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Synthesis and Spectral Properties of Amphiphilic Lipids with Linear Conjugated Polyene and Phenylpolyene Fluorescent Groups

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Lipophilic fluorescent groups with a chain-like linear conformation emitting in the visible range and with high photostability are presently unavailable. These structures would be of great interest as labels for long-chain fatty acids and phospholipids lacking intrinsic fluorescent groups. With this aim in mind, we report the synthesis and the spectroscopic characterization of a series of emitting amphiphilic lipids that may approach that ideal fluorescent tag. Each lipid was constructed by attaching a linear, *all*-(*E*) conjugated pentaene, tetraenyne, ω-phenyltetraene, or ω-phenyltrienyne chromophore to a hydrophilic head-group through a polymethylene chain spacer. The key steps of the synthesis were the Pd^0-mediated cross-coupling reaction between bromopolyenes and terminal acetylenic compounds, yielding tetraenynes or ω-phenyltrienynes, and the subsequent triple-bond partial reduction, producing the corresponding pentaenes or ω-phenyltetraenes in good overall yields. This method represents a further successful example of the so-called "acetylenic approach" to the indirect high-yield synthesis of polyene systems. In the case of ω-phenyltrienynes, a higher proportion of the *all*-(*E*) isomer was obtained using an alternative method based on the reaction of an ω-phenyldienylphosphonate with an α-acetylenic aldehyde. Some of the resulting compounds exhibit spectral and photochemical properties that warrant their use as emitting lipophilic tags. Thus, the ω-phenyltetraene and ω-phenyltrienyne members of the series show intense absorption bands in the 320–370 nm range with fluorescence emission centered at 475 nm and quantum yields up to 0.25. These parameters are appropriate for the applications noted above.

Introduction

Lipids are essential components of all living organisms and an understanding of the structures, dynamics, functions and metabolic pathways of natural lipids at a molecular level is being pursued with intense activity.[1] In addition, there is a growing number of synthetic, lipid-like compounds that present interesting biological properties, such as, anti-tumoral[2–4] or anti-protozoal[5–10] activity. At the same time, fluorescence techniques have now become the primary methods in protein and nucleic acid research.[11,12] This is due to the availability of very specific and sensitive fluorescent assays, new high-resolution fluorescence microscopes,[13] and a large variety of hydrophilic fluorophores in the form of water-soluble organic dyes, fluorescent proteins, or nanocrystals. Before these methods can be extended to lipid research a number of shortcomings need to be solved, chiefly the absence of intrinsic emitting chromophores in most natural lipids. This problem may be circumvented by attaching a fluorescent tag to the original lipid structure to produce a fluorescent lipid analogue, as in the case of proteins and nucleic acids. However, this approach still presents difficulties. Since natural lipids are usually amphipathic molecules, the emitting label might be attached to either the polar or the non-polar part of the molecule. In the first case, xanthene, cyanine, and other dyes have frequently been used, all with very convenient spectral properties in the visible range and reasonable photostability.[14] Unfortunately, the labeling dye also introduces foreign ionizable groups that were not present in the original structure as well as substantial changes of electron charge distribution, molecular size and conformation. Alternatively, the non-polar part of the lipid might be labeled with a lipophilic fluorophore such as a multiring aromatic system (anthracene, pyrene, perylene, etc.) or difluoroborodipyrromethene (BODIPY) dyes. However, the task of preserving as much as possible the structure, polarity and conformation of the original apolar chains is even more difficult in this case and often this strategy fails to produce a fully functional analogue of the parent lipid.

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Conjugated linear polyenes are strongly absorbing nonpolar chromophores that may attain modest but useful fluorescence yields. These groups retain several characteristics of the aliphatic chains of common lipids and are not strangers to the pool of natural polyunsaturated lipids.[15,16] This structural similarity has been exploited in the past to develop the natural parinaric fatty acid, *all*-(*E*)-9,11,13,15-octadecatetraenoic acid, as a fluorescent probe of lipid bilayers and cell membranes.[17–20] Extending the parinaric acid conjugated system from four to five double bonds gives rise to a new fluorophore with a red-shifted intense absorption, a fluorescence spectrum centered in the blue region (ca. 470 nm), and improved spectroscopic properties.[21–24] In this way we could show[21,22] that the fluorescent *all*-(*E*)-octadeca-8,10,12,14,16-pentaenoic acid (*t*-COPA) may be a good choice for probing important properties of lipid bilayers and membranes by means of the usual cuvette spectrofluorimetric methods. However, excitation of *t*-COPA in the near UV region (ca. 350 nm) is still unpractical for lipid imaging in standard wide-field fluorescence microscopes. In recent times new confocal optical microscopes have become available in which fluorophores can be easily excited by two-photon absorption[25,26] using, for example, a Ti:Za laser. This laser can be tuned within the 690–1000 nm range and, therefore, provides an alternative method for the two-photon excitation of the conjugated pentaene fluorophore (2×350 nm). In fact, Thiele and co-workers have recently demonstrated this possibility in a very elegant way.[27] They showed first that living mammalian cells readily take up a lipid precursor labeled with the *t*-COPA emitting group without altering the natural metabolic paths. Next, they showed that the microdomains of the cell lipids incorporating the pentaene group could be imaged in high contrast by two-photon excitation of the pentaene chromophore.

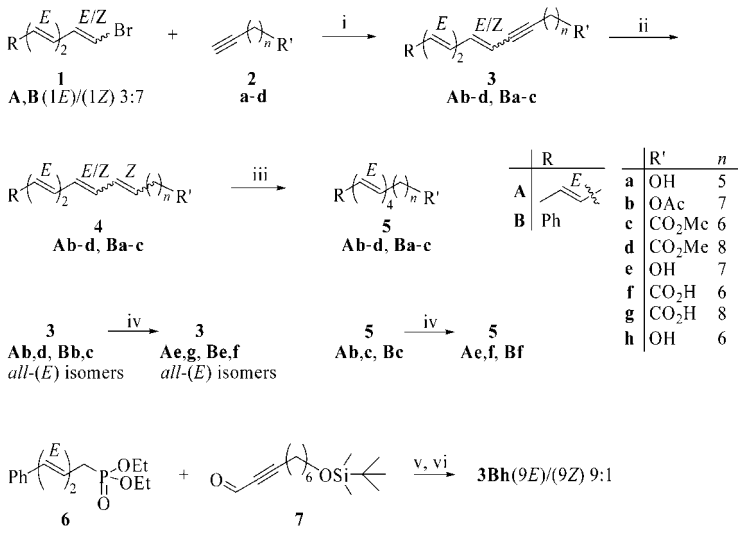
The absorbing/fluorescent properties of a polyene chain may be further improved by introducing an ω-phenyl residue with a relatively modest increase in molecular size. This approach has also been used recently to obtain an emitting analogue of the ether lipid drug edelfosine[28] in which the anti-cancer activity of the original lysophospholipid is preserved. With the purpose of exploring the use of new polyene and phenylpolyene systems to produce additional fluorescent lipid analogues, we report a general strategy for the synthesis of amphipathic structures containing diverse lipophilic, linear π-conjugated chromophores that absorb in the 350–370 nm range. In these compounds, conjugated pentaene, tetraenyne, ω-phenyltetraene, or ω-phenyltrienyne groups were attached to simple polar residues − primary alcohol, acetate, carboxylic acid, or methyl ester − through a linear aliphatic chain of 5–8 methylene groups. As we wanted to optimize the fully-extended conformation of the chromophore, *all*-(*E*) isomers were consistently selected as the double-bond systems.

Results and Discussion

Synthesis of Polyenynes 3 and Polyenes 4 and 5

The Pd/Cu-catalyzed reaction of terminal alkynes with sp^2 carbon halides (the Sonogashira–Hagihara cross-coupling reaction) is a useful way of preparing conjugated acetylenic compounds. In recent years, this reaction has emerged as a general, reliable, and efficient method for the synthesis of complex molecules.[29–31] This reaction can be combined with selective triple-bond partial reduction (the acetylenic approach) to synthesize polyene systems stereoselectively.[32] This strategy is more convenient than the use of the Stille[33] or Suzuki[34–36] reactions particularly when the respective organostannane or -borane compound required is either unavailable or too unstable. Several conjugated polyene and polyenyne systems have been prepared in our laboratory by this approach.[23,24,28] In this work, the target compounds were obtained similarly, following the sequence shown in Scheme 1. The first step was the cross-coupling[37,38] between a bromopolyene **1** [in the form of a 3:7 (1*E*,..)/(1*Z*,..) mixture of isomers] and an alkyne **2**. In preliminary assays designed to optimize reaction conditions, the coupling between bromotetraene **1A** and acetylenic ester **2d** was studied in some detail. In the presence of a 30% excess of **2d**, **1A** disappeared from the reaction medium after around 30 min at room temperature, yielding **3Ad**. A larger excess of **2d** gave rise to the **2d**–**2d** homocoupling byproduct, easily separable from the expected product **3Ad** by chromatographic methods. In contrast, both the starting compound **2d** and the product **3Ad** show almost similar chromatographic behavior. This was also observed with other compounds **2** and their corresponding cross-coupling products **3**. For this reason, at the end of the reaction, when **1A** could no longer be detected, the unreacted excess of **2d** was converted into its homocoupling product by bubbling air through the mixture for a short time in order to oxidize the Pd^0 complexes to Pd^{II} species (the species catalyzing the homocoupling). In this way, product **3Ad** can be easily purified by silica gel chromatography without degradation. This oxidation process was also carried out in the other cross-coupling reactions described herein. A thoroughly deoxygenated diethylamine/THF mixture was used as the reaction medium instead of the pure amine to completely dissolve **1A**. A mixture of dichlorobis(triphenylphosphane)palladium(II) ([Pd-$(PPh_3)_2Cl_2$]) and copper(I) iodide (5 and 17 mol-%, respectively, with regard to **1A**) was used as the catalyst. With freshly prepared tetrakis(triphenylphosphane)palladium(0) ([$Pd(PPh_3)_4$], 5 mol-%), a less efficient catalyst,[37] much lower yields of the coupling product were obtained even after longer reaction times under similar experimental conditions.

By using the optimized conditions detailed above, the complete series of compounds **3** were similarly obtained (in yields higher than 80%) by cross-coupling between the corresponding bromopolyenes **1** and alkynes **2**. In all cases, the stereochemistry of the double bond in the 1-position in **1** did not change during the reaction and the same 3:7 (*E*)/(*Z*) ratio was obtained for each compound **3**, as expected.[39] These isomers could not be separated by either chromatography on silica gel or by crystallization, although pure samples of the corresponding *all*-(*E*)-**3** isomers could be separated by selective precipitation from concentrated $CHCl_3$ or CH_2Cl_2 solutions by careful addition of *n*-pen-



Scheme 1. Reagents and conditions: i) **2/1** = 1.3 (molar), $[Pd(PPh_3)_2Cl_2]$ (5 mol-% on **1**), CuI (17 mol-% on **1**), Et_2NH, THF, Ar, room temperature, 1–3 h; ii) Zn/Cu/Ag, MeOH/H_2O, 1:1, room temperature, Ar, 24 h; iii) I_2 (trace), hexane, Ar, 15 min, reflux; iv) KOH (5 equiv.), EtOH, room temperature, Ar, 4 h; v) *t*-BuOK, THF, 0 °C, then room temperature, 1 h, 60%; vi) TBAF, THF, room temperature, 40 min, 98%.

tane. In the case of products **3A**, the (*E*)/(*Z*) mixtures obtained could be converted into the corresponding *all*-(*E*) isomers with a trace of iodine.[24] In contrast, mixtures of isomeric **3B** compounds could not be isomerized by this procedure and pure *all*-(*E*)-**3B** isomers had to be separated from the corresponding (*E*)/(*Z*) mixtures by precipitation, as above. An alternative approach that yields a much higher proportion of *all*-(*E*)-**3B** isomers is shown below.

