 min at 0 °C and 16 h at rt, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, the layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 60/40, 50/50 then petroleum ether/EtOAc: 50/50, 40/60) to afford 3.95 g (81%) of Weinreb amide **4** as a colorless oil; IR 1677, 1421, 1327, 1148, 1084, 991, 921, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (ddt, *J*=17.2, 10.3, 5.8 Hz, 1H), 5.32 (dq, *J*=17.2, 1.0 Hz, 1H), 5.23 (dq, *J*=10.3, 1.0 Hz, 1H), 4.27 (s, 2H), 4.13 (apparent br d, *J*=5.8 Hz, 2H), 3.69 (s, 3H), 3.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (s), 133.9 (d), 117.5 (t), 72.0 (t), 66.8 (t), 61.2 (q), 32.0 (q); EIMS *m*/*z* (relative intensity) 128 (M−OMe^+, 2), 103 (100), 86 (29), 74 (48), 73 (43), 71 (63), 60 (21), 58 (12), 56 (12); HRMS: M+Na^+, found 182.0787. $C_7H_{13}O_3NNa$ requires 182.0788.

*4.2.1.3. Dec-9-en-3-yn-5-one (**5**).* 1-Butyne gas (10 mL, 100 mmol, 5.0 equiv) was condensed at −78 °C and dissolved in THF (60 mL). The resulting solution was cooled to −78 °C and a solution of *n*-BuLi (20 mL, 2.5 M in hexanes, 50 mmol, 2.5 equiv) was added dropwise. After 40 min stirring from −78 to 0 °C, the resulting but-1-ynyllithium solution was cooled to −78 °C and a solution of Weinreb amide **3** (3.18 g, 20.2 mmol) in THF (10 mL) was added dropwise. After 45 min at −78 °C, the reaction mixture was warmed to −10 °C over 4 h and then poured into an ice-cold 2 M solution of hydrochloric acid. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 98/2 to 96/4) to afford 2.95 g (97%) of ketone **5** as an orange oil; IR 2212, 1670, 1641, 1315, 1238, 1162, 994, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, *J*=17.0, 10.3, 6.7 Hz, 1H), 5.03 (dq, *J*=17.0, 1.5 Hz, 1H), 4.99 (dq, *J*=10.3, 1.5 Hz, 1H), 2.54 (t, *J*=7.4 Hz, 2H), 2.38 (q, *J*=7.5 Hz, 2H), 2.12–2.06 (m, 2H), 1.80–1.74 (m, 2H), 1.21 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.0 (s), 137.6 (d), 115.3 (t), 95.1 (s), 80.1 (s), 44.6 (t), 32.7 (t), 23.0 (t), 12.7 (t), 12.5 (q); EIMS *m*/*z* (relative intensity) 150 (M^+, 5), 135 (M−Me^+, 19), 121 (13), 107 (12), 96 (59), 81 (100), 67 (11), 53 (47); HRMS: M+Na^+, found 173.0938. $C_{10}H_{14}ONa$ requires 173.0937.

*4.2.1.4. 1-(Allyloxy)hex-3-yn-2-one (**6**).* 1-Butyne gas (10 mL, 129 mmol, 6.5 equiv) was condensed at −78 °C and dissolved in THF (60 mL). The resulting solution was cooled to −78 °C and a solution of *n*-BuLi (20 mL, 2.5 M in hexanes, 50 mmol, 2.8 equiv) was added dropwise. After 40 min stirring from −78 to 0 °C, the resulting but-1-ynyllithium solution was cooled to −78 °C and a solution of Weinreb amide **4** (3.19 g, 20.0 mmol) in THF (15 mL) was added dropwise. After 45 min at −78 °C, the reaction mixture

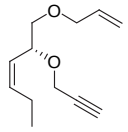
was warmed to −40 °C and then poured into an ice-cold 2 M solution of hydrochloric acid. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc: 90/10) to afford 2.68 g (88%) of ketone **6** as a yellow oil; IR 2207, 1689, 1671, 1422, 1315, 1228, 1183, 1126, 1065, 992, 927, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, J=17.0, 10.4, 5.8 Hz, 1H), 5.32 (dq, J=17.0, 1.5 Hz, 1H), 5.24 (dq, J=10.4, 1.5 Hz, 1H), 4.19 (s, 2H), 4.10 (br d, J=5.8 Hz, 2H), 2.41 (q, J=7.5 Hz, 2H), 1.22 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9 (s), 133.5 (d), 117.8 (t), 98.2 (s), 77.7 (s), 75.5 (t), 72.1 (t), 12.5 (t), 12.4 (q); HRMS: M+Na^+, found 175.0763. $C_9H_{12}O_2Na$ requires 175.0730.

*4.2.1.5. (S)-Dec-9-en-3-yn-5-ol (**7**).* To a solution of ketone **5** (731 mg, 4.86 mmol) in *i*-PrOH (48 mL) was added freshly prepared Noyori's catalyst (*S*,*S*)-Ru-**I**[26] (147 mg, 0.245 mmol, 0.05 equiv). After 1 h at rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 80/20) to afford 236 mg (32%) of alcohol **7** as a pale brown oil (ee=81%). The ee value was determined by analysis of the corresponding *p*-nitrobenzoate by super-critical fluid chromatography (SFC) on chiral stationary phase;[27] $[\alpha]_D$ −0.2 (*c* 1.23, $CHCl_3$); IR 3326, 1640, 1318, 1065, 993, 909 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, J=17.0 Hz, 10.3, 6.6 Hz, 1H), 5.03 (dq, J=17.0, 1.5 Hz, 1H), 4.97 (m, 1H), 4.36 (m, 1H), 2.22 (qd, J=7.5, 2.0 Hz, 2H), 2.10 (apparent dt, J=7.0, 1.5 Hz, 2H), 1.89 (br s, 1H, OH), 1.75–1.63 (m, 2H), 1.62–1.51 (m, 2H), 1.14 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (d), 114.7 (t), 86.9 (s), 80.5 (s), 62.5 (d), 37.5 (t), 33.3 (t), 24.4 (t), 13.8 (q), 12.3 (t); EIMS *m*/*z* (relative intensity) 137 (M−Me^+, 8), 123 (16), 119 (9), 109 (21), 105 (30), 91 (36), 83 (100), 79 (32), 67 (14), 55 (47); HRMS: M+Li^+, found 159.1353. $C_{10}H_{16}OLi$ requires 159.1356.

*4.2.1.6. (R)-1-(Allyloxy)hex-3-yn-2-ol (**8**).* To a solution of ketone **6** (2.04 g, 13.4 mmol) in *i*-PrOH (134 mL) was added freshly prepared Noyori's catalyst (*S*,*S*)-Ru-**I**[26] (403 mg, 0.672 mmol, 0.05 equiv). After 45 min at rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 70/30 to 60/40) to afford 2.00 g (97%) of alcohol **8** as a pale brown oil (ee=91%). The ee value was determined by analysis of the corresponding *p*-nitrobenzoate by super-critical fluid chromatography (SFC) on chiral stationary phase;[27] $[\alpha]_D$ −11.6 (*c* 1.07, $CHCl_3$); IR 3396, 1646, 1422, 1319, 1141, 1106, 1070, 992, 924, 883, 780, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddt, J=17.0 Hz, 10.4, 5.4 Hz, 1H), 5.30 (dq, J=17.0, 1.5 Hz, 1H), 5.21 (dq, J=10.4, 1.5 Hz, 1H), 4.54 (m, 1H), 4.07 (dm, apparent br d, J=5.4 Hz, 2H), 3.60 (dd, J=10.0, 3.4 Hz, 1H), 3.49 (dd, J=10.0, 8.0 Hz, 1H), 2.43 (d, J=4.2 Hz, 1H, OH), 2.22 (qd, J=7.5, 2.0 Hz, 2H), 1.14 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2 (d), 117.4 (t), 87.7 (s), 77.0 (s), 73.9 (t), 72.2 (t), 61.6 (d), 13.6 (q), 12.3 (t); EIMS *m*/*z* (relative intensity) 139 (M−Me^+, 1), 136 (M−H_2O^+, 1.5), 125 (M−Et^+, 5), 98 (14), 95 (10), 83 (100), 81 (9), 79 (8), 71 (12), 69 (12), 67 (8), 55 (45), 53 (15); HRMS: M+Li^+, found 161.1147. $C_9H_{14}O_2Li$ requires 161.1149.

*4.2.1.7. (Z)-(R)-1-(Allyloxy)hex-3-en-2-ol (**9**).* To a suspension of Zn dust (5.1 g, 78 mmol, 23.3 equiv) in *i*-PrOH was added 1,2-dibromoethane (0.64 mL, 7.4 mmol, 2.2 equiv) and the resulting mixture was heated at reflux for 15 min. A solution of CuBr (1.44 g, 10.1 mmol, 3.0 equiv) and LiBr (1.54 g, 17.8 mmol, 5.3 equiv) in THF (20 mL) was then added slowly. After 20 min heating at reflux, a solution of the propargylic alcohol **8** (517 mg, 3.35 mmol) in *i*-PrOH (15 mL) was added dropwise. After 8 h at reflux, and 10 h at rt, the reaction mixture was filtered through Celite (EtOAc) and the filtrate was hydrolyzed with a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc gradient: 70/30 to 60/40) to afford 502 mg (96%) of the (*Z*)-allylic alcohol **9** as a yellow oil; $[\alpha]_D$ −63.1 (*c* 0.47, $CHCl_3$); IR 3407, 1648, 1461, 1422, 1304, 1104, 1066, 996, 923, 892, 797, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, J=17.2, 10.3, 5.7 Hz, 1H), 5.56 (dtd, J=11.0, 7.4, 1.5 Hz, 1H), 5.35–5.26 (m, 2H), 5.20 (dq, J=10.3, 1.5 Hz, 1H), 4.65 (m, 1H), 4.04 (dt, J=5.7, 1.5 Hz, 2H), 3.42 (dd, J=9.7, 3.4 Hz, 1H), 3.32 (dd, J=9.7, 8.4 Hz, 1H), 2.44 (br s, 1H, OH), 2.19–2.04 (m, 2H), 0.99 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (d), 134.4 (d), 127.2 (d), 117.2 (t), 73.9 (t), 72.1 (t), 66.7 (d), 21.2 (t), 14.2 (q); EIMS *m*/*z* (relative intensity) 138 (M−H_2O^+, 46), 109 (10), 99 (21), 97 (24), 85 (100), 81 (49), 67 (88), 57 (59), 53 (23); HRMS: M+Na^+, found 179.1038. $C_9H_{16}O_2Na$ requires 179.1043.

*4.2.1.8. (Z)-(R)-1-Allyloxy-2-(prop-2-ynyloxy)hex-3-ene (**52**).*



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To a solution of alcohol **9** (830 mg, 5.32 mmol) in toluene (5 mL) were added a 35% aqueous solution of NaOH (5 mL), propargyl bromide (650 μL, 80% solution in toluene, 5.85 mmol, 1.1 equiv), and *n*-Bu_4NHSO_4 (885 mg, 2.66 mmol, 0.5 equiv). After 16 h of vigorous stirring at rt, Et_2NH (5 mL) was added. The reaction mixture was stirred for a further 1 h, poured onto ice, cautiously neutralized by addition of a 3 M solution of hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (pentane/Et_2O: 95/5) to afford 854 mg (83%) of propargyl ether **52** as a colorless oil; [Found: C, 74.21; H, 9.41. $C_{12}H_{18}O_2$ requires C, 74.19; H, 9.41%]; $[\alpha]_D$ −127 (*c* 1.00, $CHCl_3$); IR 3301, 2215, 1648, 1460, 1442, 1360, 1243, 1079, 993, 921, 748, 664, 627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, J=17.3, 10.3, 5.7 Hz, 1H), 5.72 (dtd, J=11.0, 7.6, 0.7 Hz, 1H), 5.30–5.16 (m, 3H), 4.59 (m, 1H), 4.24 (dd, J=15.8, 2.5 Hz, 1H), 4.10 (dd, J=15.9, 2.5 Hz, 1H), 4.06–4.03 (m, 2H), 3.54 (dd, J=10.5, 6.7 Hz, 1H), 3.44 (dd, J=10.5, 4.0 Hz, 1H), 2.40 (t, J=2.5 Hz, 1H), 2.26–2.08 (m, 2H), 1.01 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9 (d), 134.7 (d), 125.3 (d), 117.0 (t), 80.1 (s), 73.9 (d), 72.8 (t), 72.7 (d), 72.3 (t), 55.2 (t), 21.2 (t), 14.2 (q); EIMS *m*/*z* (relative intensity) 165 (M−Et^+, 0.1), 124 (9), 123 (M−$AllylOCH_2^+$, 100), 95 (12), 83 (39), 81 (29), 79 (8), 77 (7), 67 (19), 55 (26) 53 (8).

*4.2.1.9. {3-[(Z)-(R)-1-(Allyloxymethyl)pent-2-enyloxy]prop-1-ynyl}trimethylsilane (**10**).* To a solution of propargyl ether **52** (834 mg, 4.29 mmol) in THF (20 mL) at −78 °C was added LDA (7.5 mL, from a freshly prepared 0.62 M stock solution in THF/hexanes, 4.7 mmol, 1.1 equiv). After 1 h at 0 °C, TMSCl (712 μL, 5.57 mmol, 1.3 equiv) was added. After 1 h at 0 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with

brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (pentane/Et_2O: 96/4) to afford 966 mg (84%, 70% for the two steps from alcohol **9**) of the propargylic ether **10** as a colorless oil; [Found: C, 67.66; H, 10.04. $C_{15}H_{26}O_2Si$ requires C, 67.61; H, 9.84%]; $[\alpha]_D$ −129.0 (*c* 1.08, $CHCl_3$); IR 2173, 1648, 1250, 1081, 1012, 989, 923, 840, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J*=17.4, 10.5, 5.6 Hz, 1H), 5.71 (dtd, *J*=11.0, 7.8, 0.7 Hz, 1H), 5.30–5.16 (m, 3H), 4.61 (ddd, *J*=6.5, 4.0, 0.7 Hz, 1H), 4.24 (d, AB syst, *J*=16.0 Hz, 1H), 4.12 (d, AB syst, *J*=16.0 Hz, 1H), 4.04 (dt, *J*=5.6, 1.4 Hz, 2H), 3.55 (dd, *J*=10.5, 6.6 Hz, 1H), 3.44 (dd, *J*=10.5, 4.1 Hz, 1H), 2.28–2.08 (m, 2H), 1.01 (t, *J*=7.5 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9 (d), 134.8 (d), 125.5 (d), 117.0 (t), 102.0 (s), 90.9 (s), 72.8 (t), 72.3 (2C, d+t), 56.0 (t), 21.2 (t), 14.3 (q), −0.2 (q, 3C); EIMS *m*/*z* (relative intensity) 195 ($M-AllylOCH_2^+$, 43), 121 (20), 111 (73), 85 (17), 83 (100), 75 (37), 73 (62), 55 (16).

