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Stereoselective Total Syntheses of Polyacetylene Plant Metabolites via Ester-Tethered Ring Closing Metathesis

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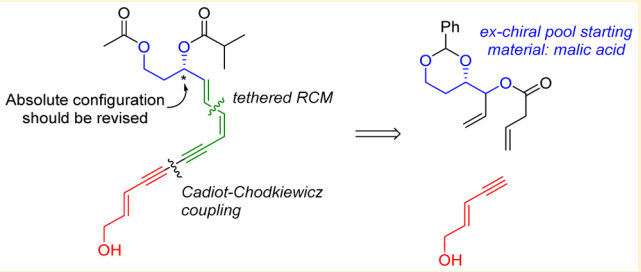
Supporting Information

ABSTRACT: Total syntheses of five naturally occurring polyacetylenes from three different plants are described. These natural products have in common an *E,Z*-configured conjugated diene linked to a di- or triyne chain. As the key method to stereoselectively establish the *E,Z*-diene part, an ester-tethered ring-closing metathesis/base-induced eliminative ring opening sequence was used. The results presented herein do not only showcase the utility of this tethered RCM variant but have also prompted us to suggest that the originally assigned absolute configurations of chiral polyacetylenes from *Atractylodes macrocephala* should be revised or at least reconsidered.



INTRODUCTION

The term "polyacetylene" applies to polymers with conjugated double bonds (i.e., polymers of acetylene)[1] but also to members of a large class of natural products that share C-C triple bonds in the main carbon chain as a common structural entity. Confusingly, compounds with just one C-C triple bond are also referred to as "polyacetylenes".[2−8] The first polyacetylene natural product, *Z*-dehydromatricaria ester, was isolated in 1826 from *Artemisia vulgaris* but not recognized as an acetylene at that time.[9] Several decades later, Arnaud correctly assigned an acetylenic structure to tairic acid, a constituent of *Picramnia species*[10] and Semmler discussed inter alia acetylenic structures for the natural product carlina oxide, which had been isolated from the carline thistle *Carlina acaulis*. Semmler eventually suggested the constitution of an allenic isomer based on the assumption that acetylenes are simply too unstable to occur in nature.[11] The correct structure, depicted in Figure 1, was assigned many years later by Gilman et al. based on total synthesis and comparison with the analytical data of the natural product (Figure 1).[12]

Since then, hundreds of polyacetylenes have been isolated not only from plants (which are still an important source) but also from insects, fungi, bacteria, moss, and lichens.[2] As for natural products in general, marine organisms have become increasingly important and thoroughly investigated sources of polyacetylenes over the past few years.[6,13] Another current prominent facet of polyacetylene research is the controversy of their role in human nutrition.[7,8] Some edible plants, in particular from the family *Apiaceae*, are rich in polyacetylenes.[4,14] Dill (*Anethum graveolens*) and ajowan (*Trachyspermum ammi* Sprague), which both contain oenanthetol,[2,15] are popular members of this family. Another example is parsnip, which has a total polyacetylene content of more than 7.5 mg per gram of dried plant material, mostly falcarindiol.[16] The cytotoxicity of falcarindiol and related polyacetylenes might be an explanation for the health promoting and chemopreventive effects of edible plants from the *Apiaceae* family.[16] In contrast to these food plants, other members of the family *Apiaceae* are highly toxic, and in these cases, polyacetylenes have been identified as potent toxins.[17] An example is water-hemlock (*Cicuta virosa*), which contains cicutoxin and the structurally closely related oenanthotoxin. Although both compounds affect the neuronal action potential leading to strong neurotoxicity, the C14-deoxygenated metabolite cicutol shows no effect on neuronal action potentials.[17] The identification of certain polyacetylenes as toxicants has probably discredited the role of these phytochemicals in food plants in general. The same study[17] revealed a significant quantitative difference in the neuronal action potential between cicutoxin and isocicutoxin, which differ only in the configuration of the C8-C9 double bond (Figure 2).

Conjugated diene-diyne and diene-triyne patterns are common in polyacetylene natural products. They are biosynthetically derived from fatty acids, which are dehydro-

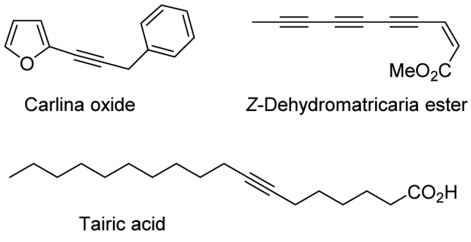


Figure 1. Early examples of naturally occurring acetylenic compounds.

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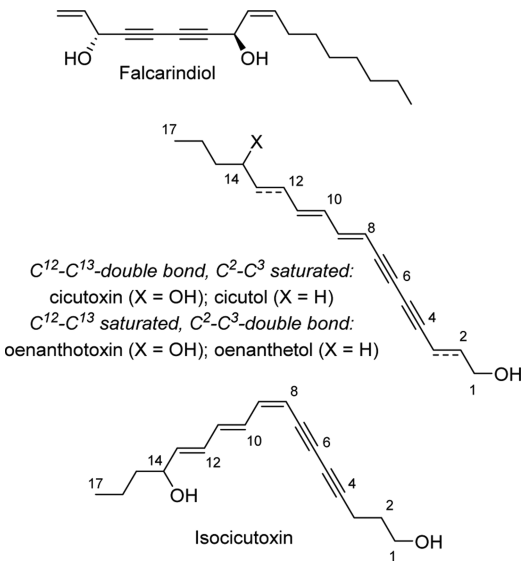

Figure 2. Examples for toxic and nontoxic polyacetylene natural products.

genated through the action of desaturases, leading to double bonds at specific sites of the carbon chain, normally in high *Z*-selectivity. Further dehydrogenation of these double bonds to alkynes proceeds in the presence of acetylenases. Certain acetylenases, however, may promote *E*-selective dehydrogenations depending on the substrate.[5] The biosynthetic formation of *E,E*-configured conjugated dienes, for example, the sex pheromone of the African cotton leafworm *Spodoptera littoralis*, has been attributed to a bifunctional desaturase that abstracts hydrogen from both allylic positions of a *Z*-configured alkene. Depending on the substrate, the same desaturase may also produce *Z,E*-configured dienes or mixtures of *E,E*- and *Z,E*-dienes.[18]

Recently, the isolation and structural characterization of seven new and eight known polyacetylenes from the rhizomes of *Atractylodes macrocephala* Koidz, a flowering plant of the family *Compositae*, was achieved by Yao and Yang through a bioactivity-guided approach.[19] The rhizomes of the plant have been used in traditional Chinese medicine for a long time, inter alia to treat malfunctions of the spleen and associated symptoms such as inappetence and abdominal distension. In their study, Yao and Yang focused on the previously described anti-inflammatory activity of *Atractylodes macrocephala* rhizomes[20] by testing the inhibitory activity of crude extracts and isolated compounds, named atractylodemaynes, against NO production.[19] The authors conclude that the polyacetylenic metabolites contribute significantly to the anti-inflammatory activity of the rhizomes. Compared to other polyacetylene-containing plants, *Atractylodes macrocephala* Koidz contains a remarkably high number of *Z,E*-configured diene-diynes: six out of 15 polyacetylenes isolated by Yao and Yang are *Z,E*-configured.[19] A literature search for this structural entity revealed that other *Z,E*-diene-di- or triynes have previously been isolated from other plant sources but that the *Z,E*-configuration appears to be much less common than the *E,E*-configuration. An example is the *E,Z,E*-diene-diyne-ene compound **5**, which has been isolated along with several other polyacetylenes from the fruits of water dropwort (*Oenanthe aquatica*), a toxic plant endemic to marshy areas in Europe.[21] *E,Z*-Diene-triyne compound **6** was isolated from the flowering plant *Leucanthemum adustum*, but no spectroscopic data have been reported (Figure 3).[2,22] Although not phototoxic to human skin, compound **6** was found to have antibiotic effects against *Candida albicans*[23] and other pathogens[24] upon UV irradiation.

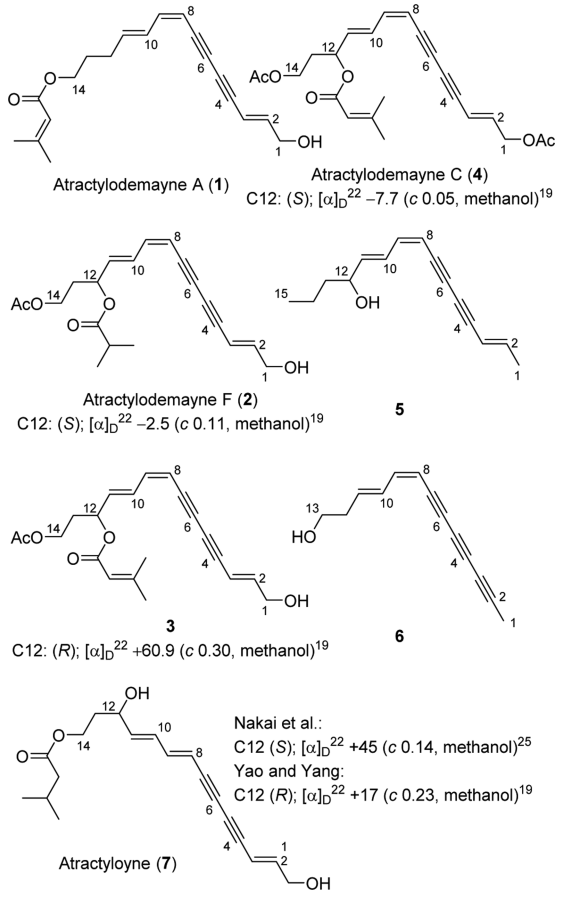

Figure 3. Naturally occurring polyacetylenes with *E,Z*-diene-di(tri)yne moieties.

The configurational diversity and sensitivity toward oxidation and light makes these natural products challenging target molecules for chemical synthesis. The motivation for organic chemists to become engaged in the total synthesis of polyacetylenes is not only to showcase a certain synthetic methodology but also to contribute to structure elucidation by confirming, revising, or completing structural assignments. For instance, Yao and Yang[19] assigned a tentative absolute configuration to the chiral atractylodemaynes **2**−**4** based on a comparison of their specific rotations with the value reported by Nakai et al. for atractyloyne **7**,[25] which was isolated by these authors from *Atractylodes chinensis*. By using Mosher's method, Nakai et al. assigned a 12*S*-configuration to (+)-atractyloyne (**7**). Yao and Yang isolated the same natural product from *Atractylodes macrocephala* Koidz and also found a positive value for the specific rotation but concluded that (+)-**7** is 12*R*-configured.[19] On the basis of this correlation, Yao and Yang assigned a 12*S*-configuration to atractylodemaynes F (**2**) and C (**4**), which were found to be levorotatory but with a rather small value for the specific rotation. Compound **3**, which had previously been isolated from the same plant by others without a reported specific rotation,[26] was reisolated by Yao and Yang in the course of their study. They found a positive value for the

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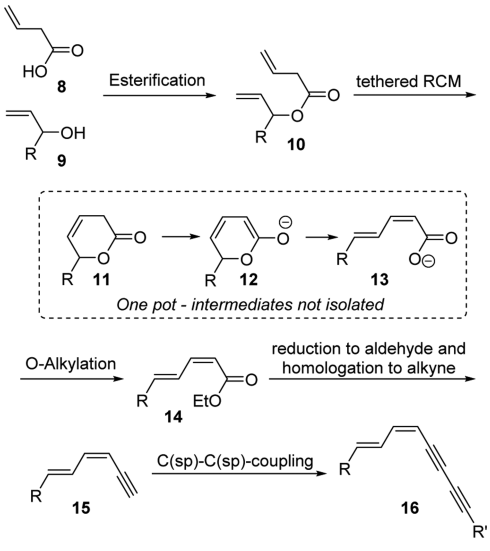
specific rotation and concluded, by analogy, that **3** should have a 12*R*-configuration.[19] We thought that a total synthesis of these polyacetylenes from a chiral pool starting material with a reliably assigned absolute configuration might substantiate or disprove these structural assignments.

Synthetic methods that have previously been used in total syntheses of polyacetylenes related to those shown in Figures 2 and 3 are Pd-catalyzed cross-coupling reactions[27−31] and a nucleophilic addition to pyrylium salts[32] for the stereoselective construction of *E,E*- and *Z,E*-configured dienes, respectively. Recently, a flexible synthetic approach to both *E,E*- and *Z,E*-dienes based on the electrocyclic ring opening of *trans*- and *cis*-cyclobutenes has been developed.[33−35] For the synthesis of the di- or triyne pattern in polyacetylenes, mostly Cu- and Pd-catalyzed couplings of the Glaser- or Cadiot−Chodkiewicz-type have been used.[36−38]

Our group has recently disclosed a novel type of tethered RCM[39−42] reaction to access (2*Z*,4*E*)-dienoates[43] and dienoic acids[44] in high yields and very high stereoselectivities. The sequence starts from allylbutenoates **10** (synthesized from allylic alcohols **9** and vinylacetic acid **8**), which are then converted in a one-pot reaction to the carboxylates **13** via RCM and base-induced eliminative ring opening of the intermediate lactones **11**. Carboxylates **13** are alkylated to yield dienoates **14**. The ester group in compounds of **14** is available for functional group transformations, e.g., as required for the target molecules in question, to terminal alkynes **15** using Corey−Fuchs homologation[45] or related reactions. For the construction of the di- or triyne part, transition metal catalyzed C(sp)-C(sp) coupling reactions were envisaged (Scheme 1).

Scheme 1. Synthetic Plan for *E,Z*-Configured Diene-di-(tri-)ynes Using an RCM Ring Opening-Alkylation Sequence

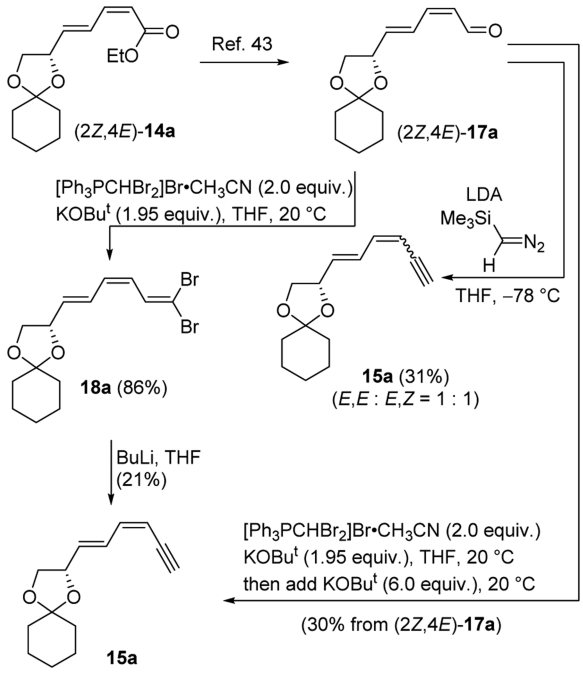


In a preliminary communication, we have recently reported the first total synthesis of atractylodemayne A (**1**, Figure 3) along these lines.[46] Herein, we report an extension of this approach to the chiral atractylodemaynes **2**−**4** and to the unnamed natural products **5** and **6**. To the best of our knowledge, none of these natural products have previously been synthesized.

RESULTS AND DISCUSSION

Our first concern was to identify conditions that allow the alkynylative carbonyl homologation of esters **14** to diene-ynes **15** with conservation of the *E,Z*-diene configuration. From previous experience, we knew that 2*Z*,4*E*-pentadiene-1-ols, the reduction products of esters **14**, tend to decompose upon purification and storage. The corresponding aldehydes are chemically more stable and can be purified by chromatography but undergo slow isomerization to *E,E*-isomers.[43] It is therefore advisable to convert esters **14** to required terminal alkynes **15** without delay and with a minimum of purification steps. Orienting experiments were performed with aldehyde (2*Z*,4*E*)-**17a**.[43] The Bestmann−Ohira reagent was discarded from the outset because *α,β*-unsaturated aldehydes are known to react with concomitant conjugate addition of methanol (the nucleophile required for activation of Bestmann−Ohira's reagent).[47] Instead, an alkynylation of (2*Z*,4*E*)-**17a** with lithiated TMS-diazomethane was initially investigated (Scheme 2).[48,49]

Scheme 2. Orienting Experiments for Carbonyl-to-Alkyne Homologation



Expected diene-yne **15a** was indeed obtained but only in low yield and with extensive isomerization of the *Z*-configured double bond. Next, we investigated a Corey−Fuchs-type homologation[45] by treating (2*Z*,4*E*)-**17a** with $[Ph_3PCHBr_2]$-$Br{\cdot}CH_3CN$ (known as Wolkoff's reagent) in the presence of KO^tBu as a base.[50] Expected triene **18a** was isolated in 80% yield and reacted with butyllithium to induce triple bond formation.[45] Although isolated only in low yield, required diene-yne **15a** was formed without any *Z,E*-isomerization or double bond migration. We sought to improve this transformation by using a protocol devised by Rassat and co-workers who conducted the carbonyl olefination step and the subsequent alkynylation in a one-pot fashion using KO^tBu as a base for both transformations.[51] Compound **15a** was again obtained as a single isomer and in a slightly increased overall yield of 30% (Scheme 2). We discovered at this point that the

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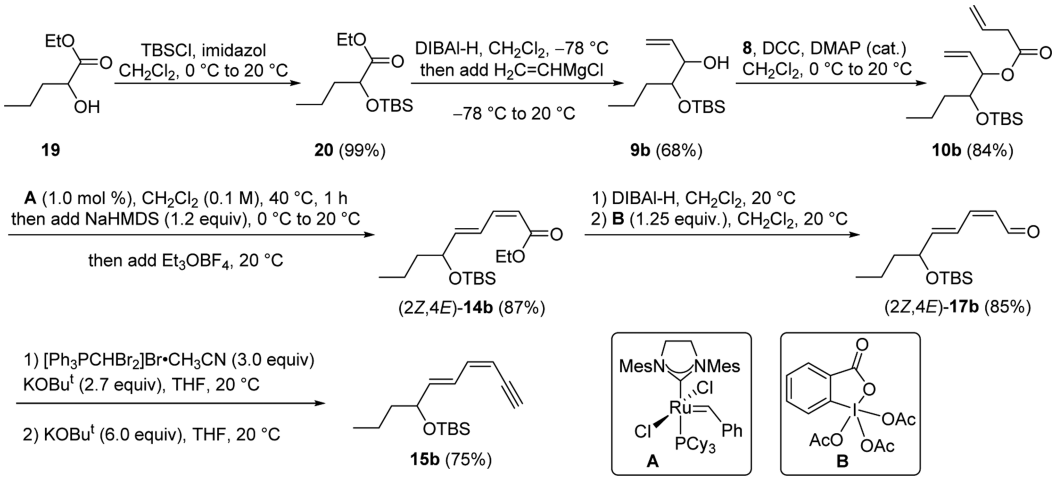
Scheme 3. Synthesis of the C6−C15 Part of Polyacetylene 5

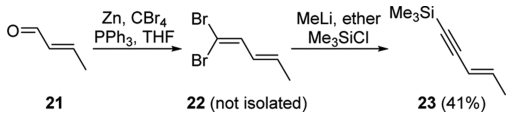


success of the one-pot protocol strongly depends on the quality of the KO^{t}Bu used. Because of its sensitivity to atmospheric humidity, it is advisible to use only recently opened containers when performing this reaction. Rather than improving the carbonyl-to-alkyne homologation for this (2*Z*,4*E*)-pentadienal any further, we decided at this stage to test Rassat's one pot method for the synthesis of polyacetylenes **5** and **6** (Figure 3).

