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Modular and Stereodivergent Approach to Unbranched 1,5,9,n-Polyenes: Total Synthesis of Chatenaytrienin-4

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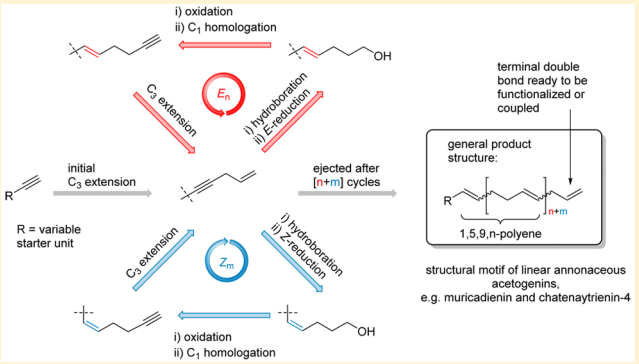
Supporting Information

ABSTRACT: An iterative strategy for the stereodivergent synthesis of unbranched 1,5,9,n-polyenes (and -polyynes) was investigated. Starting from a terminal alkyne the iteration cycle consists of a C_3 extension (allylation), a chemoselective hydroboration, an alkyne reduction, and an oxidation of the associated alcohol with subsequent C_1 homologation. Double bond geometry is controlled using stereoselective alkyne reductions, employing either the Lindlar hydrogenation protocol or an aluminum hydride reduction. In a model sequence it was demonstrated that the strategy is applicable to the synthesis of 1,5,9,n-polyenes with any possible double bond configuration accessible in equally high efficiency and selectivity. It is worth noting that our approach does not require any protecting group chemistry. Furthermore, using the same strategy, the first total synthesis of chatenaytrienin-4, the proposed unsaturated biosynthetic precursor of the bis-THF acetogenin membranacin, was examined. Thus, the all-*cis* 1,5,9-triene natural product was prepared in 15 steps from commercially available starting materials in 6% overall yield.



INTRODUCTION

Annonaceous acetogenins are a large group of fatty acid type natural products, exclusively found in different genera of the plant family Annonaceae.[1−3] The first acetogenin uvaricin (**1**, Figure 1) was isolated in 1982.[4] Since then, more than 450 natural products belonging to this class have been isolated and characterized. These compounds have attracted worldwide attention owing to their broad spectrum of bioactivities,[5] such as cytotoxic, immunosuppressive, antimalarial, pesticidal, antifeedant, and, probably most important, antitumor effects. Furthermore, some acetogenins show growth inhibitory activity against multidrug-resistant cancer cells.[6] Studies on the primary mode of action have established that acetogenins selectively inhibit cancerous cells through the blockage of the mitochondrial complex I (NADH−ubiquinone oxidoreductase), which is the main gate of energy production in cells. In addition, they are potent inhibitors of ubiquinone-linked NADH oxidase that is specifically active in plasma membranes of tumors and is inactive in normal cells. These activities suppress ATP production and thereby lead to apoptosis (programmed cell death) in malignant cells.[7]

Structurally, most acetogenins are characterized by one, two, or three THF (or less common THP) ring(s) with various stereochemistries in the center of a long hydrocarbon chain containing an α,β-unsaturated γ-lactone moiety at one end (Figure 1). The number of THF rings and the stereochemistry (including that of neighboring hydroxy groups) both have a profound effect on the biological activity. In particular, adjacent bis-THF acetogenins, e.g. membranacin[8,9] (**25**, *vide infra*), are highly potent tumor growth inhibitors.

Biosynthetically, it is assumed that these THF heterocycles originate from 1,5-dienes or 1,5,9,n-polyenes, respectively (Scheme 1). Similar to the biogenesis of polyether antibiotics,[10] it seems likely that epoxidation of the C−C double bonds delivers a di- or polyepoxide intermediate which in turn undergoes a polyepoxide cyclization cascade[11]—a process that may be catalyzed by an epoxide hydrolase or cyclase and can either be triggered by the attack of an internal hydroxy group or in the absence of such intramolecular nucleophile, by an external attack of water.[12] Other than in the case of the well-studied polyether biosynthesis where the polyene precursors are not known as natural metabolites,[13] many acyclic polyene acetogenins have been isolated from the same plant as their oxidized (and cyclized) THF derivatives.[14] Scheme 1 summarizes di- and triene-precursor substructures of the common mono-THF, nonadjacent and adjacent bis-THF, and tris-THF acetogenin motifs all of which are known as natural metabolites.[15]

It is worth noting that the stereochemistry of these 1,2-disubstituted double bonds of the polyacetate type can be fairly diverse, and while the majority of these natural products feature exclusively *Z*-configured double bonds several members have been isolated that contain one *E*-double bond (in different

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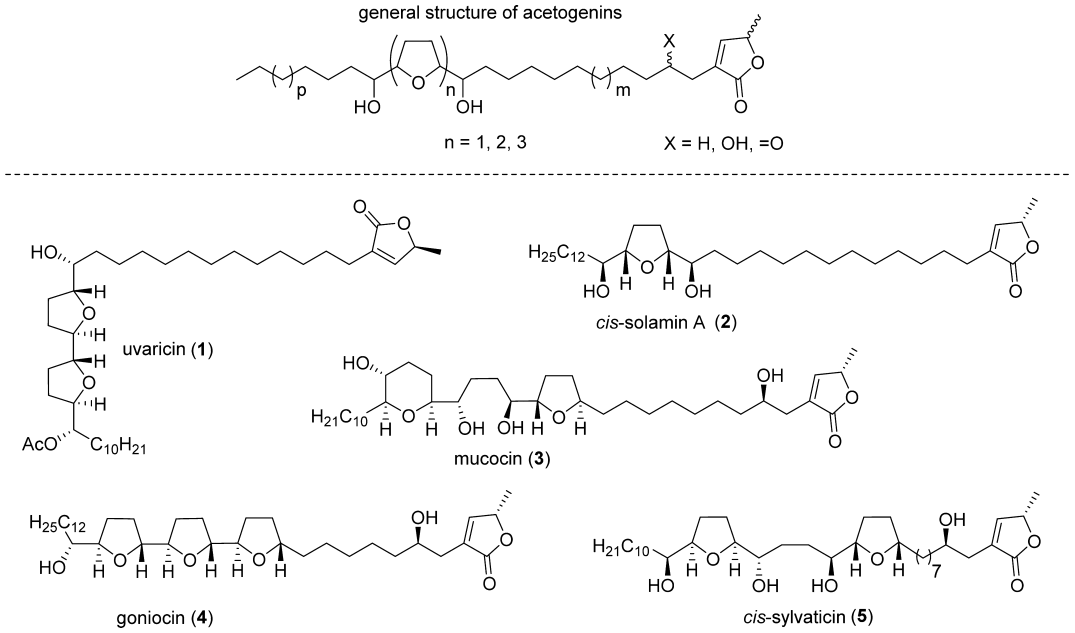
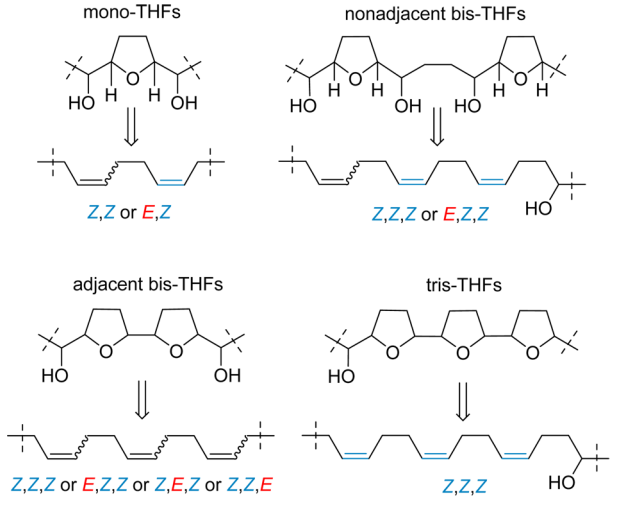


Figure 1. Representative mono-, bis-, and tris-THF acetogenins.

Scheme 1. Proposed Biosynthetic Derivation of Annonaceous Acetogenins



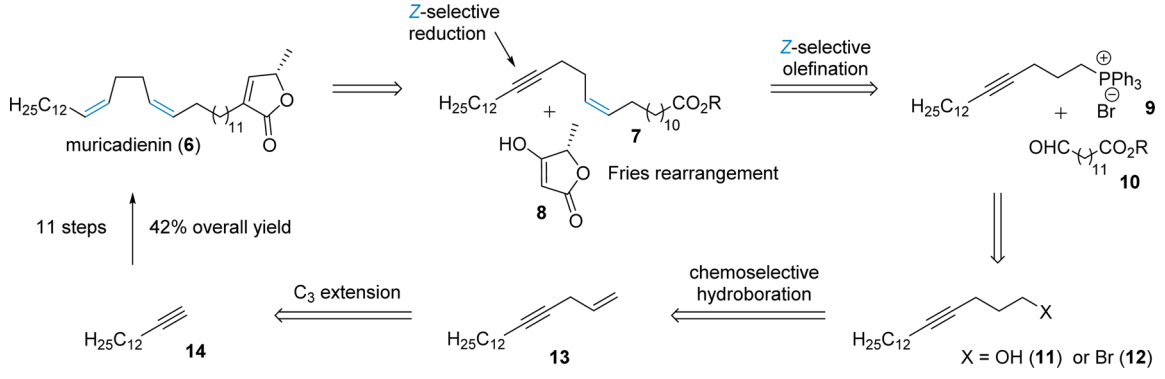
positions of the alkyl chain, e.g. annonacin A type, bullatacin type, or trilobacin type acetogenins; cf. Scheme 1).[14]

Though a number of synthetic procedures to unbranched 1,5-dienes and 1,5,9-trienes have been reported,[16−19] there is, to the best of our knowledge, no general approach to such 1,5,9,n-polyenes which allows access to all possible isomers with complete stereocontrol. In addition, it seems desirable to develop a modular and iterative process so that the same reliable and predictable chemistry can be used repetitively to establish both the carbon skeleton and the double bond stereochemistry. Based on our recent total synthesis of the *Z,Z*-1,5-diene acetogenin muricadienin,[20] the putative biosynthetic precursor of *trans*- and *cis*-solamin (**2**, Figure 1),[21,22] we here present a general stereodivergent approach to unbranched 1,5,9,n-polyenes and an application to the total synthesis of chatenaytrienin-4.

RESULTS AND DISCUSSION

Synthetic Strategy. In principle, with the aim to prepare 1,5,9,n-polyenes in a stereodivergent manner one may initially consider an iterative olefination process to be the strategy of choice.[23] However, direct olefinations frequently do not proceed with perfect stereoselectivity.[23] This limitation may not matter significantly if a single double bond formation is implemented in a synthetic strategy but may prove

Scheme 2. Summary of our Total Synthesis of Muricadienin



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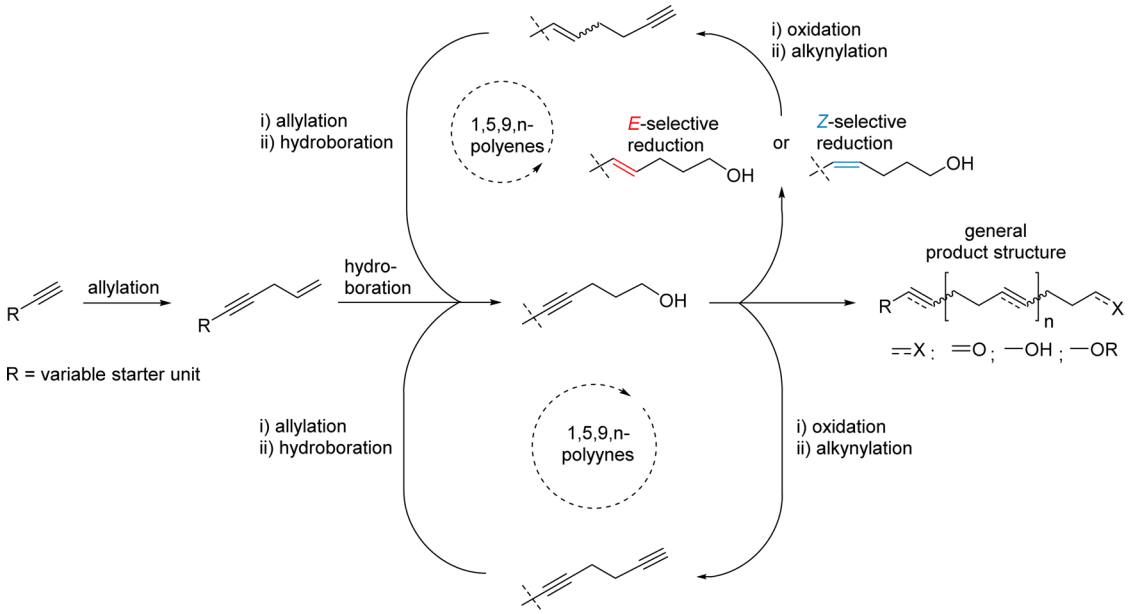
Scheme 3. Iterative Strategy for the Stereodivergent Synthesis of Unbranched 1,5,9,n-Polyenes and -Polyynes



cumbersome if this process is repeatedly used and the lipophilic isomers are not easily separable. We therefore chose to initially install C−C triple bonds and reduce these to the *E*- or *Z*-double bond in a subsequent step, processes which are known to be highly stereoselective.[24−26]

Scheme 2 summarizes our recently accomplished total synthesis of the *Z*,*Z*-diene natural product muricadienin.[20] Key steps involve a C_3 extension (allylation) starting from a terminal alkyne followed by a chemoselective hydroboration[27] and a *Z*-selective Wittig olefination.[23] The butenolide subunit was then established by an esterification using preformed tetronic acid **8** (a formal Claisen condensation product of acetic acid with lactic acid)[28] and a subsequent Fries rearrangement.[29] Finally, the alkyne was stereoselectively reduced to the *Z*-alkene using Lindlar's catalyst.[26] Thus, the natural product was obtained in 11 steps with an overall yield of 42% (Scheme 2).[20]

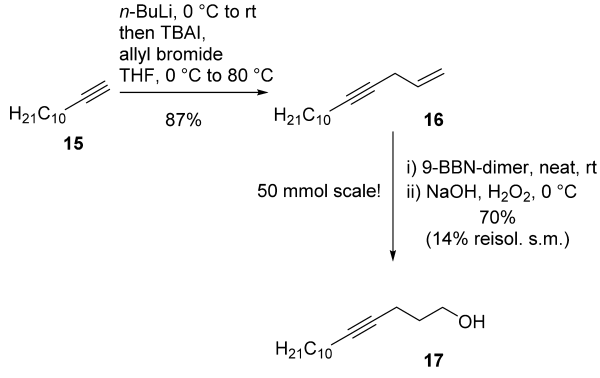
The successful total synthesis of the 1,5-diene natural product muricadienin (Scheme 2)[20] led to the idea that the same tactic may be employed for higher bis-methylene-interrupted polyenes, i.e., 1,5,9,n-polyenes. In principle, a repetitive round of C−C bond couplings and alkyne reductions should be eligible to prepare any 1,5,9,n-polyene with any double bond configuration. The respective synthetic strategy for the envisaged iterative and stereodivergent preparation of unbranched 1,5,9,n-polyenes is outlined in Scheme 3.

