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Total Synthesis of Neuroprotectin D1 Analogues Derived from Omega-6 Docosapentaenoic Acid (DPA) and Adrenic Acid (AdA) from a Common Pivotal, Late-Stage Intermediate

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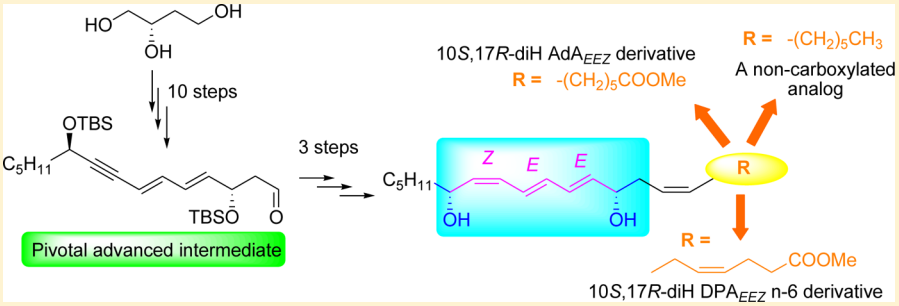
Supporting Information



ABSTRACT: The first total synthesis of three omega-6 dihydroxylated (*E*,*E*,*Z*)-docosatrienes has been successfully achieved employing a flexible strategy. The key features encompass a Boland semireduction, to create the (*E*,*E*,*Z*)-triene via an (*E*,*E*)-ynediene, and a selective deprotection of a tris(*tert*-butyldimethylsilyl) ether. The main advantage of the present strategy over previous syntheses of noncyclic dihydroxylated PUFA metabolites derived from docosahexaenoic and arachidonic acids comes from the introduction of the polar head chain at the very end of the synthesis from an advanced, pivotal aldehyde. In terms of divergency this enables late-stage modification of the head group.

INTRODUCTION

Neuroprotectin D1 (NPD1, also termed PD1) is an endogenous dihydroxylated (*E*,*E*,*Z*)-docosatriene[1,2] that protects the brain and retina against cell injury induced oxidative stress.[3] In addition to its neuroprotective activity,[4−6] this docosahexaenoic acid (DHA) derived mediator dampens inflammation, promoting its resolution process, and restores homeostasis.[7,8] Its myriad of biological properties is currently sparking a renewed interest in noncyclic omega-3 lipid mediators.[9−11]

NPD1 is biosynthesized through a 15-lipoxygenase catalyzed oxygenation of one of the *cis*,*cis*-1,4-pentadiene moieties of DHA followed by an enzymatic epoxidation and hydrolysis leading to a rearrangement of the polyenic structure (Scheme 1).[1,2,12]

Three double bonds of DHA (out of six) are directly involved in the formation of NPD1. Like DHA, the osbond acid (omega-6 docosapentaenoic acid, n-6 DPA, C22:5 n-6) and adrenic acid (docosatetraenoic acid, AdA, C22:4 n-6) are polyunsaturated fatty acids with a C22 chain length and they also contain several *cis*,*cis*-1,4-pentadiene moieties located in the same position as in DHA, relative to the terminal carboxylic acid.

Thus, n-6 DPA and AdA are surmised to be competitive substrates for the enzymes involved in NPD1 biosynthesis. We believe that, like DHA, both n-6 DPA and AdA are also susceptible to lipoxygenase-mediated metabolism. Thus, on the basis of the mechanisms suggested for the biosynthesis[1,2] of NPD1, we believe that AdA and n-6 DPA are converted in vivo into their corresponding NPD1 and aspirin-triggered analogues (Scheme 1).

Little has been reported on these two PUFAs and their metabolization. However, AdA is the third most abundant fatty acid in the brain[13−15] (mainly white matter), and it is particularly enriched in myelin[16−18] but is also found in the adrenal gland,[19] testis,[14] kidney medulla,[14] and breast milk.[20]

Despite its relative abundance and similarity to arachidonic acid, little is known about its role. It is suggested to play an important role in cardiovascular diseases[21,22] and in myelination in neural tissues,[16,23] and aberrant AdA levels are implicated in the pathogenesis of Alzheimer's disease,[13,24] depression,[25] prostatic carcinogenesis,[26] Zellweger syndrome,[27] and liver disease.[28]

In contrast, the role played by AdA metabolites has rarely been investigated. AdA was recently shown to be metabolized[19,21] to a myriad of bioactive docosanoids, including[19] dihomo-10,17-DiHETE via lipoxygenases. However, the precise stereochemical structure of these lipoxygenase-mediated metabolites has not been established.

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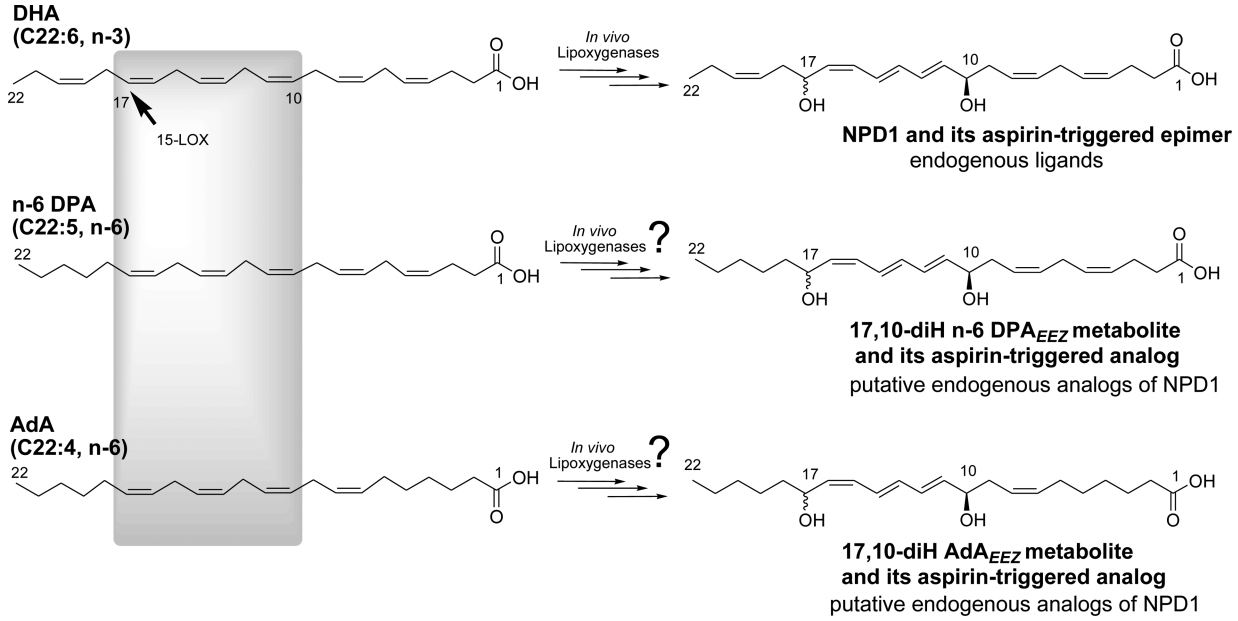
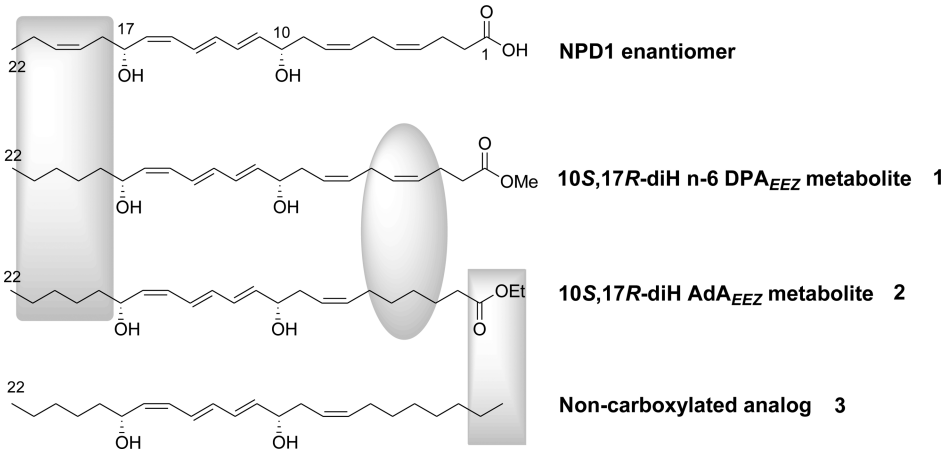
Scheme 1. Potential Metabolization of AdA and n-6 DPA Based on the Endogenous Enzymatic Synthesis of NPD1 from DHA



