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Total Synthesis of the Antidiabetic (Type 2) Lipid Mediator Protectin DX/PDX

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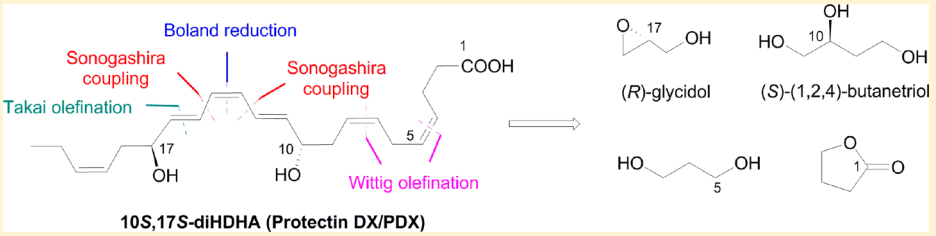
Supporting Information



ABSTRACT: The first total synthesis of a lipid mediator derived from natural ω-3-fatty acid docosahexaenoic acid (DHA), 10*S*,17*S*-diHDHA (also referred to as protectin DX/PDX), was achieved in a convergent route (29 steps). The two chiral hydroxyl groups at C-10 and C-17 were derived from readily available (*S*)-1,2,4-butanetriol and (*R*)-glycidol, respectively. The two stereodefined *E*-double bonds were generated by a Takai olefination, and the skipped diene side chain was introduced with a stereocontrolled Wittig olefination. Importantly, the sensitive conjugated *E*,*Z*,*E*-triene intermediate was generated by a Boland reduction of the central triple bond of a *E*,*E*-dienyne. Overall, this synthetic strategy should allow the preparation of a larger quantity of PDX, which is inaccessible via previously reported biosynthetic approaches.

INTRODUCTION

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the most physiologically important members of the natural ω-3 fatty acid class, being key precursors in the biosynthesis of hydroxylated metabolites that mediate resolution of inflammation process. Such lipid mediators (LMs) are divided to E-series and D-series resolvins (RvDs), protectins (PDs), and maresins (MaRs).[1,2] The founding member of the PDs is protectin D1 (**1**), or PD1, also known as neuroprotectin D1 (NPD1). PD1 is derived from DHA through the action of 15-LOX, a lipoxygenase, followed by enzymatic hydrolysis. Its molecular structure is characterized by the presence of two alcohol groups and a conjugated triene system possessing one cis olefin (Figure 1).[3] PD1 (**1**) has attracted significant attention from both synthetic chemists and biologists, owing to its interesting biochemical activities such as anti-inflammatory, immunoregulatory, and neuroprotective properties.[4]

In 2002, Hong et al. reported an additional protectin resulting from a biosynthesis through the sequential actions of two lipoxygenases on DHA.[5] The structure of this new double-oxygenated product was partially elucidated by Butovich[6] in 2005, but its complete stereochemistry was established in 2006 as 10*S*,17*S*-diHDA (**2**).[4e] In 2009, Guichardant and co-workers also reported the exact structural and configurational assignment of 10*S*,17*S*-diHDA (**2**) and named it protectin DX or PDX.[7] Interestingly, its structure differs from PD1 only by having an *E*,*Z*,*E*-geometry instead of the *E*,*E*,*Z*-geometry unit and with a (10*S*) instead of (10*R*)-configuration (Figure 1). PDX and PD1 both exert immunoresolving action, but PDX, unlike PD1, is less potent as a pro-resolving agonist.[4e] In addition, PDX inhibited the human platelet aggregation responses,[8] the replication of the influenza virus,[9] and conferred protection against sepsis in mice.[10] PDX also reversed the fibrotic process in mice with lung fibrosis.[11]

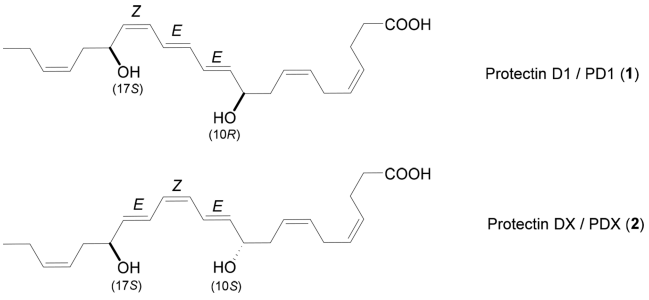


Figure 1. Structure of protectin D1 (PD1) and its structural isomer protectin DX (PDX).