Thus, starting from a terminal alkyne a C_3 extension by deprotonation of the alkyne followed by capture of the acetylide anion with allyl bromide would lead to a skipped enyne. Subsequent chemoselective hydroboration[27] would then set the stage for the crucial stereoselective alkyne reduction,[24−26] to either the *E*- or the *Z*-isomer (Scheme 3, upper half). Without the need for any protecting group chemistry the sequence would then continue with the oxidation of the primary alcohol to the aldehyde, followed by an alkynylation.[30] Thus, a new terminal alkyne moiety would be established ready to enter another round of the extension cycle. Alternatively, the extension cycle may be passed through without any reduction of the triple bonds (Scheme 3, bottom half) so that the product will be a 1,5,9,n-polyyne rather than a -polyene. This polyalkyne, itself an interesting class of compounds, would then be reduced at a late stage of the synthesis to either the all-*cis* or all-*trans* polyene isomer. It is worth noting that the terminal functional group (X in Scheme 3) of the 1,5,9,n-polyene and -polyyne, respectively, may then be employed for another C−C bond coupling such as a Wittig-type olefination to introduce yet another double bond (as for instance carried out in our total synthesis of muricadienin;[20] cf. Scheme 2).

We next focused on the practical elaboration of the concept for the stereodivergent synthesis of 1,5,9,n-polyenes using 1-dodecyne (**15**) as a model substrate. It was decided to attempt two rounds of the iteration cycle in order to test whether indeed all possible isomers (*Z*,*Z*-; *Z*,*E*-; *E*,*Z*- and *E*,*E*-) are accessible with equal efficiency and selectivity. The first two steps parallel that of the muricadienin synthesis[20] (cf. Scheme 2) except for the choice of 1-dodecyne (**15**) rather than 1-tetradecyne (**14**) as the starting material. Both the allylation and the hydroboration proceeded smoothly and yielded multigram quantities of the bis-homopropargylic alcohol **17** (Scheme 4).

Then the first round of stereoselective alkyne reductions[24−26] was carried out (Scheme 5). As expected, Lindlar reduction[26] of alkyne **17** resulted in formation of the *Z*-isomer **18a** (92%

Scheme 4. C_3 Chain Extension



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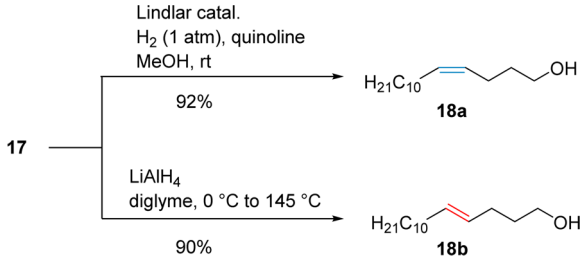
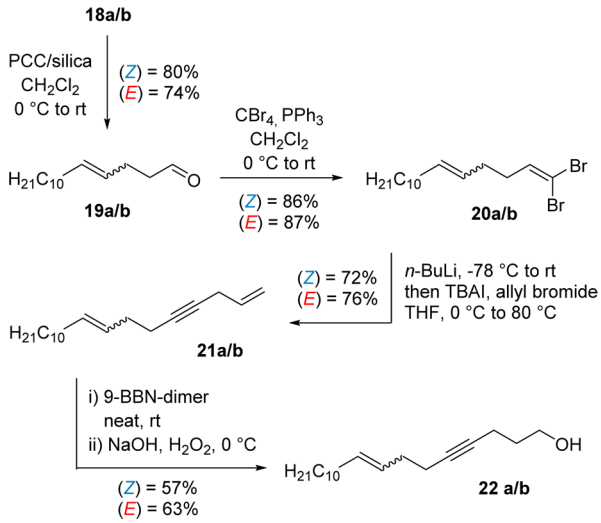
Scheme 5. *Z*- and *E*-Selective Reduction of Bis-homoallylic Alcohol 17



isolated yield) whereas alanate reduction[25] of the same substrate yielded the corresponding *E*-isomer **18b** (90% isolated yield). Both reactions were found to be highly stereoselective, and no traces of the undesired isomer or over-reduction product (i.e., formation of the alkane) were detectable.

The *Z*- and *E*-bis-homoallylic alcohols *Z*-**18a** and *E*-**18b** were then subjected to the C_4 elongation (Scheme 6) consisting of

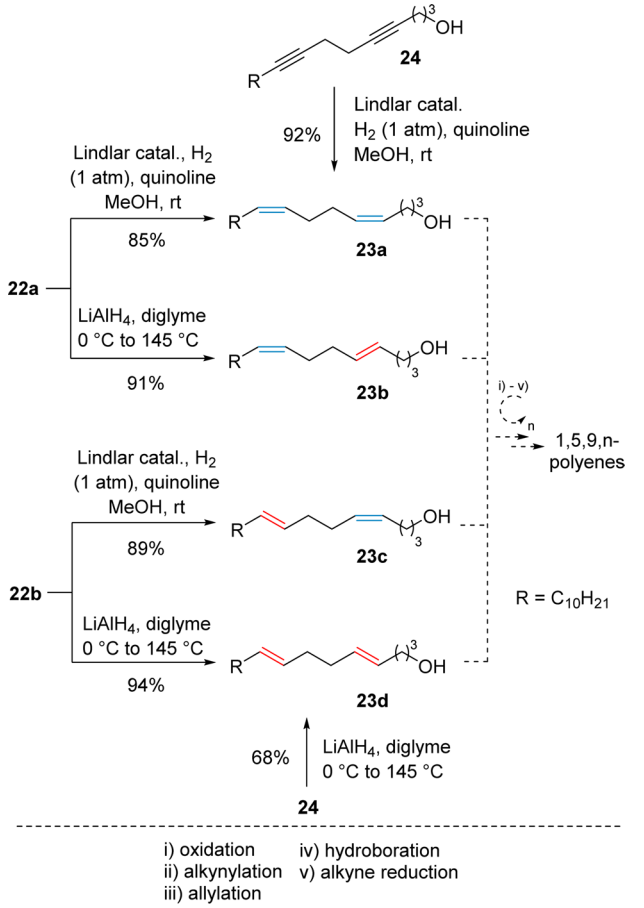
Scheme 6. C_4 Elongation of *Z*- and *E*-Configured Substrate 18a/b



alcohol oxidation, alkynylation, and allylation followed by hydroboration (cf. Scheme 3, upper half). To this end, the alcohols *Z*-**18a** and *E*-**18b** were oxidized to the corresponding aldehydes **19a/b** using PCC on silica. Dess-Martin or Swern oxidations proceeded similarly well under standard conditions (data not shown). Subsequent Corey–Fuchs homologation using carbon tetrabromide and triphenylphosphine delivered the vinyl-dibromides **20a/b**, which were then treated with an excess of *n*-butyllithium followed by addition of allyl bromide and TBAI. The ensuing hydroboration yielded alkynols **22a/b**. These steps proceeded uneventfully and with high overall yields (Scheme 6). More importantly, there was no noticeable difference in efficiency between the *Z*- and the *E*-configured series with 28% overall yield for the *Z*-isomer **22a** and 30% overall yield for the *E*-isomer **22b** over four steps.

As a final and crucial transformation for the stereodivergent model synthesis of unbranched 1,5,9,n-polyenes, we next focused on the reduction of the newly established alkynols *Z*-**22a** and *E*-**22b**, respectively (Scheme 7). Reduction of the triple bond of the *Z*-isomer under Lindlar conditions[26] yielded

Scheme 7. Stereoselective Synthesis of All Four Possible 1,5-Dienes (Starting from 22a/b) through *Z*- and *E*-Selective Enyne Reduction



the *Z*,*Z*-product *Z*,*Z*-**23a**, whereas lithium aluminum hydride reduction[25] delivered the *Z*,*E*-isomer *Z*,*E*-**23b**. Similarly, the *E*-configured substrate gave the *E*,*Z*-diastereomer using the Lindlar protocol[26] and the *E*,*E*-product when subjected to the aluminum based hydride reagent.[25] Pleasingly, all four diastereodivergent reductions proceeded with exquisite selectivity and gave the respective products in very high yields (Scheme 7). Hence, all four possible isomers, *Z*,*Z*-**23a**, *Z*,*E*-**23b**, *E*,*Z*-**23c**, and *E*,*E*-**23d**, are accessible with high efficiency without any contamination by any other double bond isomers and can be further converted to 1,5,9,n-polyenes reiterating the strategy outlined in Scheme 3. As anticipated, the *Z*,*Z*-diene **23a** is also accessible from the corresponding 1,5-diyne **24** using the Lindlar catalyst.[26] Similarly, lithium aluminum hydride reduction[25] of 1,5-diyne **24** delivered the *E*,*E*-diene **23d** in good yield (Scheme 7).

Total Synthesis of Chatenaytrienin-4. In order to explore the applicability of the concept outlined in the preceding section of this publication in target oriented total synthesis we decided to prepare chatenaytrienin-4[15a] (**26**), the putative 1,5,9-triene precursor of the adjacent bis-THF acetogenin membranacin[8,9] (**25**). Retrosynthetically, we envisaged introducing the butenolide moiety at a late stage of the synthesis in the same manner as in our published route to muricadienin.[20] The respective precursor would be the unbranched C_{32} carboxylic acid **28** with an enediyne substructure. The *Z*-double bond would be established in a

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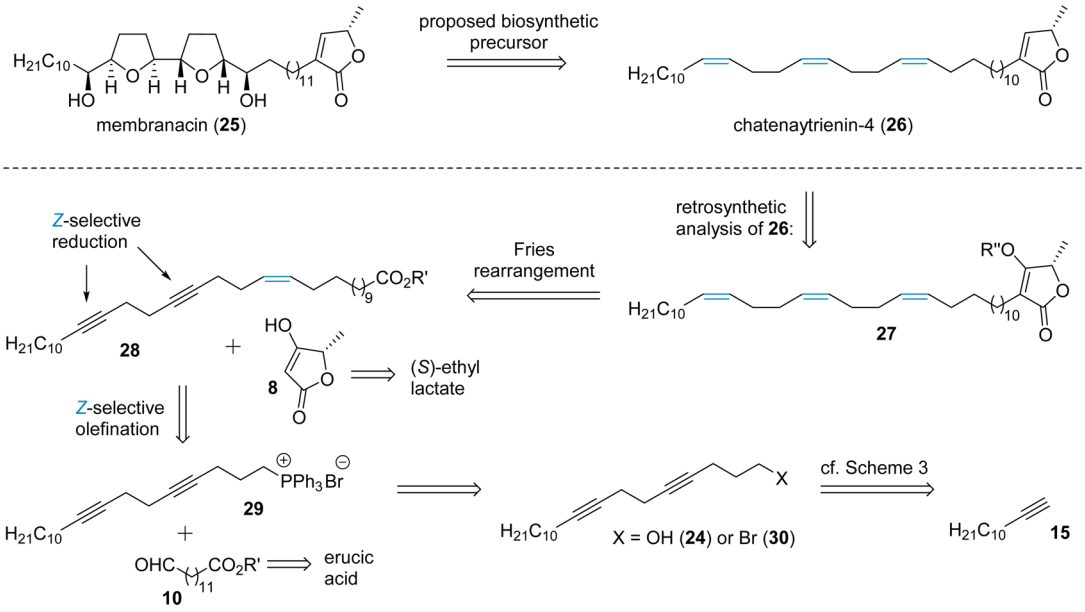
Scheme 8. Retrosynthetic Analysis of Chatenaytrienin-4, the Proposed Biosynthetic Precursor of Membranacin

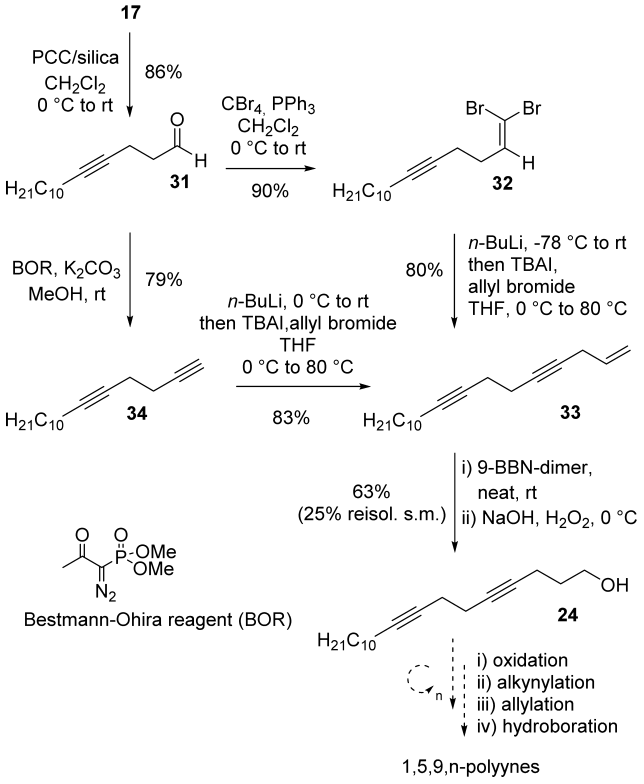


Wittig reaction as a means to terminate the iteration cycle (cf. Scheme 3). The aldehyde component **10**, for this olefination, is known to be readily accessible from erucic acid.[31] The required phosphonium salt **29** should be available from alcohol **24** via bromide **30**. Finally, hydroxydiyne **24** would be the product of two cycles of elongation (cf. Scheme 3) starting from commercially available alkyne **15**.