Scheme 2. Three Novel Docosatriene Targets (1−3) To Study Structural Influences on Inflammation Dampening Together with Their Putative Presence in Inflamed Tissues



The literature on n-6 DPA is limited. However the available data suggest it (or at least some of its lipoxygenation-derived metabolites) has beneficial health effects.[29,30] The n-6 DPA content is rather low in most mammalian tissues, except testes tissue.[31] However, its abnormal level may reflect pathology. A n-6 DPA deficiency was observed in schizophrenia and depression.[25,32] In contrast, a deficiency of n-3 fatty acids leads to a depletion of DHA and a compensatory rise in n-6 DPA level in most tissues, especially in the brain and retina.[33−35] The osbond/DHA ratio is thus a marker of dietary DHA sufficiency.[34] In addition, vitamin A deficiency enhances both DHA and n-6 DPA in the liver of rats fed with an α-linolenic acid-adequate diet.[36]

In 2009, Dangi et al. investigated the in vitro reaction of n-6 DPA with soybean 15-lipoxygenase.[37] The main products formed were (17*S*)-hydroxydocosapentaenoic acid and a dihydroxylated docosatriene which proved to have an *E,Z,E*-conjugated triene flanked by two hydroxyl groups at C10 and C17 together with a *Z,Z*-bis-allylic system as observed in PDX,[38] a stereoisomer of NPD1. Recent findings indicate that this 10,17-diHDPA$_{EZE}$ n-6 metabolite is a potent anti-inflammatory agent in vitro and in vivo, reducing leucocyte migration and edema in two animal models. Notably, it increases phagocytosis activity.[39,40]

Hence, since n-6 DPA is known to be metabolized by lipoxygenases, we speculated that n-6 DPA might also act as a precursor for production of DPA-related neuroprotectin NPD1.

More research remains to be done to further investigate the existence and biological effects of the lipoxygenase-mediated AdA and n-6 DPA metabolites.

With these molecules in hand, in addition proving their existence in vivo, we envisaged that they would provide evidence for the influence of the lateral chains (length, number of double bonds, functionalities) on the potent beneficial effects reported to date for NPD1 and its aspirin-triggered isomer (AT-NPD1), e.g. the anti-inflammatory and resolving effects, and also healing and neuroprotection.

In order to be able to discuss the influence of the carboxylic function, we also plan to prepare a noncarboxylated analogue.

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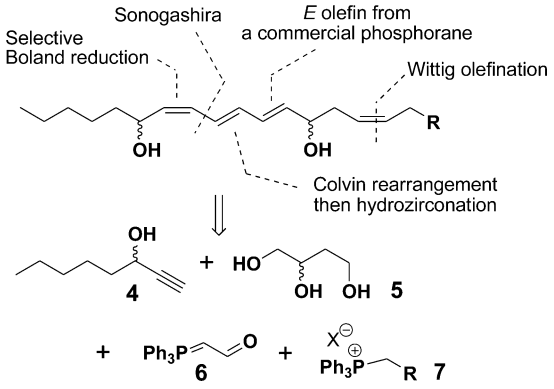
In this paper, we report an efficient entry into the omega-6 family of dihydroxylated metabolites based on our recently introduced general strategy toward the omega-3 series of protectins.[41]

According to this strategy, the head chain is introduced at a very late stage of the total synthesis by a stereoselective Wittig olefination reaction. Thus, this strategy provides convenient flexibility, enabling the preparation of several PUFA metabolites and their non-natural analogues possessing a similar tail chain. The versatility of the strategy will be exemplified with the total synthesis of the three novel targets **1**−**3** (Scheme 2). It is also noteworthy that additional diastereomers may be obtained by using the same route and by simply purchasing the suitable chiral pool derived building blocks.

RESULTS AND DISCUSSION

The retrosynthetic analysis, showing the main chemical steps and the four required starting reagents, is outlined in Scheme 3.

Scheme 3. Retrosynthetic Analysis for the Three Targets 1−3

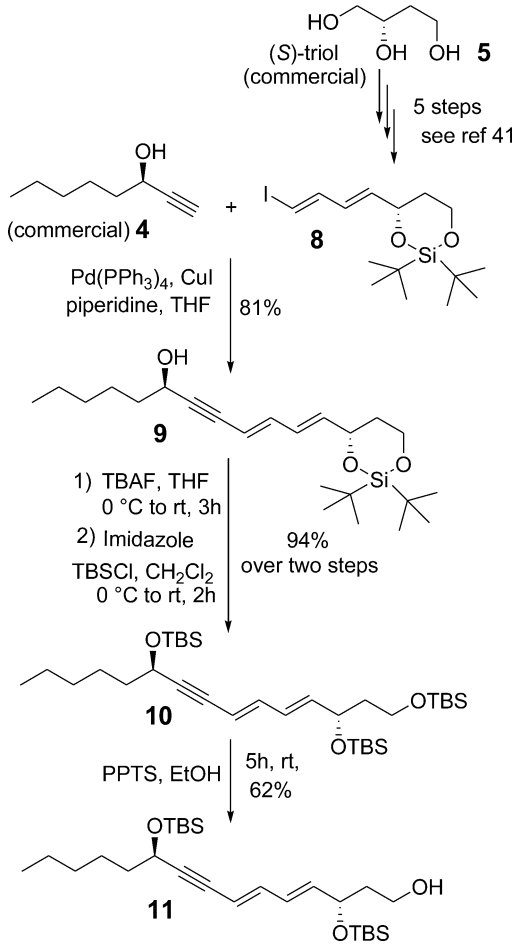


The omega-6 tail will be introduced by a Sonogashira cross-coupling reaction between the commercially available and optically active 1-octyne-3-ol **4**. The second chiral center is derived from the commercially available 1,2,4-butanetriol **5**. The conjugated (*E*,*E*)-diene is retrosynthetically dissected to an (*E*)-enyne which, in turn, results from a Colvin rearrangement[42] of an *α*,*β*-unsaturated aldehyde. The latter is derived from a two-carbon homologation using the phosphorane **6**.

The synthesis began by the conversion of the commercially available (*S*)-1,2,4-butanetriol (**5**)[43] to the (*S*)-(*E*,*E*)-iododiene **8** in 5 steps (overall 35.7% yield) as recently reported.[41]

Subsequently, as depicted in Scheme 4, a Sonogashira coupling[44,45] of the (*S*)-(*E*,*E*)-iodo diene **8** with a stoichiometric amount of the commercially available terminal alkyne (*R*)-**4** in the presence of tetrakis(triphenylphosphine)-palladium, copper iodide, and piperidine cleanly produced the expected enyne **9** in 81% yield. The ^{1}H NMR spectrum shows two large constants for the olefinic protons ($J_{6,7}$ = 15.5 Hz and $J_{4,5}$ = 15.0 Hz), in good agreement with the (*E*,*E*)-diene. Depending on the concentration and moisture, the proton H10 (at 4.47 ppm) resonates as a triplet (J = 6.0 Hz) or a quartet (J = 6.0 Hz), showing evidence of the scalar coupling with the free hydroxyl group. Both signals are broadened by a long distance coupling with proton H7 through the triple bond (J = 1.2 Hz). A correlation H7−H10 clearly appears in the COSY ^{1}H−^{1}H spectrum (see the Supporting Information).