*4.2.1.10. 3-{(Z)-(R)-1-[(Allyloxymethyl)pent-2-enyloxy]prop-1-ynyl}triisopropylsilane (**11**).* To a solution of alcohol **9** (2.28 g, 14.6 mmol) in THF (25 mL) at 0 °C were successively added *t*-BuOK (2.46 g, 21.9 mmol, 1.5 equiv) and (triisopropylsilyl)propargyl bromide[29] (4.42 g, 16.1 mmol, 1.1 equiv). After 0.5 h at 0 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 98/2) to afford 4.47 g (87%) of the propargylic ether **11** as a yellow oil; [Found: C, 71.87; H, 10.97. $C_{21}H_{38}O_2Si$ requires C, 71.94; H, 10.92%]; $[\alpha]_D$ −113.9 (*c* 0.53, $CHCl_3$); IR 1462, 1073, 987, 920, 882, 797, 748, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddt, *J*=17.2, 10.4, 5.6 Hz, 1H), 5.71 (dtd, *J*=11.0, 7.5, 0.8 Hz, 1H), 5.29–5.20 (m, 2H), 5.16 (dq, *J*=10.4, 1.4 Hz, 1H), 4.70 (m, 1H), 4.27 (d, AB syst, *J*=16.2 Hz, 1H), 4.14 (d, AB syst, *J*=16.2 Hz, 1H), 4.04 (dt, *J*=5.6, 1.4 Hz, 2H), 3.55 (dd, *J*=10.6, 6.6 Hz, 1H), 3.46 (dd, *J*=10.6, 4.0 Hz, 1H), 2.28–2.10 (m, 2H), 1.08 (m, apparent br s, 18H+3H), 1.00 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 (d), 134.8 (d), 125.5 (d), 116.7 (t), 103.9 (s), 86.8 (s), 72.6 (t), 72.1 (t), 71.8 (d), 55.7 (t), 21.1 (t), 18.5 (q, 6C), 14.3 (q), 11.1 (d, 3C); EIMS *m*/*z* (relative intensity) 280 (23), 279 ($M-AllylOCH_2^+$, 100), 237 (16), 195 (35), 169 (26), 153 (69), 139 (40), 125 (34), 11 (43), 103 (33), 97 (29), 83 (34), 75 (35), 59 (29).

*4.2.1.11. (E)-(3R,4S)-7-Allyloxy-4-ethyl-1-(trimethylsilyl)hept-5-en-1-yn-3-ol (**12**).* To a solution of ether **10** (266 mg, 1.00 mmol) in THF (10 mL) at −78 °C, was added dropwise a solution of *n*-BuLi (0.40 mL, 2.5 M in hexanes, 1.0 mmol, 1.0 equiv). After 1 h at −78 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Analysis of the residue by ^1H NMR indicated the formation of a single detectable diastereomer. After purification by flash chromatography on silica gel (pentane/Et_2O: 80/20), 239 mg (90%) of the propargylic alcohol **12** were isolated as a colorless oil; $[\alpha]_D$ +73.5 (*c* 1.19, $CHCl_3$); IR 3402, 2170, 1647, 1455, 1379, 1249, 1087, 1029, 974, 919, 839, 759, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddt, *J*=17.2, 10.5, 5.6 Hz, 1H), 5.71 (dt, *J*=15.5, 5.7 Hz, 1H), 5.61 (dd, *J*=15.5, 9.0 Hz, 1H), 5.29 (dq, *J*=17.2, 1.6 Hz, 1H), 5.19 (dq, *J*=10.5, 1.4 Hz, 1H), 4.31 (dd, *J*=7.9, 4.9 Hz, 1H), 4.05–3.95 (m, 4H), 2.21 (m, 1H), 2.11 (d, *J*=8.2 Hz, 1H, OH), 1.64–1.53 (m, 1H), 1.46–1.35 (m, 1H), 0.91 (t, *J*=7.5 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7 (d), 132.3 (d), 130.9 (d), 117.0 (t), 104.8 (s), 90.7 (s), 70.8 (t), 70.4 (t), 65.4 (d), 50.9 (d), 23.7 (t), 11.8 (q), −0.16 (q, 3C); EIMS *m*/*z* (relative intensity) 225 ($M-Allyl^+$, 0.1), 207 ($M-Allyl-H_2O^+$, 0.4), 193 (1), 179 (2), 127 (7), 111 (13), 99 (18), 83 (21), 82 (100), 73 (15), 67 (33), 55 (9); HRMS: $M+Na^+$, found 289.1594. $C_{15}H_{26}O_2NaSi$ requires 289.1594.

*4.2.1.12. (E)-(3R,4S)-7-Allyloxy-4-ethyl-1-(triisopropylsilyl)hept-5-en-1-yn-3-ol (**13**).* To a solution of ether **11** (3.09 g, 8.80 mmol) in THF (88 mL) at −78 °C was added dropwise a solution of *n*-BuLi (5.26 mL, 2.5 M in hexanes, 10.6 mmol, 1.5 equiv). After 1 h at −78 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 90/10 to 70/30) to afford 3.09 g (99%) of propargylic alcohol **13** as a colorless oil; [Found: C, 71.63; H, 11.28. $C_{21}H_{38}O_2Si$ requires C, 71.94; H, 10.92%]; $[\alpha]_D$ +52.6 (*c* 0.62, $CHCl_3$); IR 1462, 1018, 996, 973, 919, 882, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J*=17.2, 10.3, 5.7 Hz, 1H), 5.73 (dd, *J*=15.4, 5.4 Hz, 1H), 5.73–5.63 (m, 1H), 5.28 (dq, *J*=17.2, 1.5 Hz, 1H), 5.18 (dq, *J*=10.4, 1.5 Hz, 1H), 4.35 (dd, *J*=8.2, 4.7 Hz, 1H), 4.04–3.94 (m, 4H), 2.23 (m, 1H), 2.10 (br d, *J*=8.2 Hz, 1H, OH), 1.65–1.55 (m, 1H), 1.50–1.39 (m, 1H), 1.07 (m, apparent br s, 18H+3H), 0.91 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7 (d), 132.5 (d), 130.9 (d), 117.0 (t), 106.6 (s), 86.7 (s), 70.9 (t), 70.5 (t), 65.4 (d), 51.0 (d), 24.0 (t), 18.5 (q, 6C), 11.8 (q), 11.1 (d, 3C); EIMS *m*/*z* (relative intensity) 289 ($M-H_2O-i\text{-}Pr^+$, 1), 249 (6), 210 (5), 168 (10), 167 (59), 167 (59), 139 (46), 131 (14), 127 (12), 125 (16), 111 (72), 103 (22), 99 (16), 97 (28), 85 (15), 83 (48), 82 (100), 75 (25), 69 (20), 67 (38).

4.2.1.13. (E)-(1R,2S*)-5-Allyloxy-2-ethyl-1-(trimethylsilylethynyl)pent-3-enyl acrylate (±)-(**14**).* To a solution of alcohol (±)-**12** (635 mg, 2.38 mmol) (synthesized from the racemic alcohol (±)-**8** prepared by reduction of acetylenic ketone **6** with DIBAL-H, see Supplementary data) in CH_2Cl_2 (25 mL) were added DMAP (87 mg, 0.71 mmol, 0.3 equiv) and *i*-Pr_2NEt (1.24 mL, 7.12 mmol, 3.0 equiv). The resulting mixture was cooled to −78 °C and acryloyl chloride (388 μL, 4.77 mmol, 2 equiv) was added dropwise. After 3 h at −78 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 94/6) to afford 557 mg (73%) of acrylate (±)-**14** as a colorless oil; IR 1741, 1250, 1162, 1129, 1094, 1048, 990, 973, 920, 841, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.43 (dd, *J*=17.3, 1.3 Hz, 1H), 6.13 (dd, *J*=17.3, 10.5 Hz, 1H), 5.92 (ddt, *J*=17.2, 10.5, 5.6 Hz, 1H), 5.85 (dd, *J*=10.5, 1.3 Hz, 1H), 5.66–5.67 (m, 2H), 5.47 (d, *J*=5.2 Hz, 1H), 5.28 (dq, *J*=17.2, 1.5 Hz, 1H), 5.18 (dd, *J*=10.5, 1.5 Hz, 1H), 4.01–3.99 (m, 2H), 3.98 (dt, *J*=5.6, 1.5 Hz, 2H), 2.36 (m, 1H), 1.67–1.57 (m, 1H), 1.47–1.36 (m, 1H), 0.92 (t, *J*=7.4 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9 (s), 134.8 (d), 131.9 (d), 131.4 (t), 130.0 (d), 128.1 (d), 116.9 (t), 100.7 (s), 91.9 (s), 70.5 (t), 70.4 (t), 67.1 (d), 48.0 (d), 23.6 (t), 11.6 (q), −0.25 (q, 3C); HRMS: $M+Na^+$, found 343.1698. $C_{18}H_{28}O_3NaSi$ requires 343.1700.

*4.2.1.14. RRCM of acrylate (±)-**14**.* To a refluxing solution of acrylate (±)-**14** (45 mg, 0.14 mmol) in CH_2Cl_2 (10 mL) was added Grubbs II catalyst (2 mg, 0.002 mmol, 2 mol %). Three additional portions of the catalyst (2 mg, 0.002 mmol, 2 mol %) were added at 1 h interval. After a total duration of 4 h heating at reflux, the reaction mixture was cooled to rt and evaporated under reduced pressure. Analysis of the crude material by ^1H NMR showed the formation of an equimolar mixture of truncated acrylate (±)-**17** and lactone (±)-**18**. After purification by flash chromatography on silica

gel (pentane/Et_2O: 4/1 to 2/1), 11.5 mg (33%) of acrylate (±)-**17** and 11 mg (35%) of lactone (±)-**18** were isolated as colorless oils. Similar results were obtained if the RRCM of (±)-**14** was conducted in toluene at 80 °C or if Ti(O*i*-Pr)$_4$ (30 mol %) was added prior to Grubbs II catalyst.

4.2.1.15. (1R,2S*)-2-Ethyl-1-(trimethylsilylethynyl)but-3-enyl acrylate (±)-(**17**).* IR 2181, 1729, 1636, 1405, 1251, 1182, 1126, 1044, 984, 918, 842, 808, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (dd, *J*=17.3, 1.5 Hz, 1H), 6.14 (dd, *J*=17.3, 10.5 Hz, 1H), 5.85 (dd, *J*=10.5, 1.5 Hz, 1H), 5.74 (ddd, *J*=17.0, 10.2, 9.0 Hz, 1H), 5.48 (d, *J*=5.1 Hz, 1H), 5.17 (dd, *J*=10.2, 1.8 Hz, 1H), 5.09 (dd, *J*=17.0, 1.8 Hz, 1H), 2.32 (m, 1H), 1.65–1.57 (m, 1H), 1.44–1.37 (m, 1H), 0.91 (t, *J*=7.4 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (s), 136.7 (d), 131.4 (t), 128.2 (d), 118.0 (t), 100.6 (s), 91.9 (s), 67.2 (d), 49.5 (d), 23.4 (t), 11.6 (q), −0.22 (q, 3C); EIMS *m*/*z* (relative intensity) 250 (M^+, 0.3), 249 ($M-H^+$, 2), 235 ($M-Me^+$, 2), 221 ($M-Et^+$, 2), 181 (21), 163 (9), 129 (14), 111 (5), 83 (7), 75 (7), 73 (26), 55 (100); HRMS: M+Na^+, found 273.1285. $C_{14}H_{22}O_2NaSi$ requires 273.1281.

4.2.1.16. (5S,6R*)-5-Ethyl-6-(trimethylsilylethynyl)-5,6-dihydropyran-2-one (±)-(**18**).* IR 2176, 1731, 1249, 1234, 1218, 1069, 1057, 1017, 841, 822, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (ddd, *J*=9.9, 4.0, 0.4 Hz, 1H), 6.03 (dd, *J*=9.9, 1.9 Hz, 1H), 5.18 (d, *J*=4.9 Hz, 1H), 2.60–2.54 (m, 1H), 1.86–1.76 (m, 1H), 1.71–1.60 (m, 1H), 1.04 (t, *J*=7.4 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (s), 148.7 (d), 120.5 (d), 98.5 (s), 93.9 (s), 71.3 (d), 39.0 (d), 22.7 (t), 11.0 (q), −0.4 (q, 3C); EIMS *m*/*z* (relative intensity) 222 (M^+, 0.1), 192 (4), 179 (5), 164 (4), 163 (25), 149 (4), 137 (5), 135 (7), 119 (4), 111 (5), 97 (10), 96 (100), 95 (6), 81 (53), 75 (13), 73 (12), 67 (10), 53 (13); HRMS: M+Na^+, found 245.0966. $C_{12}H_{18}O_2NaSi$ requires 245.0968.

*4.2.1.17. (E)-(1R,2S)-5-Allyloxy-2-ethyl-1-[(triisopropylsilyl)ethynyl]pent-3-enyl acrylate (**19**).* To a solution of propargylic alcohol **13** (71 mg, 0.20 mmol) in CH_2Cl_2 (1.5 mL) were added DMAP (7.5 mg, 0.060 mmol, 0.3 equiv) and *i*-Pr_2NEt (0.09 mL, 0.5 mmol, 2.4 equiv). The reaction mixture was cooled to −78 °C and acryloyl chloride (0.02 mL, 0.2 mmol, 1 equiv) was added dropwise. After 1 h at −78 °C, more *i*-Pr_2NEt (0.09 mL, 0.5 mmol, 2.4 equiv) and acryloyl chloride (0.02 mL, 0.2 mmol, 1 equiv) were added. After 1 h at −78 °C, the reaction mixture was poured into brine. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 90/10) to afford 79 mg (97%) of acrylate **19** as a colorless oil; [Found: C, 71.64; H, 10.35. $C_{24}H_{40}O_3Si$ requires C, 71.23; H, 9.96%]; $[\alpha]_D$ +85.0 (*c* 0.67, $CHCl_3$); IR 1729, 1635, 1462, 1404, 1259, 1179, 1042, 970, 920, 882, 807, 675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (dd, *J*=17.3, 1.5 Hz, 1H), 6.12 (dd, *J*=17.3, 10.4 Hz, 1H), 5.91 (ddt, *J*=17.2, 10.4, 5.6 Hz, 1H), 5.84 (dd, *J*=10.4, 1.5 Hz, 1H), 5.70–5.61 (m, 1H), 5.61 (dd, *J*=15.4, 5.4 Hz, 1H), 5.49 (d, *J*=5.1 Hz, 1H), 5.27 (qd, *J*=17.2, 1.5 Hz, 1H), 5.17 (qd, *J*=10.4, 1.5 Hz, 1H), 3.99–3.95 (m, 4H), 2.41–2.34 (m, 1H), 1.70–1.59 (m, 1H), 1.50–1.39 (m, 1H), 1.06 (m, apparent br s, 18H+3H), 0.93 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9 (s), 134.8 (d), 132.3 (d), 131.1 (t), 129.8 (d), 128.3 (d), 116.9 (t), 102.6 (s), 88.1 (s), 70.5 (t, 2C), 67.2 (d), 48.0 (d), 23.8 (t), 18.5 (q, 6C), 11.6 (q), 11.1 (d, 3C); EIMS *m*/*z* (relative intensity) 361 ($M-i$-Pr^+, 2), 347 ($M-AllylO^+$, 0.5), 303 (3), 291 (4), 289 (4), 263 (0.3), 249 (10), 186 (15), 185 (100), 129 (10), 101 (9), 75 (9), 55 (42).