Partial reduction of the triple bond in any of the isomeric polyenyne compounds **3** or their mixtures with zinc activated with copper and silver (the Boland method)[32] yielded the corresponding polyenes **4**. This reduction step gave rise to compounds with a (*Z*) double bond in the position of the triple bond. Reduction of any other unsaturation moiety in the polyene system was not observed in any case. Subsequent isomerization of the mixtures of polyenes **4** with a trace of iodine provided the corresponding *all*-(*E*) compounds **5** in good overall yields. Hydrolysis of *all*-(*E*)-polyenyne esters **3Ab**,**d** and **3Bb**,**c** or of *all*-(*E*)-polyenes **5Ab**,**c** and **5Bc** gave rise to compounds **3Ae**,**g**, **3Be**,**f**, **5Ae**,**f**, and **5Bf**, respectively, with a primary alcohol or carboxylic acid as the terminal polar groups. All polyene and polyenyne compounds must be conserved completely free of traces of inorganic acids to prevent uncontrolled acid-catalyzed double-bond isomerization. The solubility of each specific amphiphilic compound depends on the type of head-group, those with a terminal carboxylic acid group being less soluble ($<10^{-5}$ M) in common organic solvents, although they are soluble in DMSO. In an acid-free $CHCl_3$ solution, conjugated tetraenyne and ω-phenyltrienyne compounds show much higher thermal and photochemical stability than the corresponding compounds with conjugated pentaene and ω-phenyltetraene systems (data not shown) such that no degradation was observed when stored for months at –20 °C and protected from exposure to light.

This approach allows access to *all*-(*E*)-polyene systems in a simple and efficient way that is more convenient than use of the Wittig reaction for the same purpose, as was described before for the synthesis of the acid **5Af** (*t*-COPA).[21,27] This method can be scaled up for the preparation of larger amounts of product and, also, it can be used to prepare other similar compounds with different polymethylene chain lengths and terminal polar groups. For example, the CH_2OH group could allow the easy introduction of a phosphate as the terminal polar group.

Alternative Synthesis of all-(*E*)-Phenyltrienynes

As discussed above, the synthesis of conjugated ω-phenyltrienyne compounds **3B**, using as starting material the 1-bromo-6-phenylhexatriene (**1B**) as a (1*E*)/(1*Z*) mixture,[28] yielded (*Z*) isomers that could not be isomerized to the corresponding (*E*) isomers with iodine as was the case for the tetraenynes **3A**, the pentaenes **4A**, and the ω-phenyltetraenes **4B**. Pure *all*-(*E*)-**3B** isomers were isolated in around 30% yield by precipitation with $CHCl_3$/pentane. In the following, we report an alternative way of obtaining much higher yields of the pure *all*-(*E*)-**3B** compounds. The method is illustrated with the obtention of alcohol **3Bh**, a homologue of **3Ba** and **3Be** with six methylene groups in the polymethylene chain (Scheme 1). Thus, the reaction between diethyl [(2*E*,4*E*)-5-phenylpenta-2,4-dienyl]phosphonate (**6**)[40] and the silylated aldehyde **7**[41] under Horner–Wadsworth–Emmons (HWE) conditions gave rise to the corresponding silylated compound with one more double bond and with a larger proportion of the (9*E*) isomer: 9:1 (9*E*)/(9*Z*), as determined by ^1H NMR spectroscopy. After deprotection with tetrabutylammonium fluoride in THF[42] the same isomeric mixture of the free

alcohol **3Bh** was produced from which *all*-(*E*)-**3Bh** could easily be isolated in the pure form by washing the crude solid with pentane. The stereochemistry of the product in the HWE reaction is sterically controlled,[43,44] yielding the (*E*) isomer as the major product.

Absorption and Fluorescence Properties

In this section, the spectroscopic properties of representative amphiphilic compounds bearing pentaene, tetraenyne, ω-phenyltetraene, and ω-phenyltrienyne conjugated groups in the 300–600 nm range are described. As expected, the absorption and emission spectra recorded in this wavelength range are characteristic of the polyunsaturated group.

The spectral properties of the *all*-(*E*)-pentaene carboxylic acid **5Af** (*t*-COPA), both in homogeneous solution and in lipid bilayers, have previously been reported in detail.[22] The main spectroscopic parameters of the compounds described herein containing the same conjugated *all*-(*E*)-pentaene system as *t*-COPA, **5Ab**–**e**, are very similar to those reported for **5Af**. Neither the type of terminal polar group nor the length of the saturated polymethylene spacer (5–8 methylene groups) affected these parameters to an appreciable extent (Table 1), indicating the lack of electronic interaction between distal groups in these molecules.

The *all*-(*E*)-tetraenyne group in *all*-(*E*)-**3Ab**–**e**,**g** absorbs in the 270–370 nm range in $CHCl_3$ solution, giving rise in the specific case of *all*-(*E*)-**3Ad** to a vibrational sequence band with maxima at 315, 329 and 347 nm (Figure 1, Table 1), and a relative intensity distribution very similar to that of the conjugated *all*-(*E*)-pentaene group, as in the carboxylic acid **5Af**. The emission spectrum of *all*-(*E*)-**3Ad** in the same solvent is a broad band with little structure (Figure 1), a maximum at around 470 nm and a large Stokes shift, indicating important differences between the electronic states involved in the absorption and emission processes. The fluorescence quantum yield is modest (0.075), similar to that of the conjugated pentaenoic acid **5Af**, and the emission does not change after several hours of irradiation in an aerated solution in a standard spectrofluorimeter.

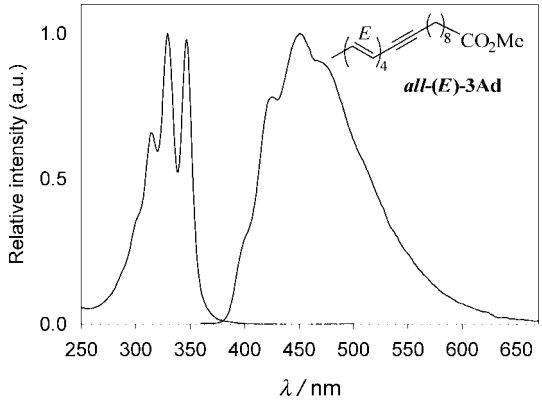


Figure 1. Absorption and corrected fluorescence spectra of the conjugated tetraenyne methyl ester *all*-(*E*)-**3Ad** in $CHCl_3$; [*all*-(*E*)-**3Ad**] = 2×10^{-5} M (absorption), 2×10^{-6} M (emission); λ_{exc} = 347 nm; 22 °C.

The absorption and fluorescence spectra of **5Bb**, which contains the *all*-(*E*)-ω-phenyltetraene fluorophore, is shown in Figure 2. In DMSO solution, the absorption maximum appears at 342 nm with an absorption coefficient value close to 10^5 $M^{-1}cm^{-1}$. In this solvent, the fluorescence emission, with a maximum at 467 nm, also shows a large Stokes shift. The absorption spectrum shifts to longer wavelengths in a non-polar microenvironment, such as in large unilamellar vesicles (LUV) of 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) (Figure 3), whereas the emission spectrum is almost insensitive to solvent polarity. The fluorescence quantum yield of **5Bb** in lipid vesicles is 0.24, significantly higher than that in EtOH solution (0.15). This effect of the ordered lipid environment on the emission quantum yield has already been observed in other polyene compounds[22,23] and is most likely due to the conformational changes that take place on photoexcitation. It is known that the electron reorganization of single and double bonds leads to large conformational variability of the polyene excited states.[45] This rotational isomerism facilitates relaxation channels that quench the fluorescence. In contrast, in a rigid environment, internal rotation modes are hindered, decreasing the radiationless deactivation.

Table 1. Absorption spectroscopic data of representative amphiphilic compounds containing the indicated *all*-(*E*) conjugated polyene.

Polyene	Polar end-group	Model compound	Solvent	λ_{max} [nm] (ε [10^4 $M^{-1}cm^{-1}$])
Pentaene	CH_2OAc	**4Ab**[a]	$CHCl_3$	319 (4.30), 335 (7.20), 353 (7.10)
	CH_2OAc	**5Ab**	$CHCl_3$	319 (4.30), 334 (6.80), 351 (6.50)
	CH_2OAc	**5Ab**	hexane	311 (4.60), 327 (7.00), 344 (6.90)
	CH_2OH	**5Ae**	EtOH	312 (6.20), 327 (10.20), 344 (10.50)
	CO_2H	**5Af**[b]	EtOH	312 (6.00), 327 (9.80), 344 (10.30)
Tetraenyne	CO_2Me	**3Ad**	$CHCl_3$	315 (4.20), 329 (6.40), 347 (6.40)
	CH_2OH	**3Ae**	$CHCl_3$	315 (4.20), 329 (6.40), 347 (6.40)
ω-Phenyltetraene	CH_2OH	**5Ba**	EtOH	325 (8.84), 340 (12.57), 360 (10.61)
	CH_2OH	**5Ba**	DMSO	333 (7.47), 349 (10.40), 368 (8.76)
ω-Phenyltrienyne	CH_2OH	**3Ba**	MeOH	321 (4.30), 335 (5.80), 353 (5.20)

[a] The (8*Z*,10*E*,12*E*,14*E*,16*E*) isomer. [b] *t*-COPA, data from ref.[22].

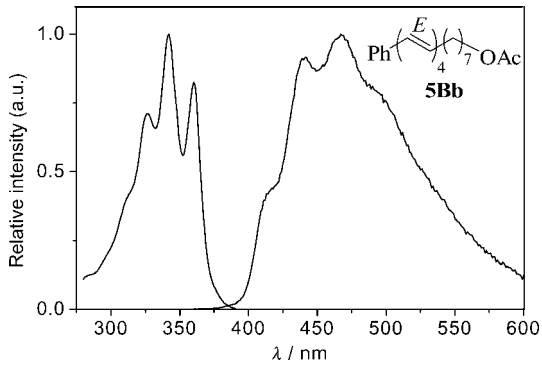


Figure 2. Absorption and corrected fluorescence spectra of *all*-(*E*)-phenyltetraene acetate **5Bb** in DMSO; [*all*-(*E*)-**5Bb**] = 2×10^{-5} M (absorption), 2×10^{-6} M (emission); λ_{exc} = 347 nm; 22 °C.