In accord with the retrosynthetic strategy outlined in Scheme 8, our synthesis started from commercially available 1-dodecyne (**15**), which was converted to the bis-homopropargylic alcohol **17** in two steps via allylation and chemoselective hydroboration[27] (cf. Scheme 4). Considering the large quantities of material required at this early stage of the synthesis, we next investigated the best method for the alkynylation[30] (Scheme 9). To this end, alcohol **17** was oxidized to ynal **31** using PCC on silica. Subsequent Corey–Fuchs homologation and allylation (cf. Scheme 6) delivered enedyine **33** in good overall yield. Alternatively, aldehyde **31** was converted to the same enediyne **33** in a sequence consisting of an Ohira–Bestmann alkynylation[32,33] followed by deprotonation of the terminal alkyne and its trapping by allyl bromide (cf. Scheme 4). Both routes to enediyne **33** proceeded with similar efficiency. For large scale application, the Corey–Fuchs pathway was preferred. Subsequent chemoselective hydroboration[27] of the terminal alkene using the 9-BBN-dimer (same conditions as before) gave alcohol **24**, which allows for the synthesis of 1,5,9,n-polyynes as mentioned above.

The synthesis of chatenaytrienin-4 continued with the bromination of diynol **24** using an Appel-type reaction (Scheme 10). Subsequent heating of this primary bromide in the presence of triphenylphosphine without any solvent provided phosphonium salt **29** which was in turn coupled to aldehyde **10** (derived from erucic acid using a procedure of Ducho and co-workers)[31] in a salt-free *Z*-selective Wittig olefination.[23] The *Z*/*E* ratio was determined as >95:5 by ^{13}C NMR analysis. Saponification of the methyl ester **35** under standard conditions delivered the free carboxylic acid **36** which was next condensed with hydroxy butenolide **8**.[28] Under these conditions in the presence of DMAP, esterification is followed by an instantaneous Fries rearrangement[29] so that the alkyl

Scheme 9. Alkynylation: Bestmann–Ohira vs Corey–Fuchs and Second C_3 Chain Extension



chain ends up in the C2-position of the butenolide (**37**, Scheme 10). Selective deoxygenation was then accomplished using sodium cyanoborohydride in acetic acid. In preparation for the defunctionalization at the C3-position of the butenolide, the hydroxy group was converted to the triflate under standard conditions. The best results for the final two steps of the synthesis were obtained when the *Z*-selective alkyne reduction using Lindlar's protocol[26] was carried out before the Pd-catalyzed reduction of the vinyl triflate. Thus, the first total

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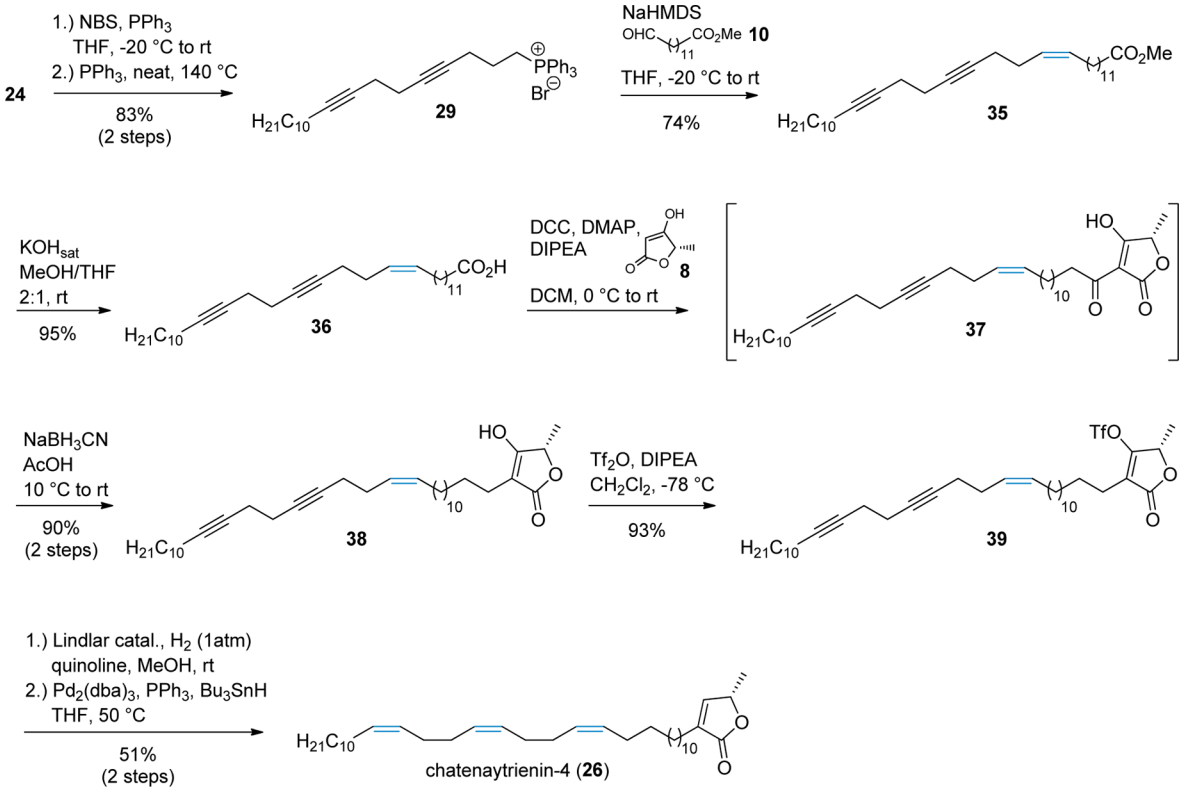
Scheme 10. Total Synthesis of Chatenaytrienin-4



synthesis of chatenaytrienin-4 (**26**) was achieved in 15 steps with an overall yield of 6% (starting from commercially available 1-dodecyne (**15**), Scheme 10).

CONCLUSION

In summary, we have presented an iterative and stereodivergent strategy for the synthesis of unbranched 1,5,9,n-polyenes (and -polyynes) using reliable and high yielding C−C bond couplings together with high yielding and stereospecific alkyne reductions. This strategy allows for the preparation of any combination of double bond isomers with complete stereocontrol. All-*trans* or all-*cis* isomers can be prepared using a late stage reduction of a corresponding polyyne intermediate. Key steps of the iterative chain elongation process are a chemoselective hydroboration, a stereoselective alkyne reduction, and an oxidation with subsequent C_1 homologation. The outlined reaction principle is relevant to the synthesis of different classes of natural products such as annonaceous acetogenins, certain groups of marine fatty acids, and lepidopteran sex pheromones. Finally, we were able to present an application of the modular and stereodivergent approach to unbranched 1,5,9,n-polyenes by presenting the first total synthesis of chatenaytrienin-4. The 1,5,9-triene natural product was obtained in a sequence of 15 linear steps, starting form commercially available starting materials. Key steps in our synthesis were a chemoselective hydroboration, a *Z*-selective Wittig olefination, and a DMAP-mediated Fries rearrangement. It is worth noting that our approach does not require any protecting groups and provides the natural all-*Z* isomer as the only detectable double bond diastereoisomer.

EXPERIMENTAL SECTION

Materials and Methods. All reagents were used as purchased from commercial suppliers. All dry solvents were purified using a solvent purification system. All reactions were performed under an atmosphere of dry nitrogen, unless otherwise mentioned. Reactions were monitored by thin layer chromatography using aluminum plates precoated with silica and visualized with potassium permanganate [$KMnO_4$ (2.4 g), K_2CO_3 (16 g), NaOH (5%, 4 mL), H_2O (196 mL)] or ceric ammonium molybdate [phosphomolybdic acid (5 g), $Ce(SO_4)_2{\cdot}2H_2O$ (2 g), concd H_2SO_4 (12 mL), H_2O (188 mL)]. Chromatographic purification was performed as flash chromatography on silica gel (particle size 0.040−0.063 mm). Yields refer to chromatographically purified and spectroscopically pure compounds. NMR spectra were recorded on a 300 MHz spectrometer (operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C acquisitions), a 400 MHz spectrometer (operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C acquisitions), or a 600 MHz spectrometer (operating at 600 MHz for ^{1}H and 150 MHz for ^{13}C acquisitions). Chemical shifts (δ) are reported in parts per million with the solvent resonance as the internal standard. Coupling constants (J) are given in hertz. Multiplicities are classified as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, or combinations thereof, or m = multiplet or br = broad signal. Two-dimensional NMR (H−COSY, HSQC, HMBC) were used for the assignment of all final compounds. Assignment of every single carbon atom of long alkyl chains was not always possible due to overlap of signals in ^{13}C NMR spectra (compounds **18b**, **19b**, **20a/b**, **21b**, **22b**, **23a/c**, **26**, **35**, **36**, **38**, **39**, **40**). High resolution mass spectra were obtained on an ESI-TOF mass spectrometer. EI mass spectra were obtained on an EI LT Large Turbo (low resolution) mass spectrometer. Elemental compositions (anal.) were determined by combustion analysis. IR spectra were recorded on an FT-IR spectroscope by attenuated total reflection (ATR). Absorbance frequencies ($\tilde{\nu}$) are reported in reciprocal centimeters (cm^{-1}). Optical rotation data were measured at 589 nm using a 100 mm path-length cell in the indicated solvent at the indicated concentration and temperature. The reported melting points are uncorrected. All compounds were named according to IUPAC rules. For simplicity,

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the numbering of the carbon atoms of a given structure does not follow the IUPAC rules (for numbering, see the Supporting Information). Compounds **6**,[20] **8**,[20,28] **9**,[20] **10**,[20,31] and **11**–**13**[20] have been prepared previously, and full data have been provided. Analytical data for these compounds were identical to published data and are not given.

Pentadec-1-en-4-yne (16). 1-Dodecyne (19.5 g, 25.0 mL, 117 mmol, 1.00 equiv) in dry THF (340 mL) was cooled to 0 °C. *n*-Butyllithium (1.6 M in hexane, 110 mL, 176 mmol, 1.50 equiv) was added slowly, and the yellowish solution was stirred for 1 h with warming to rt. 3-Bromopropene (42.6 g, 2.60 mL, 352 mmol, 3.00 equiv) and TBAI (4.33 g, 11.7 mmol, 0.10 equiv) were added, and the reaction mixture was heated to 80 °C. After complete conversion of the starting material was detected (TLC, silica), brine (250 mL) was added and the solution was extracted with ethyl acetate (3 × 170 mL). The combined organic phases were dried over $MgSO_4$ and filtrated, and the solvents were removed under reduced pressure. The crude product was codistilled with toluene to remove excess 3-bromopropene. Flash chromatography (100% hexanes, silica) of the residue gave the title compound **16** (21.0 g, 102 mmol, 87%) as a colorless liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.87–5.78 (m, 1H, H-2), 5.34–5.29 (m, 1H, H-1a), 5.11–5.07 (m, 1H, H-1b), 2.96–2.93 (m, 2H, H-3), 2.20–2.16 (m, 2H, H-6), 1.52–1.47 (m, 2H, H-7), 1.40–1.35 (m, 2H, H-8), 1.32–1.26 (m, 12H, H-9–H-14), 0.88 (t, J = 6.9 Hz, 3H, H-15). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 133.6 (C-2), 115.7 (C-1), 83.1 (C-5), 76.6 (C-4), 32.1 (C-13), 29.7, 29.7, 29.5, 29.3, 29.2, 29.1, 23.3 (C-3), 22.8 (C-14), 18.9 (C-6), 14.3 (C-15) ppm. IR (ATR): $\tilde{\nu}$ = 3086, 3014, 2923, 2854, 1642, 1465, 1421, 1401, 1378, 1331, 1284, 1110, 989, 913, 721, 558 cm^{-1}. MS (EI): m/z = 177 $[M - C_2H_5]^+$, 165 $[M - C_3H_5]^+$, 149 $[M - C_4H_9]^+$, 135 $[M - C_5H_{11}]^+$, 121 $[M - C_6H_{13}]^+$, 107 $[M - C_7H_{15}]^+$, 93 $[M - C_8H_{17}]^+$, 79 $[M - C_9H_{19}]^+$. Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 86.95; H, 12.65.

