Synthesis of Carboxyl-Tethered Symmetric Conjugated Polyenes as Fluorescent Transmembrane Probes of Lipid Bilayers

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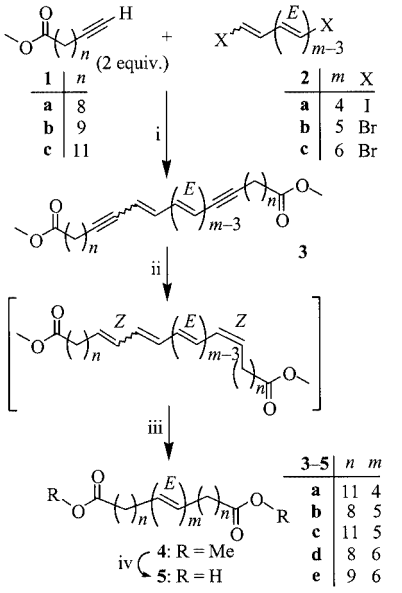
Keywords: Amphiphiles / Membranes / Lipids / Polyenes / Cross-coupling

The synthesis of a new series of fluorescent transmembrane probes in which two hydrophilic methyl ester or carboxyl groups are connected by a polymethylene chain, with four, five or six conjugated double bonds in a central position, is reported. The length of the linear structures was designed to match the width of typical lipid bilayers. These bolaamphiphilic compounds result, with overall yields higher than 80%, from an easy Pd^{II}-catalyzed double cross-coupling between terminal acetylene esters and conjugated 1,ω-dihalopolyenes, followed by selective triple bond partial reduction with activated zinc, and iodine isomerization to the all-(*E*) isomer. An alternative approach, based on a Stille double cross-coupling between the appropriate all-(*E*)-ω-halopolyenes and (*E*)-bis(tributylstannyl)ethene, yielded mixtures that could not be resolved by standard chromatographic methods due to the presence of other simultaneous coupling reactions, which are also discussed in detail. Nevertheless, the Stille method can be of utility for the obtention of carbonyl-polyene conjugated analogs.

Introduction

The biamphiphilic structure of the bipolar transmembrane lipids of *Archaebacteria* stabilizes these primitive organisms against hostile environments.[1] The same concept, with two hydrophilic groups connected by a linear apolar chain (a *bolaamphiphile*),[2] with a length matching that of natural or synthetic membranes, has been used for the inclusion of predetermined chemical groups into membranes.[3] When this group is a fluorescent chromophore,[4] the resulting structure allows one to probe the physical and chemical properties of bilayers, with the added advantage of knowing with accuracy the transverse location of the sensing group.

We have previously reported new amphiphilic fluorescent probes consisting of linear C_{12}-, C_{15}- or C_{18}-chain fatty acids with a conjugated pentaene distal group.[5] These compounds widened the scope of application of linear conjugated polyenes to membrane research, a field pioneered by Sklar and co-workers[6] with the development of fluorescent membrane probes with four conjugated double bonds (parinaric acids). To restrict the uncertainty of the transverse location within the bilayer of the distal sensing group, we have recently applied the biomimetic membrane-spanning design to a series of similar polyene groups, and communicated the preliminary data of a new family of transmembrane fluorescent probes, with a symmetric bolaamphiphile structure with methyl ester or carboxyl groups as polar heads (compounds **4** and **5**, respectively, Scheme 1) and with four, five or six conjugated all-(*E*) double bonds in



1	n
a	8
b	9
c	11

2	m	X
a	4	I
b	5	Br
c	6	Br

3–5	n	m
a	11	4
b	8	5
c	11	5
d	8	6
e	9	6

Scheme 1. i) **1/2** ratio = 3:1 (mol), $[PdCl_2(PPh_3)_2]$ (10 mol %), CuI (20 mol %), Et_2NH, THF, Ar, room temperature, 3 h, > 95%; ii) Zn(Cu/Ag), $MeOH/H_2O$ (1:1), room temperature, 24 h, ≥ 95%; iii) I_2 (trace), hexane, Ar, reflux, 15 min, > 95%; iv) KOH (10 equiv.), EtOH (95%), Ar, reflux, 5 h; then 0°, HCl (5%), ≥ 95%

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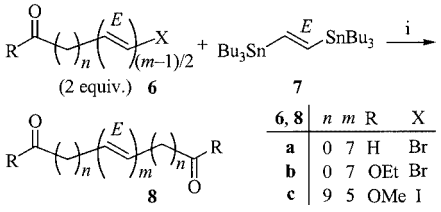
the central position of the molecule.[7] These probes were specifically designed for comparative studies of the dynamic fluctuations of the inner part of lipid bilayers as a function of lipid composition, with time-resolved fluorescence techniques.

In the present work we describe in detail the synthesis of a series of bolaamphiphilic polyenic compounds through the so-called *acetylenic approach*, which basically consists of an sp-sp^2 transition-metal-mediated cross-coupling by a Sonogashira−Hagihara reaction, followed by partial reduction of the triple bond of the ene-yne compound so generated. The Sonogashira−Hagihara reaction is a versatile C−C bond-forming reaction that has previously been used for the synthesis of related transmembrane probes with emitting fluorene[4a] or anthracene[4c] groups. We also report on the application of the Stille reaction to obtain the conjugated heptaene compounds **8a** and **8b** (Scheme 2), and discuss the divergent results found in the case of the compound **8c**, a homolog of the former esters **4**.



6, 8	n	m	R	X
a	0	7	H	Br
b	0	7	OEt	Br
c	9	5	OMe	I

Scheme 2. i) **6/7** ratio = 2:1 (mol), Pd^0 from [$PdCl_2(PPh_3)_2$] + DIBAL in THF (8 mol %), DMF, Ar, room temperature, 12 h

Results and Discussion

Synthesis of Polyene Probes by sp-sp^2 Double Cross-Coupling Followed by Selective Partial Reduction (*Acetylenic Approach*)

Probes **4** and **5** have been synthesized as shown in Scheme 1. The first step was a palladium-catalyzed Sonogashira−Hagihara double cross-coupling reaction[8] between terminal acetylenic methyl esters **1** and conjugated 1,ω-dihalopolyenes **2** with two, three or four double bonds to give polyenediyne compounds **3**, which already have a bipolar structure. Although the cross-coupling of 1,2-dihaloethenes with terminal alkynes has been frequently used to obtain the related 3-ene-1,5-diyne system,[9] and the extension of this method to two-step couplings made it possible to reach asymmetric structures, to the best of our knowledge this is the first time that conjugated 1,ω-dihalopolyenes with more than one double bond have been employed for the synthesis of symmetric polyenediyne compounds such as **3** by said double cross-coupling reaction. Terminal acetylenes are usually activated for their reaction with sp^2 centres by the formation of alkynyllithium or alkynyl Grignard intermediates or, more recently, through intermediates with other metals — mainly Zn, B or Sn — which are subsequently involved in transition-metal-catalyzed processes.[10] The reaction of dibromotriene **2b** with some of the latter intermediates has been used recently for the stereocontrolled synthesis of several conjugated trienediyne systems.[11] Nevertheless, in the present work we preferred the Sonogashira−Hagihara reaction due to its milder experimental conditions and its compatibility with many functional groups.

In our hands, compounds **3** were formed at room temperature, with yields higher than 95% after reaction times of a few hours, with a molar ratio alkyne/dihalopolyene of 3:1. As expected, (*E*)/(*Z*) mixtures of polyenes **2** yielded the same mixtures of isomeric products **3**, because the reaction proceeds with complete chemo- and stereoselectivity and stereospecificity. all-(*E*)-**3** isomers were readily separated from these mixtures by selective precipitation at room temperature from *n*-pentane, a solvent in which compounds **3** with one (*Z*)-configured double bond are soluble. This separation can be avoided if only all-(*E*) isomers **4** are sought, because (*Z*)-configured double bonds can easily be isomerized by a final treatment with traces of iodine (see below). This alternative simplifies the synthetic process and allows the use of the starting 1,ω-dihalopolyenes **2** in the form of (*E*)/(*Z*) mixtures.

Traces of the corresponding alkyne−alkyne homocoupling products were detected in some of the former cross-coupling reaction mixtures (highest observed yield 5%, products not shown), and could also be separated from the all-(*E*)-**3** products by washing with *n*-pentane. The Pd^{II}-catalyzed homocoupling process is an expected secondary reaction when Pd^{II} species are used as a metal source,[12] but the cross-coupling products **3** were formed in almost quantitative yield with 10 mol % of [$PdCl_2(PPh_3)_2$] (relative to **2**). Complete exclusion of oxygen is important to prevent oxidation of the in situ-formed Pd^0 species, the active catalyst of the cross-coupling (see below). When the Pd^0 catalyst [$Pd(PPh_3)_4$] was used instead, also under rigorous exclusion of oxygen, much longer reaction times (> 24 h) were necessary for completing the reaction, with the added disadvantage of the simultaneous degradation in the medium of both the starting dihalopolyenes **2** and the catalyst, in the latter case detected by precipitation of metallic Pd^0.