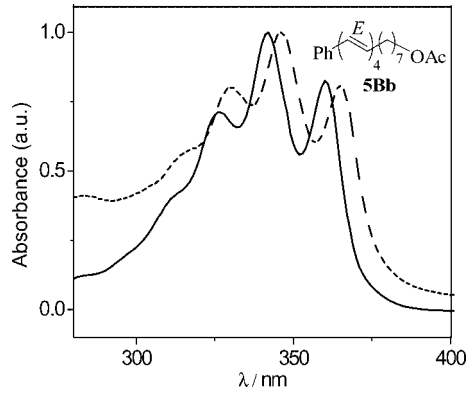


Figure 3. Absorption spectra of *all*-(*E*)-phenyltetraene acetate **5Bb** in EtOH (solid line) and in large unilamellar lipid vesicles of DMPC (dashed line) at 22 °C.

In symmetric, linear conjugated polyene compounds the first excited singlet state (S_1) is of type ^1A_g, whereas the S_2 state is ^1B_u.[46] In this case, the most intense absorption transition recorded experimentally corresponds to the $S_0 \rightarrow S_2$ excitation because $S_0 \rightarrow S_1$ is symmetry-forbidden. However, the emission takes place exclusively from the S_1 state. The absorption and emission of the *all*-(*E*) conjugated groups studied here (pentaene, tetraenyne, ω-phenyltetraene, and ω-phenyltrienyne) probably follow the same pattern, thus explaining the large Stokes shift and the different shapes of the absorption and emission spectra. These transition assignments are also consistent with the different sensitivities of the absorption and emission spectra to the medium polarity because the charge distribution in the S_1 and S_2 states is different.[22]

It is expected that the emitting polyenes obtained here would readily be incorporated into lipid bilayers because of their amphiphilic properties. To test this preferential solubility in a lipid environment, the phenyltetraene acetate **5Bb** was added to an aqueous suspension of lipid vesicles (LUVs) made up of DMPC and the fluorescence anisotropy, $<r>$, was recorded as a function of temperature (Figure 4). At low temperatures (ca. 10 °C), the anisotropy value (0.37) was close to the theoretical maximum (0.40), indicating the absence of depolarizing rotational motions of the emitting polyene within the bilayer. At higher temperatures, the fluorescence anisotropy decreased, with a sharp transition at around 23.5 °C. This value corresponds to the thermal transition between the gel and liquid-crystal phases of the DMPC lipid bilayer, as determined previously.[22,47] The changes in the anisotropy of **5Bb** reliably reflect the corresponding large changes in the fluidity of the lipid bilayer, indicating that the fluorescence emission originates from polyene molecules fully embedded in the bilayer.

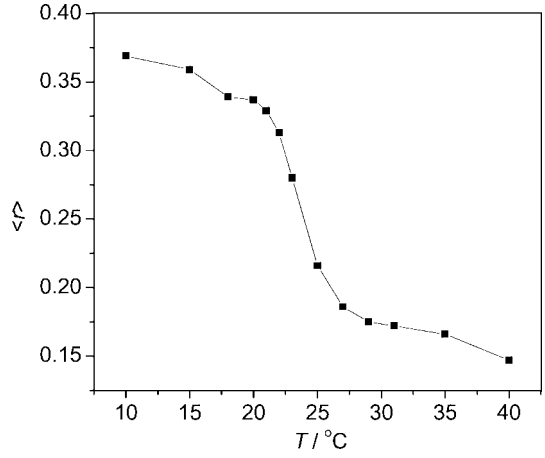


Figure 4. Fluorescence anisotropy, $<r>$, of the phenyltetraene acetate **5Bb** in lipid vesicles (LUV) of DMPC as a function of temperature. λ_{exc} = 348 nm; λ_{em} = 462 nm; [**5Bb**] ≈ 10^{-5} M; [DMPC] ≈ 10^{-3} M; [**5Bb**]/[DMPC] = 1:200.

Conclusions

A large variety of amphiphilic linear compounds incorporating the conjugated chromophore tetraenyne or ω-phenyltrienyne can be synthesized in good yields by the Sonogashira–Hagihara cross-coupling reaction. In the case of the ω-phenyltrienyne members of the series, much higher yields of the *all*-(*E*) isomers were obtained by reaction between the appropriate phosphonate and an α-acetylenic aldehyde under Horner–Wadsworth–Emmons conditions. Subsequent triple-bond partial reduction with activated zinc (Boland reduction) combined with (*Z*)→(*E*) isomerization with a trace of iodine allowed the obtention of the corresponding conjugated *all*-(*E*) compounds with pentaene or ω-phenyltetraene groups. The tetraenyne compounds prepared in this way exhibit an intense structured absorption spectrum in the 315–350 nm range and a wide fluorescent band centered at ca. 470 nm. These spectroscopic features are very similar to those of the conjugated pentaene group described previously.[22] Some of the novel chain-like chromophores obtained in this work, such as the *all*-(*E*)-phenyltetraene and *all*-(*E*)-phenyltrienyne conjugated systems, exhibit a convenient intense absorption (at ca. 360 nm) and a fluorescence yield up to 0.25 in the visible range (ca. 470 nm). These spectral properties allow these groups to be used as fluorescent labels with a variety of lipid compounds.

Experimental Section

General Remarks: Chemicals were obtained from commercial sources, and used without further purification. All solvents were freshly purified, distilled and deoxygenated thoroughly by argon-bubbling prior to use. All reactions were carried out under the total absence of oxygen in oven-dried Schlenk-type flasks. Analytical thin-layer chromatography was performed on precoated silica gel plates (Merck 60F254, 0.25 mm). Flash column chromatography was carried out on silica gel (Merck, 230–400 mesh). HPLC analysis was performed with an Agilent 1100 chromatograph equipped with a C18 reversed-phase column and a diode array detector using MeOH/H_2O mixtures as eluents. Melting points were measured with a Reichert–Kofler hot-stage microscope and are uncorrected. Yields refer to the isolated pure compound. Elemental analyses of all the compounds isolated herein were carried out with a Carlo Erba CHN-1108 microanalyser. However, results are provided only in those cases in which the experimental uncertainty is ±0.4%. The larger experimental uncertainty in some of the compounds described here was attributed to incomplete elimination of water/organic solvent molecules. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini-200 or an INOVA-300, -400 or -500 spectrometer. Chemical shifts are reported in parts per million (ppm) using as internal reference the proton signal of the trace of undeuteriated solvent or the carbon signal of the deuteriated solvent: δ = 7.26 and 77.0 ppm, respectively, in $CDCl_3$. Abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (complex multiplet). Carbon and proton assignments were based on COSY, DEPT, HSQC and HMQC experiments. (*E*)/(*Z*) ratios were calculated from the relative integrals of characteristic ^{1}H NMR signals. IR spectra (in cm^{-1}) were recorded with a Perkin–Elmer 681 or a FT-Spectrum One spectrometer. Low-resolution mass spectra were recorded by electron impact (70 eV) using a Hewlett–Packard 5973 spectrometer in direct injection mode or by electrospray ionization using a Hewlett–Packard 1100 apparatus. High-resolution mass spectra were also determined by electron impact (70 eV) in a Waters VG AutoSpec EI apparatus (Peak Match, perfluoroquerosene as internal standard). UV/Vis absorption spectra were registered on a Varian CARY-3E or a Perkin–Elmer Lambda-2 spectrophotometer. Steady-state corrected fluorescence intensity and anisotropy (<*r*>) measurements were recorded with an SLM 8000D spectrofluorimeter.[22] Fluorescence quantum yields (Φ_f) were determined by comparison of the corrected fluorescence spectra of diluted solutions of the samples with that of quinine sulfate in 0.05 M H_2SO_4 (Φ_f = 0.51), using the expression of Parker and Rees.[48] Large unilamellar vesicles (LUV) of 1,2-dimyristoyl-*sn*-*glycero*-3-phosphocholine (DMPC) containing the amphiphilic compound **5Bb** (molar ratio 200:1) were prepared by extrusion, as described elsewhere.[49,50]

Starting Compounds: 1-Bromonona-1,3,5,7-tetraene (**1A**) and 1-bromo-6-phenylhexa-1,3,5-triene (**1B**),[28] both 3:7 (1*E*)/(1*Z*) isomeric mixtures, were synthesized from *all*-(*E*)-hexa-2,4-dienal and (*E*)-cinnamaldehyde, respectively, in four steps: 1) Vinylogation (Horner–Wadsworth–Emmons reaction)[43,44,51] with the ylide from triethyl phosphonoacetate,[52] yielding the corresponding *all*-(*E*) esters with an additional (*E*) double bond; 2) reduction to the corresponding unstable primary alcohols with DIBAL-H;[53] 3) oxidation of the alcohols with MnO_2[54] to the corresponding unstable aldehydes *all*-(*E*)-octa-2,4,6-trienal[21] and *all*-(*E*)-5-phenylpenta-2,4-dienal;[28] 4) the aldehydes were treated as soon as possible with the ylide produced from (bromomethyl)triphenylphosphonium bromide (Wittig reaction). Compound **1A**, obtained in 72% overall yield (fourth step: 654 mg, 80%), must be used immediately because degradation was observed even if stored at –20 °C. Its stability increased considerably in the presence of trace amounts (ca. 1%) of 2,6-di-*tert*-butyl-4-methylphenol (BHT). Compound **1B** is stable for months if kept cool in the dark.

Data for *all*-(*E*)-**1A**: Isolated from the isomeric mixture by extracting the (1*Z*) isomer with diethyl ether. Yellow oil, m.p. 84 °C (dec). R_f = 0.86 (hexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 6.74 (dd, *J* = 13.5, 10.8 Hz, 1 H, 2-H), 6.55–6.00 (m, 6 H, 1-H, 3-H to 7-H), 5.78 (dq, *J* = 13.5, 6.9 Hz, 1 H, 8-H), 1.77 (dd, *J* = 6.9, 1.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 20 °C): δ = 137.7, 134.9, 134.0, 131.7, 131.3, 129.5, 128.7, 107.9, 18.5 ppm. FTIR (neat): $\tilde{\nu}_{max}$ = 3069, 3013, 2928, 1595, 1445, 1309, 1000, 941, 923, 751, 708, 688 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 200 (11) (nominal mass, $[M]^+$), 198 (11), 135 (26), 117 (17), 105 (12), 103 (17), 91 (77), 83 (42), 79 (36), 77 (41), 51 (29), 43 (100). Data for (1*Z*,3*E*,5*E*,7*E*)-**1A** [deduced from its 4:1 mixture with *all*-(*E*)-**1A**]: ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 6.65 (dd, *J* = 9.9, 7.2 Hz, 1 H, 2-H), 6.55–6.00 (m, 6 H, 1-H, 3-H to 7-H), 5.81 (dq, *J* = 14.1, 7.2 Hz, 1 H, 8-H), 1.80 (dd, *J* = 7.2, 1.5 Hz, 3 H, CH_3) ppm.