Scheme 4. Synthesis of Enyne 11



After a deprotection of the 1,3-diol **9** followed by TBS protection of the three hydroxyl groups, the challenging selective deprotection of the primary alcohol in the presence of both a secondary propargylic and allylic OTBS groups (compound **10**) was carried out. In our case, the difference in the rate of desilylation was less than might have been expected on the basis of literature precedent.[46,47] Partial deprotection of the secondary TBS groups was observed in most cases and could not be completely avoided, whatever the conditions tried (Table 1). The deprotection reaction was poorly selective using camphorsulfonic acid (CSA, entry 1) or HF-pyridine (entry 3). The reactivity was poor at 0 °C with TBAF (entry 4) or a catalytic amount of PPTS (entry 5) but highly dependent on the amount of PPTS (entries 5−10). Eventually, until now the best conditions required 1 equiv of PPTS in aqueous ethanol for 5 h (entry 9). The yield of the free primary alcohol **11** did not exceed 62%, but the overdeprotected mixture could be collected and reprotected to the starting trisilyl ether **10**.

In most enyne structures, the proton H3 (assignment assisted by 2D-NMR spectra) resonates with a misleading simplicity, showing a quartet multiplicity instead of its expected theoretical doublet of triplets due to similar values for its coupling constants ($J_{3,2}$ = $J_{3,4}$ = ca. 5.6−6.1 Hz).

It should be mentioned that the primary alcohol **11** was unfortunately found to be unstable on storage in the freezer at −20 °C due to silyl migration. Thus, alcohol **11** was subsequently directly converted to the corresponding aldehyde **12** (Scheme 5), which serves as a common pivotal intermediate

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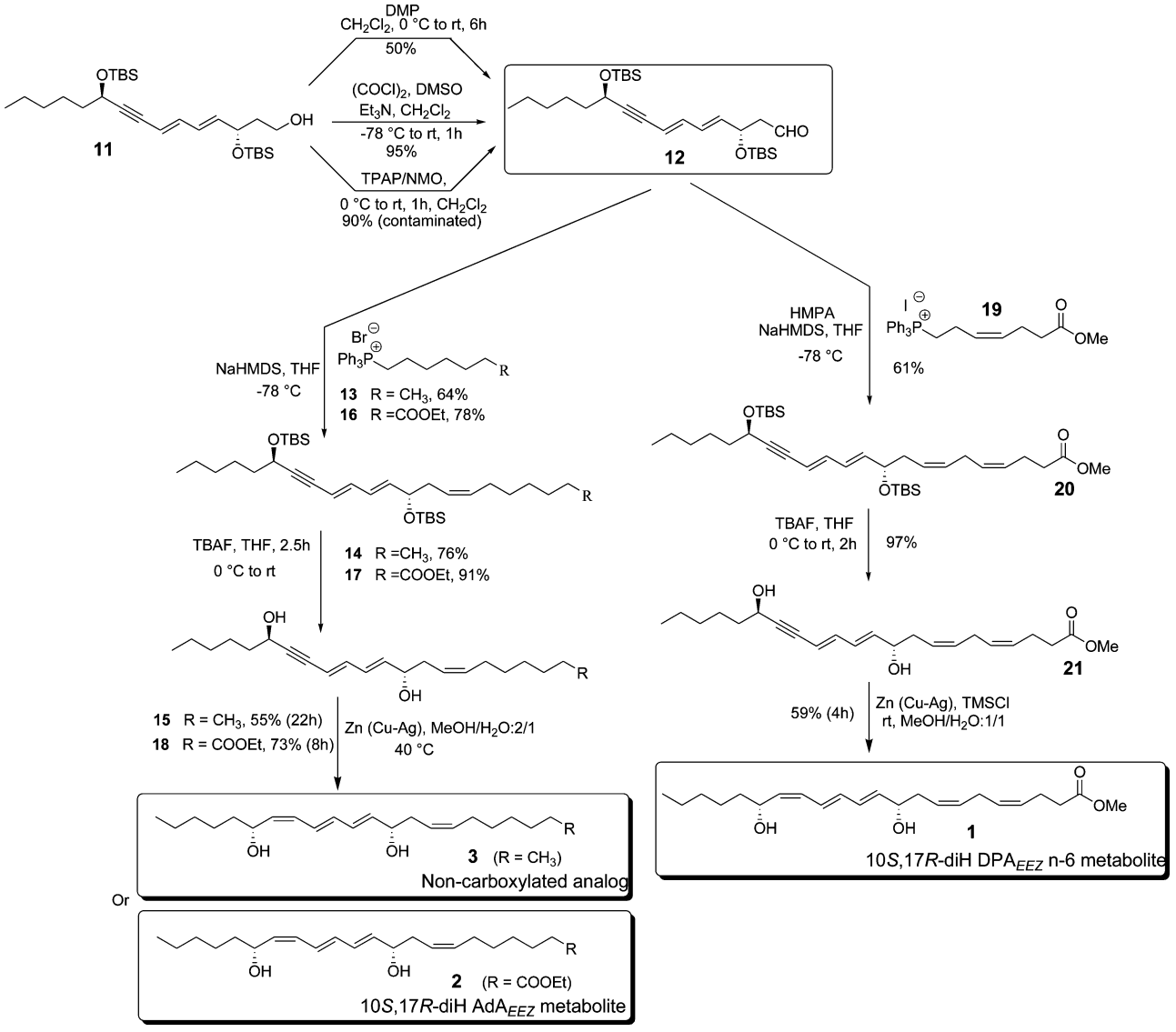
Table 1. Optimization of the Reaction Conditions for Selective Deprotection of Trisilyl Ether 10 to the Free Primary Alcohol 11

entry	reagent (amt, equiv)	solvent	*t*, °C	time	alcohol **11** yield,[c] %	diol yield, %	SM, %[a]
1	CSA (1.0)	$MeOH/CH_2Cl_2$ 1/1	0	15 min	23	43	0
2	CSA (0.3)	$MeOH/CH_2Cl_2$ 1/1	0	20 min	42	10	10
3	HF-Py (1.0)	THF	0 to room temp	7 h	29	50	0
4	TBAF (1.0)	THF	0	1 h	37	20	34
5	PPTS (0.5)	anhydrous EtOH	0	5 h	29	10	56
6	PPTS (0.1)	EtOH (96%)[b]	room temp	3 h	36	15	40
7	PPTS (0.1)	EtOH (96%)[b]	room temp	6 h	45	19	15
8	PPTS (1.0)	EtOH (96%)[b]	room temp	6 h	50	25	3
9	**PPTS (1.0)**	**EtOH (96%)[b]**	**room temp**	**5 h**	**62**	**30[d]**	**6**
10	PPTS (1.0)	EtOH (96%)[b]	room temp	4 h	50	20[d]	20

[a]SM = starting material. [b]All of the reactions with PPTS were carried out at 0.05 M concentration. [c]Isolated yields. [d]A mixture of diols and triol was obtained which can be reprotected to give trisilyl ether **10**.

Scheme 5. Synthesis of the Three Targeted Docosatrienes 1−3 from the Pivotal Late Aldehyde Precursor 12



to the three targets **1**−**3**. Several oxidation conditions were surveyed. The Dess-Martin procedure[48] gave disappointing results, providing the expected pure aldehyde **12** in only 50% yield, albeit with full conversion. Under the Ley oxidation conditions[49] the aldehyde **12** suffered from overoxidation and the carboxylic acid byproduct could not be fully removed, leading to a contaminated aldehyde sample. Eventually, the optimum yields and purities of aldehyde **12** were achieved using Swern oxidation[50] conditions.