Pentadec-4-yn-1-ol (17). 9-BBN-dimer (5.98 g, 24.5 mmol, 0.49 equiv) was added under a N_2 atmosphere to enyne **16** (10.3 g, 50.0 mmol, 1.00 equiv). The reaction mixture was warmed to 50 °C for 10 min (until all solids had been dissolved) and subsequently stirred at rt for 4 h, before adding THF (100 mL), 2 N NaOH (150 mL, 300 mmol, 6.00 equiv), and H_2O_2 (30%, 25.6 mL, 250 mmol, 5.00 equiv) at 0 °C. The reaction mixture was slowly warmed to rt overnight under vigorous stirring. The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with brine (150 mL), dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Flash chromatography (100% hexanes to 10% ethyl acetate in hexanes, silica) of the residue gave alcohol **17** (7.81 g, 34.8 mmol, 70%, brsm 81%, 14% starting material reisolated) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (t, J = 5.5 Hz, 2H, H-1), 2.27 (tt, J = 6.8, 2.3 Hz, 2H, H-3), 2.13 (tt, J = 7.1, 2.3 Hz, 2H, H-6), 1.73 (p, J = 6.5 Hz, 2H, H-2), 1.64 (br s, 1H, OH), 1.51–1.42 (m, 2H, H-7), 1.41–1.32 (m, 2H, H-8), 1.32–1.25 (m, 12H, H-9–H-14), 0.87 (t, J = 6.8 Hz, 3H, H-15) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.3 (C-5), 79.4 (C-4), 62.3 (C-1), 32.0 (C-13), 31.8 (C-2), 29.7, 29.7, 29.5, 29.3, 29.2, 29.0, 22.8 (C-14), 18.9 (C-6), 15.6 (C-3), 14.2 (C-15) ppm. IR (ATR): $\tilde{\nu}$ = 3326, 2923, 2853, 1465, 1377, 1330, 1056, 931, 721 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{29}O$ 225.2213; Found 225.2218.

(*Z*)-Pentadec-4-en-1-ol (18a). Lindlar catalyst (1.02 g, 0.50 mmol, 5.00 mol %, 0.05 equiv) and quinoline (1.20 mL, 10.0 mmol, 1.00 equiv) were added to a stirred solution of alkyne **17** (2.10 g, 9.41 mmol, 1.00 equiv) in dry MeOH (100 mL). The reaction mixture was stirred at rt for 2 h (conversion monitored by TLC, silica) under a H_2 atmosphere (1 atm). After complete conversion of the starting material, the mixture was filtrated over a short plug of Celite and silica, washed with ethyl acetate, and concentrated under reduced pressure. Flash chromatography (5% ethyl acetate in hexanes, silica) of the residue gave *Z*-alkenol **18a** (1.96 g, 8.66 mmol, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.45–5.35 (m, 2H, H-4, H-5), 3.66 (t, J = 6.5 Hz, 2H, H-1), 2.13 (dd, J = 13.6, 7.2 Hz, 2H, H-3), 2.06–2.01 (m, 2H, H-6), 1.68–1.59 (m, 2H, H-2), 1.38–1.26 (m, 16H, H-7–H-14), 0.88 (t, J = 6.7 Hz, 3H, H-15) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.0 (C-5), 128.9 (C-4), 62.9 (C-1), 32.8 (C-2), 32.1, 29.9, 29.8, 29.8, 29.7, 29.5, 29.5, 27.4 (C-6), 23.8 (C-3), 22.8 (C-14), 14.3 (C-15) ppm. IR (ATR): $\tilde{\nu}$ = 3318, 3005, 2955, 2922, 2852, 1465, 1378, 1059, 720 cm^{-1}. MS (EI): m/z = 226 $[M]^{+\bullet}$, 209 $[M - OH]^+$, 208 $[M - H_2O]^+$, 180 $[M - C_2H_6O]^+$, 166 $[M - C_3H_8O]^+$, 152 $[M - C_4H_{10}O]^+$, 138 $[M - C_6H_{12}O]^+$, 110 $[M - C_7H_{16}O]^+$, 96 $[M - C_8H_{18}O]^+$, 82 $[M - C_9H_{20}O]^+$, 68 $[M - C_{10}H_{22}O]^+$. Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.71; H, 13.29.

(*E*)-Pentadec-4-en-1-ol (18b). Under a N_2 atmosphere $LiAlH_4$ (3.42 g, 90.1 mmol, 10.0 equiv) was added portionwise to ice-cooled diglyme (150 mL). After bubbling ceased, alkynol **17** (2.02 g, 9.01 mmol, 1.00 equiv), dissolved in diglyme (30 mL), was added dropwise to the ice-cooled suspension. The temperature was raised, and the reaction mixture was stirred at 145 °C for 48 h. After cooling to 0 °C, it was diluted with Et_2O and quenched with H_2O (3.5 mL), 2 N NaOH (3.5 mL), and H_2O (10.5 mL). The mixture was stirred a further 20 min with warming to rt, dried over $MgSO_4$, filtrated to remove salts, and concentrated under reduced pressure (to remove most of diglyme, choose: 65 °C, 20 mbar). Flash chromatography (20% ethyl acetate in hexanes, silica) of the residue gave the title compound **18b** (1.84 g, 8.11 mmol, 90%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.43 (qt, J = 15.3, 6.3 Hz, 2H, H-4, H-5), 3.65 (t, J = 6.5 Hz, 2H, H-1), 2.08 (dd, J = 13.9, 7.0 Hz, 2H, H-3), 1.98 (dd, J = 13.9, 6.7 Hz, 2H, H-6), 1.66–1.60 (m, 2H, H-2), 1.38–1.26 (m, 16H, H-7–H-14), 0.88 (t, J = 7.0 Hz, 3H, H-15) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 131.5 (C-5), 129.5 (C-4), 62.8 (C-1), 32.7 (C-2), 32.7, 32.1, 29.8, 29.7, 29.7, 29.5, 29.3, 29.1, 22.8 (C-14), 14.2 (C-15) ppm. IR (ATR): $\tilde{\nu}$ = 3335, 3005, 2955, 2921, 2852, 1465, 1378, 1058, 966, 918, 720 cm^{-1}. MS (EI): m/z = 226 $[M]^{+\cdot}$, 209 $[M - OH]^+$, 208 $[M - H_2O]^+$, 180 $[M - C_2H_6O]^+$, 166 $[M - C_3H_8O]^+$, 152 $[M - C_4H_{10}O]^+$, 138 $[M - C_6H_{12}O]^+$, 110 $[M - C_7H_{16}O]^+$, 96 $[M - C_8H_{18}O]^+$, 82 $[M - C_9H_{20}O]^+$, 68 $[M - C_{10}H_{22}O]^+$. Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.29; H, 13.30.

(*Z*)-Pentadec-4-enal (19a) and (*E*)-Pentadec-4-enal (19b). Following the procedure described for the synthesis of compound **31**, alcohols **18a** (1.55 g, 6.85 mmol, 1.00 equiv) and **18b** (1.35 g, 5.97 mmol, 1.00 equiv) were converted to the corresponding aldehydes **19a** (1.22 g, 5.44 mmol, 80%) and **19b** (0.99 g, 4.41 mmol, 74%), which were obtained as colorless oils. (*Z*)-Pentadec-4-enal (**19a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.77 (t, J = 1.7 Hz, 1H, H-1), 5.47–5.39 (m, 1H, H-5), 5.36–5.28 (m, 1H, H-4), 2.51–2.44 (m, 2H, H-2), 2.41–2.32 (m, 2H, H-3), 2.07–1.99 (m, 2H, H-6), 1.38–1.26 (m, 16H, H-7–H-14), 0.88 (t, J = 6.8 Hz, 3H, H-15) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.4 (C-1), 131.9 (C-5), 127.1 (C-4), 44.0 (C-2), 32.1 (C-13), 29.8, 29.7, 29.7, 29.5, 29.5, 27.4 (C-6), 22.8 (C-14), 20.2 (C-3), 14.3 (C-15) ppm. IR (ATR): $\tilde{\nu}$ = 3008, 2955, 2922, 2853, 2716, 1727, 1465, 1409, 1388, 1351, 1056, 721 cm^{-1}. MS (EI): m/z = 224 $[M]^{+\bullet}$, 207 $[M - OH]^+$, 206 $[M - H_2O]^+$, 180 $[M - C_2H_4O]^+$, 169 $[M - C_4H_3O]^+$, 152 $[M - C_4H_8O]^+$, 138 $[M - C_5H_{10}O]^+$, 124 $[M - C_6H_{12}O]^+$, 110 $[M - C_7H_{14}O]^+$, 96 $[M - C_8H_{16}O]^+$, 82 $[M - C_9H_{18}O]^+$, 68 $[M - C_{10}H_{20}O]^+$. (*E*)-Pentadec-4-enal (**19b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (t, J = 1.7 Hz, 1H, H-1), 5.50–5.43 (m, 1H, H-5), 5.42–5.36 (m, 1H, H-4), 2.49 (td, J = 7.3, 1.7 Hz, 2H, H-2), 2.36–2.30 (m, 2H, H-3), 1.99–1.94 (m, 2H, H-6), 1.36–1.25 (m, 16H, H-7–H-14), 0.88 (t, J = 6.8 Hz, 3H, H-15) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 202.6 (C-1), 132.3 (C-5), 127.7 (C-4), 43.7 (C-2), 32.7 (C-6), 32.1 (C-13), 29.8, 29.7, 29.6, 29.5, 29.3, 25.4 (C-3), 22.8 (C-14), 14.3 (C-15) ppm. IR (ATR): $\tilde{\nu}$ = 2955, 2921, 2852, 2715, 1728, 1466, 1409, 1378, 1117, 1055, 1019, 967, 909, 722 cm^{-1}. MS (EI): m/z = 224 $[M]^{+\bullet}$, 207 $[M - OH]^+$, 206 $[M - H_2O]^+$, 180 $[M - C_2H_4O]^+$, 169 $[M - C_4H_3O]^+$, 152 $[M - C_4H_8O]^+$, 138 $[M - C_5H_{10}O]^+$, 124 $[M - C_6H_{12}O]^+$, 110 $[M - C_7H_{14}O]^+$, 96 $[M - C_8H_{16}O]^+$, 82 $(M - C_9H_{18}O]^+$, 68 $[M - C_{10}H_{20}O]^+$.

(*Z*)-1,1-Dibromohexadeca-1,5-diene (20a) and (*E*)-1,1-Dibromohexadeca-1,5-diene (20b). Following the procedure described for the synthesis of compound **32**, aldehydes **19a** (1.19 g, 5.30 mmol, 1.00 equiv) and **19b** (0.95 g, 4.23 mmol, 1.00 equiv) were converted to the corresponding dibromoalkenes **20a** (1.72 g, 4.52 mmol, 86%) and **20b** (1.42 g, 3.73 mmol, 88%), which were obtained as colorless oils. (*Z*)-1,1-Dibromohexadeca-1,5-diene (**20a**): ^{1}H NMR

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(400 MHz, $CDCl_3$): δ = 6.39 (t, J = 6.8 Hz, 1H, H-2), 5.48−5.39 (m, 1H, H-6), 5.37−5.28 (m, 1H, H-5), 2.16−2.13 (m, 4H, H-3, H-4), 2.05−1.98 (m, 2H, H-7), 1.36−1.22 (m, 16H, H-8−H-15), 0.88 (t, J = 6.8 Hz, 3H, H-16) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4 (C-1), 131.9 (C-6), 127.6 (C-5), 89.0 (C-2), 33.2 (C-3), 32.1 (C-14), 29.8, 29.7, 29.5, 29.5, 27.4 (C-7), 25.6 (C-4), 22.9 (C-15), 14.3 (C-16) ppm. IR (ATR): $\tilde{\nu}$ = 3006, 2953, 2921, 2852, 1623, 1463, 1377, 1274, 1210, 1179, 1069, 1008, 968, 809, 772, 720 cm^{-1}. (*E*)-1,1-Dibromohexadeca-1,5-diene (**20b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (t, J = 6.8 Hz, 1H, H-2), 5.50−5.41 (m, 1H, H-6), 5.41−5.31 (m, 1H, H-5), 2.20−2.06 (m, 4H, H-3, H-4), 1.98 (q, J = 6.7 Hz, 2H, H-7), 1.36−1.23 (m, 16H, H-8−H-15), 0.88 (t, J = 6.8 Hz, 3H, H-16) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4 (C-1), 132.3 (C-6), 128.2 (C-5), 88.8 (C-2), 33.2 (C-3), 32.7 (C-6), 32.1 (C-14), 30.9 (C-4), 29.8, 29.7, 29.6, 29.5, 29.3, 22.9 (C-15), 14.3 (C-16) ppm. IR (ATR): $\tilde{\nu}$ = 2954, 2921, 2851, 1622, 1464, 1377, 1269, 1211, 1129, 1070, 965, 804, 775, 721 cm^{-1}. Because of the instability of these compounds, no MS data or elemental analysis could be obtained.