The triple-to-double-bond reduction in the resulting polyenediyne compounds **3** may be carried out by several methods.[13] Isolated triple bonds in structures with several conjugated double bonds have been efficiently and selectively semihydrogenated to double bonds in the presence of Lindlar or similar catalysts,[14] although this method often fails when the triple bond is conjugated with one or more double bonds. In that case, the result depends on the number of double bonds and on the relative position of the triple bond,[15] and the isolation of the resulting polyene usually requires complex purification processes. A more promising alternative is the use of activated metals as reductants.[16] More specifically, the use of zinc activated by Cu^{II} acetate and Ag^{I} nitrate in water (Boland Zn activation[17]) is gaining importance as a clean, mild and efficient method for the selective semireduction of triple bonds conjugated with double bonds to (*Z*)-alkenes, without affecting the double bonds or any isolated triple bond in the molecule.[18]

The use of this and related methods in the synthesis of natural products with several conjugated double bonds, by semireduction of conjugated alkynes generated through metal-catalyzed sp-sp^2 cross-coupling, is known as the *acetylenic approach*.[17b] This combination has been shown to be an efficient route for obtaining conjugated polyene compounds with stereochemical control,[19] and in some cases is the only practical way for just obtaining the target product.[20]

We have successfully used this approach for the selective semireduction of the polyenediyne compounds **3** to the corresponding (*Z*,...,*Z*)-polyenes, always attaining yields higher than 95%. The resulting polyenes are not stable in wet $CHCl_3$ or wet $CDCl_3$, and shortly after the dissolution of any (*Z*,...,*Z*) isomer in nontreated $CDCl_3$, the respective (*Z*,...,*E*) and (*E*,...,*E*) isomers can be detected in the ^{1}H NMR spectrum. This isomerization must be due to traces of HCl/DCl in the solvent, because the reaction is absent in alumina-filtered and dried $CDCl_3$. Similar acid-catalyzed (*Z*) → (*E*) isomerizations have been observed in some retinoic acid derivatives and in other highly conjugated polyene systems.[21] This might be an easy, albeit slow, procedure for the isomerization of the former (*Z*,...,*Z*)-polyenes to the corresponding all-(*E*) isomers **4**. However, a gradual polyene loss was also observed in chloroform solution, even at low temperature, so that the preferred procedure was the use of traces of iodine in hexane, because in this way the isomerization reaction yielding **4** was completed in a few minutes, without product degradation. A final alkaline hydrolysis produced the target diacids **5** after careful acidification and washing.

The former sequence (Scheme 1) yielded the diacids **5** with good overall yields (≥ 80%) and can be extended to obtain similar compounds with different chain length, number of conjugated double bonds or stereochemistry. Compounds **3**−**5** are thermally stable as solids for several months if kept in a cool and dark place, and their solubility in EtOH or DMSO is in the range of 1−10 μM. These probes have been designed to span the width of typical lipid bilayers, i.e. with a maximum expanded length of 35−43 Å,[22] so that the terminal polar groups can reach the two opposite membrane surfaces, and the polyene chromophore is located in the bilayer centre.

Synthesis of Polyene Probes by Direct sp^2-sp^2 Double Cross-Coupling (*Stille Approach*)

An alternative synthetic approach, also assayed here to obtain bolaamphiphilic polyene probes, consists of the direct sp^2-sp^2 *stitching* cross-coupling between all-(*E*)-halopolyenes **6** (Scheme 2) and the easily accessible bis(stannane) (*E*)-bis(tributylstannyl)ethene (**7**), in the presence of palladium catalysts under conditions of the *Stille reaction*.[23] This initially promising approach would yield all-(*E*)-polyenes **8** in only one fully stereo- and regioselective step. (*E*)/(*Z*) isomeric mixtures of **6** may also be used in the coupling, because the reaction products could be converted into the corresponding all-(*E*) isomers with traces of iodine, as above. We first studied the reaction between the model bromotrienes **6a** and **6b**, and the bis(stannane) **7** (2:1 molar ratio), even though the expected reaction products **8a** and **8b**, respectively, do not have the proper length for their use as membrane-spanning probes. In the presence of $[PdCl_2(PPh_3)_2]$ or $[PdCl_2(CH_3CN)_2]$, two Pd^{II} catalysts widely employed in the synthesis of polyene systems by Stille coupling,[24] **8a** and **8b** were obtained with yields of 15 and 40%, respectively. Higher yields — 40 and 70% — were obtained using the Pd^0 species generated in situ by the reduction of $[PdCl_2(PPh_3)_2]$ with DIBAL (Negishi's catalyst[25]), a species used in the synthesis of highly unsaturated natural products when the former Pd^{II} catalysts were not particularly effective.[26]

The lower yield of **8a** relative to **8b**, obtained with any of the three former catalysts under comparable reaction conditions, could be a consequence of the lower electron density at the *Sn*-bound carbon atom in the intermediate monocoupling product from **6a** and **7**, with regard to the same product from **6b** and **7**. This difference would give rise to a lower reactivity of the former monocoupling product with another molecule of **6a**. In fact, traces of the monocoupling product from **6a** and **7** were detected in the ^{1}H NMR spectrum of the crude reaction mixtures.

The synthesis of the pentaene diester **8c** was then attempted by coupling the iododiene ester **6c** with **7**, in the presence of $[PdCl_2(PPh_3)_2]$/DIBAL catalyst, i.e. the catalyst that gave higher yields in the former couplings. However, even with careful exclusion of oxygen, the reaction product was always a mixture containing ca. 85% of the expected probe **8c** (as estimated from the absorption spectrum, Figure 1) and ca. 15% (overall) of the corresponding tetraene, hexaene (**4e**, formerly obtained in pure form through the *acetylenic approach*, Scheme 1), and heptaene diesters. Traces (less than 5%) of the starting iododiene **6c** were also found (^{1}H NMR spectroscopy), but not the monocoupling product from **6c** and **7** (compound **IV** in Scheme 4, below). The polyene components of the mixture, with very similar polarity, could not be separated by standard TLC on silica gel using different eluents (a single spot was always observed), even after silver nitrate impregnation. The fraction of tetraene diester was much higher (ca. 70%) using as cata-

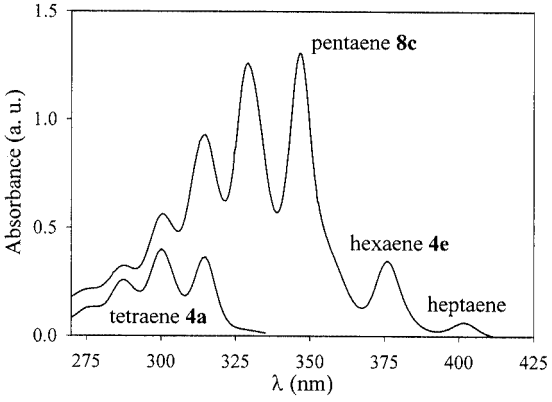
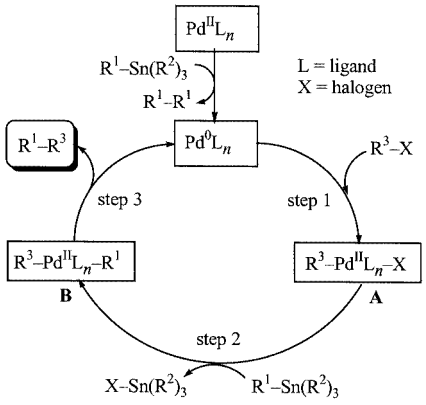


Figure 1. Absorption spectrum of the raw product from the Stille cross-coupling reaction **6c** and **7**, showing the assignments of the observed maxima (see Scheme 4); EtOH, 22 °C; the spectrum of the tetraene diester **4a** is included for comparison

lyst any of the former Pd^{II} species $[PdCl_2(PPh_3)_2]$ or $[PdCl_2(CH_3CN)_2]$. The selectivity of the reaction and the yield of tetraene diester were similar when using Pd^0 complexes having the poor electron-donating ligands trifurylphosphane or triphenylarsane (Farina's conditions[27]), although these complexes strongly increase the cross-coupling rate in Stille reactions, providing a successful route to unsaturated natural products.[28] In all these cases, the selectivity of the coupling **6c** and **7** was scarcely improved by changing the reaction time, the catalyst amount (in the range 4−10 mol % of **7**) or the sequence and way of addition of the reactants.

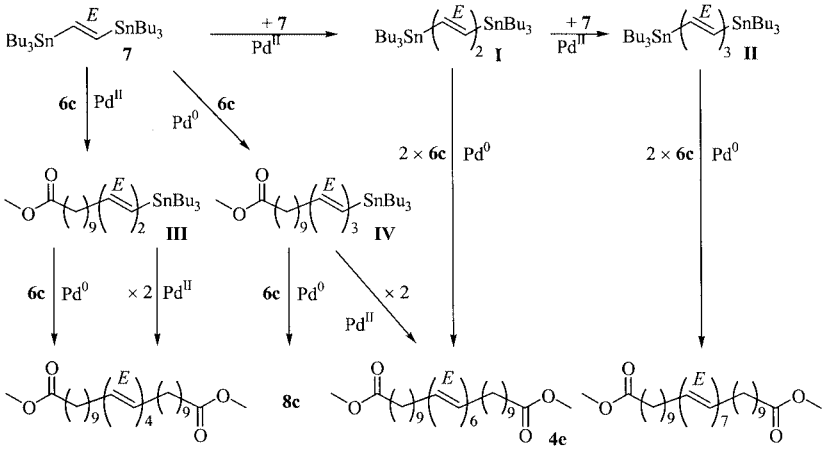
Although some aspects of the Stille reaction mechanism are not completely understood, and some formerly established points are now being questioned,[29] the former results can be understood by reference to the commonly accepted cycle of Pd^0 catalysis (Scheme 3).[23] When Pd^{II} species are used, an initial reduction to Pd^0 yields, at the same time, the stannane−stannane homocoupling by-product, a process favored by traces of oxygen due to the easy $Pd^0 \rightarrow Pd^{II}$ back oxidation, especially in stannanes with several conjugated double bonds.[30] In fact, this homocoupling has been used for synthetic purposes.[31] Step 1 of the catalytic cycle is an oxidative addition of the electrophile producing the intermediate **A**, and, when a halovinyl group is involved, the initial stereochemistry of the double bond is retained. Step 2, usually the limiting process in Stille couplings, is the Sn−Pd transmetalation with production of the intermediate **B**.[32] Step 3 is a final reductive elimination to yield the coupling product and regenerating the catalytically active Pd^0 species.

In the Pd^{II}-catalyzed process between **6c** and **7**, the initial homocoupling reaction of **7** would produce all-(*E*)-1,4-bis-(tributylstannyl)-1,3-butadiene (**I**, Scheme 4) and all-(*E*)-1,6-bis(tributylstannyl)-1,3,5-hexatriene (**II**), the reaction of any of which with two mol-equiv. of **6c** would yield the corresponding hexaene **4e** and heptaene diesters. The occurrence of the starting compound **6c** in the reaction mixtures can be partially explained by this stannane-consuming homocoupling. The formation of polyene compounds can also be explained by the Pd^{II}-catalyzed exchange of the iodine in **6c** by the tributylstannyl group from **7**, yielding compound **III**, in a process that could compete with the transmetalation of step 2 in Scheme 3. Intermediate **III** would produce the observed tetraene diester through Pd^0-catalyzed coupling with **6c**, or through Pd^{II}-catalyzed homocoupling **III** + **III**. The higher fraction of the tetraene diester when Pd^{II} species were used as catalysts supports the existence of the latter homocoupling. The homocoupling of **6c** (not shown) could also give rise to the tetraene diester. However, in our case this process does not take place because no reaction was observed when **6c** was treated under the same reaction conditions but in the absence of **7**. The hexaene diester **4e** could also result from homocoupling of **IV**, the product from the reaction **6c** and **7**.