Total Synthesis of (5*E*,7*Z*,13*E*)-Pentadeca-5,7,13-trien-9,11-diyn-4-ol (5). For the total synthesis of polyacetylene **5**, the C6−C15 fragment **15b** was required as a precursor for the C(sp)-C(sp) cross coupling. Our synthesis of **15b** starts from the commercially available α-hydroxy pentanoate **19**, which was first protected as its TBS-ether **20**. Compound **20** was converted to the allylic alcohol **9b** in one pot as a 6:1 mixture of diastereomers. As the newly generated stereocenter is not part of the target structure, the relative configuration of the major diastereomer of **9b** was not elucidated by spectroscopic means. Steglich esterification[52] of **9b** with vinyl acetic acid **8** furnished precursor **10b** for the RCM step. Under our previously established conditions,[43] **10b** was converted to (2*Z*,4*E*)-**17b** in a one flask sequence by using a catalytic amount of second generation Grubbs' catalyst (**A**) to induce the RCM followed by addition of NaHMDS to trigger the stereoselective ring opening and finally addition of Meerwein's salt[53] to trap the intermediate Na-carboxylate as the ethyl ester (2*Z*,4*E*)-**14b**. The ester was reduced to the corresponding dienol, which was immediately oxidized to pentadienal (2*Z*,4*E*)-**17b** without prior purification using Dess−Martin periodinane.[54] Although the aldehyde can be fully characterized, it should be used in the next step without delay to avoid undesirable double bond isomerization. For the subsequent aldehyde-to-alkyne homologation, we used, compared to the orienting experiments shown in Scheme 2, increased amounts of Wolkoff's reagent and KO^{t}Bu from the outset. It was also found to be advisable to perform this reaction excluded from light, as diene-ynes such as **15b** decompose when exposed to daylight or artificial light over prolonged periods of time. In due consideration of these precautions, **15b** was isolated in 75% yield as a single geometrical isomer without noticeable decomposition (Scheme 3).

As a C(sp)-C(sp) cross-coupling partner and C1−C5 building block, (*E*)-1-bromopent-3-en-1-yne **24** was envisaged. A suitable and storable precursor for this labile reagent is TMS-acetylene **23**, which had previously been synthesized via a Sonogashira coupling[55] and via a Corey−Fuchs homologation of crotonaldehyde **21**.[56] We chose the latter method, which proceeds via *gem*-dibromoalkene **22**. In accordance with the original report,[56] we found that this compound is quite unstable and refrained from any attempts to characterize this intermediate. It was instead immediately treated with methyllithium and TMS-chloride to furnish enyne **23** (Scheme 4).

Scheme 4. Synthesis of the C1−C5 Part of Polyacetylene 5



For the Cadiot−Chodkiewicz coupling,[38,57] bromoacetylene **24**[55] was required. It was obtained using Isobe's method[58] by treatment of **23** with *N*-bromosuccinimide (NBS) in the presence of $AgNO_3$. Because of its limited stability, **24** was not characterized and stored but rather was synthesized on demand (Scheme 5). In its orginal version, the Cadiot−Chodkiewicz coupling is a Cu(I)-catalyzed reaction.[59] Later, several improved variants were discovered, in particular with the aim to avoid the undesired formation of homocoupling products. Particularly noteworthy in this regard was the introduction of Pd cocatalysts, which allow the synthesis of unsymmetrical diynes in higher yields and improved selectivities at lower temperatures.[60] Examples for Pd-catalyzed Cadiot−Chodkiewicz couplings that proceed in the absence of any Cu(I) promoter are not completely unknown but are scarce.[61,62]

In the absence of a Cu(I)-catalyst, no conversion of terminal alkyne **15b** was observed (Table 1, entry 1). A similar result was obtained for the protocol devised by Wang and coworkers,[63] who found that phosphine ligands can significantly enhance the reactivity of Cu(I) catalysts in the C(sp)-C(sp) cross-coupling reaction, even in the absence of a Pd cocatalyst (entry 2). The catalyst combination of $Pd(PPh_3)_2Cl_2$ and CuI, introduced by Wityak and Chan,[60] turned out to be successful insofar as the starting material was completely consumed, but the selectivity was reproducibly unsatisfactory. Under these conditions, desired cross-coupling product **25** and homocoupling product **26** were isolated as an inseparable 1:1 mixture (Scheme 5 and Table 1, entry 3).

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Scheme 5. Completion of Total Synthesis of Polyacetylene 5 (See Table 1 for Details)

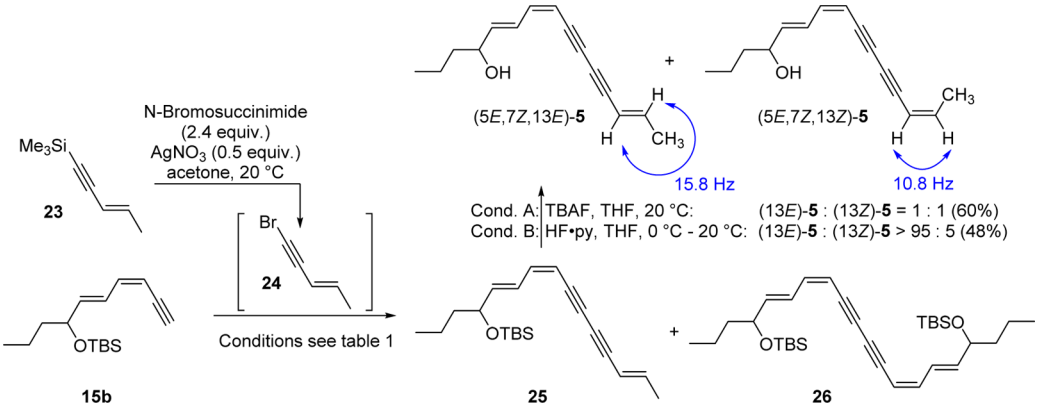


Table 1. Optimization of Conditions for the C(sp)-C(sp) Coupling of 15b and 24[a]

entry	solvent	T	catalyst(s) (mol %)	additive(s) (equiv)	ratio **25**: **26**	product (yield)
1	DMF	20 °C	$Pd(PPh_3)_4$ (5.0)	$HNPr^i_2$ (2.1)		*b*
2	ethanol	78 °C	CuI (10.0)	K_2CO_3 (2.1); P(*o*-tol)$_3$ (0.2)	*c*	<5%
3	THF	20 °C	$Pd(PPh_3)_2Cl_2$ (5.0), CuI (10.0)	$HNPr^i_2$ (2.1)	1:1	*c*,*d*
4	$HNPr^i_2$	70 °C	$Pd(OAc)_2$ (1.8), CuI (2.0)	$[NBu_4]Br$ (0.03)	7:1	**25** (64%)[e]
5[f]	THF	20 °C	$Pd(PPh_3)_2Cl_2$ (5.0), CuI (10)	$HNPr^i_2$ (2.1)		**26** (87%)

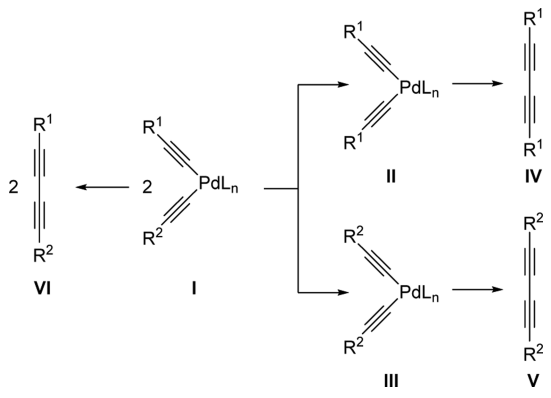
[a]Compound **24** generated from **23** (2.0 equiv) immediately prior to cross coupling. [b]No conversion. [c]Not determined. [d]Quantitative conversion to an inseparable mixture of products **25** and **26**. [e]Product contaminated with homocoupling product **26**; yield was estimated from the ^{1}H NMR spectrum. [f]Without addition of bromoacetylene **24**.

The formation of homocoupling products such as **26** from terminal alkynes is generally considered to be an oxidative process.[57] Various oxidants, such as chloroacetone,[64] iodine,[65] or air,[66] have been used in combination with Pd and Cu catalysts to selectively produce symmetrical diynes. Recently, Lei and co-workers proposed that symmetrical diynes as byproducts of cross-coupling reactions might also originate from a disproportionation of the catalytic Pd-bisacetylide-intermediate **I** into two symmetrical bisacetylides **II** and **III**, which would, upon reductive elimination, produce the homocoupling products **IV** and **V**.[67] This disproportionation is in competition with the reductive elimination of desired unsymmetrical diyne **VI** from Pd-bisacetylide **I** (Scheme 6).

In light of this mechanistic scenario, Lei and co-workers reasoned that the extent of homocoupling should decrease significantly if the catalyst loading is reduced, which would in turn require a more active catalyst. On the basis of this assumption, the authors introduced a protocol for a ligand free Cadiot−Chodkiewicz coupling that uses very small catalyst loadings of $Pd(OAc)_2$, CuI as a cocatalyst, and NBu_4Br as an additive.[67] The additive is believed to stabilize Pd nanoparticles, which might play an important role in this catalytic reaction. Gratifyingly, this protocol turned out to be successful for the cross coupling of **15b** and **24**, although we had to increase the catalyst loading substantially compared to the original conditions to achieve quantitative conversion. This might be the reason why the formation of homocoupling product **26** was not fully suppressed but the ratio of **25**:**26** was nevertheless considerably improved to 7:1 (entry 4). Although the disproportionation scenario as outlined in Scheme 6 can explain the formation of byproduct **26** up to a certain extent, the formation of larger amounts of homocoupling product, as in entry 3, points at a competing oxidative homocoupling. However, the absence of an obvious oxidizing agent under these conditions appears to be inconsistent with this assumption. To test whether formation of **26** occurs to a substantial extent through a pathway other than the above-mentioned disproportionation, **15b** was reacted under the same conditions as in entry 3 but without addition of bromoacetylene **24** (entry 5). Dimer **26** was selectively formed and isolated in high yield. A similar homocoupling of terminal alkynes in the presence of the same Pd and Cu catalysts and in the absence of intentionally added oxidant had previously been reported by Fairlamb et al.[68] It was later shown that this homocoupling is indeed an oxidative process because rigorous exclusion of air leads to an interruption of the reaction after the first catalytic cycle. This experimental finding was supported by theoretical calculations, which suggested that a closure of the catalytic cycle in the absence of any oxidant would require the thermodynamically unfavorable formation of molecular hydrogen.[69]

The final step of the total synthesis of polyacetylene **5** was the cleavage of the TBS-ether. In a first attempt to remove the

Scheme 6. Reductive Elimination Relative to Disproportionation According to Lei et al.[67]



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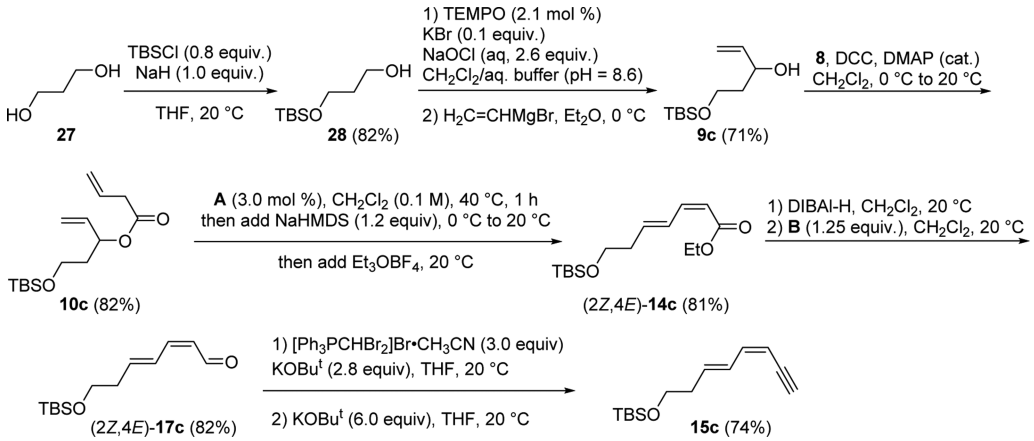
Scheme 7. Synthesis of C6−C13 Part of Polyacetylene 6

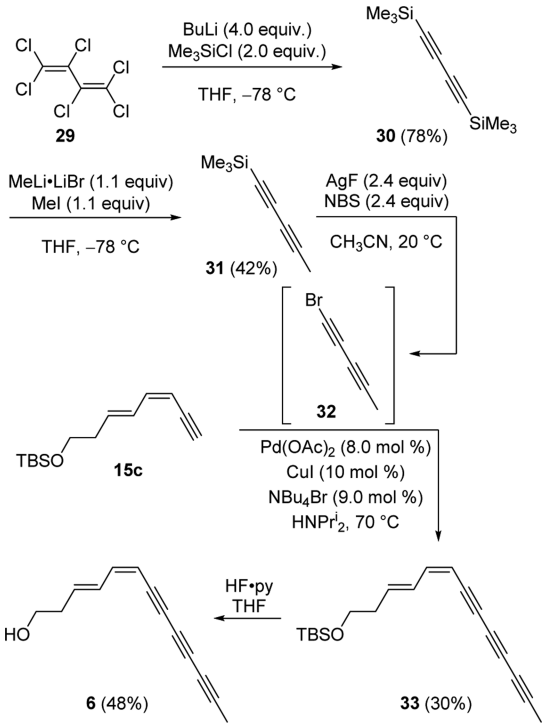


protecting group, TBAF-trihydrate was used. Although elevated temperatures were avoided in consideration of the high sensitivity of large conjugated π-systems, we surprisingly observed the formation of a 1:1 mixture of desired compound (5*E*,7*Z*,13*E*)-**5** and its geometrical isomer (5*E*,7*Z*,13*Z*)-**5**. Interestingly, the (5*E*,7*Z*)-diene moiety was not affected; only the double bond at C13 underwent partial isomerization, remarkably from *E* to *Z*. The 13*Z*-configuration of the isomerized sideproduct was proven by the appearance of a new dq for the proton at C14 with coupling constants of 10.8 and 7.0 Hz. A successful and selective deprotection of **25** was eventually achieved using HF-pyridine, giving desired (5*E*,7*Z*,13*E*)-**5** in 46% yield. In summary, this polyacetylene was synthesized in eight steps and 3.8% overall yield. In the original publication by Vincieri et al., describing the isolation and structural elucidation of **5**, selected ^{1}H NMR data were reported that match very well those found by us for the synthetic compound. The authors did not comment on the absolute configuration of the natural product or report any chiroptical data.[21]

Total Synthesis of (3*E*,5*Z*)-Trideca-3,5-dien-7,9,11-triyn-1-ol (6). For the total synthesis of this polyacetylene, diene-yne **15c** was required as a precursor for the Cadiot−Chodkiewicz coupling. Its synthesis started from propane-1,3-diol (**27**), which was first monoprotected to **28**.[70] Several methods and reagents for the oxidation of **28** to the corresponding aldehyde were tested, such as Parikh−Doering oxidation, 2-iodoxybenzoic acid (IBX), Dess-Martin's reagent, or pyridinium chlorochromate (PCC). These methods all gave the aldehyde in yields varying between 30 and 60%, but reproducibility was found to be difficult. The main reason for this is most likely the high volatility of the aldehyde, which results in loss of material upon workup. For these reasons, we sought a method that would allow a convenient workup of the reaction mixture and did not require the removal of high boiling byproducts. In our hands, Anelli's TEMPO-bromide-catalyzed oxidation[71−73] turned out to be the best method for the synthesis of volatile aldehydes because a biphasic solvent system is used. Excess oxidant (NaOCl) and coproducts of the oxidation reaction (NaCl, water) remain in the aqueous phase, whereas the organic solvent can be removed at or slightly below atmospheric pressure. The dried and concentrated solution of the aldehyde was immediately reacted with vinylmagnesium bromide to give allylic alcohol **9c** reliably in a satisfactory yield. From this point, the synthesis of **15c** was accomplished analogously to **15b** (Scheme 3) via Steglich esterification, RCM-ring opening, reduction−oxidation to aldehyde (2*Z*,4*E*)-**17c**, and eventually alkynylative homologation with Wolkoff's reagent and KO^{t}Bu. The yields for the individual steps are similar to those obtained en route to **15b** (Scheme 7).