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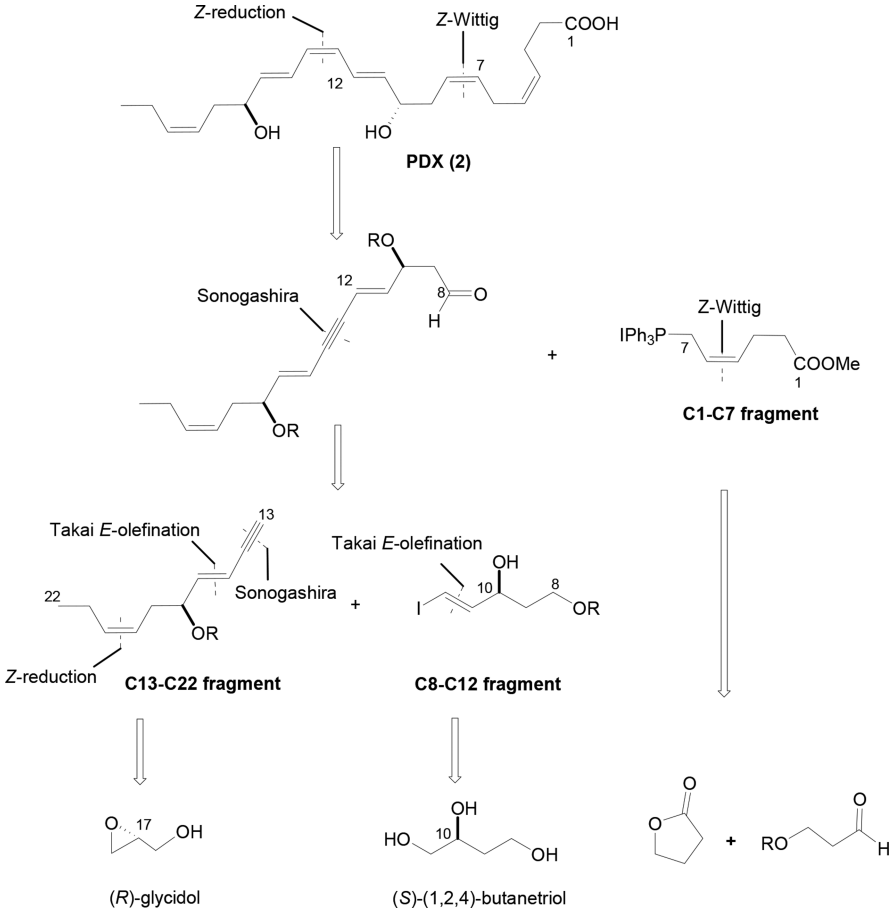

Figure 2. Retrosynthetic analysis of Protectin DX (PDX, **2**).

As another promising property, Marette and co-workers recently investigated the glucoregulatory activity of PDX, which is distinct from its antiaggregatory and anti-inflammatory actions.[12] They showed the in vitro and in vivo efficacy of PDX at submicromolar concentrations for release of the prototypic myokine interleukin-6 (IL-6) for activation of AMP-activated kinase (AMPK) and for the prevention of lipid-induced and obesity-linked insulin resistance in mouse models. Overall, these findings suggest that PDX might be a potential tool for alleviating type 2 diabetes through both anti-inflammatory and insulin-sensitizing actions. Interestingly, in the same biological tests, PD1 was ineffective at inducing IL-6 release from skeletal muscle cells.

Several total syntheses of docosatrienes having three conjugated double bonds with a characteristic *E,E,Z* geometry have already been achieved and recently reviewed.[13] However, only a few examples of syntheses of polyenes similar to PDX bearing a triene system with the isomeric *E,Z,E* geometry flanked with two carbinols have been published.[14] In fact, it has been mentioned in the literature that PDX has been obtained by total synthesis, but there is no details reported to date.[15] Unlike many other docosatrienes, this complex compound is produced from enzymatic synthesis. Unfortunately, its commercial availability is very limited and expensive, being offered only in microgram quantities.[16] For those reasons, and considering its potential therapeutic activity, we therefore investigated the total synthesis of PDX. An efficient synthesis will offer quantities allowing for further investigations into the underlying mechanisms of action of PDX, particularly in treatment of type 2 diabetes. Furthermore, a total synthesis will also provide the opportunity to obtain non-natural stereoisomers, as well as isotopically labeled materials. We thus herein describe our effort toward the development of a successful PDX total synthetic route.

RESULTS AND DISCUSSION

As for an *E,E,Z*-triene system, we suspected that the internal conjugated *E,Z,E*-triene of PDX (**2**) (Figure 1) could be sensitive to isomerization by means of heating, light, or acid to the corresponding more stable *E,E,E*-triene. For this reason, in all the strategies described to access to dihydroxylated-*E,E,Z*-docosatrienes, the conjugated *E,E,Z*-triene was built at a very late stage. Careful manipulations were also required regarding the skipped diene of the polar chain, which is potentially prone to oxidation and isomerization. Among the reported approaches to *E,E,Z*-docosatrienes, we were interested in those reported by the Balas[17] and Hansen[18] teams. Briefly, the key intermediate, a *E,E*-dienyne aldehyde, was assembled from two smaller fragments and subsequently elongated through a Wittig reaction. Finally, a semihydrogenation under Boland conditions of the alkyne portion of a *E,E*-dienyne afforded the highly sensitive *E,E,Z*-triene unit. This convergent approach could be applied to the synthesis of **2** with suitable modifications to the building blocks. Furthermore, flexibility of this strategy is amenable, especially for potential modifications of the polar head chain. Thus, inspired by the precedents in literature, we dissected the structure of **2** in three