Scheme 3. Catalytic cycle in Stille cross-coupling reactions (adapted from ref.[23c])

A similar lack of selectivity was formerly found in direct Stille cross-coupling reactions between highly unsaturated conjugated systems and unsaturated bis(stannanes). Mixtures of conjugated polyenes with a different number of double bonds,[33] or mixtures of homocoupling by-products from halogen/tin exchange[34] were obtained, but in all the cases the target products were easily separated by standard chromatography. In spite of the frequent presence of by-products, these cross-coupling reactions have been applied with success to the synthesis of carotenoids.[35]



Scheme 4. Possible competing reactions for the appearance of the observed products in the Stille cross-coupling **6c** and **7**

According to the above results, it can be concluded that the Stille reaction, as shown here, is not a convenient method for the synthesis of polyene esters such as **8c**, due to the generation of mixtures of compounds with very similar chromatographic properties on standard silica gel chromatography, although the reaction can be used for reaching the carbonyl-polyene conjugated compounds **8a** and **8b**. The previously commented *acetylenic approach* should be preferred for the synthesis of bolaamphiphilic polyene structures such as **8c**.

Experimental Section

General Remarks: All solvents were freshly distilled prior to use. THF was distilled from sodium/benzophenone; dichloromethane, hexane, and pentane from CaH_2, and diethylamine from BaO. All reactions were carried out under total absence of oxygen in oven-dried Schlenk-type flasks, and the solvents were deoxygenated by several vacuum-argon cycles. Analytical thin layer chromatography was performed on precoated aluminium silica gel plates, Merck 60F254, 0.25 mm. Flash column chromatography was carried out on silica gel (Merck, 230−400 mesh). Melting points were measured with a Reichert−Kofler hot-stage microscope and are uncorrected. Yields are referred to isolated pure compounds. Elemental analyses were done with a Carlo Erba CHN-1108 microanalyser. ^1H and ^{13}C NMR spectra were taken at 30 °C, unless otherwise noted, with Varian Gemini-200, INOVA-300, -400 or -500 spectrometers. Chemical shifts are reported in parts per million (ppm), using as internal reference the proton signal of the trace of undeuterated solvent or the carbon signal of the deuterated solvent: δ = 7.26 and 77.0 ppm in $CDCl_3$; δ = 2.45 and 39.5 ppm in $[D_6]$DMSO; and δ = 7.40 and 128.7 ppm in C_6D_6. Abbreviations: s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintet), m (complex multiplet). Carbon and proton assignments are based on DEPT, HSQC and HMQC experiments. The fractions of (*E*)/(*Z*) isomers were calculated from ^1H NMR relative integrals of characteristic signals. Infrared spectra (in cm^{-1}) were recorded with Perkin−Elmer 681 or FT-Spectrum One spectrophotometers. Mass spectra were recorded by electron impact (70 eV) with a low-resolution Hewlett−Packard 5973 spectrometer, in the direct injection mode. High resolution mass spectra were determined with an AutoSpecEQ EI apparatus. UV/Vis absorption spectra were registered with Varian CARY-3E or Perkin−Elmer Lambda-2 spectrophotometers.

Materials: Chemicals were purchased from Aldrich, Lancaster or Across, and were used without further purification. Methyl 10-undecynoate (**1a**) was obtained (95% yield) by esterification of the corresponding acid with $MeOH/SOCl_2$.[4a] ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (m, 6 H, 5-H to 7-H), 1.38 (m, 2 H, 4-H), 1.50 (quint, *J* = 6.8 Hz, 2 H, 8-H), 1.60 (quint, *J* = 7.2 Hz, 2 H, 3-H), 1.92 (t, *J* = 2.6 Hz, 1 H, 11-H), 2.16 (dt, *J* = 2.6, 6.8 Hz, 2 H, 9-H), 2.29 (t, *J* = 7.2 Hz, 2 H, 2-H), 3.63 (s, 3 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2 (C-9), 24.7 (C-3), 28.9, 28.8, 28.7, 28.5, 28.3 (C-4 to C-8), 33.8 (C-2), 51.2 (*C*H$_3$), 67.0 (C-11), 84.4 (C-10), 173.9 (*C*=O) ppm. Methyl 11-dodecynoate (**1b**) and methyl 13-tetradecynoate (**1c**) were prepared from 9-dodecyn-1-ol and 3-tetradecyn-1-ol, respectively, by triple bond *zipper* isomerization to the terminal position,[36] Jones oxidation to the corresponding carboxylic acid[37] and esterification, as above. Overall yields > 60% from 36 mmol of starting alkynol. **1b:** ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20−1.45 (m, 10 H, 4-H to 8-H), 1.50 (quint, *J* = 6.6 Hz, 2 H, 9-H), 1.60 (quint, *J* = 7.2 Hz, 2 H, 3-H), 1.92 (t, *J* = 2.7 Hz, 1 H, 12-H), 2.16 (dt, *J* = 2.7, 6.6 Hz, 2 H, 10-H), 2.29 (t, *J* = 7.2 Hz, 2 H, 2-H), 3.65 (s, 3 H, C*H*$_3$). **1c:** ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45−1.25 (m, 14 H, 4-H to 10-H), 1.51 (quint, *J* = 6.9 Hz, 2 H, 11-H), 1.62 (quint, *J* = 7.2 Hz, 2 H, 3-H), 1.94 (t, *J* = 2.6 Hz, 1 H, 14-H), 2.19 (dt, *J* = 2.6, 6.9 Hz, 2 H, 12-H), 2.29 (t, *J* = 7.2 Hz, 2 H, 2-H), 3.66 (s, 3 H, C*H*$_3$) ppm. (1*E*,3*E*)-1,4-Diiodo-1,3-butadiene (**2a**) was synthesized from acetylene, as described.[38] 1,6-Dibromo-1,3,5-hexatriene [all-(*E*)/(1*Z*,3*E*,5*E*), 1:4] (**2b**) was obtained as described.[39] 1,8-Dibromo-1,3,5,7-octatetraene [all-(*E*)/(1*Z*,3*E*,5*E*,7*E*), 1:4] (**2c**), all-(*E*)-7-bromo-2,4,6-heptatrienal (**6a**) and ethyl all-(*E*)-7-bromo-2,4,6-heptatrienoate (**6b**) were synthesized as follows: (2*E*,4*E*)-5-bromo-2,4-pentadienal[39] (1.0 g, 6.21 mmol) was treated with triethyl phosphonoacetate in 10 M K_2CO_3 in water[40] to yield ester **6b** (yield 1.33 g, 93%); this ester (0.80 g, 3.46 mmol) was reduced to the corresponding allylic alcohol with 2 equiv. of DIBAL in toluene/CH_2Cl_2 at −78 °C (yield 0.62 g, 95%). This unstable alcohol was immediately oxidized to the all-(*E*)-aldehyde **6a** with activated MnO_2 (yield 0.58 g, 95%), and this aldehyde (0.30 g, 1.6 mmol) was treated at −50 °C with the ylide generated from (bromomethyl)triphenylphosphonium bromide by treatment with *t*BuOK in THF, yielding **2c**. Purification by column chromatography (silica gel, hexane/ethyl acetate, 9:1). Yield 0.36 g, 86%. **2c:** ^1H NMR (300 MHz, $CDCl_3$): δ = 6.15−6.25 [m, 4 H, 3-H to 6-H in all-(*E*) isomer], 6.10−6.45 [m, 5 H, 3-H, 6-H, 7-H, 8-H in (1*Z*,3*E*,5*E*,7*E*) isomer], 6.37 [d, *J* = 13.5 Hz, 2 H, 1-H, 8-H in all-(*E*) isomer], 6.65 [d, *J* = 8.7 Hz, 1 H, 1-H in (1*Z*,3*E*,5*E*,7*E*) isomer], 6.50−6.70 [m, 2 H, 4-H, 5-H in (1*Z*,3*E*,5*E*,7*E*) isomer], 6.77 [dd, *J* = 10.8, 13.5 Hz, 1 H, 2-H in (1*Z*,3*E*,5*E*,7*E*) isomer], 6.80−6.70 [m, 2 H, 2-H, 7-H in all-(*E*) isomer] ppm. FT IR (KBr): $\tilde{\nu}_{max}$ = 3078, 3023, 2936, 1604, 1436, 1329, 1008, 936, 693 cm^{-1}. EI MS (70 eV): *m*/*z* (%) = 262 (8) [M^+], 185 (4), 183 (5), 174 (6), 149 (5), 104 (100), 91 (21). **6a:** ^1H NMR (400 MHz, $CDCl_3$): δ = 6.22 (d, *J* = 7.9 Hz, 1 H, 2-H), 6.46 (dd, *J* = 10.8, 15.2 Hz, 1 H, 4-H), 6.56 (dd, *J* = 10.8, 15.2 Hz, 1 H, 5-H), 6.66 (d, *J* = 13.6 Hz, 1 H, 7-H), 6.85 (dd, *J* = 10.8, 13.6 Hz, 1 H, 6-H), 7.08 (dd, *J* = 10.4, 15.6 Hz, 1 H, 3-H), 9.58 (d, *J* = 7.9 Hz, 1 H, 1-H) ppm. **6b:** ^1H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$), 4.2 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$), 5.95 (d, *J* = 15.2 Hz, 1 H, 2-H), 6.33 (dd, *J* = 10.8, 14.8 Hz, 1 H, 4-H), 6.44 (dd, *J* = 10.8, 14.8 Hz, 1 H, 5-H), 6.55 (d, *J* = 13.6 Hz, 1 H, 7-H), 6.80 (dd, *J* = 10.8, 13.6 Hz, 1 H, 6-H), 7.25 (dd, *J* = 10.8, 15.2 Hz, 1 H, 3-H) ppm. Methyl all-(*E*)-14-iodo-11,13-tetradecadienoate (**6c**) was prepared immediately prior to use as follows: 1) 11-bromoundecanoic acid was treated with triphenylphosphane to yield (11-carboxyundecyl)triphenylphosphonium bromide;[41] 2) this salt (2.70 g, 5 mmol) was converted into the corresponding ylide by reaction with sodium bis(trimethylsilyl)amide (10 mmol), and the ylide was then treated with freshly prepared (*E*)-3-iodopropenal (0.91 g, 5 mmol) in dry THF,[42] yielding 14-iodo-11,13-tetradecadienoic acid [yield 0.95 g, 54%, (11*E*,13*E*)/(11*Z*,13*E*), 4:6]; 3) the former mixture was converted into the all-(*E*) isomer with traces of iodine in wet chloroform (yield 0.90 g, 95%); 4) a final esterification of the acid as above ($MeOH/SOCl_2$) produced the unstable iododiene ester **6c** (yield 0.80 g, 85%). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (broad s, 10 H, 4-H to 8-H), 1.37 (quint, *J* = 7.2 Hz, 2 H, 9-H), 1.63 (quint, *J* = 7.2 Hz, 2 H, 3-H), 2.03 (ddt, *J* = 1.2, 6.8, 7.2 Hz, 2 H, 10-H), 2.35 (t, *J* = 7.2 Hz, 2 H, 2-H), 3.66 (s, 3 H, C*H*$_3$), 5.72 (dt, *J* = 6.8, 15.2 Hz, 1 H, 11-H), 5.96 (dddt, *J* = 0.4, 1.6, 10.8, 15.2 Hz, 1 H, 12-H), 6.15 (dt, *J* = 0.4, 14.4 Hz, 1 H, 14-H), 6.98 (ddd, *J* = 0.8, 10.8, 14.4 Hz, 1 H, 13-H) ppm. (*E*)-Bis(tributylstannyl)ethene (**7**) was obtained as described.[43] All the palladium catalysts were purchased from com-