For the next step in the total synthesis of polyacetylene **6**, the Cadiot−Chodkiewicz coupling, bromoacetylene **32** was required. Analogous to the in situ generation of coupling partner **24**, we synthesized TMS-acetylene **31** as a storable precursor (Scheme 8). Different routes to this compound, e.g.,

Scheme 8. Completion of the Total Synthesis of Polyacetylene 6



via C(sp)-C(sp) coupling,[74] have been described in the literature. Despite the moderate yield, we found the desilylative monolithiation of bis-TMS butadiyne **30** and the subsequent trapping of its lithioacetylide with methyl iodide to be more practical because desired pentadiyne **31** can be rapidly obtained in gram quantities.[75,76] Bis-TMS-butadiyne **30** was synthesized

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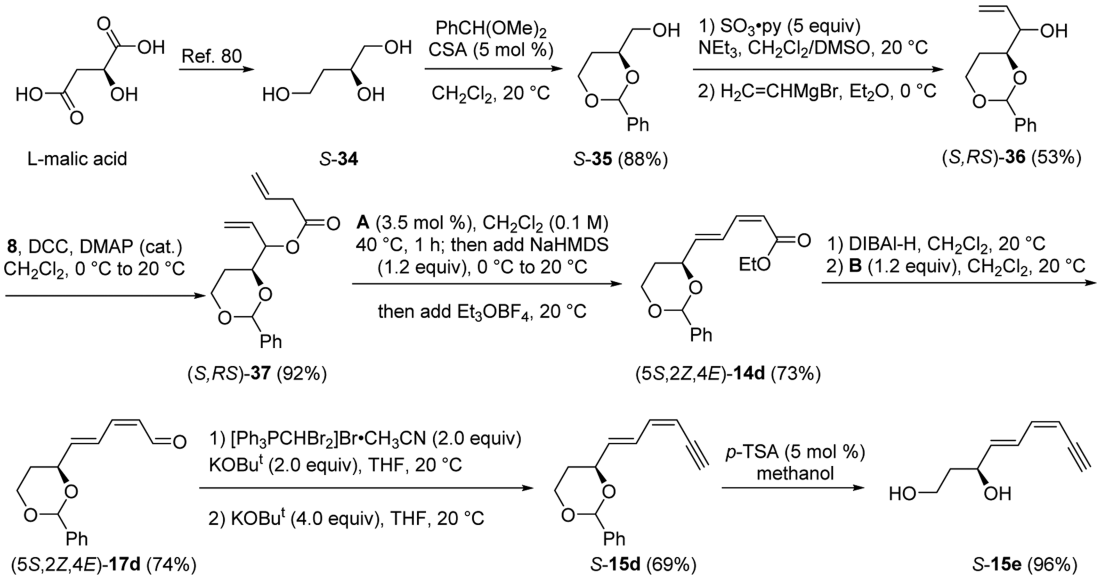
Scheme 9. Synthesis of the C6−C14 Part of Chiral Atractylodemaynes



from commercially available hexachlorobutadiene **29** via dehalogenation and trapping with TMS-chloride, as described previously.[77] For the in situ generation of bromoacetylene **32**, we first tested the same conditions used to obtain **24** (NBS and a substoichiometric amount of $AgNO_3$ in acetone), but the conversion was unsatisfactory. Better results were obtained under conditions previously established by Fiandanese et al., who used an excess of AgF in combination with NBS for the synthesis of **32**.[76] These researchers and others[78] have investigated C(sp)-C(sp) couplings of **32** with terminal alkynes for the synthesis of other polyacetylene natural products. Cross-coupling reactions of **32** with diene-ynes such as **15c** have, however, not yet been described. For this coupling, we tested initially the same conditions as for the synthesis of polyacetylene **5** (Table 1, entry 4). This resulted in only very low conversion to the desired product, which prompted us to increase the amounts of all catalysts. This eventually led to the formation of coupling product **33** in moderate yield but without noticeable formation of any homocoupling products. For the final deprotection step, the well-proven conditions from the synthesis of **5** were used. In summary, we accomplished the first synthesis of natural product (3*E*,5*Z*)-trideca-3,5-dien-7,9,11-triyn-1-ol **6** in eight steps with an overall yield of 3.4%. No NMR data were published for the natural product with this particular double bond configuration,[22] but for the (3*E*,5*E*)-isomer, which has been isolated from a different *Chrysanthemum* species, both ^1H and ^{13}C NMR data were reported.[79]

Total Syntheses of Chiral Polyacetylenes 2−4 from *Atractylodes macrocephala* Koidz. As outlined in the Introduction, a main motivation for the total synthesis of these natural products was to clarify the confusing and ambigous correlations of their absolute configuration and the sign of specific rotation.[19] Yao's and Yang's assignments refer to an absolute configuration/specific rotation correlation previously made by Nakai et al.[25] for atractyloyne (**7**). To establish an unambigous correlation via total synthesis, we required a starting material with a well-established absolute configuration, preferably from a chiral pool source. A suitable precursor in this regard should be *S*-butane-1,2,4-triol (*S*-**34**), which can be synthesized in one step from L-malic acid through reduction with borane-dimethylsulfide complex[80] but is also commercially available. Dieneyne *S*-**15e** was envisaged as a common precursor for the three polyacetylenes **2**−**4**. To minimize selectivity problems during the introduction of the ester groups at C12 and C14 (and in the case of atractylodemayne C at C1), we decided to perform the Cadiot−Chodkiewicz couplings with *S*-**15h** and *S*-**15i** (Scheme 10) in which each ester group is already located at the correct position. By the same token, *S*-**15e** and *S*-**15d** were disregarded as precursors for the cross-coupling step because this variant would necessitate the laborious differentiation of three OH groups at a late stage of the synthesis. Performing the C(sp)-C(sp) coupling with *S*-**15d** would furthermore require an acid-catalyzed deprotection in the presence of the large and hence sensitive fully conjugated π-system. For economical reasons, the synthesis of *S*-**15e** was first elaborated for the racemate and the optimized conditions were then applied to the enantiomerically pure series (Scheme 9).

Triol *S*-**34** was selectively protected as the six-membered acetal *S*-**35** following a literature procedure.[81] Oxidation of the primary alcohol to the aldehyde failed with Dess−Martin's periodinane, and Anelli's protocol resulted in cleavage of the acetal. Eventually, the oxidation was accomplished using SO_3·pyridine as previously described by Nachbauer and Brückner.[81] The aldehyde was immediately reacted with vinylmagnesium bromide to allylic alcohol (*S*,*RS*)-**36**, which was isolated in moderate yield as a 1:1 mixture of diastereomers. A vinylation of this aldehyde using divinylzinc had previously been reported with a very similar outcome.[82] From allylic alcohol (*S*,*RS*)-**36**, the synthesis of diene-yne *S*-**15d** was accomplished through the same sequence of steps and in similar yields as described above for the diene-ynes **15b** and **c**. Deprotection of *S*-**15d** to diol *S*-**15e** was achieved selectively and nearly quantitatively with a catalytic amount of *p*-TSA in methanol. The next step required a monoacetylation of the OH-group at C14. Some optimization was necessary to achieve an acceptable conversion to *S*-**15f** and suppress the formation of diacetate *S*-**15g** at the same time. For the optimization study, *rac*-**15e** was used (Table 2).

An esterification protocol developed by Twibanire and Grindley, which has been proposed to differentiate between primary and secondary alcohol groups within the same molecule,[83] worked only with limited success for the problem at hand (entry 1). Another protocol, which was especially

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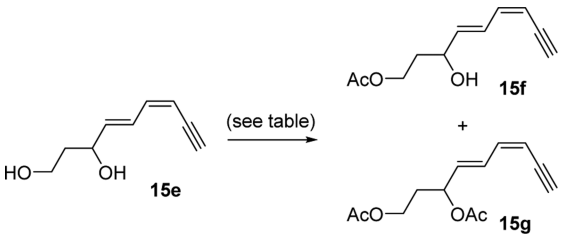
Table 2. Optimization of Monoacetylation Conditions for 15e



entry	solvent	T	base (equiv)	reagent (equiv)	**15f** (yield)[a]	**15g** (yield)[a]
1	DMF	20 °C	$NEtPr^i_2$ (2.0)	H_3CCO_2H (2.0) TBTU (1.0)[b]	40%	10%
2	THF	−90 °C → 20 °C	$NEtPr^i_2$ (2.0)	H_3CCOCl (1.4)	50%	n.d.[c]
3	THF	−90 °C → 20 °C	$NEtPr^i_2$ (2.0)	H_3CCOCl (1.7)	50%	n.d.[c]
4	CH_2Cl_2	−90 °C → 20 °C	$NEtPr^i_2$ (3.0)	H_3CCOCl (2.2)	45%	5%
5	CH_2Cl_2	0 °C	collidine (2.0)	H_3CCOCl (1.2)	20%	n.d.[c]
6	CH_2Cl_2	0 °C	$NEtPr^i_2$ (2.6)	H_3CCOCl (2.1)	40%	20%
7	CH_2Cl_2	0 °C → 20 °C	$NEtPr^i_2$ (2.0)	H_3CCOCl (1.1)	50%	n.d.[c]
8	CH_2Cl_2	0 °C → 20 °C	$NEtPr^i_2$ (1.6)	H_3CCOCl (1.0)	40%	n.d.[c]

[a]Yields from experiments carried out under the same conditions were rounded to the nearest 5%. [b]TBTU: *N,N,N′,N′*-tetramethyl-*O*-(benzotriazol-1-yl)uroniumtetrafluoroborat. [c]Not detected.

developed for selective monoacetylations of primary alcohols by Yamamoto and co-workers, uses a slight excess of acetyl chloride, an amine base, and dichloromethane at −78 °C.[84] We tested a number of variations, including a solvent switch to THF (entries 2 and 3). Under these conditions, no diacetate **15g** was observed, but conversion of the starting material remained incomplete and monoacetate **15f** was isolated in ∼50% yield. In dichloromethane, this product was isolated in a slightly lower yield but along with a small amount of **15g** (entry 3). Eventually, we discovered that for the monoacetylation of this particular diol Yamamoto's protocol is best modified by increasing the temperature to 0 °C and by using not more than 1.1 equiv of acetyl chloride (entry 7). Larger amounts of acetyl chloride will result in the formation of substantial amounts of diacetate **15g** and a diminished yield of monoacetate **15f** (entry 6). With an equimolar amount of acetyl chloride, no diacetate was formed, but the yield of **15f** decreased to ∼40% (entry 8).

The optimized conditions for the selective C14 esterification were applied to *S*-**15e**, and monoacetate *S*-**15f** was obtained in fair yield. For the synthesis of atractylodemayne F **2**, C12-isobutyrate *S*-**15h** was required as a cross-coupling precursor. This compound was cleanly obtained by acylation with the acid chloride, but addition of DMAP as a catalyst was mandatory. The synthesis of senecioate *S*-**15i**, the precursor for polyacetylene **3** and *S*-atractylodemayne C **4**, turned out to be surprisingly complicated. First attempts to acylate the secondary alcohol at C12 proceeded with unsatisfactory rates of conversion. When we tried to mend this problem by using senecioyl chloride and an amine base in large excess together with a catalytic amount of DMAP, we observed a quantitative esterification but discovered the formation of a significant amount of the isomerized byproduct *S*-**15i′**. Deconjugation reactions of similarly substituted *α,β*-unsaturated carbonyl compounds have been reported previously as unintentional side reactions[85] but have also been exploited synthetically. However, much stronger bases, in particular, lithium amides[85−87] or amine bases in combination with irradiation,[88] are normally used to initiate this deconjugation. It might, however, be possible that an amine base in combination with DMAP initiates an elimination of HCl from senecioyl chloride to a b,g-unsaturated ketene,[89] which then reacts with the alcohol *S*-**15f** to *S*-**15i′**. In our case, we found after some experimentation that the undesired deconjugation can be fully suppressed by using pyridine as a base without DMAP as an additional acylation catalyst. Desired senecioate *S*-**15i** was isolated in 61% yield as a single isomer. With *S*-**15h** and *S*-**15i** in hand, we performed the C(sp)-C(sp) cross-coupling reactions to conclude the syntheses. We used haloacetylenes **38a** and **b** as coupling partners, which were synthesized as described in our previous communication.[46] Both haloacetylenes underwent the Cadiot−Chodkiewicz coupling with the established $Pd(OAc)_2$-CuI-NBu_4Br catalyst system in comparable yields and without noticeable formation of any homocoupling products. *S*-Atractylodemayne F (*S*-**2**) and the unnamed polyacetylene *S*-**3** were obtained in yields of 43 and 47%, respectively, for the last step. *S*-Atractylodemayne C (*S*-**4**) was synthesized from *S*-**3** via acetylation with acetyl chloride (Scheme 10).

All NMR and HRMS data obtained by us for the synthetic compounds match very well those reported by Yao and Yang for natural products **2**−**4**[19] and by Chen for polyacetylene **3**[26]. However, significant discrepancies were found for the specific rotations and the assigned absolute configurations. The values and configurational assignments reported by Yao and Yang for the natural products are listed in Figure 3.[19] Unfortunately, no chiroptical data were reported in Chen's previous study on the plant constituents from *Atractylodes macrocephala*.[26] The respective values obtained by us for the synthetic compounds are shown in Scheme 10. On the basis of our total syntheses from the chiral pool derived starting material L-malic acid, we can state that the 12*S*-configured atractylodemaynes *S*-**2**, *S*-**3**, and *S*-**4** are without exception dextrorotatory. The same is true for truncated diene-ynes *S*-**15d-i**, whereas diene-yne **15a** (Scheme 2) with the reverse configuration at the allylic position is levorotatory. This observation clearly contradicts Yao and Yang's statement made for the chiral polyacetylenes from *Atractylodes macrocephala* that "$[\alpha]_D$ value is positive for the *R*-form and negative for the *S*-form".[19] It rather supports Nakai's correlation (based on Mosher's method) between a positive $[\alpha]_D$ value and a C12*S*-configuration for the structurally related atractyloyne (*S*-**7**),[25] although we would like to emphasize that configurational assignments based on

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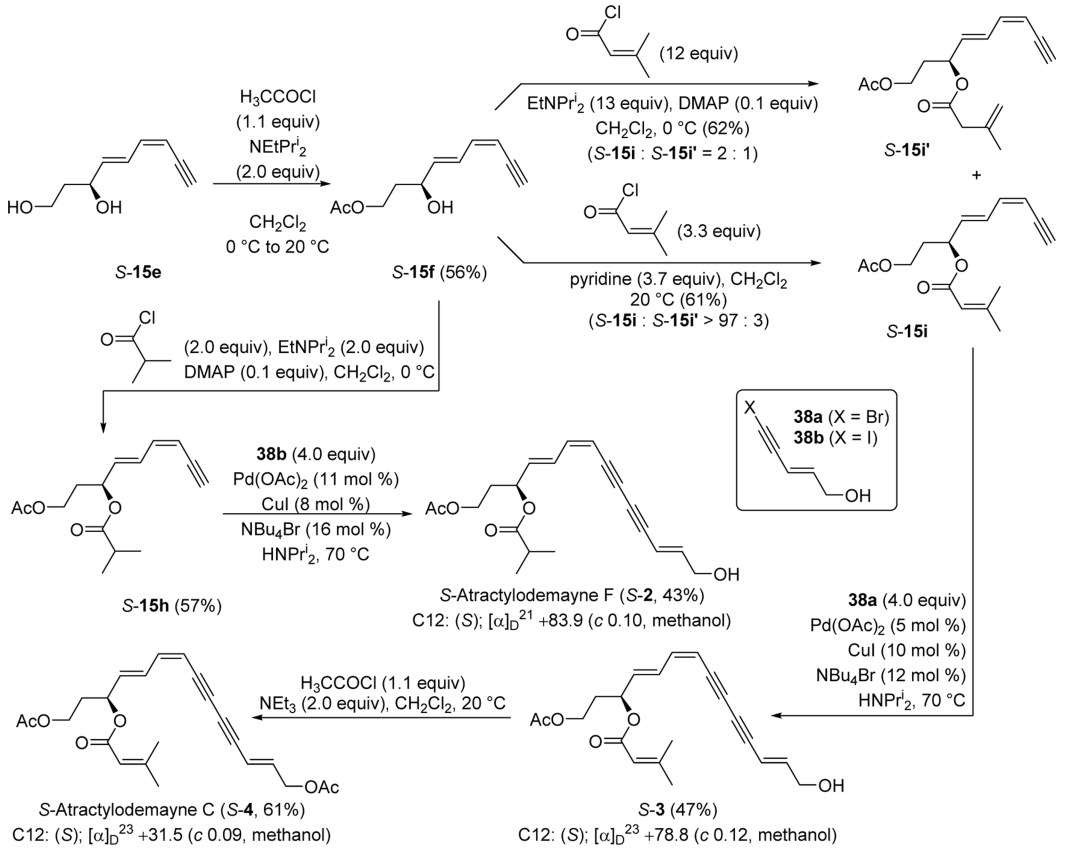
Scheme 10. Completion of the Total Syntheses of Polyacetylenes 2−4



comparison of optical rotations of structurally related compounds have only limited reliability. The confusing and contradictory configurational assignments might have been caused in part by the fact that Nakai et al. state in their discussion section that (+)-atractyloyne is *S*-configured but depicts the structure of the *R*-isomer in the corresponding figures.[25]