*4.2.1.18. RRCM of acrylate **19**.* To a solution of acrylate **19** (288 mg, 0.711 mmol) in CH_2Cl_2 (71 mL) was added Grubbs II catalyst (12 mg, 0.014 mmol, 2 mol %) and the reaction mixture was heated to reflux. Additional portions of the catalyst (12 mg, 0.014 mmol, 0.02 equiv) were added every 2 h (total quantity of catalyst used: 48 mg, 0.057 mmol, 8 mol %). After 9 h at reflux, the reaction mixture was cooled to rt and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 99/1 to 80/20) to afford 46 mg (19%) of acrylate **20** as a colorless oil and 166 mg (76%) of lactone **21** as a brown oil.

*4.2.1.19. (1R,2S)-2-Ethyl-1-[(triisopropylsilyl)ethynyl]-but-3-enyl acrylate (**20**).* $[\alpha]_D$ +83.7 (*c* 0.43, $CHCl_3$); IR 1730, 1636, 1462, 1404, 1260, 1180, 1126, 1042, 984, 917, 882, 807, 675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (dd, *J*=17.3, 1.3 Hz, 1H), 6.13 (dd, *J*=17.3, 10.4 Hz, 1H), 5.84 (dd, *J*=10.4, 1.3 Hz, 1H), 5.77 (ddd, *J*=17.1, 10.2, 9.0 Hz, 1H), 5.50 (d, *J*=5.2 Hz, 1H), 5.15 (dd, *J*=10.3, 1.5 Hz, 1H), 5.09 (dd, *J*=17.1, 1.5 Hz, 1H), 2.36–2.30 (m, 1H), 1.70–1.61 (m, 1H), 1.50–1.38 (m, 1H), 1.06 (m, apparent br s, 18H+3H), 0.92 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (s), 136.9 (d), 131.1 (t), 128.3 (d), 117.8 (t), 102.6 (s), 88.0 (s), 67.3 (d), 49.5 (d), 23.6 (t), 18.5 (q, 6C), 11.5 (q), 11.4 (d, 3C); EIMS *m*/*z* (relative intensity) 291 ($M-i$-Pr^+, 6), 185 (100), 157 (6), 55 (12); HRMS: M+Na^+, found 357.2217. $C_{20}H_{34}O_2NaSi$ requires 357.2220.

*4.2.1.20. (5S,6R)-5-Ethyl-6-[(triisopropylsilyl)ethynyl]-5,6-dihydro-pyran-2-one (**21**).* [Found: C, 70.53; H, 9.86. $C_{18}H_{30}O_2Si$ requires C, 70.53; H, 9.87%]; $[\alpha]_D$ +52.4 (*c* 0.52, $CHCl_3$); IR 1732, 1461, 1381, 1233, 1216, 1159, 1102, 1058, 1015, 996, 882, 847, 821, 732, 676 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (ddd, *J*=9.9, 3.5, 0.9 Hz, 1H), 6.04 (dd, *J*=9.9, 2.1 Hz, 1H), 5.21 (dd, *J*=5.1, 0.9 Hz, 1H), 2.68–2.61 (m, 1H), 1.86–1.77 (m, 1H), 1.75–1.65 (m, 1H), 1.05 (m, apparent br s, 18H+3H), 1.04 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (s), 148.6 (d), 120.5 (d), 100.5 (s), 90.3 (s), 71.3 (d), 39.1 (d), 23.0 (t), 18.5 (q, 6C), 11.0 (d+q, 3C+1C); EIMS *m*/*z* (relative intensity) 263 ($M-i$-Pr^+, 40), 263 (40), 221 (100), 193 (13), 177 (26), 165 (32), 149 (16), 137 (13), 111 (10), 81 (10), 75 (12), 59 (10).

*4.2.1.21. RCM of acrylate **20**.* To a solution of acrylate **20** (18 mg, 0.054 mmol) in CH_2Cl_2 (5.5 mL) was added Grubbs II catalyst (2 mg, 0.002 mmol, 0.05 equiv) and the reaction mixture was heated at reflux. Additional portions of the catalyst were added every 3 h (total quantity of catalyst used: 6 mg, 0.08 mmol, 13 mol %). After a total duration of 11 h heating at reflux, the reaction mixture was cooled to rt and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 80/20) to afford 10 mg (61%) of lactone **21** as a brown oil.

*4.2.1.22. [(E)-(3R,4S)-7-Allyloxy-4-ethyl-3-((1RS)-1-methoxyallyloxy)hept-5-en-1-ynyl]-triisopropylsilane (**23**).* To a solution of alcohol **13** (77 mg, 0.22 mmol) in C_6H_6 (20 mL) were added acrolein dimethyl acetal (0.13 mL, 1.1 mmol, 5 equiv) and PPTS (6.0 mg, 0.02 mmol, 0.1 equiv). The resulting mixture was heated at reflux with azeotropic removal of MeOH (using a small Dean/Stark apparatus filled with activated 3 Å molecular sieves). After 7 h, the reaction mixture was poured into water, the layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 98/2 to 95/5) to afford 65 mg (71%) of acetal **23** as a colorless oil (1:1 mixture of diastereomers); IR 1648, 1462, 1365, 1073, 1028, 983, 920, 882, 675 cm^{-1}; HRMS: M+Na^+, found 443.2946. $C_{25}H_{44}O_3NaSi$ requires 443.2952. To facilitate characterization, fractions obtained during chromatographic purification, enriched in one of each diastereomer, were used to record the NMR spectra.

Less polar (first eluted) diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.86–5.76 (m, 1H), 5.67–5.63 (m, 2H), 5.40 (dt, J=17.3, 1.5 Hz, 1H), 5.30–5.22 (m, 3H), 5.18–5.14 (m, 1H), 4.42 (d, J=5.4 Hz, 1H), 3.98 (d, J=5.2 Hz, 2H), 3.96 (dt, J=5.6, 1.5 Hz, 2H), 3.29 (s, 3H), 2.34–2.26 (m, 1H), 1.78–1.66 (m, 1H), 1.48–1.37 (m, 1H), 1.07 (m, apparent br s, 18H+3H), 0.91 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9 (d), 134.7 (d), 133.6 (d), 128.9 (d), 118.6 (t), 116.8 (t), 102.7 (s), 99.7 (d), 87.8 (s), 70.7 (t), 70.4 (t), 68.9 (d), 52.0 (q), 49.0 (d), 23.5 (t), 18.5 (q, 6C), 11.7 (q), 11.1 (d, 3C).

More polar (second eluted) diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (m, 1H), 5.82 (m, 1H), 5.72–5.60 (m, 2H), 5.38 (dt, J=17.3, 1.5 Hz, 1H), 5.31–5.22 (m, 3H), 5.18–5.14 (m, 1H), 4.11 (d, J=5.2 Hz, 1H), 3.98 (d, J=5.2 Hz, 2H), 3.96 (dt, J=5.6, 1.5 Hz, 2H), 3.42 (s, 3H), 2.34–2.26 (m, 1H), 1.78–1.66 (m, 1H), 1.48–1.37 (m, 1H), 1.07 (m, apparent br s, 18H+3H), 0.89 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9 (d), 134.6 (d), 133.4 (d), 129.0 (d), 118.8 (t), 116.8 (t), 105.2 (s), 104.7 (d), 87.6 (s), 70.7 (t), 70.5 (t), 68.8 (d), 54.4 (q), 49.2 (d), 23.5 (t), 18.5 (q, 6C), 11.7 (q), 11.1 (d, 3C).

*4.2.2. Synthesis of the cyclic acetal **22**.*

*4.2.2.1. Synthesis from lactone **21**.* To a solution of lactone **21** (167 mg, 0.544 mmol) in CH_2Cl_2 (11 mL) at −78 °C was added a solution of DIBAL-H (0.71 mL, 1 M in hexanes, 0.71 mmol, 1.3 equiv). After 45 min at −78 °C, the cold reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$. After extraction with EtOAc, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude lactol was dissolved in MeOH (9 mL) and PPTS (14 mg, 0.054 mmol, 0.1 equiv) was added. After 16 h at rt, the reaction was quenched by addition of Et_3N (0.2 mL) and the resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 98/2) to afford 152 mg (87%) of **22** as a colorless oil (5:1 mixture of diastereomers).

*4.2.3. Synthesis from acetal **23** by RRCM.* To a solution of mixed acetal **23** (62 mg, 0.15 mmol) in CH_2Cl_2 (16 mL) was added Grubbs II catalyst (3 mg, 0.004 mmol, 2 mol %) and the reaction mixture was heated at reflux. Additional portions of the catalyst (3 mg, 0.004 mmol, 0.02 equiv) were added every 2 h (total quantity of catalyst used: 15 mg, 0.018 mmol, 12 mol %). After 7 h at reflux, the reaction mixture was cooled to rt and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 80/20) to afford 39 mg (82%) of dihydropyran **22** as a brown oil (1:1 mixture of diastereomers). Treatment of **22** (38.6 mg, 0.120 mmol, 1:1 mixture of diastereomers) with PPTS (3.0 mg, 0.012 mmol, 10 mol %) in MeOH (2 mL) at rt for 9 h, subsequent work-up (as described for the preparation from lactone **21**) and purification by flash chromatography on silica gel (petroleum ether/Et_2O: 98/2) provided 33.5 mg (87%) of **22** as a 5:1 mixture of diastereomers.

*4.2.3.1. (2R,3S,6R and S)-3-Ethyl-6-methoxy-3,6-dihydro-2H-pyran-2-ylethynyl)triisopropylsilane (**22**).* IR 2924, 2865,1462, 1185, 1110, 1046, 1020, 964, 882, 718, 664 cm^{-1}; minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (apparent dt, J=10.3, 2.2 Hz, 1H), 5.72 (m, 1H), 4.95 (ddd, apparent q, J=1.8 Hz, 1H), 4.64 (d, J=5.5 Hz, 1H), 3.45 (s, 3H), 2.31–2.24 (m, 1H), 1.73–1.52 (m, 2H), 1.09–1.05 (m, apparent br s, 18H+3H), 0.99 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.6 (d), 125.6 (d), 104.5 (s), 96.0 (d), 86.3 (s), 63.9 (d), 55.0 (q), 39.0 (d), 24.2 (t), 18.5 (q, 6C), 11.4 (q), 11.2 (d, 3C); major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (dd, J=10.2, 5.2 Hz, 1H), 5.72 (m, 1H), 4.92 (br d, J=2.6 Hz, 1H), 4.83 (d, J=3.8 Hz, 1H), 3.45 (s, 3H), 2.08–2.03 (m, 1H), 1.92–1.82 (m, 1H), 1.73–1.52 (m, 1H), 1.09–1.05 (m, apparent br s, 18H+3H), 0.98 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.6 (d), 124.9 (d), 104.7 (s), 95.8 (d), 87.2 (s), 62.8 (d), 55.4 (q), 39.0 (d), 22.7 (t), 18.6 (q, 6C), 11.3 (q), 11.2 (d, 3C); EIMS m/z (relative intensity) 322 (M^+, 1), 291 ($M-OMe^+$, 7), 279 ($M-i$-Pr^+, 94), 247 (70), 205 (24), 177 (40), 163 (18), 149 (44), 145 (22), 117 (98), 112 (100), 103 (35), 97 (49), 89 (55), 75 (66), 59 (33); HRMS: M+Na^+, found 345.2216. $C_{19}H_{34}O_2NaSi$ requires 345.2220.

*4.2.3.2. (2R,3S,6R, and S)-3-Ethyl-2-ethynyl-6-methoxy-3,6-dihydro-2H-pyran (**24**).* To a solution of alkynylsilane **22** (136 mg, 0.420 mmol) in THF (7 mL) was added a solution of n-Bu_4NF (0.42 mL, 1 M in THF, 0.42 mmol, 1 equiv). After 2.5 h at rt, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 98/2) to afford 47 mg (67%) of the terminal alkyne **24** as a colorless oil (12:1 mixture of diastereomers); IR 3290, 1657, 1462, 1401, 1335, 1186, 1108, 1043, 1021, 962, 739, 660, 628 cm^{-1}; minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (dt, J=10.2, 2.0 Hz, 1H), 5.76 (ddd, apparent dt, J=10.4, 2.2 Hz, 1H), 4.97 (br q, J=1.9 Hz, 1H), 4.63 (dd, J=5.4, 2.4 Hz, 1H), 3.49 (s, 3H), 2.39 (d, J=2.4 Hz, 1H), 1.72–1.64 (m, 1H), 1.63–1.51 (m, 2H), 1.00 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.6 (d), 125.4 (d), 96.0 (d), 81.1 (s), 73.5 (d), 63.3 (d), 55.1 (q), 38.7 (d), 23.8 (t), 11.2 (q); EIMS m/z (relative intensity) 165 ($M-H^+$, 29), 135 ($M-OMe^+$, 53), 112 ($M-HC{\equiv}CCHO^+$, *retro Diels–Alder*, 100), 97 (62), 91 (30), 79 (29), 67 (13), 53 (10); major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (ddd, J=10.2, 5.5, 1.1 Hz, 1H), 5.90 (ddd, J=10.2, 2.8, 1.2 Hz, 1H), 4.88–4.87 (m, 1H), 4.80 (dd, apparent br t, J=3.0 Hz, 1H), 3.46 (s, 3H), 2.51 (d, J=2.4 Hz, 1H), 2.04–1.98 (m, 1H), 1.94–1.84 (m, 1H), 1.63–1.51 (m, 1H), 0.99 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.3 (d), 124.7 (d), 95.8 (d), 81.1 (s), 74.3 (d), 61.7 (d), 55.5 (q), 38.6 (d), 22.3 (t), 11.2 (q); EIMS m/z (relative intensity) 166 (M^+, 9), 135 ($M-OMe^+$, 53), 112 ($M-HC{\equiv}CCHO^+$, *retro Diels–Alder*, 100), 105 (20), 97 (77), 91 (62), 79 (47), 67 (20), 53 (15); HRMS: M+Na^+, found 189.0884. $C_{10}H_{14}O_2Na$ requires 189.0886.