mercial sources. The Pd^0 catalyst for Stille couplings was freshly generated in situ by reduction of $[PdCl_2(PPh_3)_2]$ (1 equiv.) with DIBAL (2 equiv., 1 M solution in THF) in dry THF under an inert gas, according to the Negishi method.[25] The Pd^0 catalysts used under Farina conditions[27] were prepared in situ by treating the Pd^0 complex [tris(dibenzylideneacetone)dipalladium(0)] with trifurylphosphane or triphenylarsane.

Synthesis of Polyenediyne Diesters 3 by Sonogashira−Hagihara Double Cross-Coupling

General Procedure: Deoxygenated Et_2NH (2 mL), $[PdCl_2(PPh_3)_2]$ (0.01 mmol) and CuI (0.02 mmol) were added (room temperature, stirring) to a solution of the appropriate acetylenic ester **1** (0.3 mmol) and dihalopolyene **2** (0.1 mmol) in dry THF (2.5 mL) in a Schlenk flask under argon. After completion of the reaction (ca. 3 h), the mixture was filtered through a short Celite pad, eluting with CH_2Cl_2, and the residual waxy solid remaining after solvent evaporation was purified by column chromatography [silica gel, hexane/ethyl acetate, 9:1 to 7:3], yielding **3** as the all-(*E*) isomer (reactions with **2a**) or as 1:4 mixture of (*E*/*Z*) isomers (*E*,*E*,*E*)/(*Z*,*E*,*E*) (reactions with **2b**) or (*E*,*E*,*E*,*E*)/(*Z*,*E*,*E*,*E*) (reactions with **2c**) (yields 95−97%). The all-(*E*) isomer could be separated by selective precipitation with pentane at room temperature. The acids corresponding to all-(*E*) esters **3a** and **3b** were obtained by alkaline hydrolysis (see below).

Dimethyl all-(*E*)-Dotriaconta-15,17-diene-13,19-diynedioate [all-(*E*)-3a]: Obtained from **1c** and **2a**. Yield 50 mg, 95%. White crystals, m.p. 72−73 °C. R_f = 0.61 (hexane/diethyl ether, 3:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (m, 24 H, 4-H to 9-H, 24-H to 29-H), 1.37 (quint, 4 H, *J* = 6.8 Hz, 10-H, 23-H), 1.52 (quint, 4 H, *J* = 7.6 Hz, 11-H, 22-H), 1.61 (quint, *J* = 7.2 Hz, 4 H, 3-H, 30-H), 2.30 (t, *J* = 7.2 Hz, 4 H, 2-H, 31-H), 2.32 (dt, *J* = 2.0, 7.2 Hz, 4 H, 12-H, 21-H), 3.66 (s, 6 H, 2 × C*H*$_3$), 5.62 (ddt, *J* = 2.0, 3.0, 14.4 Hz, 2 H, 15-H, 18-H), 6.50 (dd, *J* = 3.0, 14.4 Hz, 2 H, 16-H, 17-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (C-12, C-21), 25.0 (C-3, C-30), 28.7, 28.9, 29.11, 29.14, 29.2, 29.41, 29.45, 29.5 (C-4 to C-11, C-22 to C-29), 34.1 (C-2, C-31), 51.4 (*C*H$_3$), 79.8 (C-14, C-19), 94.9 (C-13, C-20), 113.2 (C-15, C-18), 139.6 (C-16, C-17), 174.3 (CO) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2870, 2800, 2155, 1710, 1145, 950 cm^{-1}. EI MS (70 eV): *m*/*z* (%) = 526 (46) [M$^+$], 495 (32), 463 (4), 328 (23), 185 (22), 171 (49), 157 (51), 141 (71), 129 (100), 117 (53), 105 (25), 91 (30). UV ($CHCl_3$): λ_{max} (ε, L·mol^{-1}·cm^{-1}) = 312 (55000), 298 nm (53000). $C_{34}H_{54}O_4$ (526.79): calcd. C 77.52, H 10.33; found C 77.25, H 9.81.

all-(*E*)-Dotriaconta-15,17-diene-13,19-diynedioic Acid: Obtained by hydrolysis of all-(*E*)-**3a**. White crystals, m.p. 178 °C. R_f = 0.70 (CH_2Cl_2/EtOH, 95:5). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 80 °C): δ = 1.26 (br. s, 24 H, 5-H to 10-H, 23-H to 28-H), 1.35 (m, 4 H, 4-H, 29-H), 1.47 (m, 8 H, 3-H, 11-H, 22-H, 30-H), 2.15 (t, *J* = 7.2 Hz, 4 H, 2-H, 31-H), 2.33 (dt, *J* = 2.0, 7.2 Hz, 4 H, 12-H, 21-H), 5.76 (m, 2 H, 15-H, 18-H), 6.52 (m, 2 H, 16-H, 17-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 70 °C): δ = 18.6 (C-12, C-21), 24.2 (C-3, C-30), 27.7, 27.8, 28.0, 28.2, 28.3, 28.40, 28.41, 30.1 (C-4 to C-11, C-22 to C-29), 33.6 (C-2, C-31), 79.7 (C-14, C-19), 94.6 (C-13, C-20), 113.2 (C-15, C-18), 139.2 (C-16, C-17), 173.9 (CO) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3080, 2960, 2890, 2250, 1715, 1490, 980, 740. EI MS (70 eV): *m*/*z* (%) = 498 (7) [M$^+$], 369 (2), 355 (4), 327 (4), 314 (5), 299 (4), 272 (4), 199 (4), 171(30), 157 (36), 143 (59), 129 (100), 117 (56), 105 (34), 91 (44). HRMS (EI): calcd. for $C_{32}H_{50}O_4$ 498.37091; found 498.37039.

Dimethyl all-(*E*)-Octacosa-12,14,16-triene-10,18-diynedioate [all-(*E*)-3b]: Obtained from **1a** and **2b**, all-(*E*)/(1*Z*,3*E*,5*E*), 1:4 isomer mixture. Yield 9 mg, 19%. Yellow crystals, m.p. 69−70 °C (pentane). R_f = 0.73 (hexane/EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (m, 12 H, 4-H to 6-H, 23-H to 25-H), 1.38 (m, 4 H, 7-H, 22-H), 1.52 (quint, *J* = 7.2 Hz, 4 H, 8-H, 21-H), 1.61 (quint, *J* = 7.3 Hz, 4 H, 3-H, 26-H), 2.30 (t, *J* = 7.6 Hz, 4 H, 2-H, 27-H), 2.33 (dt, *J* = 2.2, 7.2 Hz, 4 H, 9-H, 20-H), 3.66 (s, 6 H, 2 × C*H*$_3$), 5.63 (dt, *J* = 2.2, 15.6 Hz, 2 H, 12-H, 17-H), 6.25 (m, 2 H, 14-H, 15-H), 6.50 (ddd, *J* = 3.2, 7.2, 15.6 Hz, 2 H, 13-H, 16-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.7 (C-9, C-20), 24.9 (C-3, C-26), 28.6, 28.8, 28.9, 29.06, 29.09 (C-4 to C-8, C-21 to C-25), 34.1 (C-2, C-27), 51.5 (*C*H$_3$), 80.2 (C-11, C-18), 95.1 (C-10, C-19), 113.1 (C-12, C-17), 133.2 (C-14, C-15), 140.1 (C-13, C-16), 174.3 (CO) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2940, 2860, 2210, 1735, 1470, 1440, 1175, 990 cm^{-1}. EI MS (70 eV): *m*/*z* (%) = 468 (38) [M$^+$], 437 (5), 311 (15), 183 (21), 169 (51), 155 (100), 141 (68), 129 (62). UV ($CHCl_3$): λ_{max} (ε, L·mol^{-1}·cm^{-1}) = 343 (77000), 326 (74000), 312 nm (45000); UV (1,4-dioxane): λ_{max} (ε, L·mol^{-1}·cm^{-1}) = 310 (49000), 325 (85000), 341 nm (92000). $C_{30}H_{44}O_4$ (468.67): calcd. C 76.88, H 9.46; found C 76.63, H 9.40.