(*Z*)-Nonadeca-1,8-dien-4-yne (21a) and (*E*)-Nonadeca-1,8-dien-4-yne (21b). Following the procedure described for the synthesis of compound **33**, dibromoalkenes **20a** (1.72 g, 4.52 mmol, 1.00 equiv) and **20b** (1.45 g, 3.81 mmol, 1.00 equiv) were converted to the title compounds **21a** (838 mg, 3.22 mmol, 72%) and **21b** (754 mg, 2.90 mmol, 76%), which were obtained as colorless oils. (*Z*)-Nonadeca-1,8-dien-4-yne (**21a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (ddt, J = 16.9, 10.0, 5.3 Hz, 1H, H-2), 5.48−5.37 (m, 2H, H-8, H-9), 5.31 (dq, J = 17.0, 1.8 Hz, 1H, H-1a), 5.09 (dq, J = 10.0, 1.7 Hz, 1H, H-1b), 2.97−2.91 (m, 2H, H-3), 2.29−2.19 (m, 4H, H-6, H-7), 2.07−1.99 (m, 2H, H-10), 1.39−1.25 (m, 16H, H-11−H-18), 0.88 (t, J = 6.8 Hz, 3H, H-19) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.4 (C-1), 131.5 (C-9), 128.0 (C-8), 115.8 (C-2), 82.6 (C-5), 77.4 (C-4), 32.1 (C-17), 29.9, 29.8, 29.8, 29.7, 29.5, 29.5, 27.5 (C-10), 27.1 (C-7), 23.3 (C-3), 22.8 (C-18), 19.4 (C-6), 14.3 (C-19) ppm. IR (ATR): $\tilde{\nu}$ = 3085, 3009, 2955, 2922, 2853, 1643, 1465, 1421, 1402, 1378, 1332, 1284, 989, 914, 721, 631, 558 cm^{-1}. MS (EI) m/z = 260 $[M]^{+\bullet}$, 231 $[M - C_2H_5]^+$, 219 $[M - C_3H_5]^+$, 217 $[M - C_3H_7]^+$, 207 $[M - C_4H_5]^+$, 175 $[M - C_6H_{13}O]^+$, 161 $[M - C_7H_{15}]^+$, 147 $[M - C_8H_{17}]^+$, 133 $[M - C_9H_{19}]^+$, 119 $(M - C_{10}H_{21}]^+$, 105 $(M - C_{11}H_{23}]^+$, 91 $[M - C_{12}H_{25}]^+$. Anal. Calcd for $C_{19}H_{32}$: C, 87.62; H, 12.38. Found: C, 87.45; H, 12.38. (*E*)-Nonadeca-1,8-dien-4-yne (**21b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (ddt, J = 17.0, 10.2, 5.3 Hz, 1H, H-2), 5.53−5.40 (m, 2H, H-8, H-9), 5.31 (dq, J = 17.0, 1.9 Hz, 1H, H-1a), 5.09 (dq, J = 10.0, 1.8 Hz, 1H, H-1b), 2.97−2.91 (m, 2H, H-3), 2.27−2.15 (m, 4H, H-6, H-7), 2.03−1.94 (m, 2H, H-10), 1.37−1.26 (m, 16H, H-11−H-18), 0.88 (t, J = 6.9 Hz, 3H, H-19) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.5 (C-1), 132.0 (C-9), 128.5 (C-8), 115.7 (C-2), 82.6 (C-5), 77.0 (C-4), 32.7 (C-10), 32.4 (C-7), 32.1 (C-17), 29.8, 29.7, 29.7, 29.5, 29.3, 23.3 (C-3), 22.8 (C-18), 19.5 (C-6), 14.3 (C-19) ppm. IR (ATR): $\tilde{\nu}$ = 3085, 2955, 2922, 2853, 1642, 1465, 1421, 1402, 1378, 1284, 989, 966, 914, 721, 631, 558 cm^{-1}. MS (EI) m/z = 260 $[M]^{+\bullet}$, 231 $[M - C_2H_5]^+$, 219 $[M - C_3H_5]^+$, 217 $[M - C_3H_7]^+$, 207 $[M - C_4H_5]^+$, 175 $[M - C_6H_{13}O]^+$, 161 $[M - C_7H_{15}]^+$, 147 $[M - C_8H_{17}]^+$, 133 $[M - C_9H_{19}]^+$, 119 $(M - C_{10}H_{21}]^+$, 105 $(M - C_{11}H_{23}]^+$, 91 $[M - C_{12}H_{25}]^+$. Anal. Calcd for $C_{19}H_{32}$: C, 87.62; H, 12.38. Found: C, 87.77; H, 12.38.

(*Z*)-Nonadec-8-en-4-yn-1-ol (22a) and (*E*)-Nonadec-8-en-4-yn-1-ol (22b). Following the procedure described for the synthesis of compound **17**, alkenes **21a** (745 mg, 2.86 mmol, 1.00 equiv) and **21b** (635 mg, 2.40 mmol, 1.00 equiv) were converted to the corresponding alcohols **22a** (443 mg, 1.59 mmol, 57%, reisolated starting material 8%) and **22b** (408 mg, 1.48 mmol, 63%, reisolated starting material 12%), which were obtained as colorless oils. (*Z*)-Nonadec-8-en-4-yn-1-ol (**22a**): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.46−5.36 (m, 2H, H-8, H-9), 3.77−3.75 (m, 2H, H-1), 2.30−2.26 (m, 2H, H-3), 2.25−2.16 (m, 4H, H-6, H-7), 2.03 (q, J = 7.1 Hz, 2H, H-10), 1.74 (p, J = 6.5 Hz, 2H, H-2), 1.51 (br s, 1H, OH), 1.36−1.23 (m, 16H, H-11−H-18), 0.88 (t, J = 7.0 Hz, 3H, H-19) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 131.5 (C-9), 128.0 (C-8), 80.8 (C-5), 76.9 (C-4), 62.3 (C-1), 32.1 (C-2), 31.7, 29.9, 29.8, 29.8, 29.7, 29.5, 29.5, 27.5 (C-10), 27.1 (C-7), 22.8 (C-18), 19.3 (C-6), 15.6 (C-3), 14.3 (C-19) ppm. IR (ATR): $\tilde{\nu}$ = 3321, 3007, 2955, 2921, 2852, 1465, 1434, 1378, 1332, 1176, 1056, 933, 721 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688; Found 279.2642. (*E*)-Nonadec-8-en-4-yn-1-ol (**22b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.50−5.36 (m, 2H, H-8, H-9), 3.76 (t, J = 6.1 Hz, 2H, H-1), 2.32−2.25 (m, 2H, H-3), 2.22−2.12 (m, 4H, H-6, H-7), 2.02−1.94 (m, 2H, H-10), 1.74 (p, J = 6.5 Hz, 2H, H-2), 1.54 (br s, 1H, OH), 1.38−1.26 (m, 16H, H-11−H-18), 0.88 (t, J = 6.7 Hz, 3H, H-19) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.0 (C-9), 128.5 (C-8), 80.9 (C-5), 79.7 (C-4), 62.3 (C-1), 32.7 (C-10), 32.4 (C-7), 32.1 (C-2), 31.7, 29.8, 29.7, 29.5, 29.3, 22.8 (C-18), 19.4 (C-6), 15.6 (C-3), 14.3 (C-19) ppm. IR (ATR): $\tilde{\nu}$ = 3257, 2955, 2919, 2848, 1460, 1447, 1371, 1337, 1286, 1248, 1177, 1078, 1064, 1052, 1002, 965, 912, 724 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688; Found 279.2664.

(4*Z*,8*Z*)-Nonadeca-4,8-dien-1-ol (23a). Following the procedure described for the synthesis of compound **18a**, alcohol **22a** (63.0 mg, 0.23 mmol, 1.00 equiv) was converted to the corresponding *Z*,*Z*-alcohol **23a** (54.0 mg, 0.19 mmol, 85%), which was obtained as a colorless oil. The Lindlar catalyzed reduction of diynol **24** (276 mg, 1.00 mmol, 1.00 equiv) also delivered the title compound **23a** (257 mg, 0.92 mmol, 92%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.46−5.32 (m, 4H, H-4, H-5, H-8, H-9), 3.66 (t, J = 6.5 Hz, 2H, H-1), 2.17−1.94 (m, 8H, H-3, H-6, H-7, H-10), 1.68−1.60 (m, 2H, H-2), 1.39 (br s, 1H, OH), 1.34−1.26 (m, 16H, H-11−H-18), 0.88 (t, J = 6.8 Hz, 3H, H-19) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 130.7 ($C_{sp^2}H$), 130.2 ($C_{sp^2}H$), 129.4 ($C_{sp^2}H$), 129.1 ($C_{sp^2}H$), 62.8 (C-1), 32.8, 32.1 (C-2), 29.9, 29.8, 29.8, 29.7, 29.5, 29.5, 27.5, 27.4, 23.8, 22.8 (C-18), 14.3 (C-19) ppm. IR (ATR): $\tilde{\nu}$ = 3314, 3006, 2922, 2852, 1457, 1404, 1378, 1058, 967, 721 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{37}O$ 281.2844; Found 281.2839.

(4*E*,8*Z*)-Nonadeca-4,8-dien-1-ol (23b). Following the procedure described for the synthesis of compound **18b**, alcohol **22a** (34.0 mg, 0.12 mmol, 1.00 equiv) was converted to the corresponding *E*,*Z*-alcohol **23b** (31.0 mg, 0.11 mmol, 90%), which was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.50−5.29 (m, 4H, H-4, H-5, H-8, H-9), 3.65 (t, J = 6.5 Hz, 2H, H-1), 2.13−1.98 (m, 8H, H-3, H-6, H-7, H-10), 1.63 (p, J = 6.8 Hz, 2H, H-2), 1.35 (br s, 1H, OH), 1.34−1.26 (m, 16H, H-11−H-18), 0.88 (t, J = 6.7 Hz, 3H, H-19) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.7 ($C_{sp2}H$), 130.5 ($C_{sp2}H$), 130.0 ($C_{sp2}H$), 129.1 ($C_{sp2}H$), 62.7 (C-1), 32.8, 32.6, 32.1 (C-2), 29.9, 29.8, 29.8, 29.7, 29.5, 29.5, 29.1, 27.4, 27.4, 22.8 (C-18), 14.3 (C-19) ppm. IR (ATR): $\tilde{\nu}$ = 3313, 3006, 2921, 2852, 1457, 1378, 1059, 966, 720 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{37}O$ 281.2844; Found 281.2841.

(4*Z*,8*E*)-Nonadeca-4,8-dien-1-ol (23c). Following the procedure described for the synthesis of compound **18a**, alcohol **22b** (70.0 mg, 0.25 mmol, 1.00 equiv) was converted to the corresponding *Z*,*E*-alcohol **23c** (62.0 mg, 0.22 mmol, 89%), which was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.47−5.34 (m, 4H, H-4, H-5, H-8, H-9), 3.66 (t, J = 6.5 Hz, 2H, H-1), 2.17−1.93 (m, 8H, H-3, H-6, H-7, H-10), 1.63 (p, J = 6.8 Hz, 2H, H-2), 1.37−1.22 (m, 16H, H-11−H-18), 0.88 (t, J = 6.7 Hz, 3H, H-19) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.2 ($C_{sp2}H$), 130.3 ($C_{sp2}H$), 129.6 ($C_{sp2}H$), 129.3 ($C_{sp2}H$), 62.8 (C-1), 32.8, 32.8, 32.1 (C-2), 29.8, 29.8, 29.7, 29.5, 29.3, 27.5, 23.8, 22.8 (C-18), 14.3 (C-19) ppm. IR (ATR): $\tilde{\nu}$ = 3316, 3006, 2921, 2852, 1457, 1378, 1058, 966, 914, 758, 721 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{37}O$ 281.2844; Found 281.2871.

(4*E*,8*E*)-Nonadeca-4,8-dien-1-ol (23d). Following the procedure described for the synthesis of compound **18b**, alcohol **22b** (45.0 mg, 0.16 mmol, 1.00 equiv) was converted to the corresponding *E*,*E*-alcohol **23d** (43.0 mg, 0.15 mmol, 94%), which was obtained as a colorless oil. The $LiAlH_4$-mediated reduction of diynol **24** (138 mg, 0.50 mmol, 1.00 equiv) also delivered the title compound **23d** (94.0 mg, 0.34 mmol, 68%) under the same conditions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.50−5.33 (m, 4H, H-4, H-5, H-8, H-9), 3.65 (t, J = 6.5 Hz, 2H, H-1), 2.13−1.93 (m, 8H, H-3, H-6, H-7, H-10), 1.63 (p, J = 6.8 Hz, 2H, H-2), 1.37−1.22 (m, 16H, H-11−H-18), 0.88 (t, J = 6.7 Hz, 3H, H-19) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.0 ($C_{sp^2}H$), 130.8 ($C_{sp^2}H$), 129.9 ($C_{sp^2}H$), 129.7 ($C_{sp^2}H$), 62.7 (C-1),

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32.8, 32.8, 32.7, 32.6, 32.1 (C-2), 29.8, 29.8, 29.8, 29.7, 29.5, 29.3, 29.1, 22.8 (C-18), 14.3 (C-19) ppm. IR (ATR): $\tilde{\nu}$ = 3313, 2921, 2852, 1450, 1378, 1057, 965, 916, 721 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{37}O$ 281.2844; Found 281.2867.

Pentadec-4-ynal (31). PCC/silica (4.00 g, 9.26 mmol, 2.00 equiv; PCC containing 50 wt % of silica) was suspended in CH_2Cl_2 (80 mL) and cooled to 0 °C. Alcohol **17** (1.04 g, 4.63 mmol, 1.00 equiv), dissolved in CH_2Cl_2 (20 mL), was added dropwise. The reaction mixture was stirred vigorously with warming to rt for 2 h (conversion monitored by TLC, silica). After complete conversion of the starting material, the reaction mixture was filtrated over a plug of silica, carefully washed with Et_2O, and concentrated under reduced pressure. Flash chromatography (5% ethyl acetate in hexanes, silica) of the residue gave aldehyde **31** (0.89 g, 3.93 mmol, 86%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1H, H-1), 2.61 (t, J = 7.1 Hz, 2H, H-2), 2.51−2.45 (m, 2H, H-3), 2.11 (tt, J = 7.1, 2.3 Hz, 2H, H-6), 1.50−1.41 (m, 2H, H-7), 1.39−1.31 (m, 2H, H-8), 1.31−1.25 (m, 12H, H-9−H-14), 0.88 (t, J = 6.8 Hz, 3H, H-15) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.3 (C-1), 81.8 (C-5), 77.9 (C-4), 43.2 (C-2), 32.1 (C-13), 29.7, 29.7, 29.5, 29.3, 29.1, 29.0, 22.8 (C-14), 18.8 (C-6), 14.3 (C-15), 12.4 (C-3) ppm. IR (ATR): $\tilde{\nu}$ = 2923, 2853, 1728, 1465, 1356, 1056, 722 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{27}O$ 223.2056; Found 223.2055; $[M + Na]^+$ Calcd for $C_{15}H_{26}NaO$ 245.1876; Found 245.1861.