*4.2.3.3. (2R,3S,6R, and S)-3-Ethyl-2-((E)-2-iodovinyl)-6-methoxy-3,6-dihydro-2H-pyran (**25**).* To a solution of alkyne **24** (71 mg, 0.43 mmol) in THF (5 mL) was added Cp_2ZrHCl (143 mg, 0.554 mmol, 1.3 equiv). After 15 min at rt, I_2 (130 mg, 0.511 mmol, 1.2 equiv) was added. After 15 min at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with an aqueous solution of $Na_2S_2O_3$ and the suspension was filtered through Celite (Et_2O). The layers of the filtrate were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 98/2) to afford 68 mg (54%) of **25** as a colorless oil (12:1 mixture of diastereomers); IR 1655, 1613, 1462, 1398, 1333, 1186, 1108, 1046, 1022, 961, 909, 728 cm^{-1}; minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, J=14.5 Hz, 1H), 6.38 (ddd, J=14.4, 2.9, 1.2 Hz, 1H), 5.95 (ddd, J=10.3, 3.7, 1.5 Hz, 1H), 5.69 (ddd, J=10.3, 2.7, 1.1 Hz, 1H), 4.99 (apparent br q, J=1.8 Hz, 1H), 4.26 (ddd, J=7.3, 4.7, 1.1 Hz, 1H), 3.42 (s, 3H), 2.19–2.14 (m, 1H), 1.41–1.29 (m, 2H), 0.91 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2 (d), 133.1 (d), 125.1 (d), 96.9 (d), 76.7 (d), 72.3 (d), 54.8 (q), 38.7 (d), 23.0 (t), 11.4 (q); EIMS m/z (relative intensity) 293 ($M-H^+$, 0.4), 263 ($M-OMe^+$, 2), 167 (11), 136 (16), 112 ($M-ICH{=}CHCHO^+$, *retro Diels–Alder*, 100), 97 (72), 79 (17), 67 (8); major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (ddd, J=14.5, 4.8, 0.3 Hz, 1H), 6.40 (dd, J=14.4, 1.8 Hz, 1H), 6.11 (ddd, J=10.1, 5.6, 1.1 Hz, 1H), 5.74 (ddd,

J=10.1, 2.8, 1.2 Hz, 1H), 4.86 (apparent br d, J=2.8 Hz, 1H), 4.48 (ddd, J=4.7, 3.5, 1.7 Hz, 1H), 3.40 (s, 3H), 2.92 (m, 1H), 1.57–1.47 (m, 1H), 1.41–1.29 (m, 1H), 0.91 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3 (d), 133.1 (d), 124.9 (d), 95.8 (d), 76.7 (d), 72.0 (d), 55.2 (q), 38.7 (d), 21.6 (t), 11.5 (q); EIMS m/z (relative intensity) 294 (M^+, 0.1), 263 ($M-OMe^+$, 4), 167 (8), 136 (22), 125 (8), 112 ($M-ICH{=}CHCHO^+$, *retro Diels–Alder*, 100), 97 (72), 79 (13); HRMS: $M+Na^+$, found 317.0009. $C_{10}H_{15}O_2INa$ requires 317.0005.

4.2.4. Synthesis of the C8–C13 subunit.

*4.2.4.1. Ethyl (R)-3-(tert-butyldimethylsilyloxy)-5-(trimethylsilyl) pent-4-ynoate (**28**).* To a solution of β-hydroxyester **27**[36] (1.03 g, 4.79 mmol) in CH_2Cl_2 (25 mL) were successively added imidazole (815 mg, 12.0 mmol, 2.5 equiv), TBSCl (866 mg, 5.75 mmol, 1.2 equiv) and DMAP (29 mg, 0.24 mmol, 0.05 equiv). After 16 h at rt, the reaction mixture was hydrolyzed with water. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 98/2 to 96/4) to afford 1.53 g (97%) of silyl ether **28** as a colorless oil; [Found: C, 58.31; H, 9.71. $C_{16}H_{32}O_3Si_2$ requires C, 58.48; H, 9.82%]; $[\alpha]_D$ +55.6 (c 1.00, $CHCl_3$); IR 1740, 1250, 1165, 1092, 1029, 996, 952, 836, 778, 760 cm^{-1}; ^{1}H NMR (400 MHZ, $CDCl_3$) δ 4.82 (dd, J=9.0, 4.5 Hz, 1H), 4.20–4.07 (m, 2H), 2.71 (dd, J=15.0, 9.1 Hz, 1H), 2.62 (dd, J=15.0, 4.6 Hz, 1H), 1.26 (t, J=7.1 Hz, 3H), 0.88 (s, 9H), 0.15 (s, 9H+3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (s), 106.0 (s), 89.4 (s), 60.5 (t), 60.2 (d), 44.0 (t), 25.7 (q, 3C), 18.1 (s), 14.2 (q), −0.3 (q, 3C), −4.6 (q), −5.2 (q); EIMS m/z (relative intensity) 313 ($M-Me^+$, 3), 272 ($M-C_4H_8^+$, 24), 271 ($M-t$-Bu^+, 100), 201 (10), 147 (82), 133 (11), 103 (21), 75 (27), 73 (39).

*4.2.4.2. (R)-3-(tert-Butyldimethylsilyloxy)-N-methoxy-N-methyl-5-trimethylsilylpent-4-ynamide (**29**).* To a solution of ethyl ester **28** (2.79 g, 8.49 mmol) in THF (40 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (1.24 g, 12.7 mmol, 1.5 equiv). The reaction mixture was cooled to −40 °C and a solution of *i*-PrMgCl (12.7 mL, 2 M in THF, 25.5 mmol, 3 equiv) was added dropwise over 15 min. The reaction mixture was allowed to warm to 0 °C over 3 h and then poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 80/20) to afford 2.78 g (95%) of Weinreb amide **29** as a colorless oil; [Found: C, 55.93; H, 9.71; N, 3.99. $C_{16}H_{33}NO_3Si_2$ requires C, 55.93; H, 9.68; N, 4.08%]; $[\alpha]_D$ +70.9 (c 1.21, $CHCl_3$); IR 1664, 1385, 1250, 1086, 1063, 1013, 979, 945, 836, 778, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (dd, J=9.1, 4.3 Hz, 1H), 3.71 (s, 3H), 3.18 (s, 3H), 3.02 (dd, J=14.3, 9.6 Hz, 1H), 2.58 (dd, J=14.8, 4.3 Hz, 1H), 0.88 (s, 9H), 0.15 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.7 (s, weak), 106.8 (s), 88.9 (s), 61.5 (q), 60.4 (d), 40.7 (t), 32.0 (q, weak), 25.7 (q, 3C), 18.1 (s), −0.3 (q, 3C), −4.8 (q), −5.1 (q); EIMS m/z (relative intensity) 328 ($M-Me^+$, 5), 312 ($M-OMe^+$, 3), 287 ($M-C_4H_8^+$, 24), 286 ($M-t$-Bu^+, 100), 256 (4), 155 (4), 130 (4), 109 (5), 89 (14), 86 (5), 75 (9), 73 (30), 70 (7), 56 (6).

*4.2.4.3. 1-[(3-Iodobut-3-enyloxy)methyl]-4-methoxybenzene (**30**).* To a solution of 3-iodobut-3-en-1-ol[41] (7.92 g, 40 mmol) in toluene (150 mL) were added a solution of *p*-methoxybenzyl trichloroacetimidate (16.5 g, 80 mmol, 2 equiv) in toluene (50 mL) and $La(OTf)_3$ (234 mg, 0.400 mmol, 10 mol %). After 16 h at rt, the reaction mixture was diluted with Et_2O and poured into water. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with an aqueous solution of $Na_2S_2O_3$ (25%), brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (pentane/Et_2O: 95/5) to afford 7.8 g (61%) of ether **30** as a colorless oil; IR 1613, 1586, 1511, 1462, 1361, 1301, 1243, 1172, 1138, 1091, 1033, 896, 811 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, apparent br d, J=8.5 Hz, 2H), 6.88 (m, apparent br d, J=8.5 Hz, 2H), 6.12 (q, J=1.4 Hz, 1H), 5.78 (d, J=1.4 Hz, 1H), 4.47 (s, 2H), 3.80 (s, 3H), 3.58 (t, J=6.4 Hz, 2H), 2.67 (td, apparent br t, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (s), 130.2 (s), 129.3 (d, 2C), 127.3 (t), 113.8 (d, 2C), 107.4 (s), 72.7 (t), 68.3 (t), 55.2 (q), 45.3 (t); EIMS m/z (relative intensity) 318 (M^+, 1), 192 ($M-I^+$, 6), 191 (4), 163 (4), 137 (6), 136 (10), 135 (11), 122 (10), 121 (100), 78 (9), 77 (8), 55 (5).

*4.2.4.4. (R)-6-(tert-Butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)-3-methylene-8-(trimethylsilyl)oct-7-yn-4-one (**31**).* To a solution of alkenyl iodide **30** (1.91 g, 6.00 mmol, 2 equiv) in Et_2O (15 mL) at −78 °C was added a solution of *n*-BuLi (2.40 mL, 2.5 M in hexanes, 6.00 mmol, 1 equiv, 2 equiv). After 0.5 h at −78 °C, a solution of Weinreb amide **29** (1.03 g, 3.00 mmol) in Et_2O (30 mL) was added dropwise. After 0.5 h at −78 °C, the reaction mixture was warmed to 0 °C over 0.5 h and poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/Et_2O gradient: 94/6 to 90/10) to afford 944 mg (66%) of enone **31** as a colorless oil; [Found: C, 65.46; H, 9.02. $C_{26}H_{42}O_4Si_2$ requires C, 65.77; H, 8.92%]; $[\alpha]_D$ +45.9 (c 1.04, $CHCl_3$); IR 1679, 1613, 1513, 1361, 1247, 1173, 1086, 1037, 983, 942, 835, 778, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, apparent br d, J=8.7 Hz, 2H), 6.86 (m, apparent br d, J=8.7 Hz, 2H), 6.10 (s, 1H), 5.90 (t, J=0.9 Hz, 1H), 4.90 (dd, J=8.8, 4.1 Hz, 1H), 4.43 (d, AB syst, J=11.8 Hz, 1H), 4.40 (d, AB syst, J=11.8 Hz, 1H), 3.79 (s, 3H), 3.52 (td, J=6.7, 2.2 Hz, 2H), 3.27 (dd, J=15.6, 8.8 Hz, 1H), 2.77 (dd, J=15.6, 4.1 Hz, 1H), 2.58 (br t, J=6.6 Hz, 2H), 0.85 (s, 9H), 0.15 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2 (s), 159.1 (s), 146.0 (s), 130.5 (s), 129.2 (d, 2C), 126.9 (t), 113.7 (d, 2C), 106.7 (s), 89.1 (s), 72.5 (t), 68.5 (t), 60.0 (d), 55.2 (q), 46.0 (t), 31.2 (t), 25.7 (q, 3C), 18.1 (s), −0.27 (q, 3C), −4.7 (q), −5.2 (q).

*4.2.4.5. (4R,6R)-6-(tert-Butyldimethyl-silyloxy)-1-(4-methoxybenzyloxy)-3-methylene-8-trimethylsilyloct-7-yn-4-ol (**33**).* To a solution of oxazaborolidine (*S*)-**32** (4.9 mL, 1 M in toluene, 4.9 mmol, 2 equiv) in THF (5 mL) at 0 °C was added $BH_3{\cdot}SMe_2$ complex (0.46 mL, 4.9 mmol, 2 equiv). After 0.5 h at 0 °C, the reaction mixture was cooled to −78 °C and a pre-cooled solution of enone **31** (1.16 g, 2.45 mmol) in THF (10 mL) was added via a cannula. After 3 h at −78 °C, the reaction was quenched with MeOH (5 mL), the resulting mixture was allowed to warm to rt and was then evaporated under reduced pressure. The residue was taken-up in MeOH (10 mL) and the mixture was evaporated again under reduced pressure. The crude material was purified by flash chromatography on silica gel (pentane/Et_2O gradient: 94/6 to 90/10) to afford 884 mg (76%) of allylic alcohol **33** as a colorless oil; [Found: C, 65.45; H, 9.42. $C_{26}H_{44}O_4Si_2$ requires C, 65.50; H, 9.30%]; $[\alpha]_D$ +40.2 (c 1.10, $CHCl_3$); IR 3440, 2172, 1613, 1586, 1513, 1248, 1173, 1085, 1037, 836, 778, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, apparent br d, J=8.6 Hz, 2H), 6.87 (m, apparent br d, J=8.6 Hz, 2H), 5.13 (s, 1H), 4.91 (s, 1H), 4.63 (dd, J=6.5, 4.9 Hz, 1H), 4.45 (s, 2H), 4.41 (m, 1H), 3.80 (s, 3H), 3.64–3.54 (m, 2H), 3.36 (d, J=3.6 Hz, 1H, OH), 2.43 (m, 1H), 2.30 (m, 1H), 1.92–1.81 (m, 2H), 0.91 (s, 9H), 0.17 (s, 3H), 0.16 (s, 9H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (s), 148.6 (s), 130.1 (s), 129.3 (d, 2C), 113.8 (d, 2C), 111.5 (t), 106.8 (s), 89.5 (s), 72.7 (t), 71.4 (d), 69.5 (t), 61.6 (d), 55.2 (q), 43.6 (t), 32.4 (t), 25.7 (q, 3C), 18.1 (s), −0.27 (q,

3C), −4.5 (q), −5.1 (q); EIMS *m/z* (relative intensity) 476 (M^+, 0.1), 295 (1), 241 (6), 201 (6), 137 (5), 122 (10), 121 (100), 75 (12), 73 (11). The relative configuration of **33** was ascertained by a chemical correlation, see Supplementary data.

*4.2.4.6. (4R,6R)-6-(tert-Butyldimethylsilyl-oxy)-1-(4-methoxybenzyloxy)-3-methylene-8-trimethylsilyloct-7-yn-4-ol (**34**).* To a solution of alcohol **33** (168 mg, 0.352 mmol) in toluene (5 mL) was added *p*-methoxybenzyl trichloroacetimidate (150 mg, 0.530 mmol, 1.5 equiv) and $La(OTf)_3$ (10 mg, 0.05 mmol, 0.14 equiv). After 16 h at rt, the reaction mixture was diluted with Et_2O and poured into water. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with a saturated aqueous solution of $NaHO_3$, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (pentane/Et_2O: 91/9) to afford 133 mg (64%) of ether **34** as a colorless oil; [Found: C, 68.16; H, 9.16. $C_{34}H_{52}O_5Si_2$ requires C, 68.41; H, 8.78%]; $[\alpha]_D$ +44.7 (*c* 1.05, $CHCl_3$); IR 2171, 1613, 1586, 1512, 1246, 1172, 1089, 1035, 836, 777, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, apparent br d, *J*=8.7 Hz, 2H), 7.21 (m, apparent br d, *J*=8.7 Hz, 2H), 6.88–6.83 (m, 4H), 5.12 (m, apparent br s, 1H), 5.02 (q apparent br s, *J*=1.4 Hz, 1H), 4.56 (dd, *J*=9.8, 3.2 Hz, 1H), 4.45 (s, 2H), 4.40 (d, AB syst, *J*=10.9 Hz, 1H), 4.11 (d, AB syst, *J*=10.9 Hz, 1H), 3.97 (dd, *J*=9.6, 3.2 Hz, 1H), 3.80 (s, 6H), 3.64–3.59 (m, 2H), 2.43–2.28 (m, 2H), 1.93 (ddd, *J*=14.0, 9.6, 3.2 Hz, 1H), 1.83 (ddd, *J*=14.0, 9.8, 3.2 Hz, 1H), 0.89 (s, 9H), 0.14 (s, 3H), 0.13 (s, 9H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (s), 159.0 (s), 145.6 (s), 130.7 (s), 130.5 (s), 129.3 (d, 2C), 129.2 (d, 2C), 113.7 (d, 4C), 113.0 (t), 107.8 (s), 88.5 (s), 78.9 (d), 72.6 (t), 79.9 (t), 68.7 (t), 59.8 (d), 55.2 (q, 2C), 44.2 (t), 30.9 (t), 25.8 (q, 3C), 18.2 (s), −0.3 (q, 3C), −4.3 (q), −5.0 (q).