(12*Z*,14*E*,16*E*)-3b: Obtained from **1a** and **2b**, all-(*E*)/(1*Z*,3*E*,5*E*), 1:4 isomer mixture. Yield 36 mg, 77%. Yellow waxy oil. R_f = 0.73 (hexane/EtOAc, 7:3). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (br. s, 12 H, 5-H to 7-H, 22-H to 24-H), 1.38 (m, 4 H, 4-H, 25-H), 1.51 (q, *J* = 7.0 Hz, 4 H, 8-H, 21-H), 1.61 (q, *J* = 7.0 Hz, 4 H, 3-H, 26-H), 2.29 (t, *J* = 7.0 Hz, 2 H, 27-H), 2.30 (t, *J* = 7.0 Hz, 2 H, 2-H), 2.33 (dt, *J* = 2.5, 7.0 Hz, 2 H, 20-H), 2.39 (dt, *J* = 2.5, 7.0 Hz, 2 H, 9-H), 5.46 (dt, *J* = 2.5, 11.0 Hz, 1 H, 17-H), 5.65 (dt, *J* = 2.5, 15.0 Hz, 1 H, 12-H), 6.31 (m, 1 H, 14-H), 6.34 (dd, *J* = 7.0, 11.0 Hz, 1 H, 16-H), 6.59 (dd, *J* = 11.5, 15.5 Hz, 1 H, 15-H), 6.74 (dd, *J* = 11.5, 15.0 Hz, 1 H, 13-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.0, 28.2, 28.6, 28.66, 28.69, 28.75, 28.8, 28.9, 29.0, 33.8, 51.1, 77.9, 80.1, 94.8, 98.3, 110.9, 113.3, 130.8, 133.8, 138.0, 140.1, 173.7 (C=O) ppm.

all-(*E*)-Octacosa-12,14,16-triene-10,18-diynedioic Acid: Obtained by hydrolysis of all-(*E*)-**3b**. Light yellow solid, m.p. 140−142 °C. R_f = 0.53 (CH_2Cl_2/EtOH, 9:1). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.21 (m, 16 H, 4-H to 7-H, 22-H to 25-H), 1.29 (q, *J* = 7.0 Hz, 4 H, 8-H, 21-H), 1.43 (q, *J* = 7.0 Hz, 4 H, 3-H, 26-H), 2.13 (t, *J* = 7.0 Hz, 4 H, 2-H, 27-H), 2.29 (dt, *J* = 2.5, 7.0 Hz, 4 H, 9-H, 20-H), 5.70 (dt, *J* = 2.5, 15.5 Hz, 2 H, 12-H, 17-H), 6.34 (dd, *J* = 3.0, 7.0 Hz, 2 H, 14-H, 15-H), 6.48 (ddd, *J* = 3.0, 7.0, 15.5 Hz, 2 H, 13-H, 16-H), 11.80 (br. s, 2 H, 2 × CO_2H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 19.0 (C-9, C-20), 24.5 (C-3, C-26), 28.1, 28.3, 28.4, 28.5, 28.6 (C-4 to C-8, C-21 to C-25), 33.7 (C-2, C-27), 80.5 (C-11, C-18), 95.3 (C-10, C-19), 113.1 (C-12, C-17), 133.5 (C-14, C-15), 140.2 (C-13, C-16), 174.5 (C=O) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3000, 2920, 2860, 2210, 1700, 1470, 1269, 990 cm^{-1}. EI MS (70 eV): *m*/*z* (%) = 440 (34) [M$^+$], 297 (17), 283 (8), 169 (48), 155 (100), 141 (78), 129 (65).

Dimethyl all-(*E*)-Tetratriaconta-15,17,19-triene-13,21-diynedioate [all-(*E*)-3c]: Obtained from **1c** and **2b**, all-(*E*)/(1*Z*,3*E*,5*E*), 1:4 isomer mixture. Described in ref.[7]

Dimethyl all-(*E*)-Triaconta-12,14,16,18-tetraene-10,20-diynedioate [all-(*E*)-3d]: Obtained from **1a** and **2c**, all-(*E*)/(1*Z*,3*E*,5*E*,7*E*), 1:4 isomer mixture. Yield 9 mg, 18%. Yellow solid, m.p. 74−76 °C. R_f = 0.21 (hexane/EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (m, 12 H, 4-H to 6-H, 25-H to 27-H). 1.39 (quint, *J* = 7.2 Hz, 4 H, 7-H, 24-H), 1.53 (quint, *J* = 7.2 Hz, 4 H, 8-H, 23-H), 1.62 (quint, *J* = 7.2 Hz, 4 H, 3-H, 28-H), 2.30 (t, *J* = 7.2 Hz, 4 H, 2-H, 29-H), 2.33 (dt, *J* = 2.4, 7.2 Hz, 4 H, 9-H, 22-H), 3.66 (s, 6 H, 2 × C*H*$_3$), 5.62 (dt, *J* = 2.4, 15.6 Hz, 2 H, 12-H, 19-H), 6.27 (m, 2

H, 14-H, 17-H), 6.35 (m, 2 H, 15-H, 16-H), 6.54 (dd, J = 7.2, 15.6 Hz, 2 H, 13-H, 18-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.8 (C-9, C-22). 24.9 (C-3, C-28), 28.7, 28.77, 28.81, 28.86, 28.92, 29.1, 29.6 (C-4 to C-8, C-23 to C-27), 34.1 (C-2, C-29), 51.4 (CH_3), 80.4 (C-11, C-20), 95.0 (C-10, C-21), 112.4 (C-12, C-19), 133.7, 133.3 (C-14 to C-17), 140.4 (C-13, C-18), 174.3 (C=O) ppm. FT IR (KBr): $\tilde{\nu}_{max}$ = 2917, 2580, 2220, 1737, 1460, 1441, 1303, 1246, 1204, 1170, 1001 cm^{-1}. EI MS (70 eV): *m*/*z* (%) = 494 (44) [M$^+$], 463 (4), 337 (6), 323 (6), 207 (10), 195 (20), 181 (66), 167 (100), 155 (36), 141 (44), 129 (39), 117 (24), 105 (15), 91 (33). UV ($CHCl_3$): λ_{max} (ε, L·mol^{-1}·cm^{-1}) = 310 (59000), 353 (86000), 373 nm (90000); UV (1,4-dioxane): λ_{max} (ε, L·mol^{-1}·cm^{-1}) = 334 (63000), 351 (113000), 373 nm (128000). $C_{32}H_{46}O_4$ (494.71): calcd. C 77.69, H 9.37; found C 77.49, H 9.28.

(12*Z*,14*E*,16*E*,18*E*)-3d: Obtained from **1a** and **2c**, all-(*E*)/(1*Z*,3*E*,5*E*,7*E*), 1:4 isomer mixture. Yield 37 mg, 75%. Yellow oil. R_f = 0.21 (hexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (m, 12 H, 4-H to 6-H, 25-H to 27-H), 1.37 (m, 4 H, 7-H, 24-H), 1.51 (m, 4 H, 8-H, 23-H), 1.62 (q, J = 7.2 Hz, 4 H, 3-H, 28-H), 2.24 (m, 2 H, 9-H), 2.30 (t, J = 7.2 Hz, 4 H, 2-H, 29-H), 2.40 (dt, J = 2.4, 6.9 Hz, 2 H, 22-H), 3.66 (s, 6 H, 2 × CH_3), 5.44 (dt, J = 2.1, 11.1 Hz, 1 H, 12-H), 5.63 (dt, J = 2.4, 15.3 Hz, 1 H, 19-H), 6.34 (m, 4 H, 14-H to 17-H), 6.54 (m, 1 H, 13-H), 6.77 (m, 1 H, 18-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7 (C-9), 19.8 (C-22), 24.9 (C-3, C-28), 28.3, 28.66, 28.72, 28.8, 28.9, 28.9, 29.0, 29.0, 29.1, 29.2, 29.28, 29.3 (C-4 to C-8, C-23 to C-27), 34.0 (C-2, C-29), 51.4 (CH_3), 78.0 (C-11), 80.3 (C-20), 95.0 (C-21), 98.5 (C-10), 110.3 (C-12), 112.5 (C-19), 131.2, 133.5, 133.9, 134.4 (C-14 to C-17), 138.4 (C-13), 140.3 (C-18), 174.2 (C=O) ppm.

Dimethyl all-(*E*)-Dotriaconta-13,15,17,19-tetraene-11,21-diynedioate [all-(*E*)-3e]: Obtained from **1b** and **2c**, all-(*E*)/(1*Z*,3*E*,5*E*,7*E*), 1:4 isomer mixture. Yield 10 mg, 19%. Yellow solid, m.p. 79−81 °C. R_f = 0.60 (hexane/diethyl ether, 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (m, 16 H, 4-H to 7-H, 26-H to 29-H), 1.37 (m, 4 H, 8-H, 25-H), 1.53 (quint, J = 7.8 Hz, 4 H, 9-H, 24-H), 1.62 (quint, J = 7.2 Hz, 4 H, 3-H, 30-H), 2.30 (t, J = 7.6 Hz, 4 H, 2-H, 31-H), 2.34 (dt, J = 2.4, 7.2 Hz, 4 H, 10-H, 23-H), 3.66 (s, 6 H, 2 × CH_3), 5.61 (dt, J = 2.4, 15.3 Hz, 2 H, 13-H, 20-H), 6.30 (m, 4 H, 15-H to 18-H), 6.54 (m, 2 H, 14-H, 19-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8 (C-10, C-23), 24.9 (C-3, C-30), 28.7, 28.8, 29.0, 29.1, 29.2, 29.3 (C-4 to C-9, C-24 to C-29), 34.1 (C-2, C-31), 51.4 (CH_3), 80.4 (C-12, C-21), 95.1 (C-11, C-22), 112.4 (C-13, C-20), 133.3, 133.7 (C-15 to C-18), 140.4 (C-14, C-19), 174.3 (C=O) ppm. FT IR (KBr): $\tilde{\nu}_{max}$ = 2920, 2585, 2220, 1730, 1468, 1437, 1306, 1240, 1207, 1174, 997 cm^{-1}. EI MS (70 eV): *m*/*z* (%) = 522 (100) [M$^+$], 491 (8), 351 (10), 337 (8), 195 (18), 181 (52), 167 (74), 155 (30), 141 (33), 129 (30), 117 (19), 105 (12), 91 (25). UV: λ_{max} (ε, L·mol^{-1}·cm^{-1}) = ($CHCl_3$) 310 (59000), 353 (86000), 373 nm (90000); UV (1,4-dioxane): λ_{max} (ε, L·mol^{-1}·cm^{-1}) = 334 (63000), 351 (113000), 373 nm (128000). $C_{34}H_{50}O_4$ (522.76): calcd. C 78.12, H 9.64; found C 77.92, H 9.85.