We suggest that, at least for naturally occurring compound **3** for which both Yao and Yang ($[\alpha]_D^{22}$ +60.9 (*c* 0.30, methanol))[19] and we ($[\alpha]_D^{23}$ +78.8 (*c* 0.12, methanol)) obtained reasonably congruent $[\alpha]_D$ values, the absolute configuration should be revised from 12*R* to 12*S*. We are unable to state conclusively whether the 12*S*-configuration assigned to naturally occurring atractylodemaynes C **4** and F **2** should be revised solely based on their negative $[\alpha]_D$ values because the absolute values reported for the optical rotation of the natural products **2** ($[\alpha]_D^{22}$ −2.5 (*c* 0.11, methanol))[19] and **4** ($[\alpha]_D^{22}$ −7.7 (*c* 0.05, methanol))[19] are strikingly small compared to those obtained by us for synthetic compounds *S*-**2** ($[\alpha]_D^{21}$ +83.9 (*c* 0.10, methanol)) and *S*-**4** ($[\alpha]_D^{22}$ +31.5 (*c* 0.09, methanol)). Because of these significant discrepancies, we believe that it might be advisible to redetermine the optical rotation values for naturally occurring atractylodemaynes and to reconsider the assigned absolute configuration. We cannot comment on the reasons for the discrepancies in this specific case, but in general, several factors might be responsible for the distortion of optical rotation values, e.g., the presence of very small amounts of strongly optically active impurities with the opposite sign of rotation, partial racemization during isolation, or other chemical transformations that might occur after structure elucidation by NMR and prior to the measurement of the optical rotation. In the course of this study, we discovered a distorting effect that falls into the latter category, which prompted us to resynthesize atractylodemayne F **2** and change our standard characterization protocols in the aftermath. Because of the small amounts of material available at the final stage of the total syntheses, the same sample was used for the nondestructive characterization methods NMR and optical rotation. First, NMR spectra were recorded to confirm the identity and purity of the product, and optical rotation measurements were then performed after removing the deuterated solvent and redissolving the sample in methanol. When the optical rotation of atractylodemayne F **2** was first measured, the sample had been dissolved in $CDCl_3$ for an unusually long period of time. When we discovered the considerable difference between Yao and Yang's and our own $[\alpha]_D$ values, the sample was recovered from the methanol solution and resubmitted to NMR analysis to check the identity of the compound. Interestingly, inspection of the NMR spectra revealed the presence of an additional set of signals. The second compound was identified as the 2*Z*-isomer of atractylodemayne F (2*Z*-**2**), which probably results from an *E*/*Z*-isomerization of the C2-C3 double bond catalyzed by small amounts of acid liberated from the $CDCl_3$ solvent. The isomerization stopped after 10 days in $CDCl_3$ at a ratio of 2:1 of 2*E*-**2** and 2*Z*-**2**. The optical rotation value measured for this sample ($[\alpha]_D^{20}$ +63.5 (*c* 0.26, methanol)) was considerably smaller than the value obtained for a sample of resynthesized atractylodemayne F ($[\alpha]_D^{21}$ +83.9 (*c* 0.10, methanol)) that had not been in contact with $CDCl_3$. After recording the optical rotation value, the identity of this sample was checked by NMR (Scheme 11).

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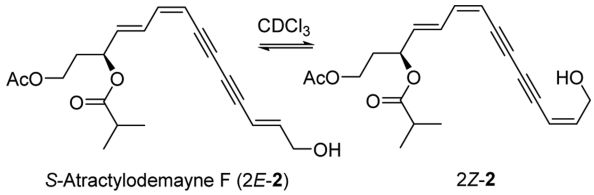
Scheme 11. Partial Isomerization of 2*E*-2 to 2*Z*-2 in $CDCl_3$



As a consequence, the two other atractylodemaynes, *S*-**3** and *S*-**4**, were spectroscopically characterized by NMR in CD_2Cl_2. The chemical shift values found in this solvent are very similar to the values reported by Yao and Yang in $CDCl_3$,[19] but the *E*/*Z*-isomerization reaction did not occur. This is in line with the assumption that this process is indeed acid catalyzed.

CONCLUSIONS

In summary, we demonstrated that an unconventional type of tethered RCM reaction that combines RCM of allylbutenoates with a highly diastereoselective elimination reaction to give *Z*,*E*-configured conjugated dienes is a useful method for the stereoselective synthesis of various naturally occurring polyacetylenes with a fully conjugated *E*/*Z*-diene-di- or -triyne backbone. For the example of three recently discovered atractylodemaynes, we could establish an unambiguous correlation between the sign of optical rotation and the absolute configuration of the C12 stereocenter, which is derived from the chiral pool compound L-malic acid. On the basis of these results, we propose that the configurational assignments of polyacetylenes isolated from *Atractylodes macrocephala* should be reconsidered. Finally, our observations during chiroptical characterization of the synthesized natural products suggest that a change in standard characterization protocols, which are probably common in many laboratories, might improve the reliability of optical rotation values.

EXPERIMENTAL SECTION

General Methods. All experiments were conducted in dry reaction vessels under an atmosphere of dry nitrogen. Solvents were purified by standard procedures. ^{1}H NMR spectra were obtained at 300, 500, or 600 MHz in $CDCl_3$ with $CHCl_3$ (δ = 7.26 ppm) as an internal standard. Coupling constants are given in Hz. ^{13}C NMR spectra were recorded at 75, 125, or 151 MHz in $CDCl_3$ with $CDCl_3$ (δ = 77.1 ppm) as an internal standard. Whenever the solubility or stability of the sample or signal separation were insufficient in $CDCl_3$, it was replaced by one of the following solvents: C_6D_6 (C_6D_5H as internal standard for ^{1}H NMR spectroscopy, δ = 7.16 ppm; C_6D_6 as internal standard for ^{13}C NMR spectroscopy, δ = 128.1 ppm), CD_2Cl_2 ($CHDCl_2$ as internal standard for ^{1}H NMR spectroscopy, δ = 5.32 ppm; CD_2Cl_2 as internal standard for ^{13}C NMR spectroscopy, δ = 53.8 ppm), acetone-d_6 (acetone-d_5 as internal standard for ^{1}H NMR spectroscopy, δ = 2.05 ppm; CD_3COCD_3 as internal standard for ^{13}C NMR spectroscopy, δ = 29.8 ppm). IR spectra were recorded as ATR-FTIR spectra. Wavenumbers (ν) are given in cm^{-1}. The peak intensities are defined as strong (s), medium (m), or weak (w). Low- and high-resolution mass spectra were obtained by EI-TOF or ESI-TOF.

Alkynylation of Aldehyde (2*Z*,4*E*)-17a with Lithiotrimethylsilyldiazomethane. A solution of $HNPr^i_2$ (0.18 mL, 1.30 mmol) in dry THF (5 mL) was cooled to 0 °C. BuLi (0.50 mL, 2.5 M in hexane, 1.30 mmol) was added dropwise, and the reaction was stirred for 0.5 h at 0 °C. After cooling to −78 °C, $TMSCHN_2$ (0.75 mL, 2.0 M in hexanes, 1.50 mmol) was added dropwise, and the mixture was stirred for 0.5 h at this temperature. A solution of aldehyde (2*Z*,4*E*)-**17a** (222 mg, 1.00 mmol) in THF (5 mL) was added dropwise and stirring was continued for 1 h at −78 °C. At this point, the reaction was brought to ambient temperature and heated to 70 °C for 3 h. After recooling to 0 °C, the reaction was quenched with brine; the organic layer was separated, and the aqueous layer was extracted with MTBE (3 × 20 mL). The combined organic phases were dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography using a hexane/MTBE mixture (20:1 v/v)) as eluent to furnish **15a** (68 mg, 0.31 mmol, 31%) as an inseparable mixture of geometrical isomers as a yellowish oil. NMR data for the 3*E*-isomer of **15a** were obtained from the mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (dd, *J* = 15.7, 10.8 Hz, 1H), 6.33 (dd, *J* = 15.2, 10.9 Hz, 1H), 5.77 (dd, *J* = 15.2, 7.4 Hz, 1H), 5.60 (dd, *J* = 15.6, 2.3 Hz, 1H), 4.55 (dt, *J* = 7.1, 6.9 Hz, 1H), 4.16−4.03 (m, 1H), 3.60 (t, *J* = 7.8 Hz, 1H), 3.04 (d, *J* = 2.4 Hz, 1H), 1.72−1.49 (m, 8H), 1.49−1.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 134.1, 131.7, 111.3, 110.4, 82.7, 80.2, 76.2, 69.2, 36.4, 35.6, 25.3, 24.1, 24.0.

(*S*)-2-((1*E*,3*Z*)-6,6-Dibromohexa-1,3,5-trien-1-yl)-1,4-dioxaspiro[4.5]decane (18a). *This compound should be synthesized and handled under exclusion of light! It decomposes slowly upon storage and should therefore be used in further transformations without delay!*

To a suspension of Wolkoff's reagent (1.110 g, 2.00 mmol) in THF (10 mL) was added KO^{t}Bu (213 mg, 1.90 mmol) and the mixture was stirred for 10 min at ambient temperature. Aldehyde (2*Z*,4*E*)-**17a** (222 mg, 1.00 mmol) was then added to the suspension. If the conversion was incomplete after 1 h (TLC), in a second flask Wolkoff's reagent (1.11 g, 2.00 mmol) in THF (10 mL) was reacted with KO^{t}Bu (213 mg, 1.90 mmol) in THF (10 mL) for 10 min. This solution was then added to the reaction mixture. After full conversion of the aldehyde, the reaction was quenched by the addition of a sat. aq NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with MTBE (3 × 20 mL). The combined organic layers were dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on silica using hexane/MTBE mixtures (20:1 (v/v)) to furnish **18a** (326 mg, 0.86 mmol, 86%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 10.8, 0.8 Hz, 1H), 6.63 (dd, *J* = 15.0, 11.3 Hz, 1H), 6.17 (dd, *J* = 11.1, 11.1 Hz, 1H), 6.01 (dd, *J* = 10.9 Hz, 10.9, 1H), 5.82 (dd, *J* = 15.0, 7.3 Hz, 1H), 4.59 (dt, *J* = 7. 1, 6.9 Hz, 1H), 4.11 (dd, *J* = 8.1, 6.3 Hz, 1H), 3.61 (dd, *J* = 8.0, 7.8 Hz, 1H), 1.69−1.55 (m, 8H), 1.45−1.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 132.3, 131.5, 127.9, 126.1, 110.5, 93.6, 76.4, 69.1, 36.4, 35.6, 25.3, 24.1, 24.0. No [M^+] signal was observed in HRMS under various ionization conditions.[90]

(*S*)-2-((1*E*,3*Z*)-Hexa-1,3-dien-5-yn-1-yl)-1,4-dioxaspiro[4.5]decane (15a). *This compound should be synthesized and handled under exclusion of light!*

Synthesis from **18a**: Compound **18a** (316 mg, 0.83 mmol) was dissolved in THF (10 mL) and cooled to −78 °C. BuLi (800 μL, 2.5 M in hexane, 2.00 mmol) was added dropwise, and the reaction was stirred for 0.5 h at this temperature. The reaction was warmed to 0 °C and stirred for another 0.5 h at this temperature. After quenching with sat. aq NH_4Cl solution, the organic layer was separated, and the aqueous layer was extracted with MTBE/hexane (2:1, 3 × 30 mL). The combined organic extracts were dried with Na_2SO_4; the organic extract was concentrated and dry-loaded on silica. The residue was purified by column chromatography on silica using a hexane/MTBE (20:1 (v/v)) mixture as eluent to furnish **15a** (40 mg, 0.18 mmol, 21%). One-pot synthesis from (2*Z*,4*E*)-**17a**: Wolkoff's reagent [Ph_3PCHBr_2]Br·CH_3CN (3.00 g, 5.4 mmol) was suspended in dry and degassed THF (25 mL). KO^{t}Bu (0.59 g, 5.3 mmol) was added, and the mixture was stirred for 10 min at ambient temperature. (2*Z*,4*E*)-**17a** (0.52 g, 2.3 mmol) was added, and the mixture was stirred for 20 min. If the conversion was incomplete after this time, a solution of Wolkoff's reagent (1.50 g, 2.7 mmol) and KO^{t}Bu (0.29 g, 2.6 mmol) in THF (10 mL) was added, and the solution was stirred at ambient temperature until the starting material was fully consumed. KO^{t}Bu (1.82 g, 16.2 mmol) was then added, and the mixture was stirred for another 5 min. The reaction was quenched by addition of brine, and the aqueous layer was separated and extracted with MTBE. The combined organic layers were dried with Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on

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silica using a hexane/MTBE mixture (20:1 v/v) as eluent to give **15a** (150 mg, 0.7 mmol, 30%) as a yellowish liquid; $[\alpha]_{27}^{D}$ −45.9 (*c* 0.99, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.83 (dd, *J* = 15.4, 11.1 Hz, 1H), 6.45 (dd, *J* = 10.9, 10.9 Hz, 1H), 5.84 (dd, *J* = 15.4, 7.6 Hz, 1H), 5.46 (dd, *J* = 10.7, 2.4 Hz, 1H), 4.61 (dt, *J* = 7.2, 6.7 Hz, 1H), 4.11 (dd, *J* = 8.2, 6.3 Hz, 1H), 3.61 (t, *J* = 7.9 Hz, 1H), 3.25 (d, *J* = 2.4 Hz, 1H), 1.67−1.54 (m, 8H), 1.43−1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 134.9, 129.9, 110.4, 109.4, 84.0, 80.4, 76.4, 69.2, 36.4, 35.6, 25.3, 24.1, 24.0; IR (ATR) ν 3287 (w), 2934 (m), 2857 (w), 1449 (w), 1278 (m), 1161 (m), 1096 (s), 1039 (m), 983 (m), 926 (s), 846 (m), 639 (m); HRMS (ESI) calcd for $C_{14}H_{18}O_2Na$ ($[M + Na]^+$) 241.1199, found 241.1201.

Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)pentanoate (20). A solution of ester **19** (3.00 g, 20.5 mmol) and imidazole (4.20 g, 61.5 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C. TBSCl (4.00 g, 26.7 mmol) was added in two portions, and the solution was warmed to ambient temperature with stirring over 12 h. The reaction mixture was washed twice with a saturated solution of $NaHCO_3$ (aq), and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with brine and dried with Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica (hexane/MTBE 20:1 (v/v)) to furnish compound **20** (5.30 g, 20.4 mmol, 99%) as a colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25−4.09 (m, 3H), 1.67 (dt, *J* = 7.9, 6.5 Hz, 2H), 1.52−1.32 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.96−0.88 (m, 12H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 72.3, 60.8, 37.5, 25.9, 18.7, 18.5, 14.4, 14.0, −4.7, −5.2; IR (ATR) ν 2959 (m), 2930 (m), 2858 (m), 1754 (m), 1733 (m), 1464 (m), 1250 (m), 1139 (s), 1096 (m), 1030 (m), 904 (m), 829 (s), 812 (m), 776 (s); HRMS (ESI) calcd for $C_{13}H_{29}O_3Si$ ($[M + H]^+$) 261.1880, found 261.1900.

4-((*tert*-Butyldimethylsilyl)oxy)hept-1-en-3-ol (9b). Compound **20** (1.040 g, 4.00 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to −78 °C (internal temperature). DIBAl-H (6.00 mL, 1.0 M in CH_2Cl_2, 6.00 mmol) was added dropwise while keeping the temperature below −75 °C. After 0.5 h at this temperature, more DIBAl-H (2.00 mL, 1.0 M in DCM, 2.00 mmol) was added. After full conversion of the starting material (TLC), vinylmagnesium chloride (8.80 mL, 1.7 M in THF, 15.0 mmol) was added dropwise while keeping the temperature below −75 °C. The reaction mixture was then warmed to ambient temperature, and the reaction was quenched by addition of sat. aq solution of NH_4Cl and an aq solution of tartaric acid (15 wt %). The aqueous phase was extracted with MTBE (3 × 30 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica (hexane/MTBE 10:1 (v/v)) to furnish **9b** as a 6:1 mixture of diastereomers (0.620 g, 2.52 mmol, 63%) as a yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (ddd, *J* = 17.3, 10.5, 6.2 Hz, 1H), 5.29 (dt, *J* = 17.3, 1.5 Hz, 1H), 5.19 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.12−4.07 (m, 1H), 3.75−3.67 (m, 1H), 2.03 (s (br), 1H), 1.55−1.18 (m, 4H), 0.92−0.87 (m, 12H), 0.11−0.06 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 116.6, 76.1, 75.3, 34.0, 26.0, 19.9, 18.3, 14.4, −4.3, −4.3; IR (ATR) ν 3400 (bw), 2957 (m), 2930 (m), 2858 (m), 1463 (m), 1253 (m), 834 (s), 774 (s); HRMS (ESI) calcd for $C_{13}H_{28}O_2SiNa$ ($[M + Na]^+$) 267.1751, found 267.1749.