1,1-Dibromohexadec-1-en-5-yne (32). Carbon tetrabromide (6.77 g, 20.4 mmol, 2.00 equiv) was dissolved in dry CH_2Cl_2 (50 mL), and triphenylphosphine (10.7 g, 40.8 mmol, 4.00 equiv) was added at 0 °C. Aldehyde **31** (2.27 g, 10.2 mmol, 1.00 equiv), dissolved in dry CH_2Cl_2 (25 mL), was added slowly to this solution. The ice bath was removed, and the reaction mixture was stirred at rt for 1 h (conversion monitored by TLC, silica). After complete conversion of the starting material, the reaction mixture was filtrated over a plug of silica, washed carefully with hexanes (precipitation of solids), and concentrated under reduced pressure. Flash chromatography (100% hexanes, silica) of the residue gave dibromoalkene **32** (3.48 g, 9.25 mmol, 90%) as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.54−6.45 (m, 1H, H-2), 2.31−2.24 (m, 4H, H-3, H-4), 2.19−2.09 (m, 2H, H-7), 1.53−1.42 (m, 2H, H-8), 1.42−1.33 (m, 2H, H-9), 1.31−1.25 (m, 12H, H-10−H-15), 0.88 (t, J = 6.7 Hz, 3H, H-16) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.4 (C-2), 89.8 (C-1), 81.9 (C-6), 78.3 (C-5), 32.8 (C-3), 32.1 (C-14), 29.8, 29.7, 29.5, 29.3, 29.1, 29.0, 22.8 (C-15), 18.9 (C-7), 17.6 (C-4), 14.3 (C-16) ppm. IR (ATR): $\tilde{\nu}$ = 2954, 2922, 2853, 1626, 1464, 1434, 1377, 1339, 1272, 1215, 1182, 1072, 805, 787, 751, 722 cm^{-1}. Because of the instability of this compound, no MS data or elemental analysis could be obtained.

Hexadeca-1,5-diyne (34). To the solution of aldehyde **31** (0.89 g, 4.00 mmol, 1.00 equiv) and fine powdered K_2CO_3 (1.38 g, 10.0 mmol, 2.50 equiv) in dry MeOH (50.0 mL) was added dimethyl-1-diazo-2-oxopropylphosphonate (Bestmann-Ohira reagent, BOR) (1.15 g, 6.00 mmol, 1.50 equiv) at rt, and stirring was continued for 3 h (conversion monitored by TLC, silica). After complete conversion of the starting material, the reaction mixture was filtrated over a plug of silica, carefully washed with ethyl acetate and concentrated under reduced pressure. Flash chromatography (100% hexanes, silica) of the residue gave diyne **34** (0.69 g, 3.16 mmol, 79%) as a colorless liquid. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.40−2.36 (m, 4H, H-3, H-4), 2.17−2.12 (m, 2H, H-7), 2.00 (t, J = 2.3 Hz, 1H, H-1), 1.50−1.45 (m, 2H, H-8), 1.38−1.34 (m, 2H, H-9), 1.32−1.26 (m, 12H, H-10−H-15), 0.88 (t, J = 7.0 Hz, 3H, H-16) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 83.3 (C-2), 81.8 (C-6), 78.2 (C-5), 69.1 (C-1), 32.1 (C-14), 29.7, 29.7, 29.5, 29.3, 29.1, 29.0, 22.8 (C-15), 19.3 (C-3 or C-4), 19.1 (C-3 or C-4), 18.9 (C-7), 14.3 (C-16) ppm. IR (ATR): $\tilde{\nu}$ = 3313, 2923, 2853, 1465, 1434, 1378, 1338, 1257, 722, 631, 561, 479 cm^{-1}. MS (EI): m/z = 203 $[M - CH_3]^+$, 189 $[M - C_2H_5]^+$, 175 $[M - C_3H_7]^+$, 141 $[M - C_6H_5]^+$, 127 $[M - C_7H_7]^+$, 85 $[M - C_{10}H_{13}]^+$, 71 $[M - C_{11}H_{15}]^+$, 57 $[M - C_{12}H_{17}]^+$. Anal. Calcd for $C_{16}H_{26}$: C, 88.00; H, 12.00. Found: C, 87.82; H, 12.04.

Nonadeca-1-en-4,8-diyne (33). *Synthesis Starting from Dibromoalkene 32.* Dibromoalkene **32** (3.48 g, 9.20 mmol, 1.00 equiv) in dry THF (100 mL) was cooled to −78 °C. *n*-Butyllithium (1.6 M in hexane, 14.4 mL, 23.0 mmol, 2.50 equiv) was added dropwise, and the yellowish solution was stirred for 2 h with warming to rt. 3-Bromopropene (3.34 g, 2.40 mL, 27.6 mmol, 3.00 equiv) and TBAI (340 mg, 0.92 mmol, 0.10 equiv) were added at 0 °C, and the reaction mixture was warmed to rt before being heated to 80 °C. After complete conversion of the starting material was detected (TLC, silica), brine (75 mL) was added and the solution was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and filtrated, and the solvents were removed under reduced pressure. The crude product was codistilled with toluene to remove excess 3-bromopropene. Flash chromatography (100% hexanes, silica) of the residue gave the title compound **33** (1.90 g, 7.35 mmol, 80%), as a colorless liquid.

Synthesis Starting from Diyne 34. Following the procedure described for the synthesis of compound **16**, diyne **34** (0.67 g, 3.07 mmol, 1.00 equiv) was converted to the title compound **33** (0.66 g, 2.55 mmol, 83%), which was obtained as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.82 (ddt, J = 16.9, 10.2, 5.2 Hz, 1H, H-2), 5.34 (dq, J = 17.0, 1.9 Hz, 1H, H-1a), 5.10 (dq, J = 10.0, 1.7 Hz, 1H, H-1b), 2.98−2.89 (m, 2H, H-3), 2.42−2.33 (m, 4H, H-6, H-7), 2.17−2.10 (m, 2H, H-10), 1.51−1.42 (m, 2H, H-11), 1.41−1.33 (m, 2H, H-12), 1.33−1.25 (m, 12H, H-13−H-18), 0.88 (t, J = 6.9 Hz, 3H, H-19) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.2 (C-2), 115.9 (C-1), 81.6 (C-5), 81.5 (C-9), 78.8 (C-8), 77.6 (C-4), 31.1 (C-17), 29.7, 29.7, 29.5, 29.3, 29.2, 29.0, 23.2 (C-3), 22.8 (C-18), 19.7 (C-6 or C-7), 19.6 (C-6 or C-7), 18.9 (C-10), 14.3 (C-19) ppm. IR (ATR): $\tilde{\nu}$ = 3085, 3013, 2923, 2853, 1642, 1465, 1433, 1402, 1378, 1339, 1285, 1258, 989, 915, 722, 634, 558 cm^{-1}. MS (EI): m/z = 258 $[M]^{+\cdot}$, 243 $[M - CH_3]^+$, 229 $[M - C_2H_5]^+$, 217 $[M - C_3H_5]^+$, 187 $[M - C_5H_{11}]^+$, 173 $[M - C_6H_{13}]^+$, 159 $[M - C_7H_{15}]^+$, 145 $[M - C_8H_{17}]^+$, 131 $[M - C_9H_{19}]^+$, 117 $[M - C_{10}H_{21}]^+$, 79 $[M - C_{13}H_{23}]^+$. Anal. Calcd for $C_{19}H_{30}$: C, 88.30; H, 11.70. Found: C, 88.40; H, 11.65.

Nonadeca-4,8-diyn-1-ol (24). Following the procedure described for the synthesis of compound **17**, alkene **33** (3.30 g, 12.8 mmol, 1.00 equiv) was converted to the alcohol **24** (2.22 g, 8.02 mmol, 63%, brsm 87%, 28% starting material reisolated), which was obtained as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.76 (dd, J = 10.7, 5.6 Hz, 2H, H-1), 2.38−2.32 (m, 4H, H-6, H-7), 2.29 (t, J = 6.9 Hz, 2H, H-3), 2.14 (t, J = 7.0 Hz, 2H, H-10), 1.78−1.70 (m, 2H, H-2), 1.51−1.43 (m, 2H, H-11), 1.40−1.33 (m, 2H, H-12), 1.33−1.25 (m, 12H, H-13−H-18), 0.88 (t, J = 6.8 Hz, 3H, H-19) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.5 (C-9), 80.4 (C-4), 79.8 (C-8), 78.7 (C-5), 62.2 (C-1), 32.1 (C-17), 31.6 (C-2), 29.7, 29.7, 29.5, 29.3, 29.2, 29.0, 22.8 (C-18), 2 × 19.6 (C-6, C-7), 18.9 (C-10), 15.6 (C-3), 14.3 (C-19) ppm. IR (ATR): $\tilde{\nu}$ = 3379, 2955, 2919, 2849, 1457, 1433, 1378, 1256, 1160, 1078, 1056, 1038, 1004, 848, 745, 723 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{33}O$: 277.2526; Found: 277.2526. Mp: 39−40 °C.

1-Bromononadeca-4,8-diyne (30). Triphenylphosphine (6.02 g, 23.0 mmol, 1.60 equiv) was added to a solution of alcohol **24** (3.97 g, 14.4 mmol, 1.00 equiv) in dry THF (40 mL) at −20 °C. *N*-Bromosuccinimide (3.83 g, 21.5 mmol, 1.50 equiv) was added, and the clear light yellow solution was stirred for 4 h (conversion monitored by TLC, silica) with warming to rt. After complete conversion of the starting material, the reaction was quenched with NH_4Cl_{aq} (30 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Filtration over a short plug of silica (100% hexanes) gave bromide **30** (4.35 g, 12.8 mmol, 90%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.54 (t, J = 6.5 Hz, 2H, H-1), 2.41−2.27 (m, 6H, H-3, H-6, H-7), 2.14 (t, J = 7.0 Hz, 2H, H-10), 2.01 (p, J = 6.4 Hz, 2H, H-2), 1.53−1.42 (m, 2H, H-11), 1.42−1.33 (m, 2H, H-12), 1.34−1.25 (m, 12H, H-13−H-18), 0.88 (t, J = 6.7 Hz, 3H, H-19) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 81.5 (C-9), 80.3 (C-5), 79.0 (C-4), 78.7 (C-8), 32.6 (C-1), 32.1 (C-17), 31.9 (C-2), 29.8, 29.7, 29.5, 29.3, 29.2, 29.0, 22.8 (C-18), 2 × 19.6 (C-6, C-7), 18.9 (C-10), 17.6 (C-3), 14.3 (C-19) ppm. IR (ATR): $\tilde{\nu}$ = 3053, 2922, 2853, 1465, 1433, 1377, 1339, 1272, 1247, 1196, 1119, 961, 853, 722, 651, 565, 542 cm^{-1}. MS (EI): m/z = 338 $[M]^{+\cdot}$, 323 $[M - CH_3]^+$, 295 $[M - C_3H_7]^+$, 281 $[M - C_4H_9]^+$, 253 $[M - C_6H_{13}]^+$, 239 $[M - C_7H_{15}]^+$, 225 $[M - C_8H_{17}]^+$,

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211 $[M - C_9H_{19}]^+$, 197 $[M - C_{10}H_{21}]^+$, 159 $[M - C_{13}H_{23}]^+$, 145 $[M - C_{14}H_{25}]^+$. Anal. Calcd for $C_{19}H_{31}Br$: C, 67.25; H, 9.12. Found: C, 67.44; H, 9.27.

Nonadeca-4,8-diyn-1-yltriphenylphosphonium Bromide (29). Triphenylphosphine (3.87 g, 14.7 mmol, 1.20 equiv) was added to bromide **30** (4.17 g, 12.3 mmol, 1.00 equiv) under a N_2 atmosphere in the absence of any solvent. The mixture was heated to 140 °C and stirred at this temperature overnight. After cooling to rt the crude reaction mixture was diluted with small amounts of $CHCl_3$ and added dropwise to Et_2O. The colorless precipitate was filtered off, and the purification procedure was repeated. The title compound **29** (6.86 g, 11.4 mmol, 93%) was isolated as a colorless foam after drying at 80 °C in vacuo overnight. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.87−7.76 (m, 9H, Ar), 7.72−7.65 (m, 6H, Ar), 3.99−3.88 (m, 2H, H-1), 2.57 (t, J = 6.1 Hz, 2H, H-3), 2.35−2.25 (m, 4H, H-6, H-7), 1.95 (t, J = 7.0 Hz, 2H, H-10), 1.86−1.76 (m, 2H, H-2), 1.41−1.30 (m, 2H, H-11), 1.29−1.19 (m, 14H, H-12−H-18), 0.85 (t, J = 6.7 Hz, 3H, H-19) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.2 (d, J = 3.0 Hz, C-23), 133.8 (d, J = 10.0 Hz, C-21), 130.6 (d, J = 12.5 Hz, C-22), 118.3 (d, J = 86.1 Hz, C-20), 81.5 (C-4), 81.0 (C-9), 79.3 (C-8), 78.6 (C-5), 32.0 (C-17), 29.7, 29.6, 29.4, 29.2, 29.0, 28.9, 22.8 (C-18), 22.5 (d, J = 3.3 Hz, C-2), 21.7 (d, J = 51.9 Hz, C-1), 19.6 (d, J = 18.3 Hz, C-3), 19.6 (C-6 or C-7), 19.5 (C-6 or C-7), 18.7 (C-10), 14.2 (C-19) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 24.3 ppm. IR (ATR): $\tilde{\nu}$ = 3386, 2922, 3053, 3006, 2853, 1587, 1465, 1437, 1338, 1338, 1191, 1111, 996, 815, 722, 689, 537, 507 cm^{-1}. HRMS (ESI-TOF) m/z: $[M - Br]^+$ Calcd for $C_{37}H_{46}P^+$: 521.3332; Found: 521.3334.