Synthesis of all-(*E*)-Polyene Diesters 4

General Procedure: A slurry of Zn powder freshly activated under Ar with $Cu(OAc)_2{\cdot}H_2O$ and $AgNO_3$ [17] in MeOH/water (1:1; 3 mL) was added to a solution of the appropriate polyenediyne **3** (0.10 mmol) in methanol (0.5 mL) at room temperature and with stirring. After 24 h, the reaction mixture was filtered (Celite, CH_2Cl_2) and the subsequent workup afforded (95% yield) the pure (*Z*,all-*E*,*Z*) isomer [products from all-(*E*)-**3** isomers] or a (*Z*,*E*,all-*E*,*Z*)/(*Z*,*Z*,all-*E*,*Z*), 1:4 mixture of isomers [products from **3** in the form of (*E*,all-*E*)/(*Z*,all-*E*), 1:4 mixtures of isomers]. Each former product in hexane (200 mL) was refluxed 15 min under Ar with iodine-saturated hexane (60 μL) and the solution was filtered through a short silica gel pad while hot, the solvent was evaporated to 5 mL and the corresponding all-(*E*) isomer **4** was separated from the cooled (−20 °C) residual solution by filtration. Yield 95%. High purity samples were obtained by crystallization from acetone at −20 °C.

Dimethyl all-(*E*)-Dotriaconta-13,15,17,19-tetraenedioate (4a): Obtained by reduction/isomerization of all-(*E*)-**3a**. Yield 48 mg, 90% overall. White crystals, m.p. 81−83 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (br. s, 28 H, 4-H to 10-H, 23-H to 29-H). 1.37 (quint, J = 7.5 Hz, 4 H, 11-H, 22-H), 1.64 (quint, J = 7.2 Hz, 4 H, 3-H, 30-H), 2.08 (dt, J = 6.9, 7.2 Hz, 4 H, 12-H, 21-H), 2.30 (t, J = 7.5 Hz, 4 H, 2-H, 31-H), 3.66 (s, 6 H, 2 × CH_3), 5.68 (dt, J = 7.2, 14.4 Hz, 2 H, 13-H, 20-H), 6.25 (m, 6 H, 14-H to 19-H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 25.0, 29.1, 29.2, 29.25, 29.3, 29.4, 29.5, 29.6, 32.9, 34.1, 51.5, 130.5, 130.8, 132.5, 135.2, 174.4 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3000, 2918, 2842, 1738, 1728, 1170, 985 cm^{-1}. EI MS (70 eV): *m*/*z* (%) = 530 (100) [M$^+$], 499 (20), 467 (5), 345 (7), 331 (20), 317 (17), 285 (10), 145 (11), 131 (23), 117 (26), 105 (31), 91 (47). UV ($CHCl_3$): λ_{max} (ε, L·mol^{-1}·cm^{-1}) = 293 (49000), 306 (73000), 321 nm (65000); UV (1,4-dioxane): λ_{max} (ε, L·mol^{-1}·cm^{-1}) = 291 (47000), 303 (64000), 318 nm (58000). $C_{34}H_{58}O_4$ (530.82): calcd. C 76.93, H 11.01; found C 76.84, H 10.89.

Dimethyl (13*Z*,15*E*,17*E*,19*Z*)-Dotriaconta-13,15,17,19-tetraenedioate [(13*Z*,15*E*,17*E*,19*Z*) Isomer of 4a]: Obtained by reduction of all-(*E*)-**3a**. Yield 50 mg, 95%. White crystals, m.p. 45−47 °C. R_f = 0.68 (hexane/diethyl ether, 3:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (br. s, 28 H, 4-H to 10-H, 23-H to 29-H), 1.38 (quint, J = 6.4 Hz, 4 H, 11-H, 22-H), 1.62 (quint, J = 7.6 Hz, 4 H, 3-H, 30-H), 2.19 (ddt, J = 1.2, 7.2, 7.6 Hz, 4 H, 12-H, 21-H), 2.30 (t, J = 7.2 Hz, 4 H, 2-H, 31-H), 3.66 (s, 6 H, 2 × CH_3), 5.45 (dt, J = 7.6, 10.8 Hz, 2 H, 13-H, 20-H), 6.03 (dt, J = 10.8, 11.2 Hz, 2 H, 14-H, 19-H), 6.26 (dd, J = 3.2, 11.2 Hz, 2 H, 15-H, 18-H), 6.50 (dt, J = 2.8, 11.2 Hz, 2 H, 16-H, 17-H) ppm. ^{1}H NMR (300 MHz, C_6D_6, 20 °C): δ = 1.44 (br. s, 28 H, 4-H to 10-H, 23-H to 29-H), 1.60 (m, 4 H, 11-H, 22-H), 1.82 (quint, J = 6.6 Hz, 4 H, 3-H, 30-H), 2.37 (t, J = 7.5 Hz, 4 H, 2-H, 31-H), 2.44 (dt, J = 6.6, 6.9 Hz, 4 H, 12-H, 21-H), 3.61 (s, 6 H, 2 × CH_3), 5.72 (dt, J = 7.8, 10.2 Hz, 2 H, 13-H, 20-H), 6.41 (m, 2 H, 14-H, 19-H), 6.55 (m, 2 H, 15-H, 18-H), 6.86 (m, 2 H, 16-H, 17-H) ppm. ^{13}C NMR (75 MHz, C_6D_6, 20 °C): δ = 25.3, 28.3, 29.4, 29.6, 29.8, 29.9, 29.96, 29.98, 30.1, 34.1, 50.9, 128.7, 129.5, 132.8, 133.5, 173.3 ppm. FT IR (KBr): $\tilde{\nu}_{max}$ = 2918, 2851, 1731, 1644, 1437, 1260, 1225, 1200, 1171, 990, 803 cm^{-1}. EI MS (70 eV): identical to the spectrum of **4a**. HRMS (EI): calcd. for $C_{34}H_{58}O_4$ 530.43351; found 530.43347. UV (1,4-dioxane): λ_{max} (ε, L·mol^{-1}·cm^{-1}) = 295 (38000), 308 (58000), 323 nm (52000).

Dimethyl all-(*E*)-Octacosa-10,12,14,16,18-pentaenedioate (4b): Obtained by reduction/isomerization of **3b**, all-(*E*)/(12*Z*,14*E*,16*E*), 1:4 isomer mixture. Yield 42 mg, 89% overall. Pale-yellow crystals. R_f = 0.75 (hexane/EtOAc, 7:3). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (br. s, 16 H, 4-H to 7-H, 22-H to 25-H), 1.37 (q, J = 6.5 Hz, 4 H, 8-H, 21-H), 1.61 (q, J = 7.0 Hz, 4 H, 3-H, 26-H), 2.09 (dt, J = 6.5, 7.0 Hz, 4 H, 9-H, 20-H), 2.30 (t, J = 7.0 Hz, 4 H, 2-H, 27-H), 3.66 (s, 6 H, 2 × CH_3), 5.70 (dt, J = 7.0, 15.0 Hz, 2 H, 10-H, 19-H), 6.07 (dd, J = 9.0, 15.0 Hz, 11-H, 18-H), 6.19 (m, 6 H, 12-H, 17-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.9 (C-3, C-26), 29.1, 29.2, 29.3 (C-4 to C-8, C-21 to C-25), 32.9 (C-9, C-20), 34.1 (C-2, C-27), 51.4 (CH_3), 130.6, 130.9, 132.4, 132.9 (C-11 to C-18), 135.6 (C-10, C-19), 177.1 (C=O) ppm. FT IR (KBr): $\tilde{\nu}_{max}$ =

2919, 2848, 1739, 1640, 1471, 1436, 1242, 1172, 1003 cm^{-1}. EI MS (70 eV): *m/z* (%) = 472 (48) [M^+], 441 (10), 315 (9), 301 (26), 145 (39), 131 (80), 117 (100), 105 (58), 91 (97). HRMS (EI): calcd. for $C_{30}H_{48}O_4$ 472.35526; found 472.35759. UV ($CHCl_3$): λ_{max} (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1}$) = 306 (29000), 320 (60000), 335 (95000), 353 nm (92000); UV (1,4-dioxane): λ_{max} (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1}$) = 306 (28000), 318 (52000), 333 (78000), 351 nm (80000).

Dimethyl (10*Z*,12*E*,14*E*,16*E*,18*Z*)-Octacosa-10,12,14,16,18-pentaenedioate [(10*Z*,12*E*,14*E*,16*E*,18*Z*) Isomer of 4b]: Obtained by reduction of all-(*E*)-**3b**. Yield 45 mg, 95%. Pale yellow crystals, m.p. 73−75 °C. R_f = 0.75 (hexane/EtOAc, 7:3). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.29 (br. s, 16 H, 4-H to 7-H, 22-H to 25-H), 1.38 (q, *J* = 6.9 Hz, 4 H, 8-H, 21-H), 1.61 (q, *J* = 7.0 Hz, 4 H, 3-H, 26-H), 2.19 (dt, *J* = 7.0, 8.0 Hz, 4 H, 9-H, 20-H), 2.30 (t, *J* = 7.5 Hz, 4 H, 2-H, 27-H), 3.66 (s, 6 H, 2 × C*H*$_3$), 5.47 (dt, *J* = 8.0, 10.5 Hz, 2 H, 10-H, 19-H), 6.04 (dd, *J* = 11.5, 11.5 Hz, 2 H, 11-H, 18-H), 6.27 (m, 4 H, 12-H, 13-H, 16-H, 17-H), 6.50 (dd, *J* = 11.5, 14.0 Hz, 2 H, 14-H, 15-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.9 (C-3, C-26), 29.1, 29.2, 29.3, 29.6 (C-4 to C-9, C-20 to C-25), 34.1 (C-2, C-27), 51.5 (*C*H$_3$), 128.4, 128.7, 132.7, 133.0, 133.2 (C-10 to C-19), 174.3 (C=O) ppm. FT IR (KBr): $\tilde{\nu}_{max}$ = 2920, 2849, 1740, 1644, 1435, 1384, 1250, 1209, 1176, 995, 710 cm^{-1}. EI MS (70 eV): identical to the spectrum of **4b**. HRMS (EI): calcd. for $C_{30}H_{48}O_4$ 472.35526; found 472.35360. UV (1,4-dioxane): λ_{max} (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1}$) = 307 (23000), 321 (41000), 337 (60000), 356 nm (61000).