4-((*tert*-Butyldimethylsilyl)oxy)hept-1-en-3-ylbut-3-enoate (10b). To a solution of alcohol **9b** (0.630 g, 2.58 mmol) in CH_2Cl_2 (26 mL) was added DMAP (88 mg, 0.72 mmol) and vinyl acetic acid (**8**, 416 μL, 4.69 mmol). The solution was cooled to 0 °C, and DCC (638 mg, 3.09 mmol) was added. The mixture was warmed to ambient temperature and stirred for 12 h. In the case of incomplete conversion, additional portions of vinyl acetic acid (110 μL, 1.29 mmol) and DCC (266 mg, 1.29 mmol) were added, and the stirring at ambient temperature was continued for another 24 h. The solution was then filtered and washed three times with CH_2Cl_2. The combined organic layers were washed with aq HCl (1.0 M) followed by a sat. aq solution of $NaHCO_3$ and dried with Na_2SO_4. The solution was filtered, and the crude mixture was dry-loaded on silica gel. Column chromatography on silica (hexane/MTBE mixtures of increasing polarity as eluent) furnished compound **10b** (0.68 g, 2.17 mmol, 84%) as a yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07−5.77 (m, 2H), 5.33−5.10 (m, 5H), 3.88−3.64 (m, 1H), 3.12 (d, *J* = 6.9 Hz, 2H), 1.47−1.26 (m, 4H), 0.91−0.87 (m, 12H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 132.8, 130.4, 119.2, 118.7, 78.4, 73.5, 39.6, 36.0, 26.0, 18.8, 18.4, 14.3, −4.2, −4.4; IR (ATR) ν 2958 (m), 2931 (m), 1741 (s), 1253 (m), 1171 (m), 1092 (m), 990 (m), 919 (m), 836 (s), 775 (s); HRMS (ESI) calcd for $C_{17}H_{32}O_3SiNa$ ($[M + Na]^+$) 335.2013, found 335.2036.

Ethyl (2*Z*,4*E*)-6-((*tert*-Butyldimethylsilyl)oxy)octa-2,4-dienoate ((2*Z*,4*E*)-14b). To a solution of butenoate **10b** (312 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added precatalyst **A** (8.5 mg, 1.0 mol %). The solution was stirred at 40 °C until full conversion of the starting material was observed (TLC). It was then cooled to 0 °C, and NaHMDS (1.2 mL, 1 M in THF, 1.20 mmol) was added. The reaction was warmed to ambient temperature and stirred until the RCM product was fully consumed (TLC). $[Et_3O]BF_4$ (285 mg, 1.50 mmol) was added, and the mixture was stirred at ambient temperature until full conversion was observed. The reaction mixture was dry-loaded on silica and purified by column chromatography on silica (hexane/MTBE 20:1 (v/v)) to furnish (2*Z*,4*E*)-**14b** (272 mg, 0.87 mmol, 87%) as a yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 15.4, 11.4 Hz, 1H), 6.54 (dd, *J* = 11.4, 11.4 Hz, 1H), 5.97 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.63 (d, *J* = 11.3 Hz, 1H), 4.28−4.14 (m, 3H), 1.60−1.34 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.92−0.87 (m, 12H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 147.6, 144.7, 125.7, 117.7, 73.2, 60.3, 40.6, 26.3, 18.8, 18.6, 14.7, 14.5, −3.9, −4.5; IR (ATR) ν 2957 (w), 2930 (w), 2856 (w), 1716 (m), 1642 (w), 1603 (w), 1254 (m), 1179 (s), 1146 (m), 1092 (m), 1034 (m), 964 (m), 835 (s), 775 (s); HRMS (ESI) calcd for $C_{17}H_{32}O_3SiNa$ ($[M + Na]^+$) 335.2013, found 335.2036.

(2*Z*,4*E*)-6-((*tert*-Butyldimethylsilyl)oxy)nona-2,4-dienal ((2*Z*,4*E*)-17b). To a solution of (2*Z*,4*E*)-**14b** (720 mg, 2.31 mmol) in CH_2Cl_2 (25 mL) was added DIBAl-H (5.00 mL, 1 M in CH_2Cl_2, 5.00 mmol) at ambient temperature. If the conversion was incomplete after stirring for 5 min, an additional portion of DIBAl-H (1.50 mL, 1 M in CH_2Cl_2, 1.50 mmol) was added. The mixture was stirred for 10 min, and the reaction was quenched by addition of sat. aq NH_4Cl solution. The mixture was diluted with CH_2Cl_2, and a minimum amount of aq HCl (1 M) was added to dissolve inorganic residues. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 times 20 mL) and Et_2O (10 mL). The combined organic layers were dried with Na_2SO_4. The solution was filtered and evaporated in vacuo (max: 400 mbar). NMR data of (2*Z*,4*E*)-6-(*tert*-Butyldimethylsilyloxy)nona-2,4-diene-1-ol (obtained from the unpurified product): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (ddt, *J* = 15.1, 11.3, 1.1 Hz, 1H), 6.08 (dd, *J* = 11.1, 11.1 Hz, 1H), 5.72 (dd, *J* = 15.1, 5.9 Hz, 1H), 5.57 (dt, *J* = 11.1, 6.9 Hz, 1H), 4.35−4.29 (m, 2H), 4.17 (q, *J* = 5.9 Hz, 1H), 1.54−1.22 (m, 4H), 0.95−0.82 (m, 12H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 130.9, 129.2, 123.7, 73.1, 59.3, 40.9, 26.3, 18.9, 14.5, −4.0, −4.4. The crude alcohol from the previous step was redissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C, and Dess−Martin periodinane (1.230 g, 2.89 mmol) was added. The mixture was warmed to ambient temperature and stirred for 2 h and then diluted with EtOAc and washed with a solution of sat. aq $NaHCO_3$ and $Na_2S_2O_3{\cdot}5H_2O$ (250 g/L, 4 × 30 mL). The organic layer was separated and dried with Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica (hexane/MTBE 20:1 (v/v)) to furnish (2*Z*,4*E*)-**17b** (530 mg, 1.97 mmol, 85%) as a yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.19 (d, *J* = 8.0 Hz, 1H), 7.18 (ddm, *J* = 14.8, 12.1 Hz, 1H), 6.96 (dd, *J* = 12.1, 11.1 Hz, 1H), 6.14 (dd, *J* = 14.8, 5.1 Hz, 1H), 5.84 (dd, *J* = 11.0, 8.1 Hz, 1H), 4.30 (q, *J* = 5.5 Hz, 1H), 1.57−1.23 (m, 4H), 0.96−0.85 (m, 12H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 148.7, 147.3, 127.2, 122.2, 72.2, 40.2, 26.0, 18.5, 18.4, 14.3, −4.4, −4.7; IR (ATR) ν 2956 (m), 2929 (m), 2856 (m), 1672 (s), 1640 (m), 1576 (w), 1463 (w), 1361 (w), 1253 (m), 1221 (w), 1082 (m), 1006 (m), 953 (m), 835 (s), 775 (s), 669 (w); HRMS (ESI) calcd for $C_{15}H_{29}O_2Si$ ($[M + H]^+$) 269.1931, found 269.1936.

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***tert*-Butyl(((5*E*,7*Z*)-deca-5,7-dien-9-yn-4-yl)oxy)dimethylsilane (15b).** *This compound was synthesized and handled under exclusion of light!*

Wolkoff's reagent $[Ph_3PCHBr_2]Br{\cdot}CH_3CN$ (2.22 g, 4.00 mmol) was suspended in THF (20 mL). KO^{t}Bu (416 mg, 3.80 mmol) was added, and the mixture was stirred for 10 min at ambient temperature. Aldehyde (2*Z*,4*E*)-**17b** (520 mg, 1.94 mmol) was added, and the mixture was stirred for 10 min. If the conversion is incomplete at this stage, a solution of Wolkoff's reagent (1.11 g, 2.00 mmol) and KO^{t}Bu (212 mg, 1.90 mmol) in THF (5 mL) was added. Upon complete consumption of the aldehyde (TLC), KO^{t}Bu (1.240 g, 12.00 mmol) was added in one portion, and the mixture was stirred for 5 min. The reaction was quenched by the addition of brine; the aqueous phase was extracted with MTBE (3 × 25 mL), and the combined organic phases were dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on silica (hexane) to yield **15b** (395 mg, 1.49 mmol 75%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (dd, J = 15.2, 11.1 Hz, 1H), 6.45 (dd, J = 10.9, 10.9 Hz, 1H), 5.87 (dd, J = 15.3, 5.8 Hz, 1H), 5.38 (dd, J = 10.6, 1.7 Hz, 1H), 4.22 (q, J = 5.6 Hz, 1H), 3.21 (d, J = 2.4 Hz, 1H), 1.52−1.21 (m, 4H), 0.98−0.83 (m, 12H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 141.6, 125.9, 107.2, 83.0, 80.7, 72.5, 40.4, 25.9, 18.5, 18.2, 14.1, −4.4, −4.8; IR (ATR) ν 3313 (w), 2957 (m), 2928 (m), 2858 (m), 1463 (w), 1253 (m), 1077 (m), 983 (m), 834 (s), 774 (s); HRMS (EI) calcd for $C_{16}H_{28}OSi$ [M^+] 264.1904, found 264.1903.

(*E*)-Trimethyl(pent-3-en-1-yn-1-yl)silane (23).[56] A solution of PPh_3 (7.70 g, 29.2 mmol) in CH_2Cl_2 (40 mL) was cooled to 0 °C. CBr_4 (9.70 g, 29.2 mmol) was added, and the solution was stirred for 10 min at this temperature. Zn dust (1.91 g, 29.2 mmol) was then added, and the mixture was warmed to ambient temperature and stirred for 22 h. The resulting suspension was cooled to 0 °C, and crotonaldehyde (**21**, 1.00 mL, 14.6 mmol) was added. The mixture was warmed to ambient temperature and stirred for 2 h. It was poored onto cold pentane (∼0 °C, 200 mL) and filtered. The filter cake was washed with cold pentane, and the combined organic solutions were concentrated in vacuo. The residue was quickly purified by flash chromatography through a short column of silica (pentane as eluent). The volatiles were removed in vacuo to give intermediate **22** (∼2.3 g), which was used without further purification and characterization in the next step: compound **22** (approximately 2.3 g, approximately 10 mmol) was dissolved in diethyl ether (4 mL) and cooled to −78 °C. MeLi (3.20 mL, 1.6 M in diethyl ether, 21.1 mmol) was slowly added, and the reaction was warmed to ambient temperature. Stirring at ambient temperature was continued for 12 h. At this point, TMSCl (1.40 mL, 11.0 mmol) was added dropwise, and the reaction was stirred for 2 h at ambient temperature. Aq HCl (1 M, 15 mL) was added, and the aqueous layer was separated and extracted with diethyl ether (3 times 10 mL). The combined organic phases were washed with water and brine and dried with Na_2SO_4. The solvent was removed at atmospheric pressure, and the residue was distilled (bp 60−70 °C at 55 mbar) to give **23** (585 mg, 4.24 mmol, 41%) as a colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (dq, J = 15.7, 6.8 Hz, 1H), 5.51 (dd, J = 15.8, 1.7 Hz, 1H), 1.77 (dd, J = 6.8, 1.7 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 111.0, 104.2, 92.5, 18.8, 0.1.

***tert*-Butyldimethyl(((5*E*,7*Z*,13*E*)-pentadeca-5,7,13-trien-9,11-diyn-4-yl)oxy)silane (25).** *This compound was synthesized and handled under exclusion of light!*

Compound **23** (69.0 mg, 0.50 mmol) and *N*-bromosuccinimide (106 mg, 0.60 mmol) were dissolved in acetone (5 mL). $AgNO_3$ (22.0 mg, 0.13 mmol) was added, and the reaction was stirred for 3.5 h at ambient temperature. Water (3 mL) was added, and the reaction mixture was extracted with pentane (3 × 25 mL). The combined organic phases were dried with Na_2SO_4 and concentrated in vacuo (600 mbar, 40 °C). Crude bromo alkyne **24** was immediately used without further purification and characterization in the next step. To a solution of **15b** (66.0 mg, 0.25 mmol), NBu_4Br (2.5 mg, 8 μmol, 3.0 mol %), and CuI (1.0 mg, 5 μmol, 2.0 mol %) in $HNPr^i_2$ (4 mL) was added a solution of the freshly prepared bromoalkyne **24** in $HNPr^i_2$ (1 mL). The resulting brown solution was stirred for 5 min at 70 °C. At this point, $Pd(OAc)_2$ (1.0 mg, 4.4 μmol, 1.8 mol %) was added, and the mixture was stirred at 70 °C for 12 h. After cooling to ambient temperatue, aq HCl (2 M, 4 mL) was added; the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried with Na_2SO_4 and evaporated in vacuo. The crude product was purified by column chromatography on silica using hexane as eluent to obtain **25** and **26** as an inseparable 7:1 mixture (66 mg, ∼64% of **25**) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (dd, J = 15.2, 11.2 Hz, 1H), 6.49 (dd, J = 10.9, 10.9 Hz, 1H), 6.32 (dq, J = 15.6, 6.9 Hz, 1H), 5.90 (dd, J = 15.3, 5.9 Hz, 1H), 5.60 (d, J = 15.8 Hz, 1H), 5.45 (d, J = 10.6 Hz, 1H), 4.22 (q, J = 6.0 Hz, 1H), 1.83 (dd, J = 6.9, 2.0 Hz, 3H), 1.59−1.24 (m, 4H), 0.92 (s, 9H), 0.91 (t, J = 7.2 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 143.2, 142.5, 126.3, 110.2, 107.3, 82.2, 80.0, 78.2, 72.7, 72.6, 40.6, 26.0, 19.1, 18.7, 18.4, 14.3, −4.2, −4.7; IR (ATR) ν 2956 (m), 2929 (m), 2856 (m), 1638 (w), 1462 (w), 1361 (w), 1253 (m), 1075 (m), 982 (m), 947 (m), 835 (s), 775 (s), 745 (m), 675 (w); HRMS (EI) calcd for $C_{21}H_{32}OSi$ [M^+] 328.2222, found 328.2236.

(6*E*,8*Z*,14*Z*,16*E*)-2,2,3,3,20,20,21,21-Octamethyl-5,18-dipropyl-4,19-dioxa-3,20-disilado-cosa-6,8,14,16-tetraen-10,12-diyne (26). *This compound was synthesized and handled under exclusion of light!*

To a solution of **15b** (39.0 mg, 147 μmol) in THF (5 mL) were added CuI (1.5 mg, 5 mol %), $HN(^iPr)_2$ (45 μL, 0.31 mmol), and $Pd(PPh_3)_2Cl_2$ (6.0 mg, 6 mol %). The reaction mixture was stirred for 12 h at ambient temperature. A sat. aq solution of NH_4Cl (5 mL) and MTBE was added. The organic layer was separated, and the aqueous layer was extracted with MTBE (2 × 10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica using hexane as eluent to obtain **26** (34.0 mg, 64 μmol, 87%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (dd, J = 15.1, 11.3 Hz, 2H), 6.50 (dd, J = 10.9, 10.9 Hz, 2H), 5.91 (dd, J = 15.2, 6.0 Hz, 2H), 5.50 (d, J = 10.4 Hz, 2H), 4.23 (q, J = 5.8 Hz, 2H), 1.59−1.26 (m, 8H), 0.94−0.88 (m, 24H), 0.06 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 142.8, 126.3, 107.4, 80.6, 80.0, 72.8, 40.6, 26.1, 18.7, 18.4, 14.3, −4.2, −4.2; IR (ATR) ν 2957 (m), 2929 (m), 2857 (m), 1638 (w), 1462 (w), 1361 (w), 1254 (m), 1076 (m), 982 (m), 835 (s), 775 (s), 676 (w); HRMS (EI) calc for $C_{32}H_{54}O_2Si_2$ [M^+] 526.3662, found 526.3685.

Attempted Deprotection of 25 with TBAF-Trihydrate. To a solution of **25** (66 mg, 0.20 mmol) in THF (3 mL) was added $NBu_4F{\cdot}3H_2O$ (95 mg, 0.30 mmol). The solution was stirred for 2 h at ambient temperature. Brine (2 mL) and MTBE (10 mL) were added; the organic layer was separated, and the aqueous layer was extracted with MTBE (2 × 10 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and evaporated. The residue was purified by chromatography on silica using hexane/MTBE (4:1 (v/v)) as eluent to furnish (5*E*,7*Z*,13*E*)-**5** and (5*E*,7*Z*,13*Z*)-**5** (60 mg, 60%) as an inseparable 1:1 mixture. NMR data for (5*E*,7*Z*,13*Z*)-**5** were obtained from the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (ddt, J = 15.2, 11.1, 1.1 Hz, 1H), 6.50 (dd, J = 10.9, 10.9 Hz, 1H), 6.16 (dq, J = 10.8, 7.0 Hz, 1H), 5.93 (ddm, J = 15.4, 6.7 Hz, 1H), 5.60 (dm, J = 10.8 Hz, 1H), 5.53 (d, J = 11.1 Hz, 1H), 4.24 (q, J = 6.0 Hz, 1H), 1.94 (dd, J = 7.0, 1.7 Hz, 3H), 1.60−1.30 (m, 4H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 143.5, 142.2, 128.2, 110.2, 109.1, 81.3, 81.1, 80.1, 79.1, 73.2, 40.2, 19.6, 17.5, 15.0.