*4.2.4.7. (4R,6R)-6-(tert-Butyldimethylsilyl-oxy)-1,4-bis-(4-methoxybenzyloxy)-8-trimethylsilyloct-7-yn-3-one (**35**).* A slow stream of ozone in oxygen was passed through a solution of **34** (411 mg, 0.688 mmol) containing Sudan red III (0.24 mL, 0.05% in MeOH) in CH_2Cl_2 (24 mL) at −78 °C. Once the red color fainted (ca. 15 min), excess ozone was immediately removed by bubbling argon through the cold reaction mixture (until the exhausted gas showed a negative test against a wet KI/starch paper). Triphenylphosphine (217 mg, 0.826 mmol, 1.2 equiv) was then added in one portion and the reaction mixture was allowed to warm to rt. After 0.5 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 90/10 to 80/20) to afford 300 mg (73%) of enone **35** as a colorless oil; [Found: C, 66.18; H, 8.34. $C_{33}H_{50}O_6Si_2$ requires C, 66.18; H, 8.41%]; $[\alpha]_D$ +31.7 (*c* 1.00, $CHCl_3$); IR 2173, 1720, 1586, 1612, 1513, 1247, 1173, 1086, 1034, 837, 778, 759, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.21 (m, 4H), 6.87–6.84 (m, 4H), 4.58 (dd, *J*=9.8, 3.1 Hz, 1H), 4.47 (d, AB syst, *J*=10.8 Hz, 1H), 4.43 (s, 2H), 4.27 (d, AB syst, *J*=10.8 Hz, 1H), 4.07 (dd, *J*=9.8, 3.0 Hz, 1H), 3.795 (s, 3H), 3.79 (s, 3H), 3.75–3.69 (m, 2H), 2.77 (td, *J*=6.1, 2.0 Hz, 2H), 2.01 (ddd, *J*=14.0, 9.8, 3.0 Hz, 1H), 1.89 (ddd, *J*=14.0, 9.8, 3.1 Hz, 1H), 0.90 (s, 9H), 0.15 (s, 3H), 0.13 (s, 9H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5 (s), 159.3 (s), 159.2 (s), 130.2 (s), 129.7 (s), 129.6 (d, 2C), 129.3 (d, 2C), 113.8 (d, 2C), 113.7 (d, 2C), 106.9 (s), 89.3 (s), 81.2 (d), 72.9 (t), 72.1 (t), 64.9 (t), 59.3 (d), 55.3 (q), 55.2 (q), 40.8 (t), 38.2 (t), 25.8 (q, 3C), 18.2 (s), −0.3 (q, 3C), −4.3 (q), −4.9 (q).

4.3. Convergent approach toward the C1–C11 subunit of PLMs and LSNs. Formal synthesis of PLM B

4.3.1. Synthesis of the C8–C11 subunit.

*4.3.1.1. 1-(tert-Butyldiphenylsilyloxy)-6-(trityloxy)hex-4-yn-3-ol ((±)-**37**).* To a solution of propargyl trityl ether[48] (7.11 g, 23.8 mmol, 1.2 equiv) in THF (32 mL) at −78 °C was added dropwise a solution of *n*-BuLi (8.70 mL, 2.5 M in hexanes, 21.8 mmol, 1.1 equiv). The reaction mixture was stirred at 0 °C for 10 min, cooled to −40 °C and a solution of 3-(*tert*-butyldiphenylsilyl-oxy) propanal [prepared from propane-1,3-diol (**36**)][47] (6.20 g, 19.9 mmol) in THF (28 mL) was then added. After 10 min at −40 °C and 20 min at 0 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 90/10 to 70/30) to afford 10.8 g (89%, 70% for the three steps from **36**) of racemic propargylic alcohol (±)-**37** as a colorless oil (see the characterization of the (*R*) enantiomer below).

*4.3.1.2. 1-(tert-Butyldiphenylsilyloxy)-6-(trityloxy)hex-4-yn-3-one (**38**).* To a solution of the racemic propargylic alcohol (±)-**37** (100 mg, 0.164 mmol) in CH_2Cl_2 (10 mL) was added MnO_2 (437 mg, 4.89 mmol, 30 equiv). After 7 h at rt, more MnO_2 (110 mg, 1.23 mmol, 7.5 equiv) was added. After 15 h at rt, the reaction mixture was filtered through Celite (CH_2Cl_2) and the filtrate was evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 90/10) to afford 88 mg (88%) of ketone **38** as a white solid; mp 110 °C; IR 1677, 1590, 1448, 1427, 1363, 1264, 1167, 1105, 1068, 908, 822, 732, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.64 (m, 4H), 7.46–7.43 (m, 6H), 7.40–7.22 (m, 15H), 3.98 (t, *J*=6.2 Hz, 2H), 3.95 (s, 2H), 2.73 (t, *J*=6.2 Hz, 2H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.6 (s), 143.1 (s, 3C), 135.6 (d, 4C), 133.4 (s, 2C), 129.7 (d, 2C), 128.6 (d, 6C), 128.0 (d, 6C), 127.7 (d, 4C), 127.4 (d, 3C), 89.0 (s), 87.9 (s), 84.3 (s), 59.2 (t), 52.8 (t), 48.1 (t), 26.8 (q, 3C), 19.2 (s); HRMS: M+Na^+, found 631.2636. $C_{41}H_{40}O_3NaSi$ requires 631.2639.

*4.3.1.3. (3R)-1-(tert-Butyldiphenylsilyloxy)-6-(trityloxy)hex-4-yn-3-ol (**37**).* To a solution of Noyori's catalyst (*R*,*R*)-Ru-**I**[26] (360 mg, 0.600 mmol, 0.05 equiv) in *i*-PrOH (120 mL) was added a solution of ketone **38** (7.3 g, 12 mmol) in CH_2Cl_2 (12 mL). After 1.5 h at rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 90/10 to 70/30) to afford 6.5 g (89%) of optically active propargyl alcohol **37** as a colorless oil (ee=97%). The ee value was determined by super-critical fluid chromatography (SFC) analysis on chiral stationary phase;[27] $[\alpha]_D$ +0.03 (*c* 0.52, $CHCl_3$); IR 1590, 1489, 1471, 1448, 1427, 1106, 1054, 822, 763, 741, 698, 632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.65 (m, 4H), 7.47–7.45 (m, 6H), 7.40–7.33 (m, 6H), 7.30–7.27 (m, 6H), 7.24–7.21 (m, 3H), 4.70 (q, *J*=5.2 Hz, 1H), 4.03–3.98 (m, 1H), 3.85–3.77 (m, 1H), 3.81 (d, *J*=1.5 Hz, 2H), 3.03 (d, *J*=6.0 Hz, 1H, OH), 2.03–1.95 (m, 1H), 1.91–1.82 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5 (s, 3C), 135.5 (d, 4C), 133.1 (s), 133.0 (s), 129.8 (d, 2C), 128.6 (d, 6C), 127.9 (d, 6C), 127.7 (d, 4C), 127.1 (d, 3C), 87.4 (s), 85.9 (s), 81.6 (s), 61.6 (t), 61.4 (d), 53.1 (t), 38.9 (t), 26.8 (q, 3C), 19.1 (s); HRMS: M+Na^+, found 633.2794. $C_{41}H_{42}O_3NaSi$ requires 633.2795.

*4.3.1.4. (R)-5-[2-(tert-Butyldiphenylsilyl-oxy)ethyl]-3-(toluene-4-sulfonyl)-4-[2-trityloxyeth-(Z)-ylidene]oxazolidin-2-one (**39**).* To a suspension of CuI (0.3 mg, 2 μmol, 0.01 equiv) in THF (0.1 mL) were added Et_3N (58 μL, 8 μmol, 0.05 equiv) and a solution of alcohol **37** (97 mg, 0.16 mmol) in THF (0.9 mL). The reaction mixture was cooled to 0 °C and tosyl isocyanate (25 μL, 0.17 mmol, 1.05 equiv) was added. After 7 h heating at reflux, the reaction mixture was filtered through Celite (CH_2Cl_2) and the filtrate was evaporated under reduced pressure. The residue was purified by

flash chromatography on silica gel (petroleum ether/Et_2O gradient: 85/15 to 70/30) to afford 118 mg (92%) of oxazolidinone **39** as a white solid; mp 68 °C; $[\alpha]_D$ +14.9 (*c* 0.43, $CHCl_3$); IR 1794, 1375, 1176, 1153, 1087, 816, 760, 744, 701, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J*=8.3 Hz, 2H), 7.65–7.61 (m, 4H), 7.47–7.33 (m, 12H), 7.29–7.20 (m, 9H), 7.08 (d, *J*=8.3 Hz, 2H), 4.97 (m, 1H), 4.84 (apparent t, *J*=6.4 Hz, 1H), 4.17 (dd, *J*=14.7, 3.0 Hz, 1H), 4.02 (dd, *J*=14.7, 7.0 Hz, 1H), 3.77–3.66 (m, 2H), 2.37 (s, 3H), 1.72–1.68 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4 (s), 145.4 (s), 144.2 (s, 3C), 143.5 (s), 135.5 (d, 4C), 135.0 (s), 133.3 (s), 133.1 (s), 129.9 (d, 2C), 129.6 (d, 2C), 128.6 (d, 6C), 128.2 (d, 2C), 127.8 (d, 10C), 127.1 (d, 3C), 113.9 (d), 87.4 (s), 78.0 (d), 62.6 (t), 58.7 (t), 36.9 (t), 26.8 (q, 3C), 21.7 (q), 19.2 (s); HRMS: M+Na^+, found 830.2939. $C_{49}H_{49}O_6NNaSSi$ requires 830.2942.

*4.3.1.5. (R)-6-(tert-Butyldiphenylsilyloxy)-4-hydroxy-1-(trityloxy)hexan-3-one (**40**).* To a solution of oxazolidinone **39** (2.06 g, 2.55 mmol) in THF (112 mL) was added a 1 M aqueous solution of NaOH (112 mL). After 2.5 h of vigorous stirring, the reaction mixture was neutralized by addition of a 1 M solution of hydrochloric acid. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 80/20 to 70/30) to afford 1.22 g (76%) of α-hydroxyketone **40** as a colorless oil (ee≥94%). The ee value was determined by super-critical fluid chromatography (SFC) analysis on chiral stationary phase;[27] $[\alpha]_D$ −7.4 (*c* 0.63, $CHCl_3$); IR 1711, 1597, 1105, 1068, 761, 736, 698, 632, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.64 (m, 4H), 7.44–7.34 (m, 12H), 7.30–7.25 (m, 6H), 7.24–7.20 (m, 3H), 4.37 (ddd, apparent dt, *J*=7.5, 4.0 Hz, 1H), 3.88–3.78 (m, 2H), 3.69 (d, *J*=4.3 Hz, 1H, OH), 3.46 (dt, *J*=9.2, 6.4 Hz, 1H), 3.41 (dt, *J*=9.2, 6.2 Hz, 1H), 2.76 (t, *J*=6.4 Hz, 2H), 2.10–2.02 (m, 1H), 1.84–1.75 (m, 1H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9 (s), 143.8 (s, 3C), 135.5 (d, 4C), 133.3 (s, 2C), 129.7 (d, 2C), 128.6 (d, 6C), 127.8 (d, 6C), 127.7 (d, 4C), 127.0 (d, 3C), 86.9 (s), 74.9 (d), 60.2 (t), 59.1 (t), 38.6 (t), 35.7 (t), 26.8 (q, 3C), 19.1 (s); HRMS: M+Na^+, found 651.2901. $C_{41}H_{44}O_4NaSi$ requires 651.2901.

*4.3.1.6. (R)-6-(tert-Butyldiphenylsilyloxy)-4-methoxymethoxy-1-(trityloxy)hexan-3-one (**41**).* To a solution of α-hydroxyketone **40** (55 mg, 0.087 mmol) in CH_2Cl_2 (2 mL) were successively added *i*-Pr_2NEt (0.15 mL, 0.87 mmol, 10 equiv), DMAP (10 mg, 0.087 mmol, 1 equiv), and NaI (13 mg, 0.087 mmol, 1 equiv). The reaction mixture was cooled to 0 °C and MOMCl (80 μL, 1.05 mmol, 12 equiv) was added. After 12 h stirring at rt, the same quantities of *i*-Pr_2NEt (0.15 mL, 0.87 mmol, 10 equiv), DMAP (10 mg, 0.09 mmol, 1 equiv), NaI (13 mg, 0.09 mmol, 1 equiv), and MOMCl (80 μL, 1.1 mmol, 12 equiv) were added. After 4 h at rt, the reaction mixture was hydrolyzed with water. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 80/20) to afford 58 mg (99%) of α-alkoxy ketone **41** as a colorless oil; $[\alpha]_D$ +5.9 (*c* 0.95, $CHCl_3$); IR 1719, 1613, 1513, 1248, 1110, 1065, 1035, 822, 745, 705, 683, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.64 (m, 4H), 7.43–7.34 (m, 12H), 7.30–7.25 (m, 6H), 7.23–7.19 (m, 3H), 4.60 (d, AB syst, *J*=6.7 Hz, 1H), 4.58 (d, AB syst, *J*=6.7 Hz, 1H), 4.30 (dd, *J*=8.6, 3.9 Hz, 1H), 3.83–3.74 (m, 2H), 3.40 (t, *J*=6.4 Hz, 2H), 3.29 (s, 3H), 2.74 (dt, *J*=6.4, 2.1 Hz, 2H), 2.00–1.91 (m, 1H), 1.82–1.75 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4 (s), 144.0 (s, 3C), 135.5 (d, 4C), 133.6 (s), 133.5 (s), 129.7 (d, 2C), 128.6 (d, 6C), 127.7 (d, 6C), 127.7 (d, 4C), 126.9 (d, 3C), 96.6 (t), 86.8 (s), 79.3 (d), 59.6 (t), 58.9 (t), 56.0 (q), 39.0 (t), 34.6 (t), 26.8 (q, 3C), 19.2 (s); HRMS: M+Na^+, found 695.31633. $C_{43}H_{48}O_5NaSi$ requires 695.31632.