The feasibility of the strategy was first validated using the commercially available heptyltriphenylphosphonium bromide (**13**), leading to the polyunsaturated compound **14**. The Wittig

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reaction was *Z* selective. No unwanted *E* isomer was observed. The main difficulty encountered in this reaction stems from the high instability of the *β*-TBSO-protected hydroxyl−aldehyde **12** under the basic reaction conditions. Aldehyde **12** tends to suffer from TBS elimination, and the yields were sensitive to the conditions employed. Although they were not fully optimized, gratifyingly yields were improved by maintaining a high phosphonium to base ratio. In our hands, no reaction occurred using the Verkade base[51,52] $P[N(i\text{-}Bu)CH_2CH_2]_3N$.

Subsequently, TBAF-mediated removal of the TBS group, followed by chemoselective semireduction of the triple bond using a freshly prepared Zn(Cu/Ag) couple, using the Boland conditions,[53,54] led to the desired noncarboxylated target **3**. Assignment of the stereochemistry of the double bonds has been established by NMR spectroscopic techniques. The presence of the (*E*,*E*)-diene unit is confirmed by the large coupling constants $J_{11,12}$ = 14.8 Hz and $J_{13,14}$ = 14.4 Hz, while the coupling constant $J_{15,16}$ = 10.9 Hz is in good agreement with the formation of a (*Z*)-olefin in conjugated (*E*,*E*,*Z*)-trienes.[41,55,56]

On the basis of the sequence described above, its application to the synthesis of the AdA and the n-6 DPA derived targets proceeded smoothly. Wittig olefination using (7-ethoxy-7-oxoheptyl)triphenylphosphonium bromide (**16**; prepared[57] in one step from the corresponding bromide), followed by fluoride-mediated silyl deprotection, afforded the expected diol **18** (91%), which was successfully converted to the desired ethyl ester dihydroxylated AdA metabolite **2**.

According to previously described NMR spectroscopic analyses of conjugated (*E*,*E*,*Z*)-trienes,[41,55,56] the coupling constant of the newly created olefinic protons ($J_{15,16}$ = 11.0 Hz) was consistent with the formation of a (*Z*)-olefin.

Thus, the first total synthesis of the 10*S*,17*R*-diH AdA_{EEZ} target **2** was completed in a total of 13 steps and 8.3% overall yield from the commercially available (*S*)-1,2,4-butanetriol **5**.

Similarly, Wittig olefination with of the *Z*-unsaturated phosphonium salt **19** (prepared in seven steps as recently described[41]), followed by TBS deprotection, and challenging chemoselective semireduction in a modified Boland procedure[58] furnished the targeted methyl ester dihydroxylated n-6 DPA metabolite **1** ($J_{11,12}$ = 14.9 Hz, $J_{13,14}$ = 14.5 Hz, and $J_{15,16}$ = 11.2 Hz).

Thus, the first synthesis of the 10*S*,17*R*-diH DPA_{EEZ} n-6 target **1** was completed in a total of 20 steps and 5.6% overall yield from the commercially available (*S*)-1,2,4-butanetriol **5**, with a longest linear sequence of 13 steps (i.e., without considering the preparation of the phosphonium salt **19**).

In conclusion, the first total synthesis of three new omega-6 docosatrienes **1**−**3** containing a conjugated (*E*,*E*,*Z*)-triene flanked by two hydroxyl groups has been achieved.

The present strategy has the relevant advantage of flexibility, as it allows the modification of the carboxylated head chain of the molecule using the late polyunsaturated pivotal aldehyde **12**: i.e., without repeating the whole synthetic sequence.

The preparation of other diastereomers and analogues is currently in progress, aiming at SAR studies.

EXPERIMENTAL SECTION

General Methods. All reactions were performed in oven-dried glassware (120 °C, minimum 12 h) under an atmosphere of argon unless otherwise specified. Inert gas was dried by passing it through solid anhydrous calcium sulfate (Drierite). Anhydrous tetrahydrofuran, benzene, and pyridine were purchased. Anhydrous dichloromethane was obtained from a PureSolv PS-400 solvent purification system. Triethylamine and hexamethylphosphoramide (HMPA) were freshly distilled over calcium hydride under an argon atmosphere. All other reagents purchased commercially were used without further purification unless otherwise noted. Thin-layer chromatography (TLC) was performed on aluminum precoated silica gel plates, and developed plates were visualized by UV light (254 nm), *p*-anisaldehyde, or potassium permanganate solution. Column chromatography was performed using flash chromatography with the indicated eluent on Davisil 40−63 *μ*m silica gel. In some cases, for flash column chromatography, deactivated silica (prepared by addition of 46 mL of water to 100 g of silica then stirring on a rotavap for 2 h at room temperature without applying vacuum) was used.

NMR spectra were recorded on spectrometers equipped with a 300 or 500 MHz magnet. Chemical shifts are reported relative to chloroform (*δ* 7.24 ppm) for ^{1}H NMR spectra and chloroform (*δ* 77.16 ppm) for ^{13}C spectra. The ^{1}H NMR spectra data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), coupling constant(s) in hertz, and integration. All of the NMR spectra were assigned with the help of 2D NMR techniques (COSY ^{1}H−^{1}H, HMQC, and HMBC). Infrared spectra were reported as wavenumbers (cm^{-1}) of significant peaks. Mass spectra and high-resolution mass spectra (HRMS) were measured using ESI or APCI (atmospheric pressure CI) techniques on Q-TOF mass spectrometers.

(*R*,9*E*,11*E*)-12-((*S*)-2,2-di-*tert*-Butyl-1,3,2-dioxasilinan-4-yl)-dodeca-9,11-dien-7-yn-6-ol (9). In an oven-dried flask under argon, CuI (75 mg, 0.392 mmol) and tetrakis(triphenylphosphine)-palladium(0) (0.226 g, 0.196 mmol) were added followed by a solution of iodo diene **8** (1.54 g, 3.92 mmol) in THF (20 mL, degassed with argon bubbling for 30 min prior to use). The solution was alternatively evacuated and flushed with argon, and then piperidine (0.77 mL, 7.84 mmol) was added. The flask was protected from light, and a solution of alkyne **4** (0.428 g, 2.0 mmol) in THF (20 mL, degassed with argon for 30 min prior to use) was added over a period of 4 h with a syringe pump. The reaction mixture was stirred for an additional 16 h and then quenched by the addition of a saturated solution of NH_4Cl (50 mL). The resulting suspension was extracted with ethyl ether (2 × 50 mL), and the organic layer was washed with brine (1 × 50 mL) and dried over Na_2SO_4. Concentration followed by flash chromatographic purification (silica gel, cyclohexane/EtOAc 97/3 to 90/10) afforded the expected ynediene **9** (1.02 g, 81%) as a colorless oil: R_f = 0.5 (eluent EtOAc/cyclohexane 1/1); IR *ν* (cm^{-1}) 3360, 2956, 2932, 2858, 2212, 1472, 1364, 1132, 972, 825, 775; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 6.55 (dd, *J* = 10.9, 15.5 Hz, 1H), 6.30 (ddd, *J* = 1.1, 10.9, 15.0 Hz, 1H), 5.77 (dd, *J* = 4.8, 15.0 Hz, 1H), 5.60 (dd, *J* = 1.2, 15.5 Hz, 1H), 4.65−4.57 (m,, 1H), 4.47 (br. q, *J* = 6.0 Hz, 1H), 4.15−4.03 (m, 2H), 1.92−1.57 (m, 5H), 1.50−1.37 (m, 2H), 1.35−1.22 (m, 4H), 1.01 (s, 9H), 0.99 (s, 9H), 0.87 (t, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 141.6, 138.8, 127.9, 110.6, 92.8, 84.1, 73.7, 64.2, 63.2, 38.0, 36.8, 31.6, 27.5, 27.3, 25.0, 22.8, 22.7, 20.1, 14.1 ppm; MS (APCI) *m*/*z* 375.27 $(M - H_2O + H)^+$ (ion peak is very small); HRMS (APCI) calcd for $C_{23}H_{39}O_2Si$ $(M - H_2O + H)^+$ 375.2719, found 375.2721.