(5*E*,7*Z*,13*E*)-Pentadeca-5,7,13-trien-9,11-diyn-4-ol (5*E*,7*Z*,13*E*)-5). A solution of compound **25** (40.0 mg, 0.12 mmol) in THF (8 mL) was cooled to 0 °C. HF·py (400 μL, 70% HF, 15.4 mmol) was added, and the reaction was stirred at this temperature for 12 h. Solid $NaHCO_3$ was then added portionwise until gas evolution ceased, followed by addition of water (10 mL) and MTBE (10 mL). The organic layer was separated, and the aqueous layer was extracted with MTBE (3 × 10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica using hexane/MTBE (4:1 (v/v)) mixture as eluent to yield (5*E*,7*Z*,13*E*)-**5** (12 mg, 56 μmol, 48%) as a yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.77 (ddt, J = 15.3, 11.1, 1.0 Hz, 2H), 6.52 (dd, J = 11.0, 11.0 Hz, 1H), 6.38 (dq, J = 15.8, 6.9 Hz, 1H), 5.96 (dd, J =

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15.3, 6.7 Hz, 1H), 5.64 (dm, J = 15.8 Hz, 1H), 5.54 (d, J = 10.7 Hz, 1H), 4.28 (q, J = 6.1 Hz, 1H), 1.87 (dd, J = 6.9, 1.8 Hz, 3H), 1.65−1.35 (m, 4H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 142.7, 141.3, 127.4, 110.1, 108.4, 82.5, 80.4, 78.0, 72.5, 72.4, 39.4, 19.1, 18.8, 14.1; IR (ATR) ν 3365 (bw), 2959 (m), 2929 (m), 2871 (m), 2197 (w), 1636 (w), 1456 (w), 1300 (m), 1260 (m), 1073 (m), 981 (s), 946 (s), 802 (m), 748 (m); HRMS (EI) calcd for $C_{15}H_{18}ONa$ $[M + Na]^+$ 237.1255, found 237.1263.

3-((*tert*-Butyldimethylsilyl)oxy)propan-1-ol (28).[70] NaH (1.20 g, 60 wt % dispersion in mineral oil, 30.0 mmol) was placed in a flask under an inert gas atmosphere and suspended in dry and degassed hexane (20 mL) with stirring. The solid was allowed to settle, and the supernatant hexane solution was removed. The solid was resuspended in THF (30 mL), and 1,3-propanediol (**27**, 2.20 mL, 30.0 mmol) was added. The suspension was stirred for 1 h at ambient temperature, and TBSCl (3.77 g, 25.0 mmol) was added in one portion. The reaction mixture was stirred for another 2 h, and then diluted with MTBE (300 mL) and subsequently washed with a sat. aq Na_2CO_3 solution and brine (20 mL each). The combined organic phases were dried with Na_2SO_4 and evaporated in vacuo. The residue was chromatographed on silica using hexane/MTBE mixtures of increasing polarity (6:1 to 2:1 (v/v)) as eluent to furnish **28** (3.91 g, 20.5 mmol, 82%) as a colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86−3.77 (m, 4H), 2.61 (s (br), 1H), 1.82−1.73 (pent, J = 5.7 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.1, 62.6, 34.3, 26.0, 18.3, −5.4; IR (ATR) ν 3350 (bw), 2953, (m), 2929 (m), 2857 (m), 1472 (w), 1254 (m), 1084 (m), 960 (m), 832 (s), 773 (s), 662 (m); HRMS (ESI) calcd for $C_9H_{23}O_2Si$ $[M + H]^+$ 191.1467, found 191.1468.

5-((*tert*-Butyldimethylsilyl)oxy)pent-1-en-3-ol (9c).[91] Oxidation of **28** to the corresponding aldehyde as previously described:[73] To a solution of $NaHCO_3$ (3.44 g, 41.0 mmol) and Na_2CO_3 (446 mg, 4.21 mmol) in water (84 mL) was added NaOCl (10 mL, 13 wt % in water, 19.4 mmol). A solution of **28** (986 mg, 5.18 mmol) in CH_2Cl_2 (40 mL) was placed in a two-necked flask equipped with a dropping funnel. KBr (63 mg, 0.53 mmol) was added, and the suspension was cooled to 0 °C followed by the addition of TEMPO (17 mg, 0.11 mmol). The previously prepared buffered aqueous NaOCl solution was added portionwise (1−2 mL) via the dropping funnel until TLC indicated full conversion (~65 mL of NaOCl solution was consumed). The reaction was quenched by the addition of MeOH (1 mL); the aqueous phase was separated and extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and evaporated in vacuo (45 °C at 500 mbar). Characterization data for 3-((*tert*-butyldimethylsilyl)oxy)propanal as obtained from the crude product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, J = 2.2 Hz, 1H), 3.95 (t, J = 6.0 Hz, 2H), 2.56 (td, J = 6.0, 2.2 Hz, 2H), 0.84 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 57.6, 46.7, 26.0, 18.4, −5.3; IR (ATR) ν 2954 (m), 2858 (m), 1716 (s), 1255 (s), 1101 (s), 831 (s), 775 (s); HRMS (ESI) calcd for $C_9H_{21}O_2Si$ $[M + H]^+$ 189.1305, found 189.1309. The crude product from the previous step was redissolved in dry and degassed diethyl ether (10 mL). This solution was added dropwise at 0 °C to a solution of vinylmagnesium bromide (6.2 mL, 1 M in THF, 6.20 mmol) in dry and degassed diethyl ether (10 mL). The mixture was warmed to ambient temperature and stirred for 12 h. The reaction was then quenched by addition of an aqueous NH_4Cl solution (sat. aq solution of NH_4Cl (10 mL) diluted with water (10 mL)). The organic layer was separated, and the aqueous layer was extracted with MTBE (3 × 20 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ and brine, dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography using hexane/MTBE mixtures of increasing polarity (20:1 to 10:1 to 8:1 (v/v)) as eluent to furnish **9c** (800 mg, 3.70 mmol, 71%) as a yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (ddd, J = 17.1, 10.4, 5.9 Hz, 1H), 5.23 (dt, J = 17.2, 1.4 Hz, 1H), 5.09 (dt, J = 10.4, 1.4 Hz, 1H), 4.16−4.10 (m, 1H), 3.95−3.76 (m, 2H), 3.32 (d, J = 3.5 Hz, 1H), 1.71−1.55 (m, 4H), 0.92 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 114.3, 72.7, 62.1, 38.4, 26.0, 18.3, −5.4, −5.4; IR (ATR) ν 3325 (bm), 2929 (m), 2857 (m), 1472 (w), 1255 (m), 1088 (m), 920 (s), 833 (s), 775 (s); HRMS (ESI) calcd for $C_{11}H_{25}O_2Si$ $[M + H]^+$ 217.1618, found 217.1617.

5-((*tert*-Butyldimethylsilyl)oxy)pent-1-en-3-ylbut-3-enoate (10c).[92] To a solution of allylic alcohol **9c** (0.780 g, 3.60 mmol) in CH_2Cl_2 (35 mL) were added DMAP (88 mg, 0.72 mmol) and vinyl acetic acid (**8**, 416 μL, 4.69 mmol). The solution was cooled to 0 °C, and DCC (966 mg, 4.69 mmol) was added. The mixture was warmed to ambient temperature and stirred for 12 h. It was filtered, and the filter cake was washed with CH_2Cl_2 (3×). The combined organic extracts were washed with aq HCl (1 M) followed by sat. aq $NaHCO_3$, dried with Na_2SO_4, filtered, and dry-loaded on silica gel. Column chromatography on silica, using hexane/MTBE mixtures of increasing polarity as eluent, gave **10c** (0.850 g, 2.95 mmol, 82%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (ddt, J = 17.3, 10.2, 6.9 Hz, 1H), 5.80 (ddd, J = 16.9, 10.5, 6.3 Hz, 1H), 5.39 (q, J = 6.9 Hz, 1H), 5.24 (dm, J = 17.3 Hz, 1H), 5.20−5.12 (m, 3H), 3.65 (t, J = 6.5 Hz, 2H), 3.09 (dm, J = 6.9 Hz, 2H), 1.95−1.75 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 136.3, 130.3, 118.5, 116.6, 72.2, 59.0, 39.4, 37.2, 25.9, 18.3, −5.4; IR (ATR) ν 2955 (w), 2929 (w), 2857 (w), 1739 (m), 1472 (w), 1251 (m), 1169 (m), 1094 (s), 985 (m), 920 (m), 833 (s), 774 (s), 662 (w); HRMS (ESI) calcd for $C_{15}H_{29}O_3Si$ $[M + H]^+$ 285.1880, found 285.1879.

5-((*tert*-Butyldimethylsilyl)oxy)pent-1-en-3-yl but-3-enoate ((2*Z*,4*E*)-14c). To a solution of **10c** (284 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added second generation Grubbs' catalyst **A** (26.0 mg, 3.0 mol %). The reaction mixture was stirred at 40 °C for 2 h and then cooled to 0 °C, and NaHMDS (1.2 mL, 1 M in THF, 1.20 mmol) was added. The mixture was warmed to ambient temperature and stirred for 12 h. Et_3OBF_4 (300 mg, 1.50 mmol) was then added, and the solution was stirred for 4 h at ambient temperature (TLC control). The reaction mixture was dry-loaded on silica gel and purified by column chromatography on silica using a hexane/MTBE mixture (20:1 (v/v)) as eluent to yield (2*Z*,4*E*)-**14c** (232 mg, 0.81 mmol, 81%) as a yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (ddm, J = 15.3, 11.3 Hz, 1H), 6.54 (dd, J = 11.3, 11.3 Hz, 1H), 6.08 (dt, J = 15.3, 7.2 Hz, 1H), 5.58 (d, J = 11.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.70 (t, J = 6.6 Hz, 2H), 2.42 (dt, J = 6.8, 6.8 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 145.1, 141.8, 128.6, 116.2, 62.5, 60.0, 36.7, 26.1, 18.5, 14.5, −5.1; IR (ATR) ν 2955 (w), 2929 (w), 2857 (w), 1715 (m), 1639 (m), 1602 (w), 1472 (w), 1420 (w), 1254 (m), 1176 (s), 1096 (s), 835 (s), 775 (s); HRMS (ESI) calcd for $C_{15}H_{29}O_3Si$ $[M + H]^+$ 285.1880, found 285.1878.

(2*Z*,4*E*)-7-((*tert*-Butyldimethylsilyl)oxy)hepta-2,4-dienal ((2*Z*,4*E*)-17c). To a solution of the ester (2*Z*,4*E*)-**14c** (880 mg, 3.09 mmol) in CH_2Cl_2 (30 mL) was added DIBAl-H (8.00 mL, 1 M in CH_2Cl_2, 8.00 mmol) at ambient temperature. The mixture was stirred for 10 min and quenched by the addition of sat. aq NH_4Cl (3 mL). It was further diluted with water (5 mL) and stirred for 5 min. At this point, a highly viscous residue had been formed from which the CH_2Cl_2 layer was removed. The residue was washed repeatedly with CH_2Cl_2. A minimum amount of aq HCl (1 M) required to dissolve the residue was added, and the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 20 mL) and Et_2O (20 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$ and brine and then dried with Na_2SO_4. The solution was filtered and evaporated in vacuo (45 °C at 450 mbar). Characterization data for (2*Z*,4*E*)-7-((*tert*-butyldimethylsilyl)oxy)hepta-2,4-dien-1-ol were obtained from the crude product: ^{1}H NMR (300 MHz, C_6D_6) δ 6.32 (ddm, J = 15.2, 11.1 Hz, 1H), 5.96 (dd, J = 11.1, 11.1 Hz, 1H), 5.62 (dt, J = 15.1, 7.1 Hz, 1H), 5.41 (dt, J = 11.0, 6.9 Hz, 1H), 4.05 (d, J = 6.5 Hz, 2H), 3.52 (t, J = 6.7 Hz, 2H), 2.23 (dt, J = 6.9, 6.7 Hz, 2H), 0.97 (s, 9H), 0.92 (s(br.), 1H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 132.9, 130.4, 129.2, 127.5, 62.9, 58.9, 36.8, 26.1, 18.5, −5.1. The crude product from the previous step was redissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C, and Dess−Martin periodinane **B** (1.600 g, 3.77 mmol) was added. The mixture was stirred at ambient temperature for 0.5 h. If the TLC control showed incomplete conversion, an additional portion of Dess−Martin periodinane **B** (280 mg, 0.66 mmol) was added, and the reaction mixture was stirred for another 5 min. The mixture was then

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diluted with CH_2Cl_2 and washed with sat. aq $NaHCO_3$ and aq $Na_2S_2O_3·5H_2O$ (250 g/L) (4 × 30 mL). The organic extract was then washed with brine and dried with Na_2SO_4, filtered, and evaporated. The residue was chromatographed on silica using hexanes/MTBE mixtures of increasing polarity (100:0 to 20:1 (v/v)) to furnish (2*Z*,4*E*)-**17c** (610 mg, 2.53 mmol, 82%) as a yellowish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.16 (d, J = 8.0 Hz, 1H), 7.09 (ddm, J = 14.5, 11.9 Hz, 1H), 6.93 (dd, J = 11.6, 11.6 Hz, 1H), 6.19 (dt, J = 14.6, 7.2 Hz, 1H), 5.80 (dd, J = 11.0, 8.0 Hz, 1H), 3.73 (t, J = 6.3 Hz, 2H), 2.48−2.41 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 147.9, 143.6, 126.3, 126.0, 62.1, 36.7, 26.0, 18.4, −5.2; IR (ATR) ν 2926 (w), 2857 (w), 1685 (m), 1640 (w), 1471 (w), 1253 (m), 1093 (s), 833 (s), 774 (s); HRMS (ESI) calcd for $C_{13}H_{24}O_2SiNa$ $[M + Na]^+$ 263.1438, found 263.1420; HRMS (ESI) calcd for $C_{13}H_{25}O_2Si$ $[M + H]^+$ 241.1618, found 241.1621.

***tert*-Butyldimethyl(((3*E*,5*Z*)-octa-3,5-dien-7-yn-1-yl)oxy)-silane (15c).** *This compound was synthesized and handled under exclusion of light!*

Wolkoff's reagent $[Ph_3PCHBr_2]Br·CH_3CN$ (1.11 g, 2.00 mmol) was suspended in THF (10 mL). KO^{t}Bu (213 mg, 1.90 mmol) was added, and the mixture was stirred for 10 min at ambient temperature. Aldehyde (2*Z*,4*E*)-**17c** (240 mg, 1.00 mmol) was added, and the reaction was monitored by TLC. If the conversion was incomplete after 10 min, a solution of Wolkoff's reagent (550 mg, 1.00 mmol) and KO^{t}Bu (106 mg, 0.95 mmol) in THF (5 mL) was added. Upon complete consumption of the starting material (TLC), KO^{t}Bu (673 mg, 6.00 mmol) was added in one portion, and the mixture was stirred for 5 min. The reaction was quenched by the addition of brine, and MTBE (25 mL) was added. The organic layer was separated, and the aqueous phase was extracted with MTBE (2 × 25 mL). The combined organic phases were dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography using hexane as eluent to furnish **15c** (175 mg, 0.74 mmol 74%) as a yello oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (ddm, J = 15.4, 10.9 Hz, 1H), 6.45 (dd, J = 10.9, 10.9 Hz, 1H), 5.94 (dt, J = 15.4, 7.1 Hz, 1H), 5.34 (dm, J = 10.8 Hz, 1H), 3.71 (t, J = 6.6 Hz, 2H), 3.23 (dm, J = 2.4 Hz, 1H), 2.40 (dt, J = 6.9, 6.6 Hz, 2H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 135.9, 129.4, 106.3, 82.9, 81.0, 62.7, 36.6, 26.1, 18.5, −5.1; IR (ATR) ν 2928 (w), 1253 (m), 1094 (s), 833 (s), 774 (s), 637 (m); HRMS (ESI) calcd for $C_{14}H_{24}OSiNa$ $[M + Na]^+$ 259.1489, found 259.1500.

Trimethyl(penta-1,3-diyn-1-yl)silane (31).[76] Synthesis of trimethyl(penta-1,3-diyn-1-yl)silane (**30**): A solution of BuLi (43.0 mL, 2.5 M in Hexan, 107.0 mmol) in THF (75 mL) was cooled to −78 °C. Hexachlorobutadiene (**29**, 7.00 g, 26.8 mmol) was added dropwise under vigorous stirring. The reaction mixture was warmed to ambient temperature over a period of 3 h and then recooled to 0 °C. TMSCl (3.90 mL, 53.7 mmol) was added dropwise, and the reaction mixture was stirred for an additional 0.5 h at 0 °C and then for 1 h at ambient temperature. Water (75 mL) was added carefully, followed by pentane (50 mL). The organic layer was separated, and the aqueous layer was extracted with pentane (2 × 50 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, and filtered through a short silica coloumn. The solvent was evaporated, and the resulting yellowish solid was purified by sublimation in vacuo to furnish **30** (4.12 g, 21.2 mmol, 78%) as colorless crystals. Synthesis of trimethyl(penta-1,3-diyn-1-yl)silane (**31**): Diyne **30** (4.00 g, 20.6 mmol) was dissolved in THF (40 mL). MeLi·LiBr (15.1 mL, 1.5 M in Et_2O, 22.6 mmol) was added at ambient temperature, and the reaction mixture was stirred for 5 h. The solution was then cooled to −78 °C, and a solution of MeI (3.20 g, 22.6 mmol) in THF (30 mL) was added. After stirring at ambient temperature for 12 h, the reaction was quenched by the addition of a sat. aq NH_4Cl solution (20 mL). The organic layer was separated, and the aqeuous layer was extracted with diethyl ether (4 × 40 mL). The solvent was evaporated in vacuo, and the residue was distilled (bp 60 to 70 °C at 15 mbar) to give **31** (1.20 g, 8.7 mmol, 42%) as a colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (s, 3H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 88.4, 82.5, 75.7, 64.7, 4.2, −0.3.