4.3.2. Synthesis of the C1–C11 subunit of the PLMs and LSNs. Formal synthesis of phoslactomycin B.

*4.3.2.1. (E)-(3R,4S)-7-Allyloxy-4-ethylhept-5-en-1-yn-3-ol (**42**).* To a solution of alkynylsilane **13** (788 mg, 2.25 mmol) in THF (7 mL) was added a solution of *n*-Bu_4NF (2.30 mL, 1 M in THF, 2.30 mmol, 1.02 equiv). After 0.5 h at rt, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 70/30 to 60/40) to afford 436 mg (100%) of the terminal alkyne **42** as a colorless oil; $[\alpha]_D$ +49.0 (*c* 1.19, $CHCl_3$); IR 3304, 1646, 1455, 1379, 1265, 1086, 1036, 974, 923, 835, 777, 628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J*=17.2, 10.4, 5.6 Hz, 1H), 5.73 (dt, *J*=15.5, 5.8 Hz, 1H), 5.63 (dd, *J*=15.5, 9.0 Hz, 1H), 5.28 (dq, *J*=17.2, 1.7 Hz, 1H), 5.19 (dq, *J*=10.4, 1.4 Hz, 1H), 4.33 (ddd, *J*=8.0, 4.8, 2.2 Hz, 1H), 4.05–3.95 (m, 4H), 2.45 (d, *J*=2.2 Hz, 1H), 2.32 (br s, 1H, OH), 2.27–2.20 (m, 1H), 1.64–1.54 (m, 1H), 1.49–1.37 (m, 1H), 0.93 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7 (d), 132.1 (d), 131.2 (d), 117.1 (t), 83.0 (s), 74.0 (d), 70.9 (t), 70.4 (t), 64.7 (d), 50.7 (d), 23.6 (t), 11.7 (q); EIMS *m*/*z* (relative intensity) 194 (0.08), 139 (7), 123 (11), 109 (6), 107 (18), 95 (58), 93 (24), 82 (100), 79 (43), 69 (78), 67 (67), 57 (20), 55 (82), 53 (19); HRMS: M+Na^+, found 217.1199. $C_{12}H_{18}O_2Na$ requires 217.1199.

*4.3.2.2. (E)-(3R,4R,7R,8S)-11-Allyloxy-1-(tert-butyldiphenylsilyloxy)-8-ethyl-3-methoxymethoxy-4-[2-(trityloxy)ethyl]undec-9-en-5-yne-4,7-diol (**43**).* To a solution of alkyne **42** (126 mg, 0.648 mmol, 3.5 equiv) in Et_2O (4 mL) at −20 °C was added dropwise a solution of *i*-PrMgCl (0.60 mL, 2.0 M in THF, 1.2 mmol, 6.5 equiv). After 1 h at 0 °C, the reaction mixture was cooled to −20 °C and a solution of ketone **41** (125 mg, 0.185 mmol) in Et_2O (5 mL) was added. After 1.5 h stirring at −20 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 70/30 to 40/60) to afford 134 mg (84%) of **43** as a colorless oil. The excess of alkyne **42** (90 mg, 2.5 equiv) was quantitatively recovered; $[\alpha]_D$ +34.7 (*c* 1.32, $CHCl_3$); IR 3439, 1449, 1428, 1153, 1087, 1031, 975, 923, 823, 763, 744, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4H), 7.46–7.34 (m, 12H), 7.32–7.28 (m, 6H), 7.25–7.20 (m, 3H), 5.85 (ddt, *J*=17.2, 10.4, 5.6 Hz, 1H), 5.63 (dt, *J*=15.4, 6.1 Hz, 1H), 5.45 (apparent br dd, *J*=15.4, 9.3 Hz, 1H), 5.22 (dq, *J*=17.2, 1.5 Hz, 1H), 5.12 (dq, *J*=10.3, 1.5 Hz, 1H), 4.69 (d, AB syst, *J*=6.6 Hz, 1H), 4.67 (d, AB syst, *J*=6.6 Hz, 1H), 4.47 (br s, 1H, OH), 4.19 (d, *J*=4.8 Hz, 1H), 3.93–3.84 (m, 4H), 3.83–3.76 (m, 2H), 3.72 (dd, *J*=9.2, 2.6 Hz, 1H), 3.63–3.55 (m, 1H), 3.52–3.47 (m, 1H), 3.27 (s, 3H), 2.19–2.06 (m, 3H), 1.84 (dt, *J*=14.1, 4.7 Hz, 1H), 1.76–1.63 (m, 2H, 1H+OH), 1.47–1.37 (m, 1H), 1.30–1.20 (m, 1H), 1.05 (s, 9H), 0.81 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8 (s, 3C), 135.6 (d, 4C), 134.8 (d), 133.8 (s), 133.7 (s), 132.5 (d), 130.9 (d), 129.6 (d, 2C), 128.6 (d, 6C), 127.9 (d, 6C), 127.6 (d, 4C), 127.1 (d, 3C), 117.0 (t), 98.4 (t), 87.6 (s), 86.8 (s), 84.9 (s), 82.2 (d), 73.7 (s), 70.9 (t), 70.6 (t), 65.0 (d), 61.7 (t), 60.8 (t), 56.0 (q), 50.9 (d), 36.1 (t), 34.4 (t), 26.9 (q, 3C), 23.5 (t), 19.2 (s), 11.8 (q); HRMS: M+Na^+, found 889.4481. $C_{55}H_{66}O_7NaSi$ requires 889.4470.

*4.3.2.3. (5E,9E)-(3R,4R,7S,8S)-11-Allyloxy-1-(tert-butyldiphenylsilyloxy)-8-ethyl-3-methoxymethoxy-4-(2-trityloxyethyl) undeca-5,9-diene-4,7-diol (**44**).* To a solution of alkynyl 1,4-diol **43** (711 mg, 0.820 mmol) in Et_2O (13 mL) at 0 °C, was added a solution of Red-Al (2 mL, 3.33 M in toluene, 6.72 mmol, 8.2 equiv). After 1.5 h and 3 h at 0 °C, more Red-Al (2 mL, 3.33 M in toluene, 6.72 mmol, 8.2 equiv)

was added. After a further 1.5 h at 0 °C, the reaction mixture was poured into a saturated aqueous solution of sodium potassium tartrate. After dilution with EtOAc and 1 h of vigorous stirring at rt, the layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 50/50) to afford 442 mg (62%) of 1,4-diol **44** as a colorless oil; $[\alpha]_D$ +18.8 (*c* 0.50, $CHCl_3$); IR 3474, 1448, 1427, 1147, 1067, 1027, 976, 921, 822, 736, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.64 (m, 4H), 7.43–7.35 (m, 12H), 7.30–7.27 (m, 6H), 7.24–7.20 (m, 3H), 5.88 (ddt, *J*=17.1, 10.7, 5.6 Hz, 1H), 5.72 (dd, *J*=15.4, 6.8 Hz, 1H), 5.59 (dt, *J*=15.5, 6.1 Hz, 1H), 5.52 (d, *J*=15.4 Hz, 1H), 5.37 (dd, *J*=15.5, 9.2 Hz, 1H), 5.24 (dm, apparent br d, *J*=17.2 Hz, 1H), 5.13 (dm, apparent br d, *J*=10.4 Hz, 1H), 4.61 (d, AB syst, *J*=6.5 Hz, 1H), 4.56 (d, AB syst, *J*=6.5 Hz, 1H), 4.06 (br s, 1H, OH), 3.97 (dd, apparent t, *J*=6.0 Hz, 1H), 3.94–3.85 (m, 4H), 3.77–3.67 (m, 2H), 3.49 (dd, *J*=8.6, 2.7 Hz, 1H), 3.36–3.24 (m, 2H), 3.26 (s, 3H), 2.12–2.02 (m, 2H), 1.95–1.87 (m, 1H), 1.82 (dt, *J*=14.3, 5.0 Hz, 1H), 1.54–1.38 (m, 3H, 2H+OH), 1.23–1.13 (m, 1H), 1.04 (s, 9H), 0.82 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8 (s, 3C), 135.6 (d, 4C), 134.9 (d), 134.3 (d), 133.8 (s), 133.7 (s), 133.6 (d), 131.0 (d), 129.7 (d), 129.6 (d, 2C), 128.6 (d, 6C), 127.9 (d, 6C), 127.6 (d, 4C), 127.1 (d, 3C), 116.9 (t), 98.2 (t), 87.5 (s), 83.5 (d), 76.6 (s), 74.8 (d), 70.8 (t), 70.7 (t), 61.1 (t), 60.9 (t), 55.9 (q), 50.7 (d), 35.7 (t), 33.9 (t), 26.9 (q, 3C), 23.1 (t), 19.2 (s), 12.0 (q); HRMS: M+Na^+, found 891.4635. $C_{55}H_{68}O_7NaSi$ requires 891.4626.

*4.3.2.4. (E)-(1S,4R,5R)-1-((E)-(S)-4-Allyloxy-1-ethylbut-2-enyl)-7-(tert-butyldiphenyl-silyloxy)-4-hydroxy-5-methoxymethoxy-4-(2-trityloxyethyl)hept-2-enyl acrylate (**45**).* To a solution of compound **44** (29.6 mg, 0.034 mmol) in CH_2Cl_2 (0.5 mL) were added DMAP (1.0 mg, 0.01 mmol, 0.3 equiv) and *i*-Pr_2NEt (0.07 mL, 0.41 mmol, 12 equiv). The reaction mixture was cooled to −78 °C and acryloyl chloride (0.022 mL, 0.27 mmol, 8 equiv) was added. After 2 h at −78 °C, the reaction mixture was poured into brine. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 70/30) to afford 31 mg (quantitative) of acrylate **45** as a colorless oil; $[\alpha]_D$ +19.9 (*c* 0.54, $CHCl_3$); IR 3476, 1721, 1635, 1618, 1598, 1448, 1427, 1403, 1266, 1189, 1147, 1067, 1030, 972, 921, 761, 743, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.63 (m, 4H), 7.41–7.34 (m, 12H), 7.28–7.24 (m, 6H), 7.22–7.18 (m, 3H), 6.32 (dd, *J*=17.4, 1.5 Hz, 1H), 6.05 (dd, *J*=17.4, 10.5 Hz, 1H), 5.87 (ddt, *J*=17.3, 10.4, 5.6 Hz, 1H), 5.78 (dd, *J*=15.4, 7.4 Hz, 1H), 5.77 (dd, *J*=10.5, 1.5 Hz, 1H), 5.61 (d, *J*=15.5 Hz, 1H), 5.52 (dt, *J*=15.5, 6.0 Hz, 1H), 5.38 (dd, *J*=15.5, 9.0 Hz, 1H), 5.29 (dd, apparent t, *J*=6.0 Hz, 1H), 5.23 (dq, *J*=17.3, 1.5 Hz, 1H), 5.13 (dq, *J*=10.4, 1.5 Hz, 1H), 4.56 (d, AB syst, *J*=6.6 Hz, 1H), 4.51 (d, AB syst, *J*=6.6 Hz, 1H), 4.07 (br s, 1H, OH), 3.90–3.88 (m, 4H), 3.75–3.65 (m, 2H), 3.42 (dd, *J*=8.6, 3.0 Hz, 1H), 3.36–3.24 (m, 2H), 3.23 (s, 3H), 2.28–2.21 (m, 1H), 2.03–1.94 (m, 1H), 1.91–1.83 (m, 1H), 1.76 (apparent dt, *J*=14.2, 5.6 Hz, 1H), 1.55–1.40 (m, 2H), 1.30–1.15 (m, 1H), 1.03 (s, 9H), 0.83 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1 (s), 143.9 (s, 3C), 136.5 (d), 135.5 (d, 4C), 134.9 (d), 133.8 (s), 133.7 (s), 132.9 (d), 130.3 (t), 129.6 (d, 2C), 129.5 (d), 128.9 (d), 128.5 (d, 6C), 127.8 (d, 6C), 127.6 (d, 4C), 127.0 (d, 3C), 126.4 (d), 116.8 (t), 98.1 (t), 87.5 (s), 83.4 (d), 76.6 (d), 76.5 (s), 70.6 (t), 70.5 (t), 61.1 (t), 60.9 (t), 55.9 (q), 48.2 (d), 35.6 (t), 33.9 (t), 26.8 (q, 3C), 23.2 (t), 19.1 (s), 11.7 (q); HRMS: M+Na^+, found 945.4734. $C_{58}H_{70}O_8NaSi$ requires 945.4732.

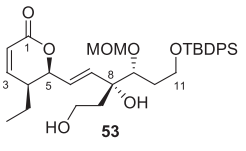
*4.3.2.5. RRCM of acrylate **45**.* To a solution of acrylate **45** (450 mg, 0.488 mmol) in CH_2Cl_2 (49 mL) was added Grubbs II catalyst (20 mg, 0.024 mmol, 0.05 equiv) and the reaction mixture was heated at reflux. Additional portions of the catalyst (10 mg, 0.012 mmol, 0.025 equiv) were added every 2 h (total quantity of catalyst used: 70 mg, 0.082 mmol, 0.17 equiv). After a total duration of 20 h at reflux, the reaction mixture was cooled to rt and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 70/30 to 50/50) to afford 353 mg (88%) of lactone **46** as a pale brown solid.

When acrylate **45** (30 mg, 0.032 mmol) was treated with Grubbs II catalyst (1.4 mg, 0.0016 mmol, 5 mol %) in CH_2Cl_2 (3.2 mL) (reflux, 2 h), ^1H NMR analysis of the crude material indicated the formation of δ-lactone **46** and the truncated acrylate **47** in a 75:25 ratio. After purification of the crude product by chromatography on a preparative TLC silica gel plate (petroleum ether/EtOAc: 70/30), 3.4 mg (13%) of **47** and 17.2 mg (65%) of **46** were isolated.

*4.3.2.6. (5S,6S)-6-[(E)-(3R,4R)-6-(tert-Butyldiphenyl-silyloxy)-3-hydroxy-4-methoxymethoxy-3-(2-trityloxyethyl)hex-1-enyl]-5-ethyl-5,6-dihydropyran-2-one (**46**).* Mp 47–49 °C; $[\alpha]_D$ +58.7 (*c* 0.88, $CHCl_3$); IR 3469, 1726, 1448, 1428, 1382, 1149, 1109, 1085, 1028, 823, 763, 745, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.45–7.36 (m, 12H), 7.32–7.27 (m, 6H), 7.25–7.21 (m, 3H), 6.87 (dd, *J*=9.8, 5.3 Hz, 1H), 5.99 (d, *J*=9.8 Hz, 1H), 5.86 (dd, *J*=15.5, 5.1 Hz, 1H), 5.78 (d, *J*=15.5 Hz, 1H), 4.91 (dd, apparent t, *J*=4.6 Hz, 1H), 4.60 (d, AB syst, *J*=6.6 Hz, 1H), 4.56 (d, AB syst, *J*=6.6 Hz, 1H), 4.26 (br s, 1H, OH), 3.78–3.69 (m, 2H), 3.49 (dd, *J*=8.7, 2.8 Hz, 1H), 3.35–3.30 (m, 2H), 3.28 (s, 3H), 2.34–2.28 (m, 1H), 2.06 (apparent dt, *J*=14.2, 7.1 Hz, 1H), 1.97–1.91 (m, 1H), 1.79 (apparent dt, *J*=14.2, 5.6 Hz, 1H), 1.57–1.37 (m, 2H), 1.32–1.18 (m, 1H), 1.04 (s, 9H), 0.84 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (s), 149.8 (d), 143.9 (s, 3C), 135.7 (d), 135.5 (d, 4C), 133.7 (s), 133.6 (s), 129.6 (d, 2C), 128.5 (d, 6C), 127.9 (d, 6C), 127.6 (d, 4C), 127.0 (d, 3C), 125.3 (d), 120.8 (d), 98.2 (t), 87.5 (s), 83.7 (d), 80.1 (d), 76.5 (s), 61.0 (t), 60.8 (t), 56.0 (q), 39.4 (d), 35.5 (t), 33.8 (t), 26.8 (q, 3C), 21.4 (t), 19.2 (s), 11.0 (q); HRMS: M+Na^+, found 847.3985. $C_{52}H_{60}O_7NaSi$ requires 847.4001.