(5*R*,8*E*,10*E*,12*S*)-12-(*tert*-Butyldimethylsilyloxy)-2,2,3,3,16,16,17,17-octamethyl-5-pentyl-4,15-dioxa-3,16-disilaoctadeca-8,10-dien-6-yne (10). Tetrabutylammonium fluoride (3.55 mL, 3.55 mmol, 1 M in THF) was added to a solution of ynediene **9** (0.56 g, 1.42 mmol) in THF (5 mL) under argon at 0 °C. After 2 min, the cooling bath was removed and the reaction mixture was stirred for 3 h. Water (10 mL) was added to the reaction mixture. The aqueous layer was extracted with EtOAc (2 × 30 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the expected triol in quantitative yield (0.36 g) as a colorless oil: R_f = 0.56 (eluent EtOAc); IR *ν* (cm^{-1}) 3319, 2931, 2859, 2207, 1453, 1334, 1106, 1050, 984; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 6.53 (dd, *J* = 10.8, 15.5 Hz, 1H), 6.26 (dd, *J* = 10.8, 15.2 Hz, 1H), 5.79 (dd, *J* = 6.0, 15.2 Hz, 1H), 5.60 (dd, *J* = 1.4, 15.5 Hz, 1H), 4.48−4.39 (m, 2H), 3.87−3.73 (m, 2H), 3.03 (br. s, 1H, OH), 2.65 (br. s, 1H, OH), 2.40 (br. s, 1H, OH), 1.89−1.64 (m,

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4H), 1.46−1.37 (m, 2H), 1.35−1.22 (m, 4H), 0.87 (t, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 138.3, 129.3, 111.2, 93.3, 83.9, 71.7, 63.1, 61.0, 38.5, 38.0, 31.6, 25.0, 22.7, 14.1 ppm; MS: (ESI) m/z: 217.2 (M − $2H_2O$ + H)$^+$, 235.2 (M − H_2O + H)$^+$, 291.2 (M + K)$^+$; HRMS (ESI) calcd for $C_{15}H_{23}O_2$ (M − H_2O + H)$^+$ 235.1698, found 235.1674.

To a solution of the resulting triol (0.36 g, 1.42 mmol) in CH_2Cl_2 (20 mL) were added imidazole (1.45 g, 21.42 mmol) and TBSCl (1.07 g, 7.14 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 2 h, before it was diluted with a saturated aqueous solution of NH_4Cl (10 mL) and ethyl ether (20 mL). After 5 min of stirring, the organic layer was separated and the aqueous layer was extracted with ethyl ether (1 × 20 mL). The combined organic layers were washed with water (1 × 20 mL) and brine (1 × 20 mL) and dried over $MgSO_4$. The volatiles were evaporated under reduced pressure, and the residue was purified by flash chromatography (silica gel, cyclohexane/ether 98/03 to 94/06) to give trisilylated- ynediene **10** (0.80 g, 94% over two steps) as a colorless oil: R_f = 0.31 (eluent ether/cyclohexane 1/9); IR ν (cm^{-1}) 2954, 2929, 2857, 1471, 1463, 1361, 1252, 1082, 982, 832, 773; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (dd, J = 10.8, 15.5 Hz, 1H), 6.15 (dd, J = 10.8, 15.2 Hz, 1H), 5.74 (dd, J = 6.4, 15.2 Hz, 1H), 5.55 (d, J = 15.5 Hz, 1H), 4.45 (td, J = 1.6, 6.4 Hz, 1H), 4.32 (q, J = 6.0 Hz, 1H), 3.70−3.56 (m, 2H), 1.72−1.61 (m, 4H), 1.41−1.26 (m, 6H), 0.89−0.85 (m, 30H), 0.11 (s, 3H), 0.09 (s, 3H), 0.03−0.00 (m, 12H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 139.6, 128.6, 110.7, 93.8, 83.4, 70.0, 63.7, 59.4, 41.5, 38.9, 31.6, 26.1, 26.0, 25.9, 25.1, 22.7, 18.4, 18.3, 18.2, 14.2, −2.8, −4.2, −4.3, −4.7, −4.8, −5.2 ppm; MS (ESI) m/z 594.5 (M)$^+$, 463.4 (M − TBSOH + H)$^+$; HRMS (ESI) calcd for $C_{27}H_{51}O_2Si_2$ (M − TBSOH + H)$^+$ 463.3428, found 463.3412.

(3*S*,4*E*,6*E*,10*R*)-3,10-Bis(*tert*-butyldimethylsilyloxy)-pentadeca-4,6-dien-8-yn-1-ol (11). The trisilyl ether **10** (1.1 g, 1.84 mmol) was taken up in 96% EtOH (37 mL), and PPTS (0.462 g, 1.84 mmol) was added at 0 °C. The mixture was stirred at room temperature. After 5 h, the reaction was diluted with saturated aqueous $NaHCO_3$ (50 mL), and the resulting aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with $NaHCO_3$ (1 × 50 mL), water (1 × 50 mL), and brine (1 × 50 mL) and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (cyclohexane/EtOAc 92/08 to 85/15) afforded alcohol **11** (0.545 g, 62%) as a colorless oil: R_f = 0.57 (eluent EtOAc/cyclohexane 2/8); IR ν (cm^{-1}) 3363, 2954, 2928, 2857, 2207, 1471, 1361, 1252, 1080, 983, 834, 775; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (dd, J = 10.8, 15.5 Hz, 1H), 6.19 (dd, J = 10.8, 15.2 Hz, 1H), 5.75 (dd, J = 6.2, 15.2 Hz, 1H), 5.58 (dd, J = 1.2, 15.2 Hz, 1H), 4.47−4.42 (m, 2H), 3.81−3.64 (m, 2H), 2.24 (br. s, 1H, OH), 1.89−1.59 (m, 4H), 1.46−1.17 (m, 6H), 0.95−0.80 (m, 21H), 0.11 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6, 138.2, 129.2, 111.4, 94.2, 83.2, 72.4, 63.7, 60.2, 39.7, 38.8, 31.6, 26.0, 25.9, 25.1, 22.7, 18.4, 18.3, 14.1, −4.2, −4.3, −4.8, −4.9 ppm; MS (ESI) m/z 217.2 (M − 2TBSOH + H)$^+$, 349.3 (M − TBSOH + H)$^+$, 433.4 (2M − 4TBSOH + H)$^+$, 565.5 (2M − 3TBSOH + H)$^+$, 697.6 (2M − 2TBSOH + H)$^+$; HRMS (ESI) calcd for $C_{21}H_{37}O_2Si$ (M − TBSOH + H)$^+$ 349.2563, found 349.2552.