(*Z*)-Methyl Dotriaconta-13-en-17,21-diynoate (35). Phosphonium salt **29** (4.04 g, 6.72 mmol, 1.00 equiv) was added to a solution of NaHMDS (2 M in THF, 3.70 mL, 7.39 mmol, 1.10 equiv) in dry THF (35 mL). The reaction mixture was stirred at rt for 30 min, and aldehyde **10** (1.79 g, 7.39 mmol, 1.10 equiv), dissolved in dry THF (15 mL), was added slowly to the orange solution at −20 °C. The reaction mixture was stirred 1 h at −20 °C before warming to rt. After complete conversion (3 h; conversion monitored by TLC, silica) the reaction was quenched with H_2O (25 mL) and extracted with Et_2O (3 × 15 mL). The combined organic phases were dried over $MgSO_4$ and filtrated, and the solvents were removed under reduced pressure. Flash chromatography (2% ethyl acetate in hexanes, silica) of the residue gave methyl ester **35** (2.40 g, 4.95 mmol, 74%; Z/E ratio of >95:5, determined by ^{13}C NMR) as a slightly yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.53−5.29 (m, 2H, H-13, H-14), 3.66 (s, 3H, H-33), 2.37−2.27 (m, 6H, H-2, H-19, H-20), 2.26−2.10 (m, 6H, H-15, H-16, H-23), 2.08−1.97 (m, 2H, H-12), 1.70−1.57 (m, 2H, H-3), 1.51−1.42 (m, 2H, H-24), 1.40−1.25 (m, 30H, H-4−H-11, H-25−H-31), 0.88 (t, J = 6.8 Hz, 3H, H-32) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5 (C-1), 131.3 (C-13), 128.1 (C-14), 81.4 (C-22), 80.8 (C-17), 79.1 (C-18), 78.8 (C-21), 51.6 (C-33), 34.3 (C-2), 32.1 (C-30), 29.9, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.0, 27.5, 27.1, 25.1 (C-3), 22.8 (C-31), 19.7 (C-19 or C-20), 19.6 (C-19 or C-20), 19.4 (C-16), 18.9 (C-23), 14.3 (C-32) ppm. IR (ATR): $\tilde{\nu}$ = 2918, 2849, 1736, 1459, 1436, 1366, 1333, 1310, 1255, 1227, 1202, 1173, 1111, 1015, 974, 881, 723, 709, 591 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{33}H_{57}O_2$ 485.4353; Found 485.4354; $[M + NH_4]^+$ Calcd for $C_{33}H_{60}NO_2$: 502.4619; Found: 502.4620. Mp: 30−31 °C.

(*Z*)-Dotriaconta-13-en-17,21-diynoic Acid (36). KOH_{aq} (sat., 8.00 mL) was added to a stirred solution of ester **35** (2.30 g, 4.74 mmol, 1.00 equiv) in MeOH/THF (2:1, 24 mL). The reaction mixture was stirred at rt for 4 h (conversion monitored by TLC, silica). After complete conversion of the starting material, the reaction mixture was acidified with a solution of 1 M $KHSO_4$. After extraction with Et_2O (3 × 15 mL) the combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. Fatty acid **36** was obtained as a pale yellow solid (2.11 g, 4.48 mmol, 95%). ^1H NMR (600 MHz, $CDCl_3$): δ = 5.45−5.35 (m, 2H, H-13, H-14), 2.37−2.24 (m, 6H, H-2, H-19, H-20), 2.24−2.10 (m, 6H, H-15, H-16, H-23), 2.06−1.98 (m, 2H, H-12), 1.67−1.59 (m, 2H, H-3), 1.52−1.42 (m, 2H, H-24), 1.40−1.21 (m, 30H, H-4−H-11, H-25−H-31), 0.88 (t, J = 7.0 Hz, 3H, H-32) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 179.1 (C-1), 131.4 (C-13), 128.1 (C-14), 81.4 (C-22), 80.9 (C-17), 79.1 (C-18), 78.9 (C-21), 34.0 (C-2), 32.1 (C-30), 29.9, 29.8, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 29.2, 29.0, 27.5, 27.1, 24.9 (C-3), 22.8 (C-31), 19.7 (C-19 or C-20), 19.6 (C-19 or C-20), 19.4 (C-16), 18.9 (C-23), 14.3 (C-32) ppm. IR (ATR): $\tilde{\nu}$ = 3012, 2953, 2917, 2847, 1693, 1459, 1433, 1331, 1310, 1286, 1259, 1233, 1209, 1187, 1109, 913, 724, 711, 590 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{55}O_2$: 471.4197; Found: 471.4190. Mp: 58−59 °C.

(*S,Z*)-3-(Dotriaconta-13-en-17,21-diyn-1-yl)-4-hydroxy-5-methylfuran-2(5*H*)-one (38).[29] DIPEA (0.83 mL, 4.91 mmol, 1.10 equiv) was added to a suspension of butenolide **8** (560 mg, 4.91 mmol, 1.10 equiv), fatty acid **36** (2.10 g, 4.46 mmol, 1.00 equiv), 4-DMAP (164 mg, 1.34 mmol, 0.30 equiv), and DCC (1.10 g, 5.35 mmol, 1.20 equiv) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was stirred overnight with warming to rt. The yellow solution was filtered, and the solid was washed with Et_2O. The filtrate was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. The organic phase was washed with a solution of 1 N HCl (20 mL) and brine (20 mL), dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. In order to remove the residual urea derivative, the mixture was dissolved in Et_2O, filtrated, and concentrated under reduced pressure to yield a brownish solid that was directly used in the subsequent reduction step. To this end, the crude product **37** was dissolved in acetic acid (15 mL) and $NaBH_3CN$ (561 mg, 8.92 mmol, 2.00 equiv) was slowly added at 10 °C. The reaction mixture was stirred overnight with warming to rt and then poured into a solution of 1 N HCl (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, filtrated, and concentrated under reduced pressure (3× codistillation with toluene to remove acetic acid). The title compound **38** (2.22 g, 4.02 mmol, 90%) was obtained in analytically pure form as a colorless solid. $[\alpha]_D^{20}$ +7.5 (c 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.48−5.32 (m, 2H, H-15, H-16), 4.80 (q, J = 6.6 Hz, 1H, H-36), 2.33 (br s, 4H, H-21, H-22), 2.26−2.08 (m, 8H, H-3, H-17, H-18, H-25), 2.07−1.96 (m, 2H, H-14), 1.53−1.22 (m, 39H, H-4−H-13, H-26−H-33, H-37), 0.87 (t, J = 6.7 Hz, 3H, H-34) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5 (C-35), 176.2 (C-1), 131.3 (C-15), 128.0 (C-16), 101.5 (C-2), 81.4 (C-24), 80.9 (C-19), 79.2 (C-20), 78.9 (C-23), 74.9 (C-36), 32.1 (C-32), 29.9, 29.9, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 29.3, 29.2, 29.0, 28.2, 27.5, 27.1, 22.8 (C-33), 21.3 (C-3), 19.7 (C-21 or C-22), 19.6 (C-21 or C-22), 19.4 (C-18), 18.9 (C-25), 18.0 (C-37), 14.3 (C-34) ppm. IR (ATR): $\tilde{\nu}$ = 3004, 2915, 2846, 1706, 1611, 1465, 1403, 1343, 1312, 1296, 1280, 1261, 1245, 1224, 1110, 1082, 1054, 923, 905, 823, 778, 756, 721, 667, 613 598 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{37}H_{61}O_3$: 553.4615; Found: 553.4617. Mp: 78−79 °C.

(*S,Z*)-4-(Dotriaconta-13-en-17,21-diyn-1-yl)-2-methyl-5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate (39). DIPEA (1.03 mL, 5.92 mmol, 1.50 equiv) was added to a stirred solution of **38** (2.18 g, 3.95 mmol, 1.00 equiv) in dry CH_2Cl_2 (40 mL) at rt. The solution was cooled to −78 °C, and Tf_2O (0.8 mL, 4.74 mmol, 1.20 equiv) was slowly added. The mixture was stirred at −78 °C for 2 h (conversion monitored by TLC, silica). After complete conversion of the starting material, CH_2Cl_2 (10 mL) was added, and the reaction mixture was extracted with a solution of 1 N HCl (35 mL). The combined organic phases were washed with H_2O (35 mL), brine (35 mL), dried over $MgSO_4$, and filtrated. The solvents were removed under reduced pressure. Flash chromatography (5% ethyl acetate in hexanes, silica) of the residue gave triflate **39** (2.52 g, 3.67 mmol, 93%) as a colorless oil. $[\alpha]_D^{20}$ +25.6 (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.45−5.35 (m, 2H, H-15, H-16), 5.11 (q, J = 6.6 Hz, 1H, H-36), 2.43−2.28 (m, 6H, H-3, H-21, H-22), 2.26−2.10 (m, 6H, H-17, H-18, H-25), 2.07−1.97 (m, 2H, H-14), 1.67−1.51 (m, 7H, H-37), 1.51−1.43 (m, 2H), 1.39−1.26 (m, 30H), 0.88 (t, J = 6.8 Hz, 3H, H-34) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.3 (C-1), 163.5 (C-35), 131.4 (C-15), 128.0 (C-16), 122.1 (C-2), 118.5 (q, J = 320.9 Hz, C-38), 81.4 (C-24), 80.8 (C-19), 79.1 (C-20), 78.8 (C-23), 74.6 (C-36), 32.1 (C-32), 29.9, 29.8, 29.8, 29.7, 29.7, 29.7, 29.6, 29.5, 29.5, 29.5, 29.3, 29.3, 29.2, 29.0, 27.5, 27.1, 26.8, 2 × 22.8 (C-3, C-33), 19.7 (C-21 or C-22), 19.6 (C-21 or C-22), 19.4 (C-18), 18.9 (C-25), 17.9

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(C-37), 14.3 (C-34) ppm. ^{19}F NMR(565 MHz, $CDCl_3$): δ = −72.9 ppm. IR (ATR): $\tilde{\nu}$ = 2923, 2853, 1780, 1699, 1433, 1339, 1218, 1136, 1066, 936, 806, 764, 722, 603, 508 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{38}H_{60}F_3O_5S$ 685.4108; Found 685.4114; $[M + Na]^+$ Calcd for $C_{38}H_{59}F_3NaO_5S$: 707.3928; Found: 707.3931.

(*S*)-4-((13*Z*,17*Z*,21*Z*)-Dotriaconta-13,17,21-trien-1-yl)-2-methyl-5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate (40). Following the procedure described for the synthesis of compound **18a**, diyne **39** (2.25 g, 3.29 mmol, 1.00 equiv) was converted to the *Z*,*Z*,*Z*-triene **40** (2.12 g, 3.08 mmol, 94%), which was obtained as a colorless oil. $[\alpha]_D^{20}$ +33 (*c* 0.2, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.41−5.34 (m, 6H, H-15, H-16, H-19, H-20, H-23, H-24), 5.11 (q, *J* = 6.7 Hz, 1H, H-36), 2.29−2.25 (m, 2H, H-3), 2.12−2.05 (m, 8H, H-17, H-18, H-21, H-22), 2.05−2.00 (m, 4H, H-14, H-25), 1.67−1.48 (m, 7H, H-37), 1.34−1.25 (m, 32H), 0.88 (t, *J* = 7.0 Hz, 3H, H-34) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.3 (C-1), 163.5 (C-33), 130.6 ($C_{sp^2}H$), 130.6 ($C_{sp^2}H$), 129.8 ($C_{sp^2}H$), 129.8 ($C_{sp^2}H$), 129.2 ($C_{sp^2}H$), 129.2 ($C_{sp^2}H$), 122.1 (C-2), 118.5 (q, *J* = 320.9 Hz, C-38), 74.6 (C-36), 32.1 (C-32), 29.9, 29.9, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 29.3, 27.6, 27.5, 27.4, 27.4, 26.9, 22.9 (C-3 or C-33), 22.8 (C-3 or C-33), 17.9 (C-37), 14.3 (C-34) ppm. ^{19}F NMR(565 MHz, $CDCl_3$): δ = −72.9 ppm. IR (ATR): $\tilde{\nu}$ = 3006, 2923, 2853, 1781, 1699, 1434, 1379, 1340, 1218, 1137, 1103, 1066, 937, 806, 764, 722, 603, 537, 508 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{38}H_{64}F_3O_5S$: 689.4421; Found: 689.4424.