*4.3.2.7. (E)-(1S,4R,5R)-7-(tert-Butyldiphenylsilyloxy)-1-((S)-1-ethyl-allyl)-4-hydroxy-5-methoxymethoxy-4-(2-trityloxyethyl)hept-2-enyl acrylate (**47**).* $[\alpha]_D$ +24.6 (*c* 0.33, $CHCl_3$); IR 3475, 1722, 1265, 1192, 1151, 1109, 1088, 1070, 1033, 982, 920, 762, 744, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.62 (m, 4H), 7.43–7.34 (m, 12H), 7.28–7.18 (m, 9H), 6.33 (dd, *J*=17.3, 1.6 Hz, 1H), 6.06 (dd, *J*=17.3, 10.4 Hz, 1H), 5.79 (dd, *J*=15.5, 7.2 Hz, 1H), 5.77 (dd, *J*=10.4, 1.6 Hz, 1H), 5.59 (d, *J*=15.5 Hz, 1H), 5.43 (ddd, apparent dt, *J*=17.0, 10.3 Hz, 1H), 5.28 (m, 1H), 5.00 (dd, *J*=10.3, 1.9 Hz, 1H), 4.95 (dd, *J*=17.0, 1.9 Hz, 1H), 4.55 (d, AB syst, *J*=6.6 Hz, 1H), 4.52 (d, AB syst, *J*=6.6 Hz, 1H), 4.05 (s, 1H, OH), 3.75–3.65 (m, 2H), 3.40 (dd, *J*=8.8, 3.0 Hz, 1H), 3.37–3.26 (m, 2H), 3.23 (s, 3H), 2.24–2.17 (m, 1H), 2.01–1.94 (m, 1H), 1.91–1.83 (m, 1H), 1.75 (apparent dt, *J*=14.0, 5.8 Hz, 1H), 1.51–1.41 (m, 2H), 1.24–1.13 (m, 1H), 1.03 (s, 9H), 0.83 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (s), 144.0 (s, 3C), 137.4 (d), 136.1 (d), 135.5 (d, 4C), 133.8 (s, 2C), 130.4 (t), 129.6 (d, 2C), 128.9 (d), 128.6 (d, 6C), 127.8 (d, 6C), 127.6 (d, 4C), 127.0 (d, 3C), 126.6 (d), 117.4 (t), 98.2 (t), 87.5 (s), 83.7 (d), 61.1 (t), 60.9 (t), 55.9 (q), 49.6 (d), 35.5 (t), 33.9 (t), 26.8 (q, 3C), 23.1 (t), 19.1 (s), 11.6 (q); HRMS: M+Na^+, found 875.4314. $C_{52}H_{64}O_7NaSi$ requires 875.4306.

*4.3.2.8. (5S,6S)-6-[(E)-(3R,4R)-6-(tert-Butyl-diphenylsilyloxy)-3-hydroxy-3-(2-hydroxy-ethyl)-4-methoxymethoxyhex-1-enyl]-5-ethyl-5,6-dihydropyran-2-one (**53**).*



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To a solution of trityl ether **46** (66 mg, 0.080 mmol) in MeOH (3.3 mL) was added $TsOH \cdot H_2O$ (1.50 mg, 0.008 mmol, 0.1 equiv). After 1.5 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and MeOH was evaporated under reduced pressure. The residue was partitioned between H_2O and EtOAc, the layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc gradient: 60/40 to 40/60) to afford 36 mg (77%) of the primary alcohol **53** as a brown oil; $[\alpha]_D$ +71.8 (*c* 0.66, $CHCl_3$); IR 3368, 1713, 1427, 1382, 1250, 1146, 1104, 1083, 1024, 982, 919, 822, 737, 701, 688, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.61 (m, 4H), 7.46–7.37 (m, 6H), 6.96 (dd, *J*=9.8, 5.4 Hz, 1H), 6.07 (dd, *J*=9.8, 1.1 Hz, 1H), 6.00 (dd, *J*=15.4, 4.1 Hz, 1H), 5.93 (dd, *J*=15.5, 1.2 Hz, 1H), 5.03 (apparent td, *J*=4.2, 1.1 Hz, 1H), 4.70 (br s, 1H, OH), 4.62 (s, 2H), 3.86–3.81 (m, 1H), 3.75–3.71 (m, 3H), 3.59 (dd, *J*=8.3, 3.6 Hz, 1H), 3.40 (s, 3H), 2.98 (br s, 1H, OH), 2.45–2.39 (m, 1H), 2.04 (ddd, *J*=14.5, 10.0, 4.2 Hz, 1H), 1.94–1.85 (m, 1H), 1.71–1.42 (m, 4H), 1.04 (s, 9H), 0.95 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (s), 150.0 (d), 135.5 (d, 4C), 134.9 (d), 133.2 (s), 133.1 (s), 129.8 (d, 2C), 127.7(d, 4C), 125.9 (d), 120.8 (d), 98.2 (t), 85.2 (d), 79.8 (d), 77.7 (s), 60.6 (t), 59.7 (t), 56.1 (q), 39.2 (d), 36.5 (t), 33.8 (t), 26.8 (q, 3C), 21.5(t), 19.1 (s), 11.0 (q); HRMS: M+Na^+, found 605.2894. $C_{33}H_{46}O_7NaSi$ requires 605.2905.

*4.3.2.9. (3R,4R)-6-(tert-Butyldiphenylsilyl-oxy)-3-[(E)-2-((2S,3S)-3-ethyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)vinyl]-3-hydroxy-4-methoxymethoxyhexyl methanesulfonate (**48**).* To a solution of alcohol **53** (42 mg, 0.072 mmol) in CH_2Cl_2 (1.3 mL) were added DMAP (3.7 mg, 0.030 mmol, 0.41 equiv), pyridine (40 μL, 0.53 mmol, 7.3 equiv) and MsCl (20 μL, 0.27 mmol, 3.8 equiv). After 14 h at rt, the reaction mixture was poured into a 0.01 M solution of hydrochloric acid. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 30/70 to 10/90) to afford 40 mg (85%) of mesylate **48** as a colorless oil; $[\alpha]_D$ +56.7 (*c* 0.96, $CHCl_3$); IR 3386, 1720, 1353, 1250, 1174, 1104, 1086, 1023, 972, 950, 822, 736, 702, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.60 (m, 4H), 7.47–7.36 (m, 6H), 6.94 (dd, *J*=9.8, 5.3 Hz, 1H), 6.07 (dd, *J*=9.8, 1.1 Hz, 1H), 6.01 (dd, *J*=15.4, 5.0 Hz, 1H), 5.91 (dd, *J*=15.4, 0.8 Hz, 1H), 5.00 (apparent t, *J*=4.0 Hz, 1H), 4.61 (d, AB syst, *J*=6.7 Hz, 1H), 4.59 (d, AB syst, *J*=6.7 Hz, 1H), 4.45–4.39 (m, 2H, 1H+OH), 4.29–4.27 (m, 1H), 3.79–3.68 (m, 2H), 3.57 (dd, *J*=8.7, 3.4 Hz, 1H), 3.40 (s, 3H), 2.99 (s, 3H), 2.45–2.39 (m, 1H), 2.16 (ddd, *J*=13.8, 8.8, 5.7 Hz, 1H), 1.97 (ddd, *J*=13.8, 8.7, 6.1 Hz, 1H), 1.90–1.81 (m, 1H), 1.66–1.44 (m, 3H), 1.04 (s, 9H), 0.94 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8 (s), 149.8 (d), 135.5 (d, 4C), 134.9 (d), 133.2 (s), 133.1 (s), 129.8 (d, 2C), 127.8 (d, 4C), 126.1 (d), 120.9 (d), 98.5 (t), 85.9 (d), 79.9 (d), 74.7 (s), 67.1 (t), 60.3 (t), 56.1 (q), 39.2 (d), 37.3 (q), 34.8 (t), 33.8 (t), 26.8 (q, 3C), 21.6 (t), 19.1 (s), 11.0 (q); HRMS: M+Na^+, found 683.2678. $C_{34}H_{48}O_9NaSSi$ requires 683.2681.

*4.3.2.10. (5S,6S)-6-[(E)-(3R,4R)-3-(2-Azidoethyl)-6-(tert-butyldiphenylsilyloxy)-3-hydroxy-4-methoxymethoxyhex-1-enyl]-5-ethyl-5,6-dihydropyran-2-one (**49**).* To a solution of mesylate **48** (40 mg, 0.061 mmol) in DMF (1.7 mL) was added NaN_3 (39.7 mg, 0.610 mmol, 10 equiv). After 3 days stirring at rt, the reaction mixture was diluted in water. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc: 80/20) to afford 26 mg (70%) of azide **49** as a colorless oil; $[\alpha]_D$ +60.5 (*c* 0.52, $CHCl_3$); IR 3425, 2094, 1725, 1253, 1107, 1027, 823, 740, 703, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.60 (m, 4H), 7.46–7.36 (m, 6H), 6.95 (dd, *J*=9.8, 5.4 Hz, 1H), 6.07 (dd, *J*=9.8, 1.0 Hz, 1H), 5.97 (dd, *J*=15.4, 4.4 Hz, 1H), 5.89 (dd, *J*=15.4, 1.0 Hz, 1H), 5.00 (apparent td, *J*=4.2, 1.0 Hz, 1H), 4.61 (s, 2H), 4.20 (s, 1H, OH), 3.78–3.69 (m, 2H), 3.58 (dd, *J*=8.6, 3.3 Hz, 1H), 3.46–3.41 (m, 1H), 3.39 (s, 3H), 3.32–3.25 (m, 1H), 2.44–2.38 (m, 1H), 1.97 (ddd, *J*=13.7, 9.5, 6.1 Hz, 1H), 1.91–1.83 (m, 1H), 1.78 (ddd, *J*=13.7, 9.4, 5.8 Hz, 1H), 1.64–1.53 (m, 2H), 1.50–1.41 (m, 1H), 1.04 (s, 9H), 0.95 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (s), 149.8 (d), 135.5 (d, 4C), 134.6 (d), 133.3 (s), 133.2 (s), 129.8 (d, 2C), 127.8 (d, 4C), 126.0 (d), 120.9 (d), 98.5 (t), 85.6 (d), 79.7 (d), 75.2 (s), 60.4 (t), 56.1 (q), 47.1 (t), 39.2 (d), 34.3 (t), 33.9 (t), 26.8 (q, 3C), 21.6 (t), 19.1 (s), 11.0 (q); HRMS: M+Na^+, found 630.2962. $C_{33}H_{45}O_6N_3NaSi$ requires 630.2970.

*4.3.2.11. Allyl {(3R,4R)-6-(tert-Butyldiphenylsilyloxy)-3-[(E)-2-((1S,2S)-2-ethyl-5-oxo-cyclohex-3-enyl)vinyl]-3-hydroxy-4-methoxymethoxyhexyl}carbamate (**50**).* To a solution of azide **49** (5.0 mg, 8.2 μmol) in THF (0.3 mL) were successively added PPh_3 (4.3 mg, 16 μmol, 2 equiv) and H_2O (1.5 μL, 82 μmol, 10 equiv). After 22 h at rt pyridine (4.0 μL, 49 μmol, 6 equiv) and allyl chloroformate (3.0 μL, 25 μmol, 3 equiv) were added. After 20 min stirring at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc gradient: 60/40 to 40/60) to afford 3.5 mg (64%) of carbamate **50** as a colorless oil; $[\alpha]_D$ +58.0 (*c* 0.50, $CHCl_3$); IR 3367, 1719, 1650, 1514, 1463, 1428, 1382, 1247, 1148, 1107, 1027, 997, 985, 924, 823, 741, 703, 689, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.60 (m, 4H), 7.46–7.37 (m, 6H), 6.95 (dd, *J*=9.8, 5.4 Hz, 1H), 6.07 (d, *J*=9.8 Hz, 1H), 5.97 (dd, *J*=15.5, 4.2 Hz, 1H), 5.96–5.87 (m, 2H), 5.43 (br s, 1H, NH), 5.29 (dq, *J*=17.2, 1.5 Hz, 1H), 5.19 (dq, *J*=10.4, 1.5 Hz, 1H), 5.01 (apparent br t, *J*=3.8 Hz, 1H), 4.61 (d, AB syst, *J*=6.8 Hz, 1H), 4.59 (d, AB syst, *J*=6.8 Hz, 1H), 4.54 (d, *J*=5.3 Hz, 2H), 4.39 (s, 1H, OH), 3.77–3.68 (m, 2H), 3.56 (dd, *J*=8.3 Hz, 3.5 Hz, 1H), 3.38 (s, 3H), 3.38–3.33 (m, 1H), 3.23–3.15 (m, 1H), 2.43–2.37 (m, 1H), 1.90–1.83 (m, 2H), 1.73–1.54 (m, 3H), 1.51–1.40 (m, 1H), 1.04 (s, 9H), 0.94 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (s), 156.2 (s), 149.9 (d), 135.5 (d, 4C), 134.8 (d), 133.3 (s), 133.2 (s), 129.8 (d, 2C), 127.8 (d, 4C), 125.9 (d, 2C), 120.9 (d), 117.4 (t), 98.4 (t), 85.7 (d), 79.7 (d), 76.5 (s), 65.3 (t), 60.5 (t), 56.1 (q), 39.3 (d), 36.9 (t), 34.7 (t), 33.9 (t), 26.8 (q, 3C), 21.6 (t), 19.2 (s), 11.0 (q); HRMS calcd for $C_{37}H_{51}NO_8NaSi$ (M+Na^+): 688.3267. Found: 688.3276.