Hept-6-yn-1-ol (**2a**) was obtained by triple-bond zipper isomerization of hept-2-yn-1-ol, as described previously.[55]

Non-8-ynyl acetate (**2b**) was synthesized from non-2-yn-1-ol by zipper isomerization to non-8-yn-1-ol and subsequent acetic anhydride/triethylamine esterification (overall yield 5.37 g, 83%), as described previously.[56] Finally, **2b** was purified by column chromatography (silica gel, hexane/EtOAc, 4:1). Yellowish oil. R_f = 0.56 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 4.04 (t, *J* = 6.7 Hz, 2 H, 1-H), 2.17 (td, *J* = 6.9, 2.6 Hz, 2 H, 7-H), 2.03 (s, 3 H, CH_3), 1.93 (t, *J* = 2.6 Hz, 1 H, 9-H), 1.61 (m, 2 H, 2-H), 1.50 (m, 2 H, 6-H), 1.34 (m, 6 H, 3-H to 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 171.2 (CO), 84.6 (C-8), 68.1 (C-9), 64.5 (C-1), 28.7, 28.6, 28.5, 28.3 (C-2, C-4 to C-6), 25.7 (C-3), 21.0 (CH_3), 18.3 (C-7) ppm. FTIR (neat): $\tilde{\nu}_{max}$ = 3296, 2935, 2859, 2095, 1739, 1464, 1366, 1242, 1042 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 182 (1) $[M]^+$, 121 (2), 107 (18), 93 (29), 81 (100).

Methyl non-8-ynoate (**2c**)[57] was obtained from non-8-yn-1-ol by Jones oxidation[58] to the corresponding carboxylic acid and subsequent esterification with MeOH/$SOCl_2$; it was purified by column chromatography (silica gel, hexane/EtOAc, 4:1). Overall yield: 2.50 g, 80%. Yellow oil. R_f = 0.55 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 3.63 (s, 3 H, CH_3), 2.23 (t, *J* = 7.2 Hz, 2 H, 2-H), 2.10 (td, *J* = 6.6, 2.7 Hz, 2 H, 7-H), 1.90 (t, *J* = 2.7 Hz, 1 H, 9-H), 1.56 (q, *J* = 7.2 Hz, 2 H, 3-H), 1.46 (q, *J* = 6.6 Hz, 2 H, 6-H), 1.35–1.10 (m, 4 H, 4-H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 173.6 (CO), 84.0 (C-8), 68.0 (C-9), 51.0 (C-2), 35.6 (CH_3), 28.3, 28.0, 27.9 (C-4 to C-6), 24.5 (C-3), 18.0 (C-7) ppm. FTIR (neat): $\tilde{\nu}_{max}$ = 3296, 2938, 2860, 2117, 1739, 1436, 1254, 1201, 1173, 1094, 1016, 879 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 168 (1) $[M]^+$, 153 (3), 121 (5), 108 (31), 79 (79), 74 (100).

Methyl undec-10-ynoate (**2d**) was obtained as described previously.[24,59]

Diethyl [(2*E*,4*E*)-5-phenylpenta-2,4-dienyl]phosphonate (**6**) was synthesized as described previously.[40] 9-(*tert*-Butyldimethylsilyloxy)non-2-ynal (**7**) was obtained from oct-7-yn-1-ol by OH protection with *tert*-butyldimethylsilyl chloride and subsequent reaction of the protected compound with *n*-butyllithium and dimethylformamide as described previously.[41] Aldehyde **7** was purified by column chromatography (silica gel, hexane/EtOAc, 9:1). Overall yield: 2.02 g, 93%. Colorless oil. R_f = 0.50 (hexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.04 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.31–1.46 (m, 4 H, 6-H, 7-H), 1.56 (m, 4 H,

2-H, 5-H), 2.42 (td, J = 7.0, 0.6 Hz, 2 H, 4-H), 3.60 (t, J = 6.4 Hz, 2 H, 9-H), 9.18 (d, J = 0.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –4.9 ($Si(CH_3)_2$), 18.7 ($C(CH_3)_3$), 19.5 (C-4), 26.3 ($C(CH_3)_3$), 25.6, 29.0 (C-6, C-7), 28.9 (C-8), 33.1 (C-5), 63.6 (C-9), 82.1 (C-2), 99.7 (C-3), 177.6 (C-1) ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 2932, 2858, 2275, 2231, 2202, 1710, 1673, 1472, 1385, 1360, 1255, 1100, 1002, 836, 776 cm^{-1}. MS (ESI$^+$): m/z = 269.2 $[M + H]^+$. The starting alcohol oct-7-yn-1-ol was synthesized from oct-3-yn-1-ol by triple-bond zipper isomerization to the terminal position with Li/1,3-diaminopropane/tBuOK, as described previously.[41] Yield: 1.49 g, 85%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.31–1.46 (m, 4 H, 3-H, 4-H), 1.55 (m, 4 H, 2-H, 5-H), 1.94 (t, J = 2.7 Hz, 1 H, 8-H), 2.19 (td, J = 7.0, 2.7 Hz, 2 H, 6-H), 3.64 (t, J = 6.6 Hz, 2 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.7 (C-6), 25.6, 28.8 (C-3, C-4), 28.9 (C-5), 33.0 (C-2), 63.3 (C-1), 70.0 (C-8), 85.0 (C-7) ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3305, 2935, 2855, 2115, 1458 1429, 1055, 1031, 999, 901 cm^{-1}. MS (ESI$^+$): m/z = 127.1 $[M + H]^+$, 149.1 $[M + Na]^+$, 275.2 $[2M + Na]^+$.

Synthesis of Polyenyne Compounds 3. General Procedure: Diethylamine (0.7 mL, 6.9 mmol), $[Pd(PPh_3)_2Cl_2]$ (70 mg, 0.1 mmol), and CuI (66 mg, 0.34 mmol) were added (Schlenk flask, room temperature, stirring, argon) to a freshly-prepared solution of bromopolyene **1**, in the form of a 3:7 (1E)/(1Z) isomeric mixture (1.35 mmol), and an alkyne **2** (1.8 mmol) in deoxygenated THF (40 mL); the mixture was kept under these conditions for 3 h. After solvent elimination, the residue was redissolved in CH_2Cl_2, the solution was filtered through a short silica gel pad, and the isolated crude product was purified by column chromatography. Compounds **3** were in all cases formed as 3:7 (E)/(Z) isomeric mixtures. Pure samples of the corresponding *all*-(E) isomers were separated from the these mixtures by precipitation with pentane from a saturated solution in $CHCl_3$ or CH_2Cl_2.

Octadeca-10,12,14,16-tetraen-8-ynyl Acetate (3Ab): The 3:7 *all*-(E)/(10Z,12E,14E,16E) isomeric mixture was obtained by coupling between polyene **1A** [3:7 *all*-(E)/(1Z,3E,5E,7E) isomeric mixture] (270 mg, 1.35 mmol) and alkyne **2b** (328 mg, 1.8 mmol). It was purified by flash column chromatography (silica gel, hexane/EtOAc, 9:1). Yield: 356 mg, 90%. Data for *all*-(E)-**3Ab**: Yellowish waxy solid. R_f = 0.64 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.53 (dd, J = 15.3, 9.9 Hz, 1 H, 11-H), 6.4–6.0 (m, 5 H, 12-H to 16-H), 5.75 (dq, J = 15.3, 7.2 Hz, 1 H, 17-H), 5.56 (dt, J = 15.3, 2.4 Hz, 1 H, 10-H), 4.06 (t, J = 6.6 Hz, 2 H, 1-H), 2.34 (dt, J = 6.6, 2.4 Hz, 2 H, 7-H), 2.05 (s, 3 H, CH_3CO), 1.80 (dd, J = 6.9, 1.2 Hz, 3 H, 18-H), 1.64 (quint, J = 6.9 Hz, 2 H, 2-H), 1.60 (quint, J = 6.9 Hz, 2 H, 6-H), 1.50–1.30 (m, 6 H, 3-H to 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.0, 140.6, 134.5, 134.4, 131.8, 131.2, 130.8, 130.0, 111.1, 93.9, 80.4, 64.5, 28.71 (2 C), 28.69, 28.6, 28.5, 25.7, 20.9, 19.6, 18.3 ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3050, 2928, 2856, 2200, 1731, 1370, 1249, 1042, 1004, 762 cm^{-1}. MS (EI, 70 eV): m/z (%) = 300 (100) $[M]^+$, 285 (2), 199 (4), 183 (10), 169 (20), 155 (45), 143 (91), 129 (94), 115 (54), 105 (32). UV ($CHCl_3$): λ_{max} (logε) = 347 (4.8), 329 (4.8), 315 nm (4.6). $C_{20}H_{28}O_2$ (300.44): calcd. C 79.96, H 9.39; found C 79.67, H 9.65.

Methyl Octadecen-10,12,14,16-tetraen-8-ynoate (3Ac): The 3:7 *all*-(E)/(10Z,12E,14E,16E) isomeric mixture was obtained by coupling between polyene **1A** [3:7 *all*-(E)/(1Z,3E,5E,7E) isomeric mixture] (270 mg, 1.35 mmol) and alkyne **2c** (303 mg, 1.8 mmol). It was purified by flash column chromatography (silica gel, hexane/EtOAc, 9:1). Yield: 336 mg, 87%. Data for the *all*-(E)-**3Ac** isomer: Yellowish waxy solid. R_f = 0.72 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.53 (dd, J = 15.3, 9.9 Hz, 1 H, 11-H), 6.40–6.00 (m, 5 H, 12-H to 16-H), 5.75 (dq, J = 15.3, 7.2 Hz, 1 H, 17-H), 5.56 (dt, J = 15.3, 2.4 Hz, 1 H, 10-H), 3.66 (s, 3 H, CH_3O), 2.33 (dt, J = 6.9, 2.4 Hz, 2 H, 7-H), 2.31 (t, J = 7.2 Hz, 2 H, 2-H), 1.79 (dd, J = 6.9, 1.4 Hz, 3 H, 18-H), 1.70–1.30 (m, 8 H, 3-H to 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 174.0, 140.6, 134.4, 134.3, 131.7, 131.1, 130.8, 130.0, 111.0, 93.8, 80.4, 51.3, 33.8, 28.5, 28.40, 28.35, 24.7, 19.5 ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3040, 2935, 2870, 2270, 1734, 1640, 1460, 999 cm^{-1}. MS (EI, 70 eV): m/z (%) = 286 (60) $[M]^+$, 185 (4), 171 (9), 158 (40), 141 (56), 129(100), 115 (61), 105 (28), 91 (58), 77 (29). UV ($CHCl_3$): λ_{max} (logε) = 347 (4.8), 329 (4.8), 315 nm (4.6). $C_{19}H_{26}O_2$ (286.41): calcd. C 79.68, H 9.15; found C 79.01, H 8.93.