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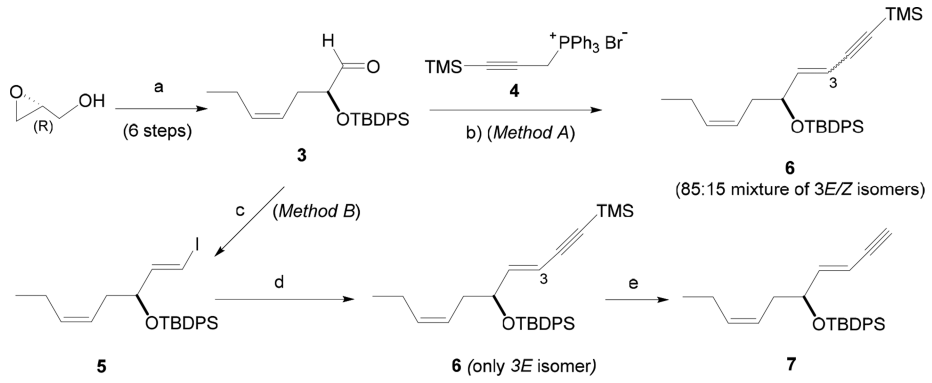
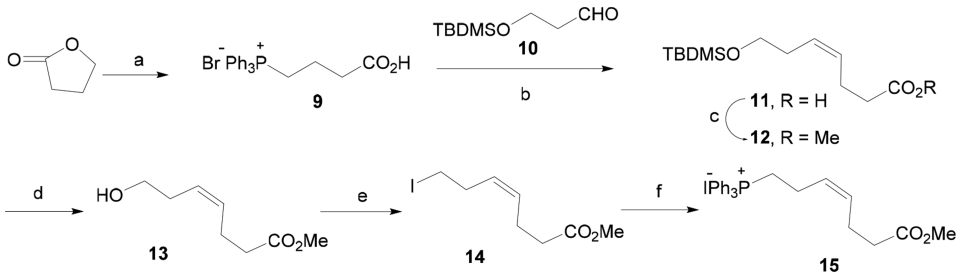
Scheme 1. Synthesis of C13−C22 Fragment 7[a]



[a]Reagents and conditions: (a) ref 19; (b) phosphonium **4**, *t*-BuOK, THF, 0 °C, 96%; (c) $CrCl_2$, CHI_3, THF−dioxane, room temperature, 54%; (d) TMS-acetylene, $Pd(PPh_3)_2Cl_2$, CuI, $(i\text{-Pr})_2NH$, THF, room temperature, 100%; (e) K_2CO_3, MeOH, room temperature, 95%.

Scheme 2. Synthesis of C1−C7 Fragment 15[a]



[a]Reagents and conditions: (a) $Ph_3P{\cdot}HBr$ neat, 180-190 °C, 94% ; (b) NaHMDS, THF, 0 °C; (c) $KHCO_3$, MeI, DMF, room temperature, 51% (from **10**); (d) TBAF, THF, room temperature, 90%; (e) I_2, Ph_3P, imidazole, 0 °C, THF, 92%; (f) Ph_3P, toluene, reflux, 96%.

fragments (C13−C22, C8−C12, and C1−C7) as shown in our retrosynthetic approach plan (Figure 2).

We initiated our synthesis by the stereoselective preparation of C13−C22 chiral fragment (compound **7**) as outlined in Scheme 1. (*S*)-Enyne **7** was obtained from (*S*)-aldehyde **3**, itself prepared from commercial (*R*)-glycidol, following standard manipulations reported by Winkler et al.[19] Overall, (*S*)-aldehyde **3** was synthesized in a stereochemically pure form in six steps and in a 40% yield from (*R*)-glycidol. We sought to prove that (*S*)-enyne **7** could directly arise from a Wittig olefination of (*S*)-aldehyde **3** using the phosphorus ylide derived from (trimethylsilylpropargyl)-triphenylphosphonium bromide (**4**)[20] (known as Yates salt). Thus, generating the ylide by treatment of the salt **4** with *n*-BuLi and condensation with the (*S*)-aldehyde **3** afforded the desired (*E*)-enyne **6** together with its (*Z*)-regioisomer. ^1H NMR analysis showed a ratio of 80:20 (*E*/*Z*), but we have observed that this *E*/*Z* ratio could be increased to 85:15 by using potassium *tert*-butoxide as a base. Disappointingly, we found that both regioisomers were not separable by flash chromatography at this time, even after deprotection of a trimethylsilyl group or at a later stage in the synthesis. For this reason, we abandoned the direct Wittig reaction and opted for a two-step preparation involving a Sonogashira reaction with (*S*)-(*E*)-vinyl iodide **5**. Employing conditions developed by Furstner and co-workers,[21] iodide **5** was obtained as a unique (*E*)-regioisomer by a Takai olefination in 54% yield.