*4.3.2.12. (5S,6S)-6-((E,3R,4R)-3-(2-(Allyloxycarbonylamino)ethyl)-3,4,6-tris(triethylsilyloxy)-3-hex-1-enyl)-5-ethyl-5,6-dihydropyran-2-one (**51**).* To a solution of compound **50** (13.5 mg, 0.020 mmol) in THF (2.4 mL) was added a 6 M solution of hydrochloric acid (2.4 mL). After 2.5 h of vigorous stirring at rt, the reaction was quenched by addition of solid $NaHCO_3$. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were directly concentrated under reduced pressure and the residue was dried by azeotropic evaporation with toluene. The crude material was purified by preparative TLC on a silica gel plate (EtOAc/EtOH: 95/5) to afford 4.3 mg (55%) of the fully deprotected triol. To a solution of this triol (3.2 mg, 8.3 μmol) in CH_2Cl_2 (0.3 mL) was added 2,6-lutidine (10 μL, 83 μmol, 10 equiv). The reaction mixture was cooled to −78 °C and TESOTf (13 μL, 58 μmol, 7 equiv) was added. After 1 h stirring at −78 °C and 1 h at 0 °C, the reaction mixture was hydrolyzed with brine. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

The crude material was purified by preparative TLC on a silica gel plate (petroleum ether/EtOAc: 70/30) to afford 4.4 mg (73%) of **51** as a colorless oil; $[\alpha]_D$ +71.8 (*c* 0.44, $CHCl_3$), lit.[8] $[\alpha]_D$ +52.2 (*c* 0.65, $CHCl_3$); IR 3351, 1720, 1520, 1459, 1381, 1239, 1100, 1006, 791, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93 (dd, *J*=9.8, 5.2 Hz, 1H), 6.05 (dd, *J*=9.8, 1.2 Hz, 1H), 5.96–5.87 (m, 2H), 5.81 (dd, *J*=15.6, 6.1 Hz, 1H), 5.29 (dd, *J*=17.2, 1.5 Hz, 1H), 5.19 (d, *J*=10.4 Hz, 1H), 5.03–5.00 (m, 1H), 4.91 (br s, 1H, NH), 4.55 (d, *J*=5.3 Hz, 2H), 3.72 (dt, *J*=9.0, 1.9 Hz, 1H), 3.69–3.57 (m, 2H), 3.34–3.27 (m, 1H), 3.19–3.11 (m, 1H), 2.44–2.39 (m, 1H), 2.08–2.01 (m, 1H), 1.89–1.80 (m, 1H), 1.79–1.72 (m, 1H), 1.68–1.44 (m, 2H), 1.33–1.26 (m, 1H), 0.99–0.92 (m, 30H), 0.69–0.53 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (s), 155.9 (s), 149.5 (d), 136.5 (d), 132.9 (d), 124.4 (d), 120.7 (d), 117.1 (t), 80.2 (d), 79.8 (s), 74.9 (d), 65.1 (t), 59.4 (t), 39.4 (d), 37.6 (t), 36.4 (t), 35.5 (t), 21.4 (t), 10.8 (q), 7.0 (q, 3C), 6.8 (q, 3C), 6.7 (t, 3C), 6.5 (q, 3C), 5.2 (t, 3C), 4.2 (q, 3C); HRMS: $M+Na^+$, found 758.4421. $C_{37}H_{71}O_7NNaSi$ requires 748.4431. The spectroscopic data of compound **51** were in agreement with those previously reported for the same advanced intermediate in Hatakeyama's total synthesis of phoslactomycin B.[8]

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Supplementary data

Determination of the optical purities of alcohols **7**, **8**, **37** and α-hydroxyketone **40**, chemical correlation for the attribution of the relative configuration of allylic alcohol **33**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.050.

References and notes

1. (a) Fushimi, S.; Nishikawa, S.; Shimazu, A.; Seto, H. *J. Antibiot.* **1989**, *42*, 1019–1025; (b) Fushimi, S.; Furihata, K.; Seto, H. *J. Antibiot.* **1989**, *42*, 1026–1036 For the isolation of structurally similar or identical phosphazomycins, see:
(c) Uramoto, M.; Shen, Y.-C.; Takizawa, N.; Kusakabe, H.; Isono, K. *J. Antibiot.* **1985**, *38*, 665–668; (d) Tomiya, T.; Uramoto, M.; Isono, K. *J. Antibiot.* **1990**, *43*, 118–121.
2. (a) Ozasa, T.; Suzuki, K.; Sasamata, M.; Tanaka, K.; Kobori, M.; Kadota, S.; Nagai, K.; Saito, T.; Watanabe, S.; Iwanami, M. *J. Antibiot.* **1989**, *42*, 1331–1338; (b) Ozasa, T.; Tanaka, K.; Sasamata, M.; Kaniwa, H.; Shimizu, M.; Matsumoto, H.; Iwanami, M. *J. Antibiot.* **1989**, *42*, 1339–1343.
3. (a) Kohama, T.; Enokita, R.; Okazaki, T.; Miyaoka, H.; Torikata, A.; Inukai, M.; Kaneko, I.; Kagasaki, T.; Sakaida, Y.; Satoh, A.; Shiraishi, A. *J. Antibiot.* **1993**, *46*, 1503–1511; (b) Kohama, T.; Nakamura, T.; Kinoshita, T.; Kaneko, I.; Shiraishi, A. *J. Antibiot.* **1993**, *46*, 1512–1519; (c) Shibata, T.; Kurihara, S.; Yoda, K.; Haruyama, H. *Tetrahedron* **1995**, *51*, 11999–12012; (d) Kohama, T.; Maeda, H.; Sakai, J. I.; Shiraishi, A.; Yamashita, K. *J. Antibiot.* **1996**, *49*, 91–94.
4. Shibata, T.; Kurihara, S.; Oikawa, T.; Ohkawa, N.; Shimazaki, N.; Sasagawa, K.; Kobayashi, T.; Kohama, T.; Asai, F.; Shiraishi, A.; Sugimura, Y. *J. Antibiot.* **1995**, *48*, 1518–1520.
5. (a) Tunac, J. B.; Graham, B. D.; Dobson, W. E. *J. Antibiot.* **1983**, *36*, 1595–1600; (b) Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Willmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. *J. Antibiot.* **1983**, *36*, 1601–1605.
6. (a) Usui, T.; Marriott, G.; Inagaki, M.; Swarup, G.; Osada, H. *J. Biochem.* **1999**, *125*, 960–965; (b) Kawada, M.; Kawatsu, M.; Masuda, T.; Ohba, S.; Amemiya, M.; Kohama, T.; Ishizuka, M.; Takeuchi, T. *Int. Immunopharmcol.* **2003**, *3*, 179–188; (c) Faulkner, N. E.; Lane, B. R.; Bock, P. J.; Markovitz, D. M. *J. Virol.* **2003**, *77*, 2276–2281.
7. (a) Wang, Y.-G.; Takeyama, R.; Kobayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3320–3323; (b) Nonaka, H.; Maeda, N.; Kobayashi, Y. *Tetrahedron Lett.* **2007**, *48*, 5601–5604.
8. (a) Shibahara, S.; Fujino, M.; Tashiro, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2008**, *10*, 2139–2142; (b) Shibahara, S.; Fujino, M.; Tashiro, Y.; Okamoto, N.; Esumi, T.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Synthesis* **2009**, 2935–2953.
9. Shimada, K.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 4048–4049.
10. (a) Miyashita, K.; Tsunemi, T.; Hosokawa, T.; Ikejiri, M.; Imanishi, T. *Tetrahedron Lett.* **2007**, *48*, 3829–3833; (b) Miyashita, K.; Tsunemi, T.; Hosokawa, T.; Ikejiri, M.; Imanishi, T. *J. Org. Chem.* **2008**, *73*, 5360–5370.
11. (a) König, C. M.; Gebhardt, B.; Schleth, C.; Dauber, M.; Koert, U. *Org. Lett.* **2009**, *11*, 2728–2731; (b) Gebhardt, B.; König, C. M.; Schleth, C.; Dauber, M.; Koert, U. *Chem.—Eur. J.* **2010**, *16*, 5934–5941.
12. Moïse, J.; Sonawane, R. P.; Corsi, C.; Wendeborn, S. V.; Arseniyadis, S.; Cossy, J. *Synlett* **2008**, 2617–2620.
13. Sarkar, S. M.; Wanzala, E. N.; Shibahara, S.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Chem. Commun.* **2009**, 5907–5909.
14. Druais, V.; Hall, M. J.; Corsi, C.; Wendeborn, S. V.; Meyer, C.; Cossy, J. *Org. Lett.* **2009**, *11*, 935–938.
15. (a) Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031–1034; (b) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1224.
16. (a) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667–3670; (b) Wang, Y.-G.; Kobayashi, Y. *Org. Lett.* **2002**, *4*, 4615–4618; (c) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666–3667.
17. (a) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885–902; (b) Marshall, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vol. 3, pp. 975–1014; (c) Kallmerten, J. In *Houben-Weyl, Methods of Organic Chemistry*; Helmchen, G., Hoffman, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. e 21d, pp 3757–3809.
18. For selected synthetic applications of [2,3]-Wittig rearrangements see: (a) Parker, K. A.; Xie, Q. *Org. Lett.* **2008**, *10*, 1349–1352; (b) Cao, H.; Parker, K. A. *Org. Lett.* **2008**, *10*, 1353–1356; (c) Liang, J.; Hoard, D. W.; Van Khau, V.; Martinelli, M. J.; Moher, E. D.; Moore, R. E.; Tius, M. A. *J. Org. Chem.* **1999**, *64*, 1459–1463.
19. Dienes RCM can be problematic in the presence of an alkyne, see: (a) Ono, K.; Nagata, T.; Nishida, A. *Synlett* **2003**, 1207–1209; (b) Vedrenne, E.; Royer, F.; Oble, J.; El Kaïm, L.; Grimaud, L. *Synlett* **2005**, 2379–2381; (c) Bressy, C.; Bargiggia, F.; Guyonnet, M.; Arseniyadis, S.; Cossy, J. *Synlett* **2009**, 565–568.
20. Dicobalt hexacarbonyl complexes of alkynes are compatible with dienes RCM, see: Ref. 19a and (a) Young, D. G. J.; Burlison, J. A.; Peters, U. *J. Org. Chem.* **2003**, *68*, 3494–3497; (b) Geng, X.; Danishefsky, S. J. *Org. Lett.* **2004**, *6*, 413–416; (c) Yang, Z.-Q.; Geng, X.; Solit, D.; Pratilas, C. A.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 7881–7889.
21. Unsaturated δ-lactones can be formed by RCM in the presence of the (triisopropylsilyl)ethynyl group, see: Langille, N. F.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3203–3206.
22. (a) Michaut, M.; Parrain, J.-L.; Santelli, M. *Chem. Commun.* **1998**, 2567–2568; (b) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211; (c) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912–1915; (d) Hoye, T.R.; Jeon, J. In *Metathesis in Natural Product Synthesis*, Cossy, J.; Arseniyadis, S.; Meyer, C.; Wiley-VCH, Weinheim, 2010.
23. Allyloxyacetic acid was prepared according to: Taillier, C.; Hameury, T.; Bellosta, V.; Cossy, J. *Tetrahedron* **2007**, *63*, 4472–4490.
24. (a) Angelastro, M. R.; Peet, N. P.; Bey, P. *J. Org. Chem.* **1989**, *54*, 3913–3916; (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
25. (a) Ng, S. M.; Bader, S. J.; Snapper, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 7315–7319; (b) Satcharoen, V.; McLean, N. J.; Kemp, S. C.; Camp, N. P.; Brown, R. C. D. *Org. Lett.* **2007**, *9*, 1867–1869.
26. Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.
27. The enantiomeric excess was determined by super-critical fluid chromatography analysis on chiral stationary phase, see Supplementary data.
28. Aerssens, M. H. P. J.; Brandsma, L. *J. Chem. Soc., Chem. Commun.* **1984**, 735–736.
29. Wright, J. M.; Jones, G. B. *Tetrahedron Lett.* **1999**, *40*, 7605–7609.
30. Wu, Y.-D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 1421–1423.
31. Mikami, K.; Uchida, T.; Hirano, T.; Wu, Y.-D.; Houk, K. N. *Tetrahedron* **1994**, *50*, 5917–5926.
32. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
33. (a) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136; (b) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651–4654.
34. Bialy, L.; Lopez-Canet, M.; Waldmann, H. *Synthesis* **2002**, 2096–2104.
35. Lawhorn, B. G.; Boga, S. B.; Wolkenberg, S. E.; Colby, D. A.; Gauss, C.-M.; Swingle, M. R.; Amable, L.; Honkanen, R. E.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 16720–16732.
36. Salit, A.-F.; Meyer, C.; Cossy, J.; Delouvrié, B.; Hennequin, L. *Tetrahedron* **2008**, *64*, 6684–6697.
37. Valverde, S.; Bernabé, M.; Garcia-Ochoa, S.; Gómez, A. M. *J. Org. Chem.* **1990**, *55*, 2294–2298.
38. (a) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160–1170; (b) Panda, J.; Ghosh, S. *Tetrahedron Lett.* **1999**, *40*, 6693–6694.
39. For the RCM of dienes containing mixed methyl acetals, see: Rutjes, F. P. J. T.; Kooistra, T. M.; Hiemstra, H.; Schoemaker, H. E. *Synlett* **1998**, 192–193.
40. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.
41. This compound was prepared from 3-iodobut-3-en-1-ol which, in turn, was obtained from homopropargyl alcohol by hydroiodination, see: (a) Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675–676; (b) Sugiyama, H.; Yokokawa, F.; Shioiri, T. *Org. Lett.* **2000**, *2*, 2149–2152.

42. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553; (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.
43. The relative configuration of the allylic alcohol **33** was ascertained by deprotection of the alcohol at C11 and comparison with authentic samples of the corresponding *syn*- and *anti*-1,3-diols, see Supplementary data.
44. Rai, A. N.; Basu, A. *Tetrahedron Lett.* **2003**, *44*, 2267–2269.
45. (a) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976; (b) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *3*, 421–433.
46. Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807–810.
47. (a) Caprio, V.; Brimble, M. A.; Furkert, D. P. *Tetrahedron* **2001**, *57*, 4023–4034; (b) Brimble, M. A.; Fares, F. A.; Turner, P. *Aust. J. Chem.* **2000**, *53*, 845–852.
48. Achmatowicz, B.; Raubo, P.; Wicha, J. *J. Org. Chem.* **1992**, *57*, 6593–6598.
49. (a) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429–438; (b) Ramón, R. S.; Marion, N.; Nolan, S. P. *Tetrahedron* **2009**, *65*, 1767–1773 and references cited therein.
50. Ohe, K.; Ishihara, T.; Chatani, N.; Kawasaki, Y.; Murai, S. *J. Org. Chem.* **1991**, *56*, 2267–2268.
51. For alternative procedures using copper, silver or gold catalysts, see: (a) Kimura, M.; Kure, S.; Yoshida, Z.; Tanaka, S.; Fugami, K.; Tamaru, Y. *Tetrahedron Lett.* **1990**, *31*, 4887–4890; (b) Ritter, S.; Horino, Y.; Lex, J.; Schmalz, H.-G. *Synlett* **2006**, 3309–3313; (c) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515–518.
52. One example dealing with the use of this strategy to prepare an α-hydroxyketone bearing an adjacent tertiary alcohol has been reported: Matsuura, T.; Nishiyama, S.; Yamamura, S. *Chem. Lett.* **1993**, 1503–1504.
53. When oxazolidinone **39** was treated with K_2CO_3 in a MeOH/H_2O (19:1) mixture, the desired α-hydroxyketone **40** was obtained in good yield (80%) but racemization was observed under those condtions (ee=80%). Less racemization occurred with KOH in MeOH/H_2O (2:1) (ee=91%) but the yield of **40** was lower (69%).
54. Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guédin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954–2961.
55. Chan, K.-K.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497–3505; (b) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595–4597.