(5*S*,6*E*,8*E*,12*R*)-2,2,3,3,14,14,15,15-Octamethyl-5-((*Z*)-non-2-enyl)-12-pentyl-4,13-dioxa-3,14-disilahexadeca-6,8-dien-10-yne (14). A solution of oxalyl chloride (0.193 mL, 2.25 mmol) and CH_2Cl_2 (15 mL) at −78 °C was treated with DMSO (0.319 mL, 4.5 mmol). After 15 min, a solution of alcohol **11** (0.54 g, 1.12 mmol) in CH_2Cl_2 (7 mL) was added dropwise though a cannula under argon. After 1 h, triethylamine (0.626 mL, 4.5 mmol) was added dropwise and the reaction mixture was warmed to room temperature over 30 min. It was diluted with CH_2Cl_2 (10 mL) and washed sequentially with water (1 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (deactivated silica, pentane/ethyl ether 95/5) to afford aldehyde **12** (0.51 g, 95%) as a colorless syrup: R_f = 0.37 (eluent EtOAc/cyclohexane 2/8); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, J = 2.3 Hz, 1H), 6.47 (dd, J = 10.8, 15.5 Hz, 1H), 6.22 (dd, J = 10.8, 15.0 Hz, 1H), 5.76 (dd, J = 6.0, 15.0 Hz, 1H), 5.60 (dd, J = 1.2, 15.5 Hz, 1H), 4.67 (q, J = 5.6 Hz, 1H), 4.44 (td, J = 1.7, 6.3 Hz, 1H), 2.49 (ddd, J = 2.6, 6.8, and 15.7 Hz, 1H) and 2.39 (ddd, J = 2.2, 5.3, and 15.7 Hz, 1H), 1.69−1.60 (m, 2H), 1.44−1.33 (m, 2H), 1.32−1.21 (m, 4H), 0.90−0.83 (m, 21H), 0.10 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 140.2, 137.1, 129.6, 112.0, 94.5, 83.1, 68.7, 63.7, 51.6, 38.8, 31.6, 26.0, 25.9, 25.1, 22.7, 18.4, 18.2, 14.1, −4.2, −4.3, −4.8, −4.9 ppm.

NaHMDS (0.418 mL, 0.418 mmol, 1.0 M solution in THF) was added dropwise to a suspension of *n*-heptyltriphenylphosphonium bromide (**13**; 0.221 g, 0.501 mmol) in THF (4 mL) at −5 °C. The resulting dark orange mixture was stirred for 30 min at the same temperature. The mixture was cooled to −78 °C. A solution of aldehyde **12** (80 mg, 0.167 mmol) in THF (2 mL) was then added. After it was stirred for 2.5 h at −78 °C, the reaction mixture was quenched with saturated NH_4Cl (5 mL) and warmed to room temperature. The reaction mixture was extracted with ethyl ether (2 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL) and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by chromatography on deactivated silica gel (pentane/ethyl ether 99.5/0.5) provided the title product **14** (60 mg, 64%) as a colorless oil: R_f = 0.09 (eluent ethyl ether/pentane 1/9); IR ν (cm^{-1}) 2927, 2856, 2177, 1466, 1463, 1252, 1080, 983, 835, 775; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48 (dd, J = 10.8, 15.5 Hz, 1H), 6.16 (dd, J = 10.8, 15.2 Hz, 1H), 5.74 (dd, J = 6.0, 15.2 Hz, 1H), 5.56 (dd, J = 1.3, 15.5 Hz, 1H), 5.45−5.27 (m, 2H), 4.45 (td, J = 1.6, 6.4 Hz, 1H), 4.15 (q, J = 6.0 Hz, 1H), 2.33−2.14 (m, 2H), 2.04−1.90 (m, 2H), 1.70−1.58 (m, 2H), 1.46−1.17 (m, 14H), 0.95−0.78 (m, 24H), 0.11 (s, 3H), 0.09 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 139.3, 132.3, 128.6, 125.0, 110.7, 93.8, 83.4, 73.0, 63.7, 38.9, 36.4, 31.9, 31.6, 29.7, 29.1, 27.6, 27.4, 26.0 (2C), 25.1, 22.8, 22.7, 18.4, 14.2, 14.1, −4.2, −4.3, −4.6, −4.8 ppm; MS, molecule too apolar, no ionization could be detected by ESI or APCI.

(6*R*,9*E*,11*E*,13*S*,15*Z*)-Docosa-9,11,15-trien-7-yne-6,13-diol (15). Tetrabutylammonium fluoride (0.30 mL, 0.30 mmol, 1 M solution in THF) was added to a solution of TBS ether **14** (0.06 g, 0.107 mmol) in THF (2 mL) under argon at 0 °C. The cooling bath was removed, and the reaction mixture was stirred for 2.5 h at room temperature. Water (5 mL) was added. The resulting mixture was extracted with ethyl ether (2 × 10 mL). The organic extracts were combined, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified via column chromatography (deactivated silica, cyclohexane/EtOAc 97/03 to 93/07) to give the diol **15** (27 mg, 76% yield) as a colorless oil: R_f = 0.48 (eluent EtOAc/cyclohexane 2/8); IR ν (cm^{-1}) 3338, 2954, 2923, 2855, 2207, 1457,1168, 1026, 982, 724; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (dd, J = 10.8, 15.5 Hz, 1H), 6.26 (dd, J = 10.8, 15.2 Hz, 1H), 5.79 (dd, J = 6.0, 15.2 Hz, 1H), 5.62−5.51 (m, 2H), 5.37−5.29 (m, 1H), 4.47 (td, J = 1.6, 6.5 Hz, 1H), 4.19 (q, J = 6.1 Hz, 1H), 2.30 (t, J = 6.9 Hz, 2H), 2.01 (q, J = 6.6 Hz, 2H), 1.81 (br. s, 2H, 2 × OH), 1.73−1.64 (m, 2H), 1.47−1.38 (m, 2H), 1.31−1.23 (m, 12H), 0.92−0.83 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 138.3, 134.2, 129.4, 124.0, 111.0, 93.1, 84.0, 71.7, 63.2, 38.0, 35.4, 31.9, 31.6, 29.7, 29.1, 27.6, 25.0, 22.8, 22.7, 14.2, 14.1 ppm; MS (APCI) m/z 297.2 (M − $2H_2O$ + H)$^+$, 315.2 (M − H_2O + H)$^+$; HRMS (APCI) calcd for $C_{22}H_{33}$ (M − $2H_2O$ + H)$^+$ 297.2582, found 297.2600; HRMS (APCI) calcd for $C_{22}H_{35}O$ (M − H_2O + H)$^+$ 315.2688, found 315.2693.

(6*R*,7*Z*,9*E*,11*E*,13*S*,15*Z*)-Docosa-7,9,11,15-tetraene-6,13-diol (3). To a suspension of a Zn(Cu/Ag) mixture (0.30 g) in MeOH/water (1/1, 10 mL) was added the alkyne **15** (9 mg, 0.043 mmol) in MeOH (5 mL), and the reaction mixture was stirred at room temperature for 22 h. CH_3CN (20 mL) was added. The reaction mixture was filtered through a short plug of Celite and washed with EtOAc (10 mL). The combined organic phases were dried over $MgSO_4$, and then removal of the solvents afforded a residue that was purified by column chromatography (deactivated silica, cyclohexane/EtOAc 95/05 to 75/25), providing the (*E*,*E*,*Z*)-triene **3** (5 mg, 55% yield) as a colorless oil (procedure based on ref 59): R_f = 0.75 (eluent EtOAc/cyclohexane 3/7); IR ν (cm^{-1}) 3363, 2955, 2925, 2855, 1459, 1019, 993; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48 (dd, J = 11.6, 14.4 Hz,

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1H), 6.32−6.19 (m, 2H), 6.06 (t, J = 10.9 Hz, 1H), 5.76 (dd, J = 6.3, 14.8 Hz, 1H), 5.60−5.51 (m, 1H), 5.44−5.38 (m, 2H), 4.55 (q, J = 6.8 Hz, 1H), 4.25−4.14 (m, 1H), 2.38−2.24 (m, 2H), 2.02 (q, J = 6.7 Hz, 2H), 1.68−1.56 (m, 2H), 1.43−1.17 (m, 16H), 1.53−0.82 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 134.5, 134.1, 133.9, 130.4, 130.1, 127.9, 124.2, 72.1, 68.3, 37.6, 35.5, 31.9, 29.8, 29.7, 29.1, 27.6, 25.1, 22.8, 22.7, 14.2, 14.1 ppm; MS (ESI) m/z 299.2 (M − $2H_2O$ + H)$^+$, 317.2 (M − H_2O + H)$^+$; HRMS (ESI) calcd for $C_{22}H_{37}O$ (M − H_2O + H)$^+$ 317.2844, found 317.2823.