Dimethyl (10*Z*,12*Z*,14*E*,16*E*,18*Z*)-Octacosa-10,12,14,16,18-pentaenedioate [(10*Z*,12*Z*,14*E*,16*E*,18*Z*) Isomer of 4b]: Obtained by reduction of (12*Z*,14*E*,16*E*)-**3b**. Yield 46 mg, 97%. Yellow crystals, m.p. 69−70 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (br. s, 16 H, 4-H to 7-H and 22-H to 25-H), 1.38 (q, *J* = 6.8 Hz, 4 H, 8-H, 21-H), 1.61 (q, *J* = 7.2 Hz, 4 H, 3-H, 26-H), 2.19 (dt, *J* = 7.2, 7.6 Hz, 4 H, 9-H, 20-H), 2.30 (t, *J* = 7.2 Hz, 4 H, 2-H, 27-H), 3.66 (s, 6 H, 2 × C*H*$_3$), 5.50 (m, 2 H, 10-H, 19-H), 6.05 (dd, *J* = 10.8, 11.2 Hz, 2 H, 11-H, 18-H), 6.27 (m, 3 H, 12-H, 13-H, 17-H), 6.47, 6.52, 6.69 (3 m, each 1 H, 14-H to 16-H) ppm.

Dimethyl all-(*E*)-Tetratriaconta-13,15,17,19,21-pentaenedioate (4c): Obtained by reduction/isomerization of **3c**, all-(*E*)/(15*Z*,17*E*,19*E*), 1:4 isomer mixture. Described in ref.[7]

Dimethyl all-(*E*)-Triaconta-10,12,14,16,18,20-hexaenedioate (4d): Obtained by reduction/isomerization of **3d**, all-(*E*)/(12*Z*,14*E*,16*E*,18*E*), 1:4 isomer mixture. Yield 45 mg, 90% overall. Yellow crystals, m.p. 90−92 °C. R_f = 0.3 (hexane/EtOAc, 7:3). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.29 (br. s, 16 H, 4-H to 7-H, 24-H to 27-H), 1.38 (quint, *J* = 7.5 Hz, 4 H, 8-H, 23-H), 1.61 (quint, *J* = 7.2 Hz, 4 H, 3-H, 28-H), 2.09 (dt, *J* = 6.9, 7.2 Hz, 4 H, 9-H, 22-H), 2.30 (t, *J* = 7.5 Hz, 4 H, 2-H, 29-H), 3.66 (s, 6 H, 2 × C*H*$_3$), 5.71 (dt, *J* = 7.2, 14.7 Hz, 2 H, 10-H, 21-H), 6.09 (dd, *J* = 9.3, 14.7 Hz, 11-H, 20-H), 6.22 (m, 8 H, 12-H to 19-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9 (C-3, C-26), 29.1, 29.2, 29.3 (C-4 to C-8, C-23 to C-27), 32.9 (C-9, C-22), 34.1 (C-2, C-29), 51.5 (*C*H$_3$), 130.5, 130.9, 132.5, 132.9, 133.3 (C-11 to C-20), 135.8 (C-10, C-21), 174.4 (C=O) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2919, 2849, 1738, 1622, 1436, 1174, 1005 cm^{-1}. EI MS (70 eV): *m/z* (%) = 498 (100) [M^+], 467 (10), 341 (6), 327 (19), 171 (11), 157 (15), 143 (21), 129 (33), 117 (36), 105 (23), 91 (36). UV ($CHCl_3$): λ_{max} (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1}$) = 306 (34000), 320 (71000), 362 (120000), 382 nm (124000). $C_{32}H_{50}O_4$ (498.74): calcd. C 77.06, H 10.10; found C 76.99, H 10.53.

Dimethyl all-(*E*)-Dotriaconta-11,13,15,17,19,21-hexaenedioate (4e): Obtained by reduction/isomerization of **3e**, all-(*E*)/(1*Z*,3*E*,5*E*,7*E*), 1:4 isomer mixture. Yield 47 mg, 89% overall. Yellow crystals, m.p. 96−98 °C. R_f = 0.84 (hexane/EtOAc, 7:3). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (br. s, 20 H, 4-H to 8-H, 25-H to 29-H), 1.37 (quint, *J* = 7.2 Hz, 4 H, 9-H, 4-H), 1.61 (quint, *J* = 7.2 Hz, 4 H, 3-H, 30-H), 2.09 (dt, *J* = 6.9, 7.2 Hz, 4 H, 10-H, 23-H), 2.30 (t, *J* = 7.2 Hz, 4 H, 2-H, 31-H), 3.66 (s, 6 H, 2 × C*H*$_3$), 5.71 (dt, *J* = 6.9, 14.7 Hz, 2 H, 11-H, 22-H), 6.15 (m, 10 H, 12-H to 21-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9 (C-3, C-30), 29.12, 29.14, 29.20, 29.27, 29.3, 29.4 (C-4 to C-9, C-24 to C-29), 32.9 (C-10, C-23), 34.1 (C-2, C-31), 51.4 (*C*H$_3$), 130.6, 130.9, 132.5, 132.9, 133.3 (C-12 to C-21), 135.8 (C-11, C-22), 174.3 (C=O) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3000, 2918, 2842, 1738, 1728, 1170, 985 cm^{-1}. EI MS: *m/z* (%) = 526 (100) [M^+], 495 (9), 355 (7), 341 (22), 171 (17), 129 (52), 117 (59), 105 (40), 91 (62). UV ($CHCl_3$): λ_{max} (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1}$) = 306 (34000), 320 (71000), 362 (120000), 382 nm (124000). $C_{34}H_{54}O_4$ (526.79): calcd. C 77.52, H 10.33; found C 77.64, H 10.42.

Hydrolysis of Diesters 4 to the Corresponding Diacids 5

General Procedure: A suspension of each ester **4** (0.10 mmol) in 95% EtOH (2 mL) with powdered KOH (10 mmol) was refluxed for 5 h, the reaction mixture was cooled, acidified (pH = 1, 5% HCl), and the precipitated solid was filtered, washed successively with water, EtOH and toluene, and dried. Yield 95%. Pure samples of diacids **5** were obtained by crystallization from toluene at −20 °C.

all-(*E*)-Dotriaconta-13,15,17,19-tetraenedioic Acid (5a): Yield 48 mg, 96%. White crystals, m.p. 126−128 °C. R_f = 0.22 (CH_2Cl_2/EtOH, 95:5). ^1H NMR (300 MHz, [D_6]DMSO, 70 °C): δ = 1.26 (br. s, 28 H, 4-H to 10-H, 23-H to 29-H), 1.36 (quint, *J* = 6.9 Hz, 4 H, 11-H, 22-H), 1.50 (quint, *J* = 7.2 Hz, 4 H, 3-H, 30-H), 2.07 (dt, *J* = 6.6, 6.9 Hz, 4 H, 12-H, 21-H), 2.18 (t, *J* = 7.2 Hz, 4 H, 2-H, 31-H), 5.70 (dt, *J* = 6.9, 14.4 Hz, 2 H, 13-H, 20-H), 6.07 (dd, *J* = 9.6, 14.8 Hz, 2 H, 14-H, 19-H), 6.20 (m, 4 H, 15-H to 18-H), 11.90 (br. s, 2 H, 2 × CO_2H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 70 °C): δ = 24.1 (C-3, C-30), 28.2, 28.3, 28.40, 28.43, 28.5 (C-4 to C-11, C-21 to C-29), 31.7 (C-12, C-21), 33.4 (C-2, C-31), 130.2, 130.4, 132.0 (C-14 to C-19), 134.3 (C-13, C-20), 173.8 (C=O) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3050, 2960, 2875, 2800, 1690, 1680, 1210, 918 cm^{-1}. EI MS (70 eV): *m/z* = 502 (36) [M^+], 303 (14), 171 (3), 159 (4), 131 (28), 117 (39), 105 (53), 91 (100), 79 (48), 69 (38). HRMS (EI): calcd. for $C_{32}H_{54}O_4$ 502.40221; found 502.40165.

all-(*E*)-Octacosa-10,12,14,16,18-pentaenedioic Acid (5b): Yield 42 mg, 95%. Pale yellow crystals, m.p. 146−148 °C. R_f = 0.43 (CH_2Cl_2/EtOH, 95:5). ^1H NMR (500 MHz, [D_6]DMSO): δ = 1.20 (br. s, 16 H, 4-H to 7-H, 22-H to 25-H), 1.30 (quint, *J* = 7.0 Hz, 4 H, 8-H, 21-H), 1.43 (quint, *J* = 7.0 Hz, 4 H, 3-H, 26-H), 2.02 (dt, *J* = 7.0, 7.0 Hz, 4 H, 9-H, 20-H), 2.13 (t, *J* = 7.0 Hz, 4 H, 2-H, 27-H), 5.68 (dt, *J* = 7.0, 15.5 Hz, 2 H, 10-H, 19-H), 6.05 (dd, *J* = 9.5, 15.0 Hz, 2 H, 11-H, 18-H), 6.18 (m, 6 H, 12-H to 17-H), 11.82 (br. s, 2 H, 2 × CO_2H) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 24.4 (C-3, C-26), 28.4, 28.6 (C-4 to C-8, C-21 to C-25), 32.1 (C-9, C-20), 35.6 (C-2, C-27), 130.6, 130.8, 132.4, 132.8 (C-11 to C-18), 135.2 (C-10, C-19), 174.3 (C=O) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3011, 2920, 2849, 1705, 1433, 1253, 996 cm^{-1}. EI MS (70 eV): *m/z* (%) = 444 (46) [M^+], 287 (8), 145 (24), 131 (53), 117 (67), 105 (43), 91 (100). HRMS (EI): calcd. for $C_{28}H_{44}O_4$ 444.32396; found 444.32528.