***tert*-Butyldimethyl(((3*E*,5*Z*)-trideca-3,5-dien-7,9,11-triyn-1-yl)oxy)silane (33).** *This compound was synthesized and handled under exclusion of light!*

To a solution of **31** (36.0 mg, 264 μmmol) in CH_3CN (3 mL) were added NBS (56.0 mg, 320 μmol) and AgF (40.0 mg, 315 μmol) at ambient temperature. The mixture was stirred for 1 h, and a sat. aq solution of NH_4Cl (5 mL) was added, followed by pentane (25 mL). The organic layer was separated, and the aqueous layer was extracted with pentane (4 × 25 mL). The combined organic phases were dried with Na_2SO_4 and concentrated in vacuo (40 °C at 600 mbar). Crude bromoacetylene **32** was immediately used without further purification in the next step: To a solution of **15c** (31.0 mg, 131 μmol), NBu_4Br (4.0 mg, 12.4 μmol, 9.0 mol %), and CuI (2.5 mg, 13.1 μmol, 10.0 mol %) in $HNPr^i_2$ (4 mL) was added a solution of freshly prepared bromodiyne **32** in $HNPr^i_2$ (1 mL). The resulting solution was stirred for 5 min at 70 °C, and $Pd(OAc)_2$ (2.5 mg, 11.1 μmol, 8.0 mol %) was added. The mixture was stirred for 12 h at 70 °C and cooled to ambient temperature, and aq HCl (2 M, 4 mL) and ethyl acetate (10 mL) were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (4 × 10 mL). The combined organic phases were dried with Na_2SO_4 and evaporated in vacuo. The crude product was purified by column chromatography using hexane as eluent to furnish **33** (12 mg, 40 μmol, 30%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (dd, J = 14.7, 10.5 Hz, 1H), 6.54 (dd, J = 10.5, 10.5 Hz, 1H), 5.99 (dt, J = 14.5, 7.2 Hz, 1H), 5.34 (d, J = 10.4 Hz, 1H), 3.69 (t, J = 6.5 Hz, 2H), 2.39 (dt, J = 7.2, 6.5 Hz, 2H), 2.00 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 137.8, 129.7, 105.4, 80.2, 79.0, 73.3, 68.8, 65.2, 62.6, 59.3, 36.6, 26.1, 18.5, 4.9, −5.1; IR (ATR) ν 2953 (m), 2928 (m), 2856 (m), 2218 (w), 2178 (w), 1634 (w), 1471 (w), 1254 (m), 1098 (s), 981 (m), 938 (m), 834 (s), 775 (s), 742 (w), 662 (w); HRMS (ESI) calcd for $C_{19}H_{27}OSi$ $[M + H]^+$ 299.1831, found 299.1828.

(3*E*,5*Z*)-Trideca-3,5-dien-7,9,11-triyn-1-ol (6).[22] A solution of compound **33** (27 mg, 90 μmol) in THF (8 mL) was cooled to 0 °C. HF·py (100 μL, 70 wt % HF, 3.90 mmol) was added, and the reaction was stirred at 0 °C for 2 h. Solid $NaHCO_3$ was then added portionwise until gas evolution had ceased, followed by addition of water (10 mL) and MTBE (10 mL). The organic layer was separated, and the aqueous layer was extracted with MTBE (3 × 10 mL). The combined organic phases were dried with Na_2SO_4 and evaporated in vacuo. The residue was chromatographed on silica using hexane/MTBE mixtures of increasing polarity (2:1 to 1:2 (v/v)) as eluent to furnish **6** (8.0 mg, 43 μmol, 48%) as a yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.68 (ddq, J = 15.3, 11.1, 1.2 Hz, 1H), 6.55 (dd, J = 10.9, 10.9 Hz, 1H), 5.98 (dt, J = 15.3, 7.3 Hz, 1H), 5.38 (d, J = 10.7 Hz, 1H), 3.73 (t, J = 6.3 Hz, 2H), 2.46 (dt, J = 7.3, 6.3 Hz, 2H), 2.00 (s, 3H), 1.74 (bs, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.2, 136.8, 130.4, 106.0, 80.4, 79.2, 73.0, 69.0, 65.1, 61.9, 59.2, 36.4, 4.9; IR (ATR) ν 3338 (bm), 2925 (m), 2881 (m), 2217 (s), 2177 (m), 1633 (s), 1562 (w), 1411 (m), 1373 (m), 1040 (s), 980 (s), 940 (m), 800 (w), 741 (m), 682 (w), 482 (w); HRMS (EI) calcd for $C_{13}H_{12}O$ $[M^+]$ 184.0883, found 184.0884.

((4*S*)-2-Phenyl-1,3-dioxan-4-yl)methanol (*S*-35).[81] To a solution of triol *S*-**34** (3.17 g, 29.9 mmol) in CH_2Cl_2 (120 mL) were added camphor sulfonic acid (333 mg, 1.43 mmol) followed by benzaldehyde dimethyl acetal (6.00 mL, 40.0 mmol). The solution was stirred at ambient temperature for 12 h and then quenched by addition of imidazol (200 mg, 3.00 mmol). All volatiles were evaporated in vacuo, and the residue was purified by chromatography on silica using hexanes/MTBE mixtures of increasing polarity (2:1 to 1.5:1 (v/v)) as eluent to furnish *S*-**35** (5.12 g, 26.4 mmol, 88%) as a colorless liquid; $[\alpha]_D^{23}$ +9.6 (*c* 0.35, CH_2Cl_2); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.50−7.40 (m, 2H), 7.38−7.29 (m, 3H), 5.53 (s, 1H), 4.20 (dd, J = 11.3, 5.1 Hz, 1H), 4.01−3.90 (m, 2H), 3.78 (dd, J = 6.6, 5.9 Hz, 1H), 3.65−3.50 (m, 2H), 1.75 (qd, J = 12.9, 5.1 Hz, 1H), 1.52 (dm, J = 12.9 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 140.5, 129.3, 128.7, 127.2, 101.8, 78.9, 67.3, 66.1, 28.5; IR (ATR) ν 3423 (bw), 2861 (w), 1455 (w), 1103 (s), 1065 (s), 1024 (s), 757 (m), 699 (s); HRMS (EI) calcd for $C_{11}H_{14}O_3$ $[M^+]$ 194.0943, found 194.0948.

1-((4*S*)-2-Phenyl-1,3-dioxan-4-yl)prop-2-en-1-ol (*S*,*RS*)-36).[82] The Parikh−Doering oxidation was carried out following a literature

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procedure:[81] To a solution of *S*-**35** (2.98 g, 15.3 mmol) and NEt_3 (21.3 mL, 153 mmol) in a CH_2Cl_2/DMSO solvent mixture (4:1 (v/v) 150 mL) was added SO_3·py (12.20 g, 76.7 mmol) at ambient temperature in one portion. The reaction mixture was stirred for 3 h at this temperature, and then water (150 mL) and brine (100 mL) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with water (2 × 50 mL), and the combined aqueous phases were extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with brine (100 mL) and dried with Na_2SO_4, and all volatiles were evaporated in vacuo. The crude aldehyde was dissolved in diethyl ether (30 mL), and the solution was added dropwise to a solution of vinylmagnesium bromide (18.4 mL, 1.0 M in THF, 18.4 mmol) in diethyl ether (18 mL) at 0 °C. The reaction was stirred for 12 h at ambient temperature and then quenched by addition of a sat. aq NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with MTBE (3 × 30 mL). The combined organic phases were washed with brine (100 mL) and dried with Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica using hexanes/MTBE mixtures of increasing polarity (3:1 to 2:1 (v/v)) as eluent to furnish (*S*,*RS*)-**36** (1.2:1.0 mixture of diastereomers, 1.80 g, 8.1 mmol, 53%) as a yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.45 (m, 2H), 7.43−7.33 (m, 3H), 5.99−5.79 (m, 1H), 5.56 (s, 0.5H), 5.54 (s, 0.5H), 5.46−5.23 (m, 2H), 4.35−4.27 (m, 1H), 4.14−3.73 (m, 3H), 2.24 (bs, 1H), 2.05 (qd, *J* = 12.7, 5.1 Hz, 0.5H), 1.88 (qd, *J* = 12.3, 5.2 Hz, 0.5H), 1.56−1.44 (m, 1H); major isomer: ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 135.7, 129.1, 128.4, 126.2, 117.3, 101.4, 79.5, 74.4, 66.9, 25.0; minor isomer: ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 135.6, 129.2 128.4, 126.3, 118.4, 101.4, 79.9, 75.8, 66.7, 27.2; IR (ATR) ν 3443 (bw), 2857 (w), 1454 (w), 1241 (w), 1105 (s), 1025 (s), 991 (s), 759 (m), 698 (s); HRMS (EI) calcd for $C_{13}H_{16}O_3$ [M^+] 220.1099, found 220.1093.

1-((4*S*)-2-Phenyl-1,3-dioxan-4-yl)allyl But-3-enoate (*S*,*RS*)-37). A solution of allylic alcohol (*S*,*RS*)-**36** (1.66 g, 7.5 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C, and DMAP (91 mg, 0.75 mmol) and vinyl acetic acid (**8**, 0.67 g, 7.8 mmol) were added. A solution of DCC (1.55 g, 7.5 mmol) in CH_2Cl_2 (20 mL) was added dropwise at this temperature, and the reaction mixture was warmed to ambient temperature. If the conversion of the alcohol remained incomplete after 3 h (TLC), an additional portion of vinyl acetic acid (**8**, 0.17 g, 2.0 mmol) and DCC (0.39 g, 1.9 mmol) were added, and the mixture was stirred at ambient temperature for 12 h. This process was repeated if necessary. The reaction mixture was then cooled to 0 °C to facilitate precipitation of the urea byproduct and filtered. Silica was added to the filtrate, and all volatiles were removed in vacuo. The product was isolated by chromatography on silica using a hexanes/MTBE mixture (4:1 (v/v)) as eluent to furnish (*S*,*RS*)-**37** (1.2:1.0 mixture of diastereomers, 1.99 g, 6.9 mmol, 92%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.43 (m, 2H), 7.43−7.29 (m, 3H), 6.05−5.81 (m, 2H), 5.51 (s, 1H), 5.48−5.28 (m, 3H), 5.26−5.12 (m, 2H), 4.37−4.23 (m, 1H), 4.08−3.90 (m, 2H), 3.22−3.10 (m, 2H), 2.07−1.80 (m, 1H), 1.62−1.42 (m, 1H); major isomer: ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 138.5, 132.5, 130.2, 128.9, 128.3, 126.2, 119.1, 118.9, 101.2, 77.8, 76.2, 66.8, 39.4, 26.6; minor isomer: ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 138.5, 132.3, 130.3 128.9, 128.3, 126.1, 119.2, 118.8, 101.2, 77.4, 75.9, 66.8, 39.3, 26.8; IR (ATR) ν 2857 (w), 1738 (s), 1643 (w), 1243 (m), 1170 (s), 1108 (s), 1024 (m), 989 (s), 927 (m), 698 (m); HRMS (EI) calcd for $C_{17}H_{20}O_4$ [M^+] 288.1362, found 288.1373.

Ethyl (2*Z*,4*E*)-5-((4*S*)-2-Phenyl-1,3-dioxan-4-yl)penta-2,4-dienoate ((5*S*,2*Z*,4*E*)-14d). To a solution of (*S*,*RS*)-**37** (1.80 g, 6.2 mmol) in CH_2Cl_2 (60 mL) was added second generation Grubbs' catalyst A (185 mg, 3.5 mol %). The reaction was heated at 40 °C until full conversion of starting material was observed (TLC). It was then cooled to 0 °C, and NaHMDS (5.00 mL, 1.50 M in THF, 7.50 mmol) was added. The mixture was stirred at ambient temperature for 3 h. $[Et_3O]BF_4$ (1.90 g, 9.5 mmol) was added, and the reaction was stirred for an additional 3 h at ambient temperature. Silica gel was then added to the solution, and the solvent was removed in vacuo. The product was isolated by chromatography on silica using hexanes/MTBE mixtures (4:1 (v/v)) as eluent to furnish (5*S*,2*Z*,4*E*)-**14d** (1.30 g, 4.5 mmol, 73%) as a yellowish oil; $[\alpha]_D^{23}$ +43.1 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (ddm, *J* = 15.6, 11.3 Hz, 1H), 7.53−7.50 (m, 2H), 7.38−7.31 (m, 3H), 6.57 (dd, *J* = 11.4, 11.4 Hz, 1H), 6.10 (dd, *J* = 15.6, 5.9 Hz, 1H), 5.70 (d, *J* = 11.4 Hz, 1H), 5.58 (s, 1H), 4.55 (ddm, *J* = 10.9, 6.0 Hz, 1H), 4.31 (ddd, *J* = 11.4, 4.9, 1.1 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.03 (ddd, *J* = 12.0, 11.5, 2.5 Hz, 1H), 2.00 (dddd, *J* = 13.3, 12.4, 11.5, 4.9 Hz, 1H), 1.66 (dm, *J* = 13.3 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 143.7, 141.8, 138.5, 129.0, 128.4, 127.1, 126.3, 118.9, 101.4, 77.2, 66.9, 60.3, 31.1, 14.4; IR (ATR) ν 2979 (w), 2854 (w), 1711 (s), 1643 (w), 1604 (w), 1186 (s), 1147 (m), 1106 (m), 1024 (m), 881 (w), 819 (w), 756 (w), 698 (w); HRMS (EI) calcd for $C_{17}H_{20}O_4$ [M^+] 288.1362, found 288.1367.

(2*Z*,4*E*)-5-((4*S*)-2-phenyl-1,3-dioxan-4-yl)penta-2,4-dienal (5*S*,2*Z*,4*E*)-17d. To a solution of (5*S*,2*Z*,4*E*)-**14d** (1.15 g, 4.0 mmol) in CH_2Cl_2 (30 mL) was added DIBAl-H (9.50 mL, 1.0 M in DCM, 9.5 mmol) at ambient temperature. The mixture was stirred for 10 min and quenched by addition of brine (10 mL). It was diluted with CH_2Cl_2 (10 mL), and a minimum amount of aq HCl (1 M) necessary to dissolve any inorganic precipitates was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ solution and brine and dried with Na_2SO_4. The solution was filtered, and all volatiles were evaporated in vacuo. The residue was immediately redissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C, and Dess−Martin periodinane B (2.03 g, 4.8 mmol) was added. The mixture was warmed to ambient temperature, stirred for 1 h, diluted with CH_2Cl_2, and washed with a solution of sat. aq $NaHCO_3$ and $Na_2S_2O_3$·$5H_2O$ (250 g/L) (4 × 10 mL). The organic solution was dried with Na_2SO_4, filtered, and dry-loaded on silica. The residue was purified by chromatography on silica using a hexanes/MTBE mixture (2:1 (v/v)) as eluent to furnish (5*S*,2*Z*,4*E*)-**17d** (0.72 g, 2.9 mmol, 74%) as a yellowish oil; $[\alpha]_D^{23}$ +31.5 (*c* 0.41, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.19 (d, *J* = 7.9 Hz, 1H), 7.53−7.50 (m, 2H), 7.41−7.34 (m, 3H), 7.30 (ddt, *J* = 15.1, 11.9, 1.2 Hz, 1H), 6.95 (dd, *J* = 11.6, 11.6 Hz, 1H), 6.19 (dd, *J* = 15.1, 5.1 Hz, 1H), 5.90 (dd, *J* = 11.0, 7.9 Hz, 1H), 5.61 (s, 1H), 4.58 (dm, *J* = 11.5 Hz, 1H), 4.33 (ddd, *J* = 11.5, 4.9, 1.3 Hz, 1H), 4.04 (ddd, *J* = 12.2, 11.6, 2.5 Hz, 1H), 1.97 (dddd, *J* = 13.3, 12.3, 11.7, 5.0 Hz, 1H), 1.69 (dm, *J* = 13.3 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 190.6, 146.5, 143.0, 138.3, 129.2, 128.5, 128.2, 126.2, 123.8, 101.4, 76.4, 66.9, 31.2; IR (ATR) ν 2856 (w), 1668 (s), 1642 (m), 1225 (m), 1127 (s), 1105 (s), 1004 (s), 954 (m), 753 (m), 699 (s); HRMS (EI) calcd for $C_{15}H_{16}O_3$ [M^+] 244.1099, found 244.1089.

(4*S*)-4-((1*E*,3*Z*)-Hexa-1,3-dien-5-yn-1-yl)-2-phenyl-1,3-dioxane (*S*-15d). *This compound was synthesized and handled under exclusion of light!*

Wolkoff's reagent $[Ph_3PCHBr_2]Br$·CH_3CN (915 mg, 1.65 mmol) was suspended in THF (10 mL), and KO^{t}Bu (180 mg, 1.60 mmol) was added. The mixture was stirred for 10 min at ambient temperature. Then, aldehyde (5*S*,2*Z*,4*E*)-**17d** (201 mg, 0.82 mmol) was added, and the mixture was stirred until TLC indicated complete conversion (~10 min). KO^{t}Bu (369 mg, 3.29 mmol) was added in one portion, and stirring was continued for an additional 5 min. The reaction was quenched by addition of brine, and MTBE (20 mL) was added. The organic layer was separated, and the aqueous layer was extracted with MTBE (2 × 20 mL). The combined organic phases were dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by chromatography on silica using a hexanes/MTBE mixture (4:1 (v/v)) as eluent to furnish *S*-**15d** (135 mg, 0.56 mmol, 69%) as an off-white solid; mp 72−73 °C; $[\alpha]_D^{23}$ +106.4 (*c* 0.27, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.46 (m, 2H), 7.42−7.31 (m, 3H), 6.85 (dd, *J* = 15.0, 11.3 Hz, 1H), 6.47 (dd, *J* = 10.8, 10.8 Hz, 1H), 5.98 (dd, *J* = 15.5, 6.0 Hz, 1H), 5.59 (s, 1H), 5.47 (d, *J* = 10.6 Hz, 1H), 4.58−4.45 (m, 1H), 4.31 (dd, *J* = 11.5, 4.7 Hz, 1H), 4.04 (td, *J* = 12.0, 2.2 Hz, 1H), 3.25 (d, *J* = 1.7 Hz, 1H), 2.00 (qd, *J* = 12.5, 5.0 Hz, 1H), 1.64 (dm, *J* = 13.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 138.6, 136.7, 129.0, 128.4, 128.1, 126.3, 109.1, 101.4, 83.8, 80.6, 77.3,

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67.0, 31.4; IR (ATR) ν 3286 (m), 2855 (w), 2093 (w), 1454 (w), 113 (s), 1022 (s), 984 (s), 751 (m), 698 (s), 652 (m); HRMS (ESI) calcd for $C_{16}H_{16}O_2Na$ $[M + Na]^+$ 263.1048, found 263.1058.