(7*Z*,10*S*,11*E*,13*E*,17*R*)-Ethyl 10,17-Bis(*tert*-butyldimethylsilyloxy)docosa-7,11,13-trien-15-ynoate (17). NaHMDS (0.4 mL, 0.8 mmol, 2.0 M solution in THF) was added dropwise to a suspension of (7-ethoxy-7-oxoheptyl)-triphenylphosphonium bromide (**16**; 0.56 g, 1.13 mmol; prior to use the phosphonium salt was washed with benzene (4 × 4 mL) and then dried under vacuum over P_2O_5 for 48 h, at 75 °C) in THF (8 mL) at −78 °C and stirred at −50 °C for 1 h. After this time, the dark orange mixture was added through a cannula to the aldehyde **12** (75 mg, 0.156 mmol) in THF (4 mL) at −78 °C. The reaction mixture was warmed to 0 °C over 2 h. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and warmed to room temperature. The reaction mixture was extracted with ethyl ether (2 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL) and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by chromatography (silica, cyclohexane/ether 97/03) afforded the title product **17** (75 mg, 78%) as a colorless oil: R_f = 0.43 (eluent ethyl ether/cyclohexane 0.5/9.5); IR ν (cm^{-1}) 2946, 2928, 2856, 1737, 1462, 1250, 1070, 983, 833, 774; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (dd, J = 10.8, 15.5 Hz, 1H), 6.18 (dd, J = 10.1, 14.5 Hz, 1H), 5.75 (dd, J = 5.9, 15.1 Hz, 1H), 5.58 (dd, J = 1.3, 15.5 Hz, 1H), 5.46−5.40 (m, 1H), 5.38−5.32 (m, 1H), 4.47 (t, J = 7.6 Hz, 1H), 4.16 (q, J = 5.6 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.32−2.17 (m, 4H), 2.00 (q, J = 6.7 Hz, 2H), 1.71−1.57 (m, 4H), 1.38−1.29 (m, 10H), 1.26 (t, J = 7.1 Hz, 3H) 0.90−0.86 (m, 21H), 0.21 (s, 3H), 0.11 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 141.0, 139.1, 131.9, 128.7, 125.4, 110.8, 93.8, 83.4, 72.9, 63.6, 60.2, 38.8, 36.4, 34.5, 31.6, 29.4, 28.9, 27.4, 26.0 (2C), 25.0 (2C), 22.7, 18.4 (2C), 14.4, 14.1, −4.3, −4.4, −4.6, −4.8 ppm; MS (APCI) m/z 355.2 (M − 2TBSOH + H)$^+$, 487.3 (M − TBSOH + H)$^+$; HRMS (APCI) calcd for $C_{30}H_{51}O_3Si$ (M − TBSOH + H)$^+$ 487.3607, found 487.3602.

(7*Z*,10*S*,11*E*,13*E*,17*R*)-Ethyl 10,17-Dihydroxydocosa-7,11,13-trien-15-ynoate (18). The deprotection was performed according to the procedure described for diol **15**. Thus, starting from TBS ether **17** (50 mg, 0.08 mmol), the diol **18** (28.5 mg, 91% yield) was obtained as a colorless oil after column chromatography (deactivated silica, cyclohexane/EtOAc 80/20 to 65/35): R_f = 0.48 (eluent EtOAc/cyclohexane 4/6); IR ν (cm^{-1}) 3391, 2929, 2857, 2203, 1733, 1463, 1261, 1029, 984, 725; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (dd, J = 10.8, 15.5 Hz, 1H), 6.25 (dd, J = 11.5, 15.2 Hz, 1H), 5.79 (dd, J = 6.0, 15.2 Hz, 1H), 5.59 (dd, J = 1.3, 15.5 Hz, 1H), 5.56−5.49 (m, 1H), 5.38−5.30 (m, 1H), 4.47 (t, J = 6.6 Hz, 1H), 4.19 (q, J = 6.2 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 2.35−2.24 (m, 4H), 2.02 (q, J = 6.2 Hz, 2H), 1.86 (br. s, 1H, OH), 1.73−1.52 (m, 6H), 1.48−1.39 (m, 2H), 1.35−1.25 (m, 7H), 1.22 (t, J = 7.1 Hz, 3H), 0.87 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 141.4, 138.3, 133.8, 129.3, 124.3, 111.0, 93.1, 83.9, 71.7, 63.2, 60.4, 38.0, 35.4, 34.5, 31.6, 29.4, 28.9, 27.4, 25.0 (2C), 22.7, 14.4, 14.1 ppm; MS (APCI) m/z 355.1 (M − $2H_2O$ + H)$^+$, 373.1 (M − H_2O + H)$^+$, 391.1 (M + H)$^+$; HRMS (APCI) calcd for $C_{24}H_{35}O_2$ (M − $2H_2O$ + H)$^+$ 355.2637, found 355.2620.

(7*Z*,10*S*,11*E*,13*E*,15*Z*,17*R*)-Ethyl 10,17-Dihydroxydocosa-7,11,13,15-tetraenoate (2). The semireduction was performed according to the procedure described for triene **3**. Thus, starting from ynediene **18** (11 mg, 0.028 mmol), the reaction yielded (*E*,*E*,*Z*)-triene **2** (8 mg, 73% yield) as a colorless oil after column chromatography (deactivated silica, cyclohexane/EtOAc 80/20 to 75/25): R_f = 0.52 (eluent EtOAc/cyclohexane 3/7); IR ν (cm^{-1}) 3382, 2929, 2857, 1734, 1461, 1260, 1089, 1025, 995, 802; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48 (dd, J = 11.6, 14.4 Hz, 1H), 6.29 (ddd, J = 0.9, 10.7, 14.7 Hz, 1H), 6.21 (dd, J = 10.8, 14.4 Hz, 1H), 6.06 (t, J = 11.0 Hz, 1H), 5.75 (dd, J = 6.2, 14.8 Hz, 1H), 5.58−5.49 (m, 1H), 5.43−5.31 (m, 2H), 4.55 (q, J = 6.5 Hz, 1H), 4.20 (q, J = 6.4 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 2.38−2.23 (m, 4H), 2.03 (q, J = 6.4 Hz, 2H), 1.69−1.54 (m, 5H), 1.50−1.40 (m, 2H), 1.39−1.19 (m, 12H), 0.86 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 136.7, 134.5, 133.9, 133.6, 130.4, 130.0, 127.9, 124.6, 72.0, 68.2, 60.3, 37.6, 35.5, 34.5, 31.9, 29.3, 28.9, 27.4, 25.1, 25.0, 22.7, 14.4, 14.1 ppm; MS (ESI) m/z 375.2 (M − H_2O + H)$^+$, 357.2 (M − $2H_2O$ + H)$^+$; HRMS (ESI) calcd for $C_{24}H_{39}O_3$ (M − H_2O + H)$^+$ 375.2899, found 375.2882.