all-(*E*)-Tetratriaconta-13,15,17,19,21-pentaenedioic Acid (5c): Described in ref.[7]

all-(*E*)-Triaconta-10,12,14,16,18,20-hexaenedioic Acid (5d): Yield 45 mg, 96%. Yellow crystals. R_f = 0.5 (CH_2Cl_2/EtOH, 95:5). ^1H NMR (400 MHz, [D_6]DMSO, 70 °C): δ = 1.26 (br. s, 16 H, 4-H

to 7-H, 24-H to 27-H), 1.36 (quint, J = 7.2 Hz, 4 H, 8-H, 23-H), 1.50 (quint, J = 7.2 Hz, 4 H, 3-H, 28-H), 2.08 (dt, J = 7.2, 7.8 Hz, 4 H, 9-H, 22-H), 2.18 (t, J = 7.6 Hz, 4 H, 2-H, 29-H), 5.74 (dt, J = 7.2, 14.8 Hz, 2 H, 10-H, 21-H), 6.10 (dd, J = 9.6, 15.3 Hz, 2 H, 11-H, 20-H), 6.20 (m, 8 H, 12-H to 19-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 70 °C): δ = 24.1 (C-3, C-28), 28.14, 28.16, 28.23, 28.3, 28.4 (C-4 to C-8, C-23 to C-27), 31.8 (C-9, C-22), 33.4 (C-2, C-29), 130.3, 130.5, 132.1, 132.5, 132.9 (C-11 to C-20), 135.0 (C-10, C-21), 173.9 (C=O) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3060, 2916, 2849, 1701, 1616, 1423, 1166, 998 cm^{-1}. EI MS (70 eV): m/z (%) = 470 (40) [M$^+$], 313 (8), 181 (9), 171 (20), 155 (33), 143 (44), 129 (78), 117 (78), 105 (51), 91 (100).

all-(*E*)-Dotriaconta-11,13,15,17,19,21-hexaenedioic Acid (5e): Yield 48 mg, 96%. Yellow crystals. R_f = 0.51 (CH_2Cl_2/EtOH, 95:5). ^{1}H NMR (300 MHz, 70 °C): δ = 1.26 (br. s, 20 H, 4-H to 8-H, 25-H to 29-H), 1.36 (quint, J = 6.9 Hz, 4 H, 9-H, 24-H), 1.50 (quint, J = 7.2 Hz, 4 H, 3-H, 30-H), 2.08 (dt, J = 6.9, 6.9 Hz, 4 H, 10-H, 23-H), 2.18 (t, J = 7.2 Hz, 4 H, 2-H, 31-H), 5.74 (dt, J = 6.9, 14.7 Hz, 2 H, 11-H, 22-H), 6.09 (m, 2 H, 12-H, 21-H), 6.24 (m, 8 H, 13-H to 20-H), 11.66 (br. s, 2 H, 2 × CO_2H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 70 °C): δ = 24.1 (C-3, C-30), 28.1, 28.2, 28.36, 28.38 (C-4 to C-9, C-24 to C-29), 31.8 (C-10, C-23), 33.4 (C-2, C-31), 130.3, 130.5, 132.1, 132.5, 132.8 (C-12 to C-21), 135.0 (C-11, C-22), 173.8 (C=O) ppm. IR (KBr): $\tilde{\nu}_{max}$ 3058, 2912, 2853, 1706, 1620, 1410, 1128, 1008 cm^{-1}. EI MS (70 eV): m/z (%) = 498 (100) [M$^+$], 484 (4), 420 (3), 341 (8), 327 (29), 171 (15), 157 (23), 143 (34), 129 (60), 117 (69), 105 (47), 91 (75).

Synthesis of Polyene Compounds 8 by Stille Double Cross-Coupling

General Procedure: A THF solution of Pd^0 catalyst, freshly prepared by reduction of [$PdCl_2(PPh_3)_2$] with DIBAL[25] (0.4 mL, ca. 11 μmol), was added to a mixture of the appropriate all-(*E*)-ω-halopolyene **6** (280 μmol) and (*E*)-bis(tributylstannyl)ethane (**7**) (84 mg, 139 μmol) in dry DMF, with stirring and under argon. After 12 h, the subsequent workup yielded a solid that was purified by column chromatography (silica gel, hexane/ethyl acetate, 1:1). The remaining halopolyene **6** was recovered in the same chromatography. Very pure samples of polyenes **8a** and **8b** were isolated by crystallization from hexane with traces of ethanol. Product **8c** was a mixture of polyene compounds.

all-(*E*)-Hexadeca-2,4,6,8,10,12,14-heptaene-1,16-dial (8a): Obtained from **6a** and **7**. Yield 27 mg, 40%. Reddish crystals, m.p. > 60 °C (dec.). R_f = 0.57 (hexane/EtOAc, 1:1); R_f = 0.17 (hexane/EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.18 (dd, J = 8.0, 15.2 Hz, 2 H, 2-H, 15-H), 6.50 (m, 8 H, 5-H to 12-H), 6.73 (dd, J = 11.2, 14.8 Hz, 2 H, 4-H, 13-H), 7.14 (dd, J = 11.2, 15.2 Hz, 2 H, 3-H, 14-H), 9.58 (d, J = 8.0 Hz, 2 H, 1-H, 16-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 131.0, 131.5, 133.5, 135.5, 138.0 (C-4 to C-13), 142.0 (C-2, C-15), 151.0 (C-3, C-14), 193.2 (C=O) ppm. FT IR (KBr): $\tilde{\nu}_{max}$ = 3436, 2917, 1663, 1617, 1586, 1261, 1149, 1016, 802 cm^{-1}. EI MS (70 eV): m/z (%) = 240 (22) [M$^+$], 231 (4), 214 (3), 205 (4), 165 (8), 153 (9), 141 (14), 135 (15), 128 (19), 115 (26), 105 (13), 97 (14), 91 (100). UV ($CHCl_3$): λ_{max} (ε, L·mol^{-1}·cm^{-1}) = 413.2 (63000), 434.0 (92000), 458.2 nm (88000). HRMS (EI): calcd. for $C_{16}H_{16}O_2$ 240.11503; found 240.11509.

Diethyl all-(*E*)-Hexadeca-2,4,6,8,10,12,14-heptaenedioate (8b): Obtained from **6b** and **7**. Yield 64 mg, 70%. Reddish crystals, m.p. >60 °C (decomp.). R_f = 0.22 (hexane/EtOAc, 9:1); R_f = 0.62 (hexane/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.2 Hz, 3 H, CH_3), 4.21 (c, J = 7.2 Hz, 2 H, CH_2), 6.5−6.3 (m, 8 H, 5-H to 12-H), 5.89 (d, J = 15.2 Hz, 1 H, 2-H, 15-H), 6.61 (dd, J = 10.4, 14.4 Hz, 1 H, 4-H, 13-H), 7.32 (dd, J = 11.2, 15.2 Hz, 1 H, 3-H, 14-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3 (CH_3), 60.4 (CH_2), 121.4, 131.3, 134.1, 136.4, 140.1 (C-2, C-4 to C-13, C-15), 144.0 (C-3, C-14), 167.0 (C=O) ppm. FT IR (KBr): $\tilde{\nu}_{max}$ = 3435, 2990, 1703, 1622, 1375, 1305, 1239, 1135, 1014 cm^{-1}. EI MS (70 eV): m/z (%) = 328 (100) [M$^+$], 309 (2), 283 (13), 255 (10), 235 (13), 219 (8), 209 (29), 191 (14), 179 (28), 165 (35), 153 (25), 141 (43), 128 (41), 115 (69), 105 (29), 91 (78). HRMS (EI): calcd. for $C_{20}H_{24}O_4$ 328.16746; found 328.16675. UV ($CHCl_3$): λ_{max} (ε, L·mol^{-1}·cm^{-1}) = 397.3 (31000), 416.0 (49000), 441.8 nm (52000). The corresponding octaene diesters **8** (n = 0, m = 8, R = OEt) and nonaene diesters **8** (n = 0, m = 9, R = OEt) were detected by EI MS in the raw material separated by column chromatography {respective [M$^+$] signals at m/z (%) = 354 (31) and 380 (2)}, as well as by UV/Vis spectroscopy.

Dimethyl all-(*E*)-Triaconta-11,13,15,17,19-pentaenedioate (8c): Impure compound, obtained from **6c** and **7**. Mixture of **8c** (85%) and the corresponding tetraene diester **8** (n = 9, m = 4, R = OMe), hexaene diester **4e** and heptaene diester **8** (n = 9, m = 7, R = OMe) (15% total). Yield 85 mg, ca. 60% overall. Data deduced for the main product **8c**: R_f = 0.49 (hexane/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): δ = 1.30 (m, 4-H, 8-H, 23-H, 27-H), 1.4 (m, 9-H, 22-H), 1.63 (m, 3-H, 28-H), 2.09 (dt, J = 6.6, 7.2 Hz, 10-H, 21-H), 2.30 (t, J = 7.5 Hz, 2-H, 29-H), 3.66 (s, 2 × CH_3), 5.69 (m, 11-H, 20-H), 6.15 (m, 12-H to 19-H) ppm. FT IR (neat): $\tilde{\nu}_{max}$ = 2923, 2851, 1738, 1437, 1260, 1172, 993, 802 cm^{-1}. EI MS (70 eV): m/z (%) = 500 (14) [M$^+$], 329 (3), 289 (6), 213 (6), 183 (4), 157 (8), 143 (15), 131 (52) 117 (66), 105 (58), 91 (100). Signal of hexaene **4e** at m/z (%) = 526 (1) [M$^+$].

Acknowledgments

Supported by the Spanish Dirección General de Enseñanza Superior e Investigación Científica, Ministerio de Educación y Cultura (Projects PB96-0852 and BQU2000-1500). E. Q. acknowledges a doctoral fellowship from the same source.

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Received October 8, 2002
[O02556]