(*S*,4*E*,6*Z*)-Nona-4,6-dien-8-yne-1,3-diol (*S*-15e). *This compound was synthesized and handled under exclusion of light!*

To a solution of *S*-**15d** (122 mg, 508 μmol) in methanol (50 mL) was added *p*-TSA·H_2O (4.3 mg, 5.0 mol %) at ambient temperature, and the solution was stirred for 12 h. A sat. aq $NaHCO_3$ solution (2 mL) and water (2 mL) were added, and the mixture was concentrated in vacuo (40 °C at 100 mbar). The concentrated aqueous solution was extracted with ethyl acetate (5 × 20 mL). The combined organic phases were dried with Na_2SO_4 and concentrated in vacuo. The residue was filtered through a short pad of Celite and eluted with chloroform. All volatiles were removed in vacuo to furnish *S*-**15e** (74 mg, 486 μmol, 96%), which was used in the next step without further purification as a yellowish oil; $[\alpha]_D^{21}$ +43.0 (*c* 0.21, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.46 (dd, *J* = 10.9, 10.9 Hz, 1H), 5.95 (dd, *J* = 15.4, 6.2 Hz, 1H), 5.45 (dd, *J* = 10.6, 1.6 Hz, 1H), 4.56−4.47 (m, 1H), 3.94−3.80 (m, 2H), 3.25 (d, *J* = 1.6 Hz, 1H), 2.22 (s (br), 2H), 1.87−1.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 139.7, 127.1, 108.8, 83.9, 80.6, 72.2, 61.3, 38.4; IR (ATR) ν 3336 (bs), 3289 (s), 3943 (w), 2090 (w), 1419 (w), 1052 (s), 985 (s), 754 (w), 642 (m); HRMS (ESI) calcd for $C_9H_{13}O_2$ $[M + H]^+$ 153.0916, found 153.0926; HRMS (ESI) calcd for $C_9H_{12}O_2Na$ $[M + Na]^+$ 175.0735, found 175.0742.

(*S*,4*E*,6*Z*)-3-Hydroxynona-4,6-dien-8-yn-1-yl Acetate (*S*-15f). *This compound was synthesized and handled under exclusion of light!*

A solution of diol *S*-**15e** (35.7 mg, 234 μmol) and $NEtPr^i_2$ (62 μL, 469 μmol) CH_2Cl_2 (5 mL) was cooled to 0 °C. Freshly destilled acetyl chloride (20 μL, 281 μmol) was added, and the solution was stirred for 12 h at ambient temperature. Diluted aq. HCl (1 M, 3 mL) was added; the organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried with Na_2SO_4, and the solvent was removed in vacuo. The residue was chromatographed on silica using hexanes/MTBE mixtures of increasing polarity (3:1 to 2:1 to 1:1 (v/v)) to furnish *S*-**15f** (25.5 mg, 131 μmol, 56%) as a yellowish oil; $[\alpha]_D^{23}$ +38.7 (*c* 0.21, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.45 (dd, *J* = 10.9, 10.9 Hz, 1H), 5.91 (dd, *J* = 15.4, 6.3 Hz, 1H), 5.45 (dd, *J* = 10.6, 1.6 Hz, 1H), 4.39−4.26 (m, 2H), 4.16 (dt, *J* = 11.3, 5.7 Hz, 1H), 3.26 (d, *J* = 1.6 Hz, 1H), 2.07 (s, 3H), 1.94−1.80 (m, 2H), 1.60 (s(br), 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 141.0, 139.3, 127.5, 109.0, 83.9, 80.5, 69.3, 61.3, 36.1, 21.1; IR (ATR) ν 3446 (bw), 3289 (w), 2961 (w), 1733 (s), 1245 (s), 1042 (m), 986 (m), 608 (w); HRMS (ESI) calcd for $C_{11}H_{14}O_3Na$ $[M + Na]^+$ 217.0841, found 217.0838. Analytical data for (4*E*,6*Z*)-nona-4,6-dien-8-yne-1,3-diyl diacetate (**15g**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (dd, *J* = 15.4, 11.0 Hz, 1H), 6.42 (dd, *J* = 10.8, 10.8 Hz, 1H), 5.82 (dd, *J* = 15.4, 6.9 Hz, 1H), 5.51−5.42 (m, 2H), 4.19−4.06 (m, 2H), 3.27 (d, *J* = 1.7 Hz, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 2.03−1.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.5, 140.8, 134.6, 129.6, 110.1, 84.5, 80.6, 71.2, 60.8, 33.7, 21.5, 21.3; IR (ATR) ν 3285 (w), 2936 (w), 1734 (s), 1369 (m), 1229 (s), 1042 (m), 846 (w), 756 (w), 638 (w), 606 (w); HRMS (ESI) calcd for $C_{13}H_{16}O_4Na$ $[M + Na]^+$ 259.0946, found 259.0946.

(*S*,4*E*,6*Z*)-1-Acetoxynona-4,6-dien-8-yn-3-yl isobutyrate(*S*-15h). *This compound was synthesized and handled under exclusion of light!*

A solution of *S*-**15f** (31.0 mg, 160 μmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C. $NEtPr^i_2$ (54.5 μL, 351 μmol), isobutyryl chloride (33.5 μL, 319 μmol), and DMAP (2 mg, 16 μmol, 10 mol %) were added, and the solution was warmed to ambient temperature and stirred for 12 h. Silica gel was added, and the solvent was evaporated in vacuo. The residue was chromatographed on silica using hexanes/MTBE mixtures of increasing polarity (10:1 to 8:1 to 6:1) to furnish *S*-**15h** (24.2 mg, 91.5 μmol, 57%) as a yellowish oil; $[\alpha]_D^{21}$ +7.3 (*c* 0.14, DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (dd, *J* = 15.4, 11.2 Hz, 1H), 6.42 (dd, *J* = 10.7, 10.7 Hz, 1H), 5.83 (dd, *J* = 15.5, 6.3 Hz, 1H), 5.51−5.42 (m, 2H), 4.15−4.08 (m, 2H), 3.25 (d, *J* = 1.6 Hz, 1H), 2.57 (sept., *J* = 7.0 Hz, 1H), 2.05 (s, 3H), 2.03−1.96 (m, 2H), 1.22−1.19 (m, 3H), 1.19 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 171.1, 140.6, 134.6, 128.8, 109.6, 84.1, 80.4, 70.4, 60.5, 34.3, 33.5, 21.1, 19.1, 19.1; IR (ATR) ν 3267 (w), 2973 (w), 2930 (w), 1737 (s), 1367 (w), 1240 (m), 1154 (m); HRMS (ESI) calcd for $C_{15}H_{20}O_4Na$ $[M + Na]^+$ 287.1259, found 287.1270.

(*S*,4*E*,6*Z*)-1-Acetoxynona-4,6-dien-8-yn-3-yl 3-methylbut-2-enoate (*S*-15i). *This compound was synthesized and handled under exclusion of light!*

To a solution of *S*-**15f** (15.8 mg, 81.4 μmol) and pyridine (24.0 μL, 297 μmol) in CH_2Cl_2 (4 mL) was added 3,3-dimethylacryloyl chloride (31.0 μL, 266 μmol) at ambient temperature, and the reaction mixture was stirred for 12 h. The mixture was dry-loaded on silica and chromatographed on silica using a hexanes/MTBE mixture (5:1 (v/v)) as eluent to furnish *S*-**15i** (13.9 mg, 50.3 μmol, 61%) as a yellow oil; $[\alpha]_D^{23}$ +78.9 (*c* 0.12, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (ddm, *J* = 15.6, 11.1 Hz, 1H), 6.41 (dd, *J* = 10.9, 10.9 Hz, 1H), 5.85 (dd, *J* = 15.5, 6.8 Hz, 1H), 5.68 (sept, *J* = 1.2 Hz, 1H), 5.50 (q, *J* = 6.5 Hz, 1H), 5.45 (dd, *J* = 10.7, 2.3 Hz, 1H), 4.15−4.09 (m, 2H), 3.25 (dd, *J* = 2.4, 0.6 Hz, 1H), 2.16 (d, *J* = 1.2 Hz, 3H), 2.04 (s, 3H), 2.03−1.98 (m, 2H), 1.90 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 165.7, 157.8, 140.7, 135.1, 129.0, 115.9, 109.5, 84.1, 80.4, 69.9, 60.7, 33.5, 27.6, 21.1, 20.5; IR (ATR) ν 3287 (w), 2093 (w), 1737 (s), 1717 (s), 1648 (m), 1222 (s), 1140 (s), 1074 (m), 982 (m); HRMS (ESI) calcd for $C_{16}H_{20}O_4Na$ $[M + Na]^+$ 299.1259, found 299.1254. Characteristic signals of the byproduct *S*-**15i′** formed during esterification with Hünig's base: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (s, 1H), 4.86 (s, 1H), 3.05 (s, 2H).

(*S*)-Atractylodemayne F (*S*-2).[19] *This compound was synthesized and handled under exclusion of light!*

To a solution of *S*-**15h** (10.3 mg, 39.0 μmol), NBu_4Br (2.0 mg, 6.20 μmol, 16 mol %), and CuI (0.6 mg, 3.2 μmol, 8 mol %) in $HNPr^i_2$ (4 mL) was added iodoacetylene **38b** (32.4 mg, 156 μmol). The solution was heated at 70 °C for 5 min with stirring, and $Pd(OAc)_2$ (1.0 mg, 4.45 μmol, 11 mol %) was added. Stirring at 70 °C was continued for 12 h. The mixture was cooled to ambient temperature, and diluted aq HCl (2 M, 4 mL) was added, followed by ethyl acetate (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic phases were dried with Na_2SO_4 and evaporated in vacuo. The crude product was purified by column chromatography using hexanes/MTBE mixtures of increasing polarity (2:1 to 1:1 (v/v)) as eluent to furnish (*S*)-atractylodemayne F (*S*-**2**, 6.3 mg, 18.3 μmol, 43%) as a yellow oil; $[\alpha]_D^{21}$ +83.9 (*c* 0.10, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (ddt, *J* = 15.4, 11.1, 1.0 Hz, 1H), 6.48 (dd, *J* = 10.9, 10.9 Hz, 1H), 6.42 (dt, *J* = 15.9, 4.8 Hz, 1H), 5.89 (dm, *J* = 15.9 Hz, 1H), 5.86 (dd, *J* = 15.4, 6.3 Hz, 1H), 5.54 (d, *J* = 10.6 Hz, 1H), 5.48 (q, *J* = 6.4 Hz, 1H), 4.27 (dd, *J* = 4.7, 1.7 Hz, 2H), 4.17−4.07 (m, 2H), 2.58 (sept, *J* = 7.0 Hz, 1H), 2.06 (s, 3H), 2.03−1.98 (m, 2H), 1.57 (s, 1H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 170.9, 145.4, 142.1, 135.3, 128.7, 109.2, 109.0, 81.5, 80.4, 78.3, 74.5, 70.2, 62.7, 60.3, 34.2, 33.4, 20.9, 19.0, 18.9; IR (ATR) ν 3454 (w), 2972 (w), 2903 (w), 2856 (w), 2198 (w), 1736 (s), 1368 (m), 1241 (m), 1154 (m), 1100 (m), 1041 (m), 984 (m), 753 (w), 700 (w); HRMS (ESI) calcd for $C_{20}H_{24}O_5Na$ $[M + Na]^+$ 367.1521, found 367.1521. Selected analytical data of the 2*E*/2*Z*-isomerization product 2*Z*-**2** (obtained from the mixture after keeping the sample in $CDCl_3$ for 30 days): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (ddt, *J* = 15.4, 11.1, 1.1 Hz, 1H), 6.50 (dd, *J* = 10.9, 10.9 Hz, 1H), 6.26 (dt, *J* = 11.1, 6.4 Hz, 1H), 5.70 (dm, *J* = 11.1 Hz, 1H), 5.56 (d, *J* = 10.9 Hz, 1H), 4.45 (dd, *J* = 6.4, 1.5 Hz, 1H).

(*S*,4*E*,6*Z*,12*E*)-1-Acetoxy-14-hydroxytetradeca-4,6,12-trien-8,10-diyn-3-yl 3-methylbut-2-enoate (*S*-3).[19,26] *This compound was synthesized and handled under exclusion of light!*

To a solution of *S*-**15i** (13.2 mg, 47.8 μmol), NBu_4Br (2.0 mg, 6.20 μmol, 13 mol %), and CuI (0.9 mg, 4.8 μmol, 10 mol %) in $HNPr^i_2$ (4 mL) was added bromoacetylene **38a** (30.8 mg, 191 μmol). The solution was heated to 70 °C with stirring for 5 min. $Pd(OAc)_2$ (0.5 mg, 2.39 μmol, 5 mol %) was then added, and the mixture was heated to 70 °C with stirring for 12 h. It was then cooled to ambient temperature and diluted with ethyl acetate (30 mL). The mixture was washed with diluted aq HCl (2 M, 2 × 4 mL) to remove the amine.

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The aqueous washing solution was extracted with ethyl acetate (2 × 10 mL); the combined organic extracts were washed with sat. aq $NaHCO_3$ solution and brine, dried with Na_2SO_4, filtered, and evaporated in vacuo. The residue was chromatographed on silica using hexanes/MTBE mixtures of increasing polarity (2:1 to 1:1 (v/v)) to give *S*-**3** (8.0 mg, 22.5 μmol, 47%) as a yellow oil; $[\alpha]_D^{23}$ +78.8 (*c* 0.12, methanol); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 6.74 (ddt, *J* = 15.3, 11.2, 1.0 Hz, 1H), 6.52 (dd, *J* = 11.0, 11.0 Hz, 1H), 6.45 (dt, *J* = 15.9, 4.7 Hz, 1H), 5.91 (dd, *J* = 15.3, 6.8 Hz, 1H), 5.90 (dm, *J* = 15.9 Hz, 1H), 5.70 (sept, *J* = 1.3 Hz, 1H), 5.56 (d, *J* = 10.7 Hz, 1H), 5.47 (q, *J* = 6.7 Hz, 1H), 4.24 (dd, *J* = 4.7, 1.6 Hz, 2H), 4.09 (t, *J* = 6.1 Hz, 2H), 2.16 (d, *J* = 1.2 Hz, 3H), 2.02 (s, 3H), 2.01−1.96 (m, 2H), 1.90 (d, *J* = 1.2 Hz, 3H), 1.70 (s(br), 1H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 171.1, 165.8, 158.2, 146.7, 142.9, 136.8, 129.1, 115.9, 109.1, 108.5, 82.1, 80.4, 78.6, 74.3, 70.2, 62.9, 60.8, 33.8, 27.6, 21.1, 20.4; IR (ATR) ν 3450 (w), 2919 (w), 2854 (w), 2199 (w), 1737 (s), 1718 (s), 1648 (m), 1444 (m), 1367 (m), 1224 (s), 1142 (s), 1076 (m), 1042 (m), 981 (m), 946 (m); HRMS (ESI) calcd for $C_{21}H_{24}O_5Na$ $[M + Na]^+$ 379.1521, found 379.1517.

(*S*)-Atractylodemayne C (*S*-4).[19] *This compound was synthesized and handled under exclusion of light!*

To a solution of compound *S*-**3** (7.30 mg, 20.5 μmol) in CH_2Cl_2 (4 mL) were added NEt_3 (34.0 μL, 245 μmol) and acetyl chloride (14.5 μL, 202 μmol). The solution was stirred at ambient temperature for 12 h, dry-loaded on silica, and chromatographed on silica using hexanes/MTBE mixtures of increasing polarity (4:1 to 2:1 (v/v)) as eluent to yield (*S*)-atractylodemayne C (*S*-**4**, 5.0 mg, 12.6 μmol, 61%) as a yellowish oil; $[\alpha]_D^{23}$ +31.5 (*c* 0.09, methanol); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 6.74 (ddt, *J* = 15.3, 11.2, 1.0 Hz, 1H), 6.54 (dd, *J* = 11.1, 11.1 Hz, 1H), 6.35 (dt, *J* = 15.9, 5.7 Hz, 1H), 5.92 (dd, *J* = 15.3, 6.7 Hz, 1H), 5.87 (dm, *J* = 15.9 Hz, 1H), 5.70 (sept., *J* = 1.3 Hz, 1H), 5.56 (d, *J* = 10.7 Hz, 1H), 5.47 (q, *J* = 6.7 Hz, 1H), 4.63 (dd, *J* = 5.7, 1.8 Hz, 2H), 4.09 (t, *J* = 6.2 Hz, 2H), 2.16 (d, *J* = 1.2 Hz, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.01−1.96 (m, 2H), 1.90 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 171.3, 170.7, 166.0, 158.3, 143.3, 141.0, 137.2, 129.2, 116.1, 111.8, 109.1, 81.4, 80.4, 79.3, 75.2, 70.4, 64.0, 61.0, 34.0, 27.7, 21.2, 21.1, 20.6; IR (ATR) ν 2921 (w), 2852 (w), 2200 (w), 1737 (s), 1718 (m), 1648 (w), 1443 (w), 1363 (w), 1221 (s), 1140 (s), 1074 (m), 1038 (m), 980 (m), 946 (m), 849 (w); HRMS (ESI) calcd for $C_{23}H_{26}O_6Na$ $[M + Na]^+$ 421.1627, found 421.1628.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02987.

Copies of ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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