Finally, coupling of **5** with TMS-acetylene under Sonogashira conditions ($Pd(PPh_3)_2Cl_2$, $(i\text{-Pr})_2NH$, CuI) cleanly produced quantitatively the TMS-protected (*S*)-dienyne **6**. Removal of the TMS group with K_2CO_3 in methanol afforded the terminal conjugated (*S*)-dienyne **7** (95% yield) in a stereochemically pure form.

As depicted in Scheme 2, the C1−C7 fragment (a phosphonium salt **15**) was prepared from known propanaldehyde derivative **10**.[22] A Wittig reaction with the readily available (3-carboxypropyl)triphenylphosphonium bromide (**9**) and aldehyde **10** furnished the desired (*Z*)-olefin **11** (100% isomeric purity by ^1H NMR), which was directly converted into the corresponding methyl ester **12** ($KHCO_3$, MeI in DMF) in 51% yield. Cleavage of the silyl ether with TBAF afforded in 90% yield the alcohol **13**, which was then transformed uneventfully into the desired phosphonium salt **15** via iodide **14** (88%, two steps).

The C8−C12 fragment, (*S*)-vinyl iodide **8** (Scheme 3), was prepared in four steps (overall 36% yield) from commercially available (*S*)-1,2,4-butanetriol, as described by Balas's group.[17] As a key step, these authors selectively protected the 1,3-diol functionality of (*S*)-1,2,4-butanetriol as a stable six-membered di-*tert*-butylsilylene ketal.

The first C13−C22 and second C18−C12 fragments were assembled as outlined in Scheme 3. Conjugated (*S*)-alkyne **7** and (*S*)-vinylic iodide **8** were thus coupled via a Sonogashira reaction ($Pd(PPh_3)_2PdCl_2$, $(i\text{-Pr})_2NH$, CuI) to quantitatively afford the tris-protected (*S*,*S*)-trienyne **16**. Manipulations of the protecting group were required to ensure selective oxidation of the primary alcohol. First, both the TBDPS and silylene groups were removed in the presence of TBAF to yield triol **17** in 72% yield. Selective tritylation of the primary alcohol with chlorotriphenylmethane (Et_3N, DMAP, CH_2Cl_2) followed by protection of the two residual hydroxyls of **17** as TBDPS ethers (chloro-*tert*-butyldiphenylsilane, Et_3N, CH_2Cl_2)

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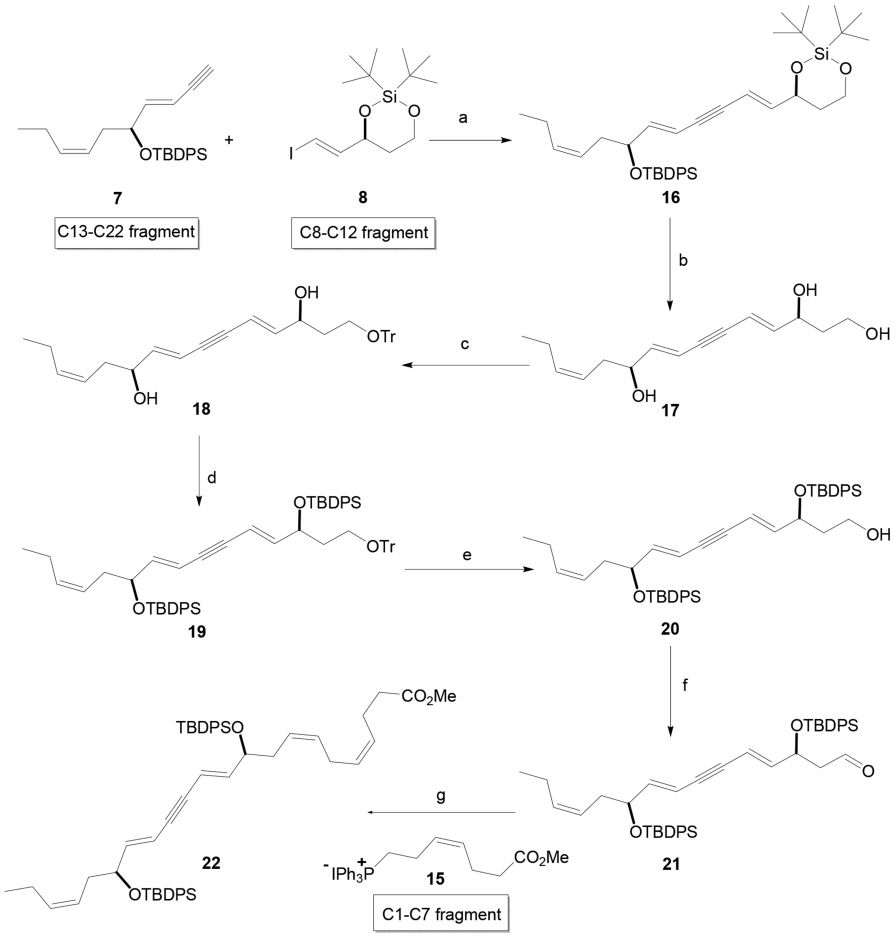
Scheme 3. Fragment Assembly (Synthesis of Intermediate 22)[a]