(4*Z*,7*Z*,10*S*,11*E*,13*E*,17*R*)-Methyl 10,17-Bis(*tert*-butyldimethylsilyloxy)docosa-4,7,11,13-tetraen-15-ynoate (20). NaHMDS (0.4 mL, 0.8 mmol, 2.0 M solution in THF) was added dropwise to a suspension of (*Z*)-(7-methoxy-7-oxohept-3-enyl)triphenylphosphonium iodide (**19**; 0.60 g, 1.13 mmol; prior to use the phosphonium salt was washed with benzene (4 × 4 mL) and then dried under vacuum over P_2O_5 for 48 h, at 75 °C) in THF (10 mL) and HMPA (1.63 mL) at −78 °C and warmed to −20 °C in 1 h and then cooled to −78 °C. The dark orange mixture was added to the aldehyde **12** (85 mg, 0.177 mmol) in THF (5 mL) through a cannula at −78 °C. The reaction mixture was warmed to 0 °C over 2 h. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and warmed to room temperature. The reaction mixture was extracted with ethyl ether (2 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL) and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by chromatography (silica, cyclohexane/ethyl ether 98/02 to 97/03) provided the title product **20** (65 mg, 61%) as a colorless oil: R_f = 0.25 (eluent EtOAc/cyclohexane 1/9); IR ν (cm^{-1}) 3017, 2953, 2929, 2857, 1742, 1471, 1251, 1081, 985, 836, 776; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48 (dd, J = 10.8, 15.5 Hz, 1H), 6.17 (dd, J = 10.8, 15.1 Hz, 1H), 5.73 (dd, J = 5.9, 15.1 Hz, 1H), 5.56 (d, J = 15.5 Hz, 1H), 5.44−5.25 (m, 4H), 4.48 (td, J = 1.4, 6.4 Hz, 1H), 4.17 (q, J = 6.0 Hz, 1H), 3.65 (s, 3H), 2.76 (t, J = 5.3 Hz, 2H), 2.40−2.20 (m, 6H), 1.70−1.60 (m, 2H), 1.45−1.20 (m, 6H), 0.95−0.80 (m, 21H), 0.11 (s, 3H), 0.09 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 141.0, 139.0, 129.8, 129.4, 128.7, 127.9, 125.7, 110.9, 93.8, 83.2, 72.7, 63.6, 51.7, 38.8, 36.4, 34.2, 31.6, 26.0 (2C), 25.9, 25.1, 22.9, 22.7, 18.4 (2C), 14.2, −4.3, −4.4, −4.6, −4.8 ppm. No ions could be detected using ESI or APCI mass spectroscopy. Combustion analytical data are unavailable due to the compound being unstable.

(4*Z*,7*Z*,10*S*,11*E*,13*E*,17*R*)-Methyl 10,17-Dihydroxydocosa-4,7,11,13-tetraen-15-ynoate (21). The deprotection was performed according to the procedure described for diol **15**. Thus, starting from TBS ether **20** (40 mg, 0.066 mmol), the diol **21** (24 mg, 97% yield) was obtained as a colorless oil after column chromatography (deactivated silica, cyclohexane/EtOAc 80/20 to 70/30): R_f = 0.62 (eluent EtOAc/cyclohexane 4/6); IR ν (cm^{-1}) 3389, 3013, 2951, 2929, 2858, 2202, 1737, 1437, 1164, 1026, 984; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (dd, J = 10.9, 15.5 Hz, 1H), 6.27 (dd, J = 10.9, 15.1 Hz, 1H), 5.80 (dd, J = 5.9, 15.2 Hz, 1H), 5.60 (dd, J = 1.5, 15.5 Hz, 1H), 5.56−5.47 (m, 1H), 5.44−5.29 (m, 3H), 4.47 (t, J = 6.6 Hz, 1H), 4.21 (q, J = 6.2 Hz, 1H), 3.64 (s, 3H), 2.88−2.70 (m, 2H), 2.43−2.26 (m, 6H), 2.00 (br. s, 1H, OH), 1.92−1.60 (m, 3H), 1.56−1.37 (m, 2H), 1.35−1.24 (m, 4H), 0.87 (t, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 141.3, 138.1, 131.6, 129.4, 129.1, 128.2, 124.8, 111.0, 93.0, 83.9, 71.6, 63.2, 51.8, 37.9, 35.5, 34.1, 31.6, 25.9, 25.0, 22.9, 22.7, 14.2 ppm; MS (APCI) m/z 339.23 (M − $2H_2O$ + H)$^+$, 357.24 (M − H_2O + H)$^+$, 397.24 (M+Na)$^+$, 695.47 (2M − $3H_2O$ + H)$^+$, 713.48 (2M − $2H_2O$ + H)$^+$; HRMS (APCI) calcd for $C_{23}H_{31}O_2$ (M − $2H_2O$ + H)$^+$ 339.2324, found 339.2323; HRMS (APCI) calcd for $C_{23}H_{33}O_3$ (M − H_2O + H)$^+$ 357.2430, found 357.2429; HRMS (APCI) calcd for $C_{23}H_{34}O_4Na$ (M + Na)$^+$ 397.2355, found 397.2356.

(4*Z*,7*Z*,10*S*,11*E*,13*E*,15*Z*,17*R*)-Methyl 10,17-Dihydroxydocosa-4,7,11,13,15-pentaenoate (1). To a suspension of the Zn(Cu/Ag) mixture (0.27 g) in H_2O (2 mL), the substrate (12 mg, 0.032 mmol) in methanol (2 mL) was added followed by the addition of TMSCl (40 μL, 0.32 mmol). The reaction mixture was stirred at room

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temperature for 4 h. EtOAc (10 mL) was added. The reaction mixture was filtered through a short plug of desactivated silica gel and eluted with EtOAc (10 mL). The combined organic phases were washed with water (10 mL). The organic layer was separated and dried ($MgSO_4$), and then removal of the solvent afforded a residue that was purified by column chromatography (desactivated silica, hexane/EtOAc 90/10 to 80/20) afforded the title product **1** (7.0 mg, 59% yield) as a colorless oil: IR ν (cm^{-1}) 3374, 3014, 2951, 2929, 2858, 1738, 1437, 1161, 995; ^1H NMR (500 MHz, $CDCl_3$) δ 6.48 (dd, J = 11.6, 14.5 Hz, 1H), 6.30 (dd, J = 10.8, 14.9 Hz, 1H), 6.21 (dd, J = 10.8, 14.5 Hz, 1H), 6.06 (t, J = 11.2 Hz, 1H), 5.76 (dd, J = 6.2, 14.9 Hz, 1H), 5.57−5.48 (m, 1H), 5.44−5.30 (m, 4H), 4.55 (q, J = 7.1 Hz, 1H), 4.26−4.17 (m, 1H), 3.65 (s, 3H), 2.90−2.73 (m, 2H), 2.42−2.26 (m, 6H), 1.80 (d, J = 3.7 Hz, 1H, OH), 1.51−1.38 (m, 2H), 1.37−1.20 (m, 6H), 0.86 (t, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 136.6, 134.5, 133.8, 131.4, 130.4, 130.0, 129.2, 128.2, 127.9, 125.0, 71.9, 68.2, 51.8, 37.6, 35.5, 34.1, 31.9, 25.9, 25.1, 23.0, 22.7, 14.2 ppm; MS (APCI) m/z 341.25 $(M - 2H_2O + H)^+$, 359.26 $(M - H_2O + H)^+$, 399.25 $(M + Na)^+$; HRMS (APCI) calcd for $C_{23}H_{33}O_2$ $(M - 2H_2O + H)^+$ 341.2481, found 341.2487; HRMS (APCI) calcd for $C_{23}H_{35}O_3$ $(M - H_2O + H)^+$ 359.2586, found 359.2590; HRMS (APCI) calcd for $C_{23}H_{36}O_4Na$ $(M+Na)^+$ 399.2511, found 399.2516.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^1H and ^{13}C NMR spectra for all new compounds and 2D-NMR spectra (COSY45, HMQC, HMBC) for enynes **9** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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