Methyl Icosa-12,14,16,18-tetraen-10-ynoate (3Ad): The 3:7 *all*-(E)/(12Z,14E,16E,18E) isomeric mixture was obtained by coupling between polyene **1A** [3:7 *all*-(E)/(1Z,3E,5E,7E) isomeric mixture] (270 mg, 1.35 mmol) and alkyne **2d** (353 mg, 1.8 mmol). It was purified by flash column chromatography (silica gel, hexane/EtOAc, 9:1). Yield: 360 mg, 85%. Data for the *all*-(E)-**3Ad** isomer: Yellow solid, m.p. 83–85 °C. R_f = 0.66 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.52 (dd, J = 15.3, 9.9 Hz, 1 H, 13-H), 6.32–6.05 (m, 5 H, 14-H to 18-H), 5.75 (dq, J = 15.3, 7.2 Hz, 1 H, 19-H), 5.56 (dt, J = 15.3, 2.1 Hz, 1 H, 12-H), 3.66 (s, 3 H, CH_3O), 2.33 (dt, J = 6.9, 2.1 Hz, 2 H, 9-H), 2.30 (t, J = 7.2 Hz, 2 H, 2-H), 1.79 (dd, J = 6.9, 1.2 Hz, 3 H, 20-H), 1.60 (quint, J = 7.2 Hz, 2 H, 3-H), 1.50 (quint, J = 7.2 Hz, 2 H, 8-H), 1.41–1.30 (m, 2 H, 4-H), 1.29 (m, 6 H, 5-H to 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 174.3, 140.7, 134.5, 134.4, 131.8, 131.3, 130.9, 130.1, 111.2, 94.2, 80.4, 51.4, 34.1, 29.1 (2 C), 28.9, 28.8, 28.7, 24.9, 19.7, 18.4 ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3017, 2929, 2855, 2204, 1739, 1637, 1439, 1322, 1247, 1209, 1172, 1002, 730 cm^{-1}. MS (EI, 70 eV): m/z (%) = 314 (16) $[M]^+$, 157 (25), 143 (55), 129 (56), 117 (49), 105 (46), 91 (72), 83 (70), 74 (30), 67 (31), 55 (86), 41 (100). HRMS (peak matching): calcd. for $C_{21}H_{30}O_2$ 314.2246; found 314.2248. UV ($CHCl_3$): λ_{max} (logε) = 347 (4.8), 329 (4.8), 315 nm (4.6). UV (MeOH/H_2O, 9:1): λ_{max} = 310, 324 (max.), 340 nm. $C_{21}H_{30}O_2$ (314.46): calcd. C 80.21, H 9.62; found C 79.97, H 9.38.

13-Phenyltrideca-8,10,12-trien-6-yn-1-ol (3Ba): The 3:7 *all*-(E)/(8Z,10E,12E) isomeric mixture was obtained by coupling between polyene **1B** [3:7 *all*-(E)/(1Z,3E,5E) isomeric mixture] (317 mg, 1.35 mmol) and alkyne **2a** (202 mg, 1.8 mmol). It was purified by column chromatography (silica gel, hexane/EtOAc, 4:1). Yield: 287 mg, 80%. Data for the *all*-(E)-**3Ba** isomer: Yellowish waxy solid. R_f = 0.51 (hexane/EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 7.38 (m, 2 H, H_o), 7.29 (m, 2 H, H_m), 7.22 (m, 1 H, H_p), 6.81 (dd, J = 15.6, 9.8 Hz, 1 H, 12-H), 6.60 (dd, J = 15.4, 10.0 Hz, 1 H, 9-H), 6.59 (d, J = 15.6 Hz, 1 H, 13-H), 6.39 (m, 2 H, 10-H, 11-H), 5.64 (dt, J = 15.4, 2.0 Hz, 1 H, 8-H), 3.67 (t, J = 5.5 Hz, 2 H, 1-H), 2.38 (td, J = 6.7, 2.0 Hz, 2 H, 5-H), 1.70–1.45 (m, 6 H, 2-H to 4-H) ppm.^{13}C NMR ($CDCl_3$, 75 MHz, 30 °C): δ = 140.6 (C-9), 137.2 (C_i), 134.3 (C-11), 132.5 (C-10), 133.7 (C-13), 128.7 (C-12), 128.6 (C_m), 127.7 (C_p), 126.4 (C_o), 111.9 (C-8), 94.2 (C-6), 80.5 (C-7), 62.8 (C-1), 32.3 (C-2), 28.5 (C-4), 25.0 (C-3), 19.7 (C-5) ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3435, 3014, 2927, 2855, 1632, 1049, 995, 746, 688 cm^{-1}. MS (EI, 70 eV): m/z (%) = 266 (84) $[M]^+$, 205 (16), 191 (50), 179 (100), 165 (67), 152 (26), 141 (23), 128 (27), 115 (58), 91 (68), 77 (15). HRMS (peak matching): calcd. for $C_{19}H_{22}O$ 266.1671; found 266.1667. UV (MeOH): λ_{max} (logε) = 321 (4.64), 335 (4.76), 353 nm (4.72).

15-Phenylpentadeca-10,12,14-trien-8-ynyl Acetate (3Bb): The 3:7 *all*-(E)/(10Z,12E,14E) isomeric mixture was obtained by coupling between polyene **1B** [3:7 *all*-(E)/(1Z,3E,5E) isomeric mixture]

(317 mg, 1.35 mmol) and alkyne **2b** (328 mg, 1.8 mmol). It was purified by flash column chromatography (silica gel, hexane/EtOAc, 4:1). Yield: 387 mg, 85%. Data for the *all*-(*E*)-**3Bb** isomer: Yellow solid. R_f = 0.63 (hexane/EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.40 (d, J = 7.5 Hz, 2 H, H_o), 7.31 (t, J = 7.5 Hz, 2 H, H_m), 7.22 (t, J = 7.5 Hz, 1 H, H_p), 6.80 (dd, J = 15.5, 9.8 Hz, 1 H, 14-H), 6.59 (dd, J = 15.4, 10.0 Hz, 1 H, 11-H), 6.58 (d, J = 15.5 Hz, 1 H, 15-H), 6.43 (dd, J = 14.7, 9.8 Hz, 1 H, 13-H), 6.35 (dd, J = 14.7, 10.0 Hz, 1 H, 12-H), 5.64 (dt, J = 15.4, 2.1 Hz, 1 H, 10-H), 4.06 (t, J = 6.9 Hz, 2 H, 1-H), 2.36 (td, J = 7.0, 2.1 Hz, 2 H, 7-H), 2.05 (s, 3 H, CH_3), 1.64 (quint, J = 6.9 Hz, 2 H, 2-H), 1.55 (m, 2 H, 6-H), 1.50–1.30 (m, 6 H, 3-H to 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.2 (CO), 140.5 (C-11), 137.2 (C_i), 134.3 (C-13), 133.7 (C-15), 132.5 (C-12), 128.7 (C-14), 128.6 (C_m), 127.7 (C_p), 126.4 (C_o), 112.0 (C-10), 94.5 (C-8), 80.4 (C-9), 64.6 (C-1), 28.8, 28.7, 28.6, 28.5 (C-2, C-4 to C-6), 25.8 (C-3), 21.0 (CH_3), 19.7 (C-7) ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3436, 3014, 2928, 2847, 2195, 1734, 1631, 1243, 1001, 926, 890, 746, 689 cm^{-1}. MS (ESI$^+$): m/z = 337.3 [M + H]$^+$. MS (EI, 70 eV): m/z (%) = 336 (86) [M]$^+$, 205 (17), 193 (53), 179 (100), 165 (52), 152 (17), 141 (23), 129 (30), 115 (53), 91 (70). HRMS (peak matching): calcd. for $C_{23}H_{28}O_2$ 336.2089; found 336.2080. UV ($CHCl_3$): λ_{max} = 334, 346 (max.), 358 nm. UV (MeOH/H_2O, 9:1): λ_{max} = 332, 336 (max.), 354 nm.

Methyl 15-Phenylpentadeca-10,12,14-trien-8-ynoate (3Bc): The 3:7 *all*-(*E*)/(10*Z*,12*E*,14*E*) isomeric mixture was obtained by coupling between polyene **1B** [3:7 *all*-(*E*)/(1*Z*,3*E*,5*E*) isomeric mixture] (317 mg, 1.35 mmol) and alkyne **2c** (303 mg, 1.8 mmol). It was purified by flash column chromatography (silica gel, hexane/EtOAc, 4:1). Yield: 371 mg, 80%. Data for the *all*-(*E*)-**3Bc** isomer: Brown oil. R_f = 0.59 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 7.40 (d, J = 7.5 Hz, 2 H, H_o), 7.31 (t, J = 7.5 Hz, 2 H, H_m), 7.22 (t, J = 7.5 Hz, 1 H, H_p), 6.80 (dd, J = 15.5, 9.8 Hz, 1 H, 14-H), 6.59 (dd, J = 15.4, 10.0 Hz, 1 H, 11-H), 6.58 (d, J = 15.5 Hz, 1 H, 15-H), 6.43 (dd, J = 14.7, 9.8 Hz, 1 H, 13-H), 6.35 (dd, J = 14.7, 10.0 Hz, 1 H, 12-H), 5.64 (dt, J = 15.4, 2.1 Hz, 1 H, 10-H), 3.67 (s, 3 H, CH_3), 2.35 (td, J = 6.9, 2.0 Hz, 2 H, 7-H), 2.31 (t, J = 7.5 Hz, 2 H, 2-H), 1.74–1.30 (m, 8 H, 3-H to 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 173.7 (CO), 140.5 (C-11), 137.2 (C_i), 134.3 (C-13), 133.7 (C-15), 132.5 (C-12), 128.7 (C-14), 128.6 (C_m), 127.7 (C_p), 126.4 (C_o), 112.0 (C-10), 94.2 (C-8), 80.4 (C-9), 51.1 (C-2), 33.7 (CH_3), 28.4, 28.3, 28.2 (C-4, C-5, C-6), 24.6 (C-3), 19.5 (C-7) ppm. MS (ESI$^+$): 323.5 [M + H]$^+$. UV ($CHCl_3$): λ_{max} = 334, 346 (max.), 358 nm.

Synthesis of Polyene Compounds 4 and 5. General Procedure: A slurry of zinc power (3 g, 46 mmol), freshly activated under Ar, with $Cu(OAc)_2{\cdot}H_2O$ (0.3 g, 1.51 mmol) and $AgNO_3$ (0.3 g, 1.75 mmol) (Boland procedure)[32,60] in MeOH/H_2O (1:1, 6 mL) was added to a solution of each polyenyne **3Ab**–**d**, **3Ba**–**c** [all 3:7 (*E*)/(*Z*) isomeric mixtures] (0.33 mmol) in MeOH (1 mL) at room temperature and with stirring. After 24 h, the reaction mixture was filtered through Celite with CH_2Cl_2 and the subsequent work up afforded the corresponding reduced products **4** as 3:7 (*Z*,*E*,..)/(*Z*,*Z*,..) mixtures of isomers with a (*Z*) double bond in the position of the original triple bond. A solution of each crude product in hexane (200 mL) was refluxed for 15 min under Ar with iodine-saturated hexane (60 μL) and the solution was filtered through a short silica gel pad while hot. After solvent evaporation, the corresponding *all*-(*E*) isomer **5** was purified by column chromatography and subsequent precipitation with pentane from a CH_2Cl_2 solution and/or by crystallization from acetone at –20 °C.