[a]Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, $(i\text{-}Pr)_2NH$, benzene, room temperature, 100%; (b) TBAF, THF, room temperature, 72%; (c) trityl chloride, Et_3N, DMAP, CH_2Cl_2, room temperature; (d) TBDPS-Cl, imidazole, DMAP, CH_2Cl_2, room temperature, 80% (from **17**); (e) CSA, CH_2Cl_2–MeOH, 0 °C, 80%; (f) Dess–Martin periodinane, CH_2Cl_2, room temperature, 80%; (g) NaHMDS, THF–HMPA, −78 to 0 °C, 75%.

provided the fully protected triol **19**. Chemoselective cleavage of the trityl ether in acidic conditions (CSA, CH_2Cl_2) gave the bis-protected triol **20** (80% overall yield from trienyne **17**). Oxidation of primary alcohol was achieved using Dess–Martin reagent in CH_2Cl_2 giving a 80% yield of **21**. Interestingly, we obtained a higher yield than those reported in the literature[17] when this oxidation was performed on a similar substrate having full TBDMS protection. The sensitive protected *β*-hydroxy aldehyde **21**, which is prone to elimination of the OTBDPS group, was immediately reacted with the ylide generated from phosphonium **15** and NaHMDS in THF at −78 °C in the presence of HMPA.[17] Under these conditions, the Wittig reaction proceeds with a high (*Z*)-selectivity (>95%) to give a 75% yield of **22**.

The synthesis of PDX was completed as outlined in Scheme 4 via deprotection of the TBDPS groups of *E,E*-enynene **22** with TBAF to give diol **23** (80% yield, 96% HPLC purity).

To achieve the crucial chemoselective reduction of the central triple bond of **23**, we chose to use zinc-activated by copper(II) acetate and silver(I) nitrate (Zn (Cu/Ag)) in aqueous methanol according to a modified Boland procedure.[23] These conditions have proven to be more efficient to reduce alkyne in conjugated polyunsaturated systems over other hydrogenation catalysts.[24] Thus, conjugated *E,E*-enynene **23** was treated in the dark with Zn(Cu/Ag), aqueous methanol, and chlorotrimethylsilane leading *E,Z,E* triene **24** in 51% yield. Careful analysis of the ^{1}H NMR spectrum of the crude material revealed the presence of a byproduct (∼5%, estimated by ^{1}H NMR analysis) that we suspect to be the *E,E,E* regioisomer of PDX (**2**). Indeed, we observed a broad signal at 6.25 ppm that could correspond to those of vinylic protons of an all *E*-conjugated triene.[25]

The final saponification of ester **24** was accomplished with an excess of LiOH in diluted aqueous methanol–THF at 0 °C, followed by acidification with NaH_2PO_4 to provide PDX (**2**) in 77% yield after chromatography on deactivated silica gel (96% HPLC purity). The chromatographic behavior in LC–MS/MS of commercial PDX (from the Cayman Chemical Company) and synthetic PDX (**2**) were found to be identical (Figure 3). In fact, the multiple reaction monitoring (MRM) chromatogram gave a peak at t_R = 14.20 min (Figure 3A), while the MRM chromatogram of synthetic PDX (**2**) gave also a major peak at t_R = 14.21 min (Figure 3B). These results confirmed that synthetic PDX (**2**) matched perfectly with natural PDX. Furthermore, our ^{1}H and ^{13}C NMR and UV–vis absorption spectral data of **2** were in perfect agreement with those previously published.[6,7]

In summary, the above results represent the first total synthesis of PDX (**2**). This complex molecule was prepared by a convergent approach in 29 steps, which favorably compares