(+)-Chatenaytrienin-4 (26). $Pd_2(dba)_3$ (4.12 mg, 0.0045 mmol 1.5 mol %, 0.015 equiv) and triphenylphosphine (12.0 mg, 0.045 mmol, 15 mol %, 0.15 equiv) were dissolved in dry THF (6.00 mL). After stirring for 5 min at rt, triflate **40** (207 mg, 0.30 mmol, 1.00 equiv) and Bu_3SnH (243 μL, 0.90 mmol, 3.00 equiv) were added to the greenish solution. The mixture was heated to 50 °C and stirred at this temperature for 5 h (conversion monitored by TLC, silica). After complete conversion of the starting material, the reaction was cooled to rt, diluted with H_2O (3.00 mL), and extracted with Et_2O (3 × 5.00 mL). The combined organic phases were dried over $MgSO_4$ and filtrated, and the solvents were removed under reduced pressure. Flash chromatography (2% ethyl acetate in hexanes, KF/silica 9:1) of the residue gave (+)-chatenaytrienin-4 (**26**) (101 mg, 0.19 mmol, 63%) as a colorless waxy solid. $[\alpha]_D^{20}$ +16 (*c* 0.2, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.98 (d, *J* = 1.4 Hz, 1H, H-35), 5.42−5.33 (m, 6H, H-15, H-16, H-19, H-20, H-23, H-24), 5.01−4.96 (m, 1H, H-36), 2.29−2.24 (m, 2H, H-3), 2.16−2.03 (m, 8H, H-17, H-18, H-21, H-22), 2.05−1.98 (m, 4H, H-14, H-25), 1.57−1.51 (m, 2H, H-4), 1.40 (d, *J* = 6.8 Hz, 3H, H-37), 1.36−1.25 (m, 34H, H-5−H-13, H-26−H-33), 0.88 (t, *J* = 7.0 Hz, 3H, H-34) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.0 (C-1), 149.0 (C-35), 134.5 (C-2), 130.6 ($C_{sp^2}H$), 130.5 ($C_{sp^2}H$), 129.8 ($C_{sp^2}H$), 129.8 ($C_{sp^2}H$), 129.2 ($C_{sp^2}H$), 129.2 ($C_{sp^2}H$), 77.5 (C-36), 32.1 (C-32), 29.9, 29.8, 29.8, 29.8, 29.7, 29.7, 29.5, 29.5, 29.4, 27.6, 27.6, 27.5, 27.4, 25.3 (C-3), 22.8 (C-33), 19.4 (C-37), 14.3 (C-34) ppm. IR (ATR): $\tilde{\nu}$ = 3005, 2922, 2852, 1757, 1655, 1456, 1373, 1317, 1198, 1118, 1075, 1027, 966, 856, 721 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{37}H_{65}O_2$: 541.4979; Found: 541.4969.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01051.

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

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Dr. Dr. h.c. mult. Wittko Francke on the occasion of his 75th birthday.

■ REFERENCES

(1) For selected reviews, see: (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540. (b) Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269−303. (c) Makabe, H.; Konno, H.; Miyoshi, H. *Curr. Drug Discovery Technol.* **2008**, *5*, 213−229. (d) Smith, R. S.; Tran, K.; Richards, K. M. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier B. V.; 2014; Vol. *41*, pp 95−117.

(2) For recent reviews on the total synthesis of annonaceous acetogenins, see: (a) Makabe, H. *Biosci., Biotechnol., Biochem.* **2007**, *71*, 2367−2374. (b) Li, N.; Shi, Z.; Tang, Y.; Chen, J.; Li, X. *Beilstein J. Org. Chem.* **2008**, *4*, 1−62. (c) Spurr, I. B.; Brown, R. C. D. *Molecules* **2010**, *15*, 460−501. See also ref 1b.

(3) Representative acetogenin total syntheses: (a) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 971−975. (b) Bäurle, S.; Hoppen, S.; Koert, U. *Angew. Chem., Int. Ed.* **1999**, *38*, 1263−1266. (c) Hoppen, S.; Bäurle, S.; Koert, U. *Chem. - Eur. J.* **2000**, *6*, 2382−2396. (d) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3622−3626. (e) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790−12791. (f) Nattrass, G. L.; Diez, E.; McLachlan, M. M.; Dixon, D. J.; Ley, S. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 580−584. (g) Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R.-A. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245−4248. (h) Morris, C. L.; Hu, Y.; Head, G. D.; Brown, L. J.; Whittingham, W. G.; Brown, R. C. D. *J. Org. Chem.* **2009**, *74*, 981−988. (i) Sohn, T.; Kim, M. J.; Kim, D. *J. Am. Chem. Soc.* **2010**, *132*, 12226−12227. (j) Florence, G. J.; Morris, J. C.; Murray, R. G.; Osler, J. D.; Reddy, V. R.; Smith, T. K. *Org. Lett.* **2011**, *13*, 514−517. See also refs 9 and 22.

(4) Tempesta, M. S.; Kriek, G. R.; Bates, R. B. *J. Org. Chem.* **1982**, *47*, 3151−3153.

(5) Liaw, C.-C.; Wu, T.-Y.; Chang, F.-R.; Wu, Y.-C. *Planta Med.* **2010**, *76*, 1390−1404 and references cited therein. See also ref 1.

(6) Oberlies, N. H.; Croy, V. L.; Harrison, M. L.; McLaughlin, J. L. *Cancer Lett.* **1997**, *115*, 73−79.

(7) (a) Ahammadsahib, K. I.; Hollingworth, R. M.; McGovern, P. J.; Hui, Y.-H.; McLaughlin, J. L. *Life Sci.* **1993**, *53*, 1113−1120. (b) Morré, D. J.; de Cabo, R.; Farley, C.; Oberlies, N. H.; McLaughlin, J. L. *Life Sci.* **1994**, *56*, 343−348.

(8) For the isolation of membranacin, see: González, M. C.; Lavaud, C.; Gallardo, T.; Zafra-Polo, M.-C.; Cortes, D. *Tetrahedron* **1998**, *54*, 6079−6088.

(9) For the synthesis of membranacin, see: Head, G. D.; Whittingham, W. G.; Brown, R. C. D. *Synlett* **2004**, 1437−1439.

(10) For selected reviews, see: (a) Liu, T.; Cane, D. E.; Deng, Z. In *Methods in Enzymology*; Hopwood, D. A., Ed.; Elsevier, 2009; Vol. *459*, pp 187−214. (b) Gallimore, A. R. *Nat. Prod. Rep.* **2009**, *26*, 266−280.

(11) (a) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831−4832. (b) Schmidt, J.; Stark, C. B. W. *Org. Lett.* **2012**, *14*, 4042−4045. (c) Morimoto, Y.; Takeuchi, E.; Kambara, H.; Kodama, T.; Tachi, Y.; Nishikawa, K. *Org. Lett.* **2013**, *15*, 2966−2969. (d) Schmidt, J.; Khalil, Z.; Capon, R. J.; Stark, C. B. W. *Beilstein J. Org. Chem.* **2014**, *10*, 1228−1232.

(12) (a) Koert, U. *Synthesis* **1995**, *1995*, 115−132. (b) McDonald, F. E.; Tong, R.; Valentine, J. C.; Bravo, F. *Pure Appl. Chem.* **2007**, *79*, 281−291. (c) Vilotijevic, I.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250−5281. (d) Ueberbacher, B. T.; Hall, M.; Faber, K. *Nat. Prod. Rep.* **2012**, *29*, 337−350.

DOI: 10.1021/acs.joc.6b01051
J. Org. Chem. 2016, 81, 8175−8186

(13) It has recently been established that such polyenes are indeed precursors in polyether biosynthesis through feeding studies and knockout mutants lacking the epoxidase activity of the natural Streptomyces strain, e.g. in the monensin and lasalocid biosynthesis. For monensin, see reference: (a) Bhatt, A.; Stark, C. B. W.; Harvey, B. M.; Gallimore, A. R.; Demydchuk, Y. A.; Spencer, J. B.; Staunton, J.; Leadlay, P. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 7075−7078. For lasalocid, see: (b) Hotta, K.; Chen, X.; Paton, R. S.; Minami, A.; Li, H.; Swaminathan, K.; Mathews, I. I.; Watanabe, K.; Oikawa, H.; Houk, K. N.; Kim, C.-Y. *Nature* **2012**, *483*, 355−358. (c) Minami, A.; Migita, A.; Inada, D.; Hotta, K.; Watanabe, K.; Oguri, H.; Oikawa, H. *Org. Lett.* **2011**, *13*, 1638−1641.

(14) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275−306. See also ref 1b.

(15) For the isolation of selected linear acetogenins, see: (a) Gleye, C.; Raynaud, S.; Hocquemiller, R.; Laurens, A.; Fourneau, C.; Serani, L.; Laprévote, O.; Roblot, F.; Leboeuf, M.; Fournet, A.; Rojas de Arias, A.; Figadère, B.; Cavé, A. *Phytochemistry* **1998**, *47*, 749−754. (b) Jiang, Z.; Chen, Y.; Chen, R.-Y.; Yu, D.-Q. *Phytochemistry* **1998**, *49*, 769−775. (c) Yu, J.-G.; Gui, H.-Q.; Luo, X.-Z.; Sun, L. *Phytochemistry* **1998**, *49*, 1689−1692. See also ref 1b.

(16) Carballeira, N. M.; Emiliano, A.; Guzmán, A. *Chem. Phys. Lipids* **1999**, *100*, 33−40.

(17) Liblikas, I.; Mozūraitis, R.; Santangelo, E. M.; Noreika, R.; Borg-Karlson, A.-K. *Chem. Biodiversity* **2009**, *6*, 1388−1403.

(18) Carballeira, N. M.; Montano, N.; Alvarez-Velilla, R.; Prada, C. F.; Reguera, R. M.; Balaña-Fouce, R. *Mar. Drugs* **2013**, *11*, 3661−3675.

(19) D'yakonov, V. A.; Makarov, A. A.; Dzhemileva, L. U.; Makarova, E.; Khusnutdinova, E. K.; Dzhemilev, U. M. *Chem. Commun.* **2013**, *49*, 8401−8403.

(20) Adrian, J.; Stark, C. B. W. *Org. Lett.* **2014**, *16*, 5886−5889.

(21) For biosynthetic hypotheses, see: (a) Hu, Y.; Cecil, A. R. L.; Frank, X.; Gleye, C.; Figadère, B.; Brown, R. C. D. *Org. Biomol. Chem.* **2006**, *4*, 1217−1219 and references cited therein. See also refs 10b and 12d.

(22) For syntheses of *trans*-solamin, see: (a) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891−4892. (b) Trost, B. M.; Shi, Z. P. *J. Am. Chem. Soc.* **1994**, *116*, 7459−7460. (c) Makabe, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1975−1981. (d) Kuriyama, W.; Ishigami, K.; Kitahara, T. *Heterocycles* **1999**, *50*, 981−988. (e) Prestat, G.; Baylon, C.; Heck, M.-P.; Grasa, G. A.; Nolan, S. P.; Mioskowski, C. *J. Org. Chem.* **2004**, *69*, 5770−5773. (f) Raghavan, S.; Subramanian, S. G.; Tony, K. A. *Tetrahedron Lett.* **2008**, *49*, 1601−1604. For syntheses of *cis*-solamin A, see: (g) Makabe, H.; Hattori, Y.; Tanaka, A.; Oritani, T. *Org. Lett.* **2002**, *4*, 1083−1085. (h) Cecil, A. R. L.; Brown, R. C. D. *Org. Lett.* **2002**, *4*, 3715−3718. (i) Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4766−4768. (j) Göksel, H.; Stark, C. B. W. *Org. Lett.* **2006**, *8*, 3433−3436. See also refs 2a and 22g.

(23) For reviews, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−92. (b) Vedejs, E.; Peterson, M. J. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons: New York, 1994; Vol. *21*, pp 1−158. (c) Byrne, P. A.; Gilheany, D. G. *Chem. Soc. Rev.* **2013**, *42*, 6670−6696.

(24) For a recent review on alkyne reductions, see: Oger, C.; Balas, L.; Durand, T.; Galano, J.-M. *Chem. Rev.* **2013**, *113*, 1313−1350.

(25) Generally, the reduction of acetylenes to (*E*)-alkenes is carried out using Li or Na in liquid NH_3; see reference: (a) Brandsma, L.; Nieuwenhuizen, W. F.; Zwikker, J. W.; Mäeorg, U. *Eur. J. Org. Chem.* **1999**, *1999*, 775−779. $LiAlH_4$ in Et_2O or THF is used for long-chain alk-2-ynes. For *β*-, *γ*-, or *ω*-alkynes, higher temperatures are needed for the reduction, and diglyme or a mixture of diglyme and THF is the solvent of choice; see references: (b) Rossi, R.; Carpita, A. *Synthesis* **1977**, *1977*, 561−562. (c) Vyvyan, J. R.; Holst, C. L.; Johnson, A. J.; Schwenk, C. M. *J. Org. Chem.* **2002**, *67*, 2263−2265.

(26) Lindlar's catalyst is the most popular catalyst for the selective hydrogenation of alkynes to (*Z*)-alkenes; see references: (a) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446−450. (b) Lindlar, H.; Dubois, R. *Org. Synth., Coll.* **1973**, *V*, 880−883. (c) Lindlar Hydrogenation. *Comprehensive Organic Name Reactions and Reagents, Lindlar Hydrogenation*; pp 1758−1763, DOI: 10.1002/9780470638859.

(27) (a) Brown, C. A.; Coleman, R. A. *J. Org. Chem.* **1979**, *44*, 2328−2329. For the synthesis of 9-BBN-dimer, see: (b) Soderquist, J. A.; Negron, A. *Org. Synth.* **1998**, *9*, 95; **1992**, *70*, 169.

(28) (a) Brandänge, S.; Flodman, L.; Norberg, A. *J. Org. Chem.* **1984**, *49*, 927−931. (b) Spence, J. T. J.; George, J. H. *Org. Lett.* **2013**, *15*, 3891−3893.

(29) Ghobril, C.; Kister, J.; Baati, R. *Eur. J. Org. Chem.* **2011**, *2011*, 3416−3419.

(30) For a recent review on the conversion of carbonyl compounds to alkynes, see: Habrant, D.; Rauhala, V.; Koskinen, A. M. P. *Chem. Soc. Rev.* **2010**, *39*, 2007−2017.

(31) Ries, O.; Ochmann, A.; Ducho, C. *Synthesis* **2011**, *2011*, 2357−2368.

(32) (a) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, *2004*, 59−62. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *1996*, 521−522. (c) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564. (d) Pietruszka, J.; Witt, A. *Synthesis* **2006**, *2006*, 4266−4268.

(33) For a recent application of the Bestmann−Ohira alkynylation, see: Brunner, A.; Hintermann, L. *Chem. - Eur. J.* **2016**, *22*, 2787−2792.

DOI: 10.1021/acs.joc.6b01051
J. Org. Chem. 2016, 81, 8175−8186