(8*Z*,10*E*,12*E*,14*E*,16*E*)-Octadeca-8,10,12,14,16-pentaenyl Acetate (4Ab): The (*Z*,*E*,*E*,*E*,*E*) isomer was obtained from **3Ab** [3:7 (10*E*,12*E*,14*E*,16*E*)/(10*Z*,12*E*,14*E*,16*E*) isomeric mixture] (100 mg, 0.33 mmol) after Zn reduction and precipitation with pentane. Pale yellow oil. Yield: 30 mg, 30%. R_f = 0.68 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 6.48 (m, 1 H, 11-H), 6.30–6.10 (m, 5 H, 10-H, 12-H to 16-H), 6.04 (m, 1 H, 9-H), 5.73 (dq, J = 15.3, 6.9 Hz, 1 H, 17-H), 5.44 (dt, J = 10.2, 7.8 Hz, 1 H, 8-H), 4.05 (t, J = 6.6 Hz, 2 H, 1-H), 2.2 (dt, J = 6.9, 6.6 Hz, 2 H, 7-H), 2.04 (s, 3 H, CH_3CO), 1.79 (dd, J = 6.6, 1.2 Hz, 3 H, 18-H), 1.62 (quint, J = 6.9 Hz, 2 H, 2-H), 1.45–1.25 (m, 8 H, 3-H to 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 171.1, 133.2, 133.1, 132.85, 132.79, 132.4, 132.0, 130.6, 130.2, 128.9, 128.0, 64.6, 29.6, 29.1 (×2), 28.6, 27.9, 25.9, 21.0, 18.4 ppm. UV ($CHCl_3$): λ_{max} (logε) = 353 (4.85), 335 (4.86), 319 nm (4.63).

Methyl 15-Phenylpentadeca-8,10,12,14-tetraenoate (4Bc): The 1:1 (8*Z*,10*E*,12*E*,14*E*)/(8*Z*,10*Z*,12*E*,14*E*) isomeric mixture was obtained by Zn reduction of **3Bc** [1:1 *all*-(*E*)/(10*Z*,12*E*,14*E*) isomeric mixture] (106 mg, 0.33 mmol); it was purified by column chromatography (silica gel, hexane/EtOAc, 4:1 as eluent). Yield: 86 mg, 80%. Yellowish waxy oil. R_f = 0.57 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 7.41 (d, J = 7.4 Hz, 1 H, H_o of (8*Z*,10*Z*)), 7.40 (d, J = 7.4 Hz, 1 H, H_o of (8*Z*,10*E*)), 7.32 (t, J = 7.4 Hz, 1 H, H_m of (8*Z*,10*Z*)), 7.31 (t, J = 7.3 Hz, 1 H, H_m of (8*Z*,10*Z*)), 7.22 (t, J = 7.4 Hz, 0.5 H, H_p of (8*Z*,10*Z*)), 7.21 (t, J = 7.4 Hz, 0.5 H, H_p of (8*Z*,10*E*)), 6.86 (m, 1 H, 14-H), 6.59 (d, J = 15.2 Hz, 0.5 H, 15-H of (8*Z*,10*Z*)), 6.54 (d, J = 15.3 Hz, 0.5 H, 15-H of (8*Z*,10*E*)), 6.56–6.24 (m, 4 H, 10-H to 13-H), 6.09 (m, 1 H, 9-H), 5.57 (dt, J = 10.7, 7.5 Hz, 0.5 H, 8-H of (8*Z*,10*Z*)), 5.47 (dt, J = 10.4, 7.5 Hz, 0.5 H, 8-H of (8*Z*,10*E*)), 3.67 (s, 3 H, CH_3), 2.31 (t, J = 7.5 Hz, 2 H, 2-H), 2.22 (q, J = 7.5 Hz, 2 H, 7-H), 1.64 (quint, J = 7.5 Hz, 2 H, 3-H), 1.48–1.25 (m, 6 H, 4-H to 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 174.1 (CO), 137.4, 137.3, 133.8, 133.7, 133.6, 133.0, 132.9, 132.7, 132.6, 132.2, 129.1, 129.0, 128.8, 128.6 (C-8 to C-13, C-15), 128.5 (C_m), 127.4, 127.3 (C_p), 126.3, 126.2 (C_o), 124.8, 123.7 (C-14), 51.3 (CH_3), 34.0 (C-2), 29.3, 29.2, 28.9, 28.8, 27.8, 27.4 (C-4 to C-7), 24.8 (C-3) ppm. MS (EI, 70 eV): m/z (%) = 324 (72) [M]$^+$, 195 (21), 181 (73), 167 (47), 155 (20), 141 (27), 128 (26), 117 (59), 104 (25), 91 (100).

***all*-(*E*)-Octadeca-8,10,12,14,16-pentaenyl Acetate (5Ab):** Acetate **5Ab** was obtained by reduction/isomerization of **3Ab** (100 mg, 0.33 mmol). It was purified by column chromatography (silica gel, hexane/EtOAc, 4:1). Yield: 87 mg, 87%. Yellow waxy solid. R_f = 0.68 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 6.30–6.10 (m, 8 H, 9-H to 16-H), 5.72 (dq, J = 15.3, 7.2 Hz, 1 H, 17-H), 5.7 (m, 1 H, 8-H), 4.05 (t, J = 6.9 Hz, 2 H, 1-H), 2.1 (dt, J = 7.2, 6.9 Hz, 2 H, 7-H), 2.04 (s, 3 H, CH_3CO), 1.78 (dd, J = 7.2, 1.2 Hz, 3 H, 18-H), 1.61 (quint, J = 6.9 Hz, 2 H, 2-H), 1.39 (quint, J = 6.9 Hz, 2 H, 6-H), 1.32 (m, 6 H, 3-H to 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 171.0, 135.4, 132.9, 132.8, 132.5, 132.4, 132.0, 130.9, 130.7, 130.66, 129.9, 64.6, 32.8, 29.2, 29.1, 29.0, 28.6, 25.8, 21.0, 18.4 ppm. FTIR (neat): $\tilde{\nu}_{max}$ = 3015, 2926, 2854, 1739, 1466, 1367, 1247, 1002 cm^{-1}. MS (EI, 70 eV): m/z (%) = 302 (34) [M]$^+$, 290 (4), 277 (16), 185 (3), 173 (4), 159 (12), 147 (9), 143 (22), 131 (20), 117 (36), 105 (38), 91 (63), 81 (56), 67 (41), 55 (59), 43 (100). UV ($CHCl_3$): λ_{max} (logε) = 351 (4.81), 334 (4.83), 319 nm (4.63). UV (hexane): λ_{max} (logε) = 344 (4.84), 327 (4.85), 311 nm (4.66).

Methyl *all*-(*E*)-Octadeca-8,10,12,14,16-pentaenoate (5Ac): Compound **5Ac** was obtained by reduction/isomerization of **3Ac** (95 mg, 0.33 mmol). It was purified by column chromatography (silica gel, hexane/EtOAc, 4:1). Yield: 78 mg, 82%. Yellowish waxy solid. R_f = 0.7 (hexane/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): δ = 6.30–6.00 (m, 8 H, 9-H to 16-H), 5.80–5.60 (m, 2 H, 8-H, 17-H),

3.65 (s, 3 H, CH_3O), 2.29 (t, J = 7.2 Hz, 2 H, 2-H), 2.1 (dt, J = 7.2, 6.9 Hz, 2 H, 7-H), 1.78 (dd, J = 6.9, 1.5 Hz, 3 H, 18-H), 1.60 (quint, J = 7.2 Hz, 2 H, 3-H), 1.45–1.20 (m, 6 H, 4-H to 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 174.1, 135.1, 132.78, 132.75, 132.4, 132.35, 132.0, 130.9, 130.7, 130.6, 129.7, 51.2, 33.9, 32.7, 29.0, 28.9, 28.7, 24.8, 18.2 ppm. FTIR (neat): $\tilde{\nu}_{max}$ = 2927, 2830, 1737, 1436, 1175, 1003 cm^{-1}. MS (EI, 70 eV): m/z (%) = 288 (1) $[M]^+$, 277 (5), 199 (3), 179 (3), 171 (13), 157 (6), 141 (22), 129 (21), 121 (17), 107 (26), 95 (59), 83 (55), 74 (38), 55 (100). UV ($CHCl_3$): λ_{max} ($\log\varepsilon$) = 351 (4.81), 334 (4.83), 319 nm (4.63). UV (hexane): λ_{max} ($\log\varepsilon$) = 344 (4.84), 327 (4.85), 311 nm (4.66).

Methyl *all*-(*E*)-Icosa-10,12,14,16,18-pentaenoate (5Ad): Compound **5Ad** was obtained by reduction/isomerization of **3Ad** (104 mg, 0.33 mmol). It was purified by column chromatography (silica gel, hexane/EtOAc, 4:1). Yield: 99 mg, 95%. Bright yellowish crystals, m.p. 113–115 °C. R_f = 0.70 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 6.30–6.00 (m, 8 H, 11-H to 18-H), 5.80–5.65 (m, 2 H, 10-H, 19-H), 3.66 (s, 3 H, CH_3O), 2.30 (t, J = 7.2 Hz, 2 H, 2-H), 2.09 (dd, J = 14.1, 6.9 Hz, 2 H, 2-H), 1.78 (d, J = 6.9 Hz, 3 H, 20-H), 1.62 (quint, J = 7.2 Hz, 2 H, 3-H), 1.38 (quint, J = 6.9 Hz, 2 H, 8-H), 1.29 (br. s, 8 H, 4-H to 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 135.6 (C-10), 132.9, 132.8, 132.4, 132.41, 132.0, 130.8, 130.7, 130.6, 129.9 (C-11 to C-19), 51.5 (CH_3O), 34.1 (C-2), 32.9 (C-9), 29.26 (×2), 29.17, 29.10 (×2) (C-4 to C-8), 24.9 (C-3), 18.4 (C-20) ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3011, 2921, 2848, 1737, 1471, 1436, 1243, 1207, 1176, 1003 cm^{-1}. MS (EI, 70 eV): m/z (%) = 316 (5) $[M]^+$, 277 (2), 199 (7), 169 (10), 157 (11), 145 (18), 131 (23), 125 (21), 117 (23), 105 (30), 91 (47), 55 (100). UV ($CHCl_3$): λ_{max} ($\log\varepsilon$) = 351 (4.81), 334 (4.83), 319 nm (4.63). UV (hexane): λ_{max} ($\log\varepsilon$) = 344 (4.84), 327 (4.85), 311 nm (4.66). $C_{21}H_{32}O_2$ (316.48): calcd. C 79.70, H 10.19; found C 79.60, H 10.40.