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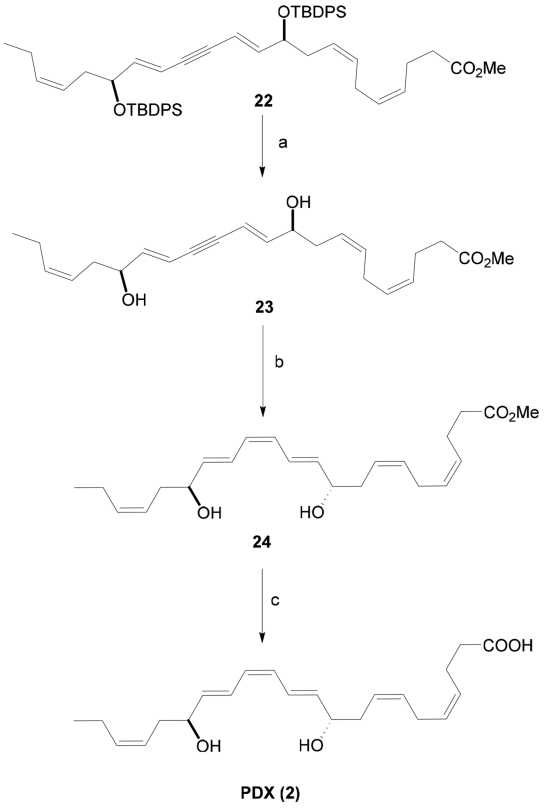
Scheme 4. Completion of the Synthesis of PDX (2)[a]



[a]Reagents and conditions: (a) TBAF, THF, room temperature, 80%; (b) Zn(Cu/Ag), MeOH−H_2O, room temperature, 51% (c) LiOH, MeOH−THF−H_2O, 5 °C, 77%.

with other previously reported syntheses of docosatrienes, where at least 26 steps were necessary, no matter the targets and chosen strategies. The configuration of the two asymmetric carbons was secured by the chiron approach using traditional chiral precursors ((*R*)-glycidol and (*S*)-1,2,4-butanetriol). Since the stereochemistry of the six double bonds was highly controlled, particularly the Boland semireduction, this work opens an access to the preparation of larger amounts of PDX (**2**).

EXPERIMENTAL SECTION

General Experimental Procedure. Reagents and solvents were obtained from commercial suppliers (Sigma-Aldrich, Strem, Combi-blocks, Alfa Aesar) and used without further purification unless otherwise mentioned. Optical rotations of commercial (*R*)-glycidol and (*S*)-1,2,4-butanetriol were checked before use. Natural PDX, used as a standard reference, was purchased from Cayman Chemical Company. All reactions that were moisture and air-sensitive were carried out in flame-dried glassware and under an argon atmosphere. Reaction progress was monitored by thin-layer chromatography using EMD silica gel 60 F254 aluminum plates. The spots were visualized with UV light (254 nm), followed by staining with cerium ammonium molybdate (CAM) solution or potassium permanganate, and then heated on a hot plate. Silicycle R10030B 230−400 mesh silica gel (Québec, QC, Canada) was used for flash chromatography. When indicated, deactivated silica gel was prepared by mixing silica gel (100 g) with water (46 mL) and stirring the mixture on a rotavapor for 2 h without applying vacuum. Optical rotations were measured on a JASCO DIP-370 digital polarimeter (Easton, MD) using a cylindrical glass cell (50 mm length). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 digital spectrometer (Billerica, MA) at 400 MHz for ^{1}H NMR and 100.6 MHz for ^{13}C NMR. Spectra are referenced relative to the central residual proton solvent resonance in ^{1}H NMR ($CDCl_3$ δ = 7.26 ppm, MeOH-d_4 δ = 3.31 ppm and DMSO-d_6 δ = 2.50 ppm) and to the central carbon solvent resonance in ^{13}C NMR ($CDCl_3$ δ = 77.0 ppm, MeOH-d_4 δ = 49.0 ppm and DMSO-d_6 δ = 39.4 ppm). High-performance liquid chromatography (HPLC) analyses for chemical purities were performed on a Shimadzu Prominence instrument (Kyoto, Japan) using a diode array detector (PDA) and an Altima C18 analytical reversed-phase column (5 μm, 4.6 × 250 mm), applying the conditions as stated (wavelength detection and solvent gradient). Low-resolution mass spectra (LRMS) were recorded on a Shimadzu Prominence instrument (Kyoto, Japan) equipped with a Shimadzu LCMS-2020 mass spectrometer and an APCI probe. ESI-TOF HRMS, APCI-TOF HRMS, or APPI-TOF HRMS spectra were provided by Pierre Audet at the Laval University Chemistry Department (Québec, QC, Canada). LC−MS/MS analysis for comparison assays with natural PDX (**2**) was performed by Jocelyn Trottier (Bioanalytical Services-CHU de Québec Research Center) as previously reported.[12a]

*Preparation of (2S,4Z)-2-(tert-Butyldiphenylsilyloxy)hept-4-enal (**3**).* Aldehyde **3**, which was prepared in seven steps from commercially available (*R*)-glycidol, was obtained in a 40% overall yield as a colorless oil as previously reported.[19a] ^{1}H NMR data were in full agreement with those reported in the literature:[19a] $[\alpha]^{21}_D$ +13 (*c* 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H, H_1), 7.67−7.62 (m, 4H), 7.45−7.26 (m, 6H), 5.59−5.42 (m,1H, H_5), 5.40−5.31 (m, 1H, H_4), 4.04 (qd, 1H, *J* = 6.5, 1.7 Hz, H_2), 2.45 (m, 1H), 2.34 (m, 1H), 1.91 (m, 2H), 1.11 (s, 9H), 0.88 (t, 3H, *J* = 7.5 Hz); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 203.4, 135.8, 135.7, 134.9, 133.3, 132.9, 130.1, 130.0, 127.8, 127.7, 122.0, 77.8, 31.0, 26.9, 20.6, 20.5, 14.0.

*Preparation of (3E)-Enyne **7** (C13−C22 Fragment). (3S,1E,5Z)-3-(tert-Butyldiphenylsilyloxy)-1-iodoocta-1,5-diene (**5**).* Iodo vinylic compound **5** was prepared using a Takai olefination following the previously described Furstner's procedure.[21] A 250 mL flask was charged with commercially $CrCl_2$ (5 g, 40.6 mmol). The solid was dried using a heat gun under high vacuum. After being cooled to room temperature under argon, the flask was protected from light with an aluminum foil, and then dry THF (7 mL) and dry dioxane (40 mL) were added followed at 0 °C by CHI_3 (8 g, 20.3 mmol). The initial dark-green mixture was stirred at room temperature for 2 h until it had turned brown. Aldehyde **3** (2 g, 5.1 mmol) in dioxane (5 mL) was added and the mixture stirred for 2 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl, and the aqueous phase was extracted with Et_2O. The combined organic phase was washed successively with a saturated aqueous solution of $Na_2S_2O_3$ and brine solution, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash chromatography on deactivated silica gel with hexanes afforded iodide **5** as a light yellow oil (1.4 g, 54%): ^{1}H NMR data were in full agreement with those reported in the literature:[19] $[\alpha]^{21}_D$ −41 (*c* 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.66 (m, 4H,) 7.51−7.41 (m, 6H), 6.56 (dd, 1H, *J* = 14.4, 6.5 Hz, H_2), 6.15 (dd, 1H, *J* = 14.4, 1.1 Hz, H_1), 5.45−5.38 (m, 1H, H_6), 5.30−5.24 (m, 1H, H_5), 4.24 (qd, 1H, *J* = 6.6, 1.2 Hz, H_3), 2.32−2.18 (m, 2H), 1.91−1.84 (m, 2H), 1.07 (s, 9H), 0.87 (t, 3H, *J* = 7.5 Hz, H_8); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 147.9, 135.9, 135.7, 134.4, 133.8, 133.5, 129.8, 129.6, 123.0, 75.7, 35.1, 26.9, 20.6, 19.3, 14.2.

*(5S,3E,7Z)-5-(tert-Butyldiphenylsilyloxy)-1-(trimethylsilyl)deca-3,7-dien-1-yne (**6**).* Method A: To a cooled (salt−ice mixture) solution of TMS-propargyl triphenylphosphonium bromide (**4**) (prepared by reaction of TMS-propargyl bromide and triphenylphosphine in refluxing toluene)[20] (668 mg, 1.47 mmol) in THF (5 mL) was added potassium *tert*-butoxide (183 mg, 1.63 mmol). The mixture was stirred under argon for 30 min. Aldehyde **3** (360 mg, 0.98 mmol) was added in THF (2 mL), and the mixture was stirred for 1 h before being quenched by the addition of a saturated solution of NH_4Cl. The resulting mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduce pressure. Purification on silica gel with hexanes afforded TMS-dienyne **6**