***all*-(*E*)-13-Phenyltrideca-6,8,10,12-tetraen-1-ol (5Ba):** Compound **5Ba** was obtained by reduction/isomerization of **3Ba** (88 mg, 0.33 mmol). It was purified by column chromatography (silica gel, hexane/EtOAc, 4:1). Yield: 80 mg, 90%. Yellowish waxy solid. R_f = 0.13 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 7.39 (d, J = 7.3 Hz, 2 H, H_o), 7.30 (m, 2 H, H_m), 7.20 (m, 1 H, H_p), 6.83 (ddd, J = 15.5, 6.7, 3.6 Hz, 1 H, 12-H), 6.53 (d, J = 15.5 Hz, 1 H, 13-H), 6.37 (dd, J = 6.7, 3.6 Hz, 2 H, 10-H, 11-H), 6.23 (m, 2 H, 8-H, 9-H), 6.11 (m, 1 H, 7-H), 5.74 (dt, J = 14.8, 7.0 Hz, 1 H, 6-H), 3.64 (t, J = 6.4 Hz, 2 H, 1-H), 2.14 (dt, J = 7.0, 6.8 Hz, 2 H, 5-H), 1.56 (m, 2 H, 2-H), 1.50–1.30 (m, 4 H, 3-H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 30 °C): δ = 137.5 (C_i), 135.7 (C-6), 133.7, 133.6 (C-9, C-10), 132.4 (C-11), 131.9 (C-13), 130.8, 130.7 (C-7, C-8), 129.3 (C-12), 128.6 (C_m), 127.3 (C_p), 126.2 (C_o), 62.9 (C-1), 32.8 (C-5), 32.6 (C-2), 29.0 (C-4), 25.3 (C-3) ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3349, 3021, 2930, 2857, 1673, 1448, 1072, 1001, 746, 690 cm^{-1}. MS (EI, 70 eV): m/z (%) = 268 (100) $[M]^+$, 195 (16), 181 (62), 167 (35), 155 (26), 141 (25), 128 (28), 117 (56), 104 (29), 91 (94), 77 (24). HRMS (peak matching): calcd. for $C_{19}H_{24}O$ 268.1827; found 268.1823. UV (EtOH): λ_{max} ($\log\varepsilon$) = 325 (4.95), 340 (5.10), 360 nm (5.03). UV (DMSO): λ_{max} ($\log\varepsilon$) = 333 (4.87), 349 (5.02), 368 nm (4.94).

***all*-(*E*)-15-Phenylpentadeca-8,10,12,14-tetraenyl Acetate (5Bb):** Compound **5Bb** was obtained by reduction/isomerization of **3Bb** (111 mg, 0.33 mmol). It was purified by column chromatography (silica gel, hexane/EtOAc, 4:1). Yield: 103 mg, 92%. Waxy oil. R_f = 0.60 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 7.38 (m, 2 H, H_o), 7.30 (m, 2 H, H_m), 7.20 (m, 1 H, H_p), 6.83 (ddd, J = 15.5, 6.6, 3.2 Hz, 1 H, 14-H), 6.53 (d, J = 15.5 Hz, 1 H, 15-H), 6.37 (dd, J = 6.6, 3.2 Hz, 2 H, 12-H, 13-H), 6.24 (m, 2 H, 10-H, 11-H), 6.11 (m, 1 H, 9-H), 5.74 (dt, J = 14.4, 7.0 Hz, 1 H, 8-H), 4.05 (t, J = 6.8 Hz, 2 H, 1-H), 2.12 (q, J = 7.0 Hz, 2 H, 7-H), 2.04 (s, 3 H, CH_3), 1.62 (q, J = 6.8 Hz, 2 H, 2-H), 1.33 (m, 8 H, 3-H to 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 171.2 (CO), 137.5 (C_i), 135.9 (C-8), 133.7, 133.6 (C-11, C-12), 132.3 (C-13), 131.9 (C-15), 130.7, 130.6 (C-9, C-10), 129.3 (C-14), 128.6 (C_m), 127.3 (C_p), 126.3 (C_o), 64.6 (C-1), 33.7 (C-7), 32.8, 29.2, 29.0, 28.8 (C-2, C-4, C-5, C-6), 25.8 (C-3), 21.0 (CH_3) ppm. UV ($CHCl_3$): λ_{max} = 332, 347 (max.), 365 nm.

Hydrolysis of Polyenyne Esters 3 and Polyene Esters 5. General Procedure: A solution of a polyenyne ester [**3Ab**,**d**, **3Bb**,**c**, pure *all*-(*E*) isomers] or of a polyene ester (**5Ab**,**c**, **5Bc**) (0.6 mmol) in EtOH (7 mL) with potassium hydroxide (0.17 g, 3 mmol) was stirred at room temperature for 4 h. The reaction mixture was then acidified with 5% aqueous HCl, poured into water, extracted with dichloromethane (3 × 20 mL), and the organic extract washed with water. Work up yielded a crude product that was purified by column chromatography (silica gel, hexane/EtOAc, 4:1). When the (*E*)/(*Z*) isomeric mixtures of polyenyne esters **3** were hydrolyzed instead, pure *all*-(*E*) isomers **3Ae**,**g** and **3Be**,**f** were obtained from the reaction mixtures by precipitation with pentane or hexane or, in the case of compounds **3A**, by isomerization with traces of iodine, as before. Compounds **3B** could not be isomerized by the latter treatment.

***all*-(*E*)-Octadeca-10,12,14,16-tetraen-8-yn-1-ol (3Ae):** Compound **3Ae** was obtained by hydrolysis of *all*-(*E*)-**3Ab** (180 mg, 0.6 mmol). Yield: 135 mg, 87%. Yellow waxy solid. R_f = 0.24 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 6.52 (dd, J = 15.3, 9.9 Hz, 1 H, 11-H), 6.32–6.05 (m, 5 H, 12-H to 16-H), 5.75 (dq, J = 15.3, 7.2 Hz, 1 H, 17-H), 5.56 (dt, J = 15.3, 2.4 Hz, 1 H, 10-H), 3.63 (t, J = 6.9 Hz, 2 H, 1-H), 2.33 (dt, J = 6.9, 2.4 Hz, 2 H, 7-H), 1.79 (dd, J = 6.9, 1.5 Hz, 3 H, 18-H), 1.58 (quint, J = 6.9 Hz, 2 H, 2-H), 1.55 (quint, J = 6.9 Hz, 2 H, 6-H), 1.5–1.3 (m, 6 H, 3-H to 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 140.6, 134.5, 134.4, 131.2, 130.8, 130.0, 111.0, 94.1, 80.4, 62.9, 32.7, 28.9, 28.8, 28.7, 25.6, 19.7, 18.4 ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3435, 2926, 2850, 1630, 1467, 1065, 998, 749 cm^{-1}. MS (EI, 70 eV): m/z (%) = 258 (30) $[M]^+$, 199 (3), 169 (7), 157 (34), 143 (98), 129 (100), 115 (57), 91 (59), 79 (29). UV ($CHCl_3$): λ_{max} ($\log\varepsilon$) = 347 (4.80), 329 (4.80), 315 nm (4.62). $C_{18}H_{26}O$ (258.40): calcd. C 83.67, H 10.14; found C 83.25, H 10.34.

***all*-(*E*)-Icosa-12,14,16,18-tetraen-10-ynoic Acid (3Ag):** Compound **3Ag** was obtained by hydrolysis of *all*-(*E*)-**3Ad** (188 mg, 0.6 mmol). Yield: 177 mg, 98%. Yellowish waxy solid. R_f = 0.65 (CH_2Cl_2/EtOH, 9:1). ^{1}H NMR (300 MHz, [D_6]acetone, 30 °C): δ = 10.6 (br. s, 1 H, CO_2H), 6.69 (dd, J = 15.3, 10.2 Hz, 1 H, 13-H), 6.60–6.20 (m, 5 H, 14-H to 18-H), 5.96 (dq, J = 15.3, 6.9 Hz, 1 H, 19-H), 5.79 (dt, J = 15.3, 2.4 Hz, 1 H, 12-H), 2.49 (dt, J = 6.9, 2.4 Hz, 2 H, 9-H), 2.43 (t, J = 7.2 Hz, 2 H, 2-H), 1.91 (d, J = 6.9 Hz, 3 H, 20-H), 1.74 (m, 2 H, 3-H), 1.70–1.45 (m, 10 H, 4-H to 8-H) ppm. ^{13}C NMR (75 MHz, [D_6]acetone): δ = 173.6, 138.5, 135.2, 134.9, 131.8, 130.1, 129.0, 108.9, 93.6, 80.2, 33.1, 28.72, 28.48, 28.45, 28.44, 24.6, 19.0, 17.4 ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3435, 3060, 2929, 2860, 2126, 1705, 1001 cm^{-1}. MS (EI, 70 eV): m/z (%) = 300 (45) $[M]^+$, 199 (3), 185 (5), 171 (9), 157 (39), 143 (100), 129 (90), 115 (46), 105 (27), 91 (52), 79 (26). UV (MeOH/H_2O, 9:1): λ_{max} = 310, 324, 340 nm (max.). $C_{18}H_{26}O$ (300.44): calcd. C 79.96, H 9.39; found C 79.60, H 9.99.

***all*-(*E*)-15-Phenylpentadeca-10,12,14-trien-8-yn-1-ol (3Be):** Compound **3Be** was obtained by hydrolysis of *all*-(*E*)-**3Bb** (202 mg, 0.6 mmol). Yield: 175 mg, 99%. Yellowish waxy solid. R_f = 0.24 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 7.39

(d, J = 7.3 Hz, 2 H, H_o), 7.31 (t, J = 7.3 Hz, 2 H, H_m), 7.22 (t, J = 7.5 Hz, 1 H, H_p), 6.81 (dd, J = 15.5, 9.8 Hz, 1 H, 14-H), 6.59 (dd, J = 15.4, 10.0 Hz, 1 H, 11-H), 6.58 (d, J = 15.5 Hz, 1 H, 15-H), 6.43 (dd, J = 14.7, 9.8 Hz, 1 H, 13-H), 6.35 (dd, J = 14.7, 10.0 Hz, 1 H, 12-H), 5.64 (dt, J = 15.4, 2.4 Hz, 1 H, 10-H), 3.65 (t, J = 6.5 Hz, 2 H, 1-H), 2.36 (td, J = 6.9, 2.4 Hz, 2 H, 7-H), 1.63–1.49 (m, 4 H, 2-H, 6-H), 1.37 (m, 6 H, 3-H to 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 140.5 (C-11), 137.2 (C_i), 134.2 (C-13), 133.6 (C-15), 132.5 (C-12), 128.7 (C-14), 128.6 (C_m), 127.7 (C_p), 126.4 (C_o), 112.0 (C-10), 94.5 (C-8), 80.4 (C-9), 63.0 (C-1), 32.7 (C-2), 28.9, 28.8, 28.7 (C-4, C-5, C-6), 25.6 (C-3), 19.7 (C-7) ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3435, 2956, 2928, 2847, 1631, 1447, 1261, 1096, 1020, 802, 746, 688 cm^{-1}. MS (EI, 70 eV): m/z (%) = 294 (42) $[M]^+$, 205 (7), 193 (45), 179 (100), 165 (57), 152 (22), 141 (26), 129 (30), 115 (68), 91 (90). HRMS (peak matching): calcd. for $C_{21}H_{26}O$ 294.1984; found 294.1979. UV ($CHCl_3$): λ_{max} = 334, 346 (max.), 358 nm. UV (MeOH/H_2O, 9:1): λ_{max} = 322, 336 (max.), 354 nm.