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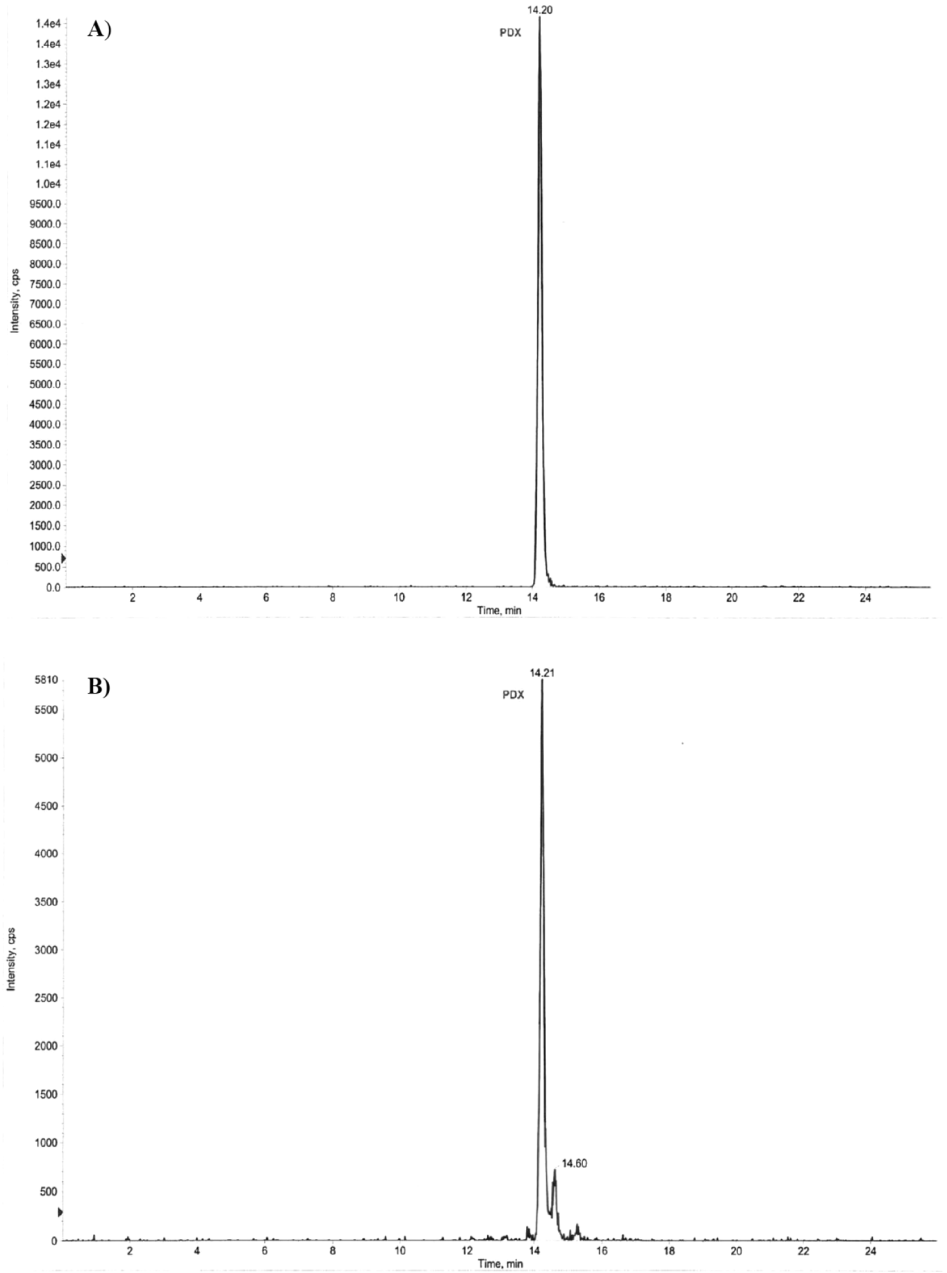

Figure 3. Comparison of LC−MS/MS profiles. Multiple reaction monitoring chromatograms for selected ion pair *m*/*z* 359−206 of PDX (**2**) from Cayman Chemical Company (A) and synthetic compound (B).

(390 mg, 96%) as a mixture of (*E*/*Z*)-isomers (85:15 ratio based on ^{1}H NMR analysis). For the (*E*)-isomer: see below (method B) for ^{1}H data. For the (*Z*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.60 (m, 4H), 7.45−7. 32 (m, 6H), 5.93 (dd, 1H, *J* = 11.1, 8.9 Hz), 5.80 (m, 3H), 4.80 (m, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 1.88 (m, 2H), 1.11 (s, 9H), 0.89 (t, 3H,, *J* = 7.4 Hz), 0.04 (s, 9H). Method B: A Schlenk tube was charged with iodovinyle **5** (1.4 g, 2.94 mmol), THF (20 mL), and $(i\text{-Pr})_2NH$ (20 mL). Argon was bubbled through the mixture for 5 min, and then dichlorobis(triphenylphosphine) palladium II (206 mg, 0.294 mmol) and copper(I) iodide (112 mg, 0.59 mmol) were added followed by the addition of TMS-acetylene (0.84 mL, 5.9 mmol). The tube was sealed, and the resulting black mixture was stirred for 18 h. After filtration on a pad of Celite and washing with EtOAc, the filtrate was concentrated under vacuum. The oily residue was purified by flash chromatography on silica gel via gradient elution (98/2 hexanes−CH_2Cl_2 to 90/10 hexanes−CH_2Cl_2) to yield (3*E*)-dienyne **6** as a dark yellow oil (1.2 g, 100%). We have observed that pure compound **6** can easily lose its TMS group in chloroform solution at room temperature: $[\alpha]^{21}_D$ −34 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.61 (m, 4H), 7.44−7.34 (m, 6H), 6.20 (dd, 1H, *J* = 15.9, 5.3 Hz, H_4), 5.88−5.80 (m, 1H,, H_6), 5.67 (dd, 1H, *J* = 15.9, 1.5 Hz, H_3), 5.62−5.71 (m, 1H, H_5), 4.22 (tdd, 1H, *J* = 6.4, 5.3, 1.3 Hz, H_4), 2.30−2.16 (m, 1H), 2