***all*-(*E*)-15-Phenylpentadeca-10,12,14-trien-8-ynoic Acid (3Bf):** Compound **3Bf** was obtained by hydrolysis of *all*-(*E*)-**3Bc** (194 mg, 0.6 mmol). Yield: 183 mg, 99%. Yellowish crystals. R_f = 0.41 (hexane/EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 7.39 (d, J = 7.3 Hz, 2 H, H_o), 7.31 (t, J = 7.3 Hz, 2 H, H_m), 7.22 (t, J = 7.5 Hz, 1 H, H_p), 6.81 (dd, J = 15.5, 9.8 Hz, 1 H, 14-H), 6.59 (dd, J = 15.4, 10.0 Hz, 1 H, 11-H), 6.58 (d, J = 15.5 Hz, 1 H, 15-H), 6.43 (dd, J = 14.7, 9.8 Hz, 1 H, 13-H), 6.35 (dd, J = 14.7, 10.0 Hz, 1 H, 12-H), 5.64 (dt, J = 15.4, 2.4 Hz, 1 H, 10-H), 2.37 (m, 4 H, 1-H, 7-H), 1.66 (q, J = 7.3 Hz, 2 H, 3-H), 1.56 (quint, J = 6.9 Hz, 2 H, 6-H), 1.40 (m, 4 H, 4-H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 179.5 (CO), 140.6 (C-11), 137.2 (C_i), 134.3 (C-13), 133.7 (C-15), 132.5 (C-12), 128.7 (C-14), 128.6 (C_m), 127.7 (C_p), 126.4 (C_o), 112.0 (C-10), 94.3 (C-8), 80.5 (C-9), 33.9 (C-2), 28.6, 28.5, 28.4 (C-4 to C-6), 24.5 (C-3), 19.7 (C-7) ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3434, 3014, 2934, 2855, 1711, 1631, 996, 757, 688 cm^{-1}. MS (EI, 70 eV): m/z (%) = 308 (27) $[M]^+$, 193 (43), 179 (100), 165 (48), 152 (18), 141 (19), 129 (22), 115 (57), 91 (69). HRMS (peak matching): calcd. for $C_{21}H_{24}O_2$ 308.1776; found 308.1770. UV ($CHCl_3$): λ_{max} = 334, 342 (max.), 359 nm. UV (MeOH/H_2O, 9:1): λ_{max} = 322, 336 (max.), 354 nm.

***all*-(*E*)-Octadeca-8,10,12,14,16-pentaen-1-ol (5Ae):** Compound **5Ae** was obtained by hydrolysis of acetate **5Ab** (181 mg, 0.6 mmol). Yield: 94 mg, 60%. Bright white crystals. R_f = 0.22 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, [D_6]DMSO, 70 °C): δ = 6.40–6.00 (m, 8 H, 9-H to 16-H), 5.73 (m, 2 H, 8-H, 17-H), 4.40 (br. s, 1 H, OH), 3.37 (t, J = 6.6 Hz, 2 H, 1-H), 2.07 (dt, J = 7.2, 6.9 Hz, 2 H, 7-H), 1.74 (d, J = 6.9 Hz, 3 H, 18-H), 1.40 (quint, J = 6.6 Hz, 2 H, 2-H), 1.36 (quint, J = 6.6 Hz, 2 H, 6-H), 1.27 (m, 6 H, 3-H to 5-H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 70 °C): δ = 134.7, 132.4, 132.3, 131.88, 131.86, 131.5, 130.3, 130.14, 130.11, 128.1, 60.3, 32.0, 31.7, 28.2 (×2), 28.1, 25.0, 17.4 ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3401, 2927, 2850, 1633, 1633, 1465, 1070, 1002 cm^{-1}. MS (EI): m/z (%) = 260 (100) $[M]^+$, 159 (22), 145 (90), 131 (66), 117 (81), 105 (63), 91 (65), 79 (63). UV (EtOH): λ_{max} (logε) = 344 (4.02), 327 (4.01), 312 (4.79), 298 nm (4.48). $C_{18}H_{28}O$ (260.41): calcd. C 83.02, H 10.38; found C 82.26, H 10.37.

***all*-(*E*)-Octadeca-8,10,12,14,16-pentaenoic Acid (5Af) (*t*-COPA):** Compound **5Af** was obtained by hydrolysis of ester **5Ac** (173 mg, 0.6 mmol). Yield: 156 mg, 95%. Ivory crystals; m.p. 139 °C. R_f = 0.33 (hexane/EtOAc, 4:1). This is a known compound; it was previously obtained through a Wittig olefination approach.[21]

***all*-(*E*)-15-Phenylpentadeca-8,10,12,14-tetraenoic Acid (5Bf):** Compound **5Bf** was obtained from **4Bc** (195 mg, 0.6 mmol) by iodine isomerization to **5Bc** and subsequent hydrolysis. Yield: 167 mg, 90%. Yellow amorphous solid. R_f = 0.13 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 7.39 (m, 2 H, H_o), 7.27 (m, 2 H, H_m), 7.17 (m, 1 H, H_p), 6.80 (ddd, J = 15.5, 6.6, 3.2 Hz, 1 H, 14-H), 6.49 (d, J = 15.5 Hz, 1 H, 15-H), 6.34 (dd, J = 6.6, 3.2 Hz, 2 H, 12-H, 13-H), 6.20 (m, 2 H, 10-H, 11-H), 6.07 (m, 1 H, 9-H), 5.70 (dt, J = 14.4, 7.0 Hz, 1 H, 8-H), 2.32 (t, J = 7.2 Hz, 2 H, 2-H), 2.08 (q, J = 7.0 Hz, 2 H, 7-H), 1.61 (q, J = 7.2 Hz, 2 H, 3-H), 1.42–1.24 (m, 6 H, 4-H to 6-H) ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3435, 3007, 2920, 2847, 1631, 1001, 742, 688 cm^{-1}. MS (ESI$^-$): m/z = 309 $[M - H]^-$. UV (MeOH): λ_{max} = 326, 339 (max.), 358 nm.

Synthesis of 14-Phenyltetradeca-9,11,13-trien-7-yn-1-ol (3Bh): A solution of potassium *tert*-butoxide (340 mg, 3.02 mmol) in dry THF (7 mL) was added with stirring and under argon to a solution of phosphonate **6** (846 mg, 3.02 mmol) and aldehyde **7** (675 mg, 2.51 mmol) in THF (20 mL) at 0 °C. After stirring the mixture at room temperature for 1 h, the solvent was evaporated in vacuo. Column chromatography of the crude product (silica gel, hexane/EtOAc 9:1) yielded a 9:1 (9*E*,11*E*,13*E*)/(9*Z*,11*E*,13*E*) isomeric mixture of the protected alcohol *tert*-butyldimethyl(14-phenyltetradeca-9,11,13-trien-7-ynyloxy)silane. Yield: 590 mg, 60%. Pale yellow amorphous solid. R_f = 0.70 (EtOAc/hexane, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.30 (d, J = 7.0 Hz, 2 H, H_o), 7.31 (t, J = 7.3 Hz, 2 H, H_m), 7.22 (t, J = 7.3 Hz, 1 H, H_p), 6.86 (m, 1 H, 13-H), 6.59 (d, J = 15.6 Hz, 1 H, 14-H), 6.59 (dd, J = 10.5, 15.5 Hz, 1 H, 10-H), 6.42 (m, 2 H, 11-H, 12-H), 5.64 (dt, J = 15.2, 2.1 Hz, 0.9 H, 9-H of isomer (9*E*)), 5.46 (dt, J = 10.2, 2.2 Hz, 0.1 H, 9-H isomer (9*Z*)), 3.61 (t, J = 6.5 Hz, 2 H, 1-H), 2.43 (td, J = 7.0, 2.2 Hz, 0.2 H, 6-H of isomer (9*Z*)), 2.35 (td, J = 7.0, 2.1 Hz, 1.8 H, 6-H of isomer (9*E*)), 1.54 (m, 4 H, 2-H, 5-H), 1.46–1.31 (m, 4 H, 3-H, 4-H), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.05 (s, 6 H, $Si(CH_3)_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 137.6 (C_i), 134.6, 134.0 (C-10, C-14), 140.9, 133.0, 129.2 (C-11 to C-13), 129.1 (C_m), 128.1 (C_p), 126.8 (C_o), 112.5 (C-9), 94.9 (C-7), 80.8 (C-8), 63.6 (C-1), 33.1, 29.1, 28.9, 25.8 (C-2 to C-5), 26.4 ($SiC(CH_3)_3$), 20.1 (C-6), 18.7 ($SiC(CH_3)_3$), –4.9 ($Si(CH_3)_2$) ppm. MS (EI, 70 eV): m/z (%) = 394 (15) $[M]^+$, 337 (4), 263 (7), 193 (22), 178 (30), 165 (22), 117 (51).

The resulting 9:1 mixture of isomers was deprotected to give the corresponding isomeric alcohols as follows: A solution of tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 1 mL, 0.95 mmol) was added dropwise to the solution of the protected alcohol (9:1 (9*E*)/(9*Z*) mixture) (260 mg, 0.63 mmol) in THF (10 mL) at room temperature and the mixture was stirred for 20 min. Then more TBAF solution was added (0.5 mL, 0.48 mmol) and the reaction mixture was stirred for another 20 min. Work up yielded a crude product that was purified by column chromatography with hexane/EtOAc (7:3) as eluent. Yield: 180 mg, 98%. Pure *all*-(*E*)-**3Bh** was separated by washing the solid (9*E*)/(9*Z*) mixture with *n*-pentane. Data for *all*-(*E*)-**3Bh**: M.p. 98–100 °C. R_f = 0.65 (hexane/EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.40 (d, J = 7.3 Hz, 2 H, H_o), 7.32 (t, J = 7.3 Hz, 2 H, H_m), 7.22 (t, J = 7.3 Hz, 1 H, H_p), 6.86 (dd, J = 9.5, 15.3 Hz, 1 H, 13-H), 6.59 (d, J = 15.7 Hz, 1 H, 14-H), 6.59 (dd, J = 9.2, 15.2 Hz, 1 H, 10-H), 6.41 (m, 2 H, 11-H, 12-H), 5.64 (d, J = 15.3 Hz, 1 H, 9-H), 3.66 (t, J = 6.0 Hz, 2 H, 1-H), 2.37 (t, J = 5.9 Hz, 2 H, 6-H), 1.58 (m, 4 H, 2-H, 5-H), 1.48–1.31 (m, 4 H, 3-H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 137.6 (C_i), 129.1 (C-13), 141.0, 134.7, 134.1, 132.9 (C-10, C-11, C-12, C-14), 129.1 (C_m), 128.1 (C_p), 126.8 (C_o), 112.4 (C-9), 94.9 (C-7), 80.8 (C-8), 63.4 (C-1), 33.1, 29.1, 29.1, 25.7 (C-2 to C-5), 20.1 (C-6) ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 3435, 2927, 2855, 1631, 1447, 1071, 995, 746, 688 cm^{-1}. MS (EI, 70 eV): m/z (%) = 280 (43) $[M]^+$, 193 (45), 179 (100), 165 (58), 152 (21), 141 (25), 128 (29), 115

(63), 91 (80). HPLC (C_{18} reversed-phase column, MeOH/H_2O, 9:1, 1.8 mL min^{-1}, λ_{anal} 356, 345 and 250 nm): R_t = 3.06 min (100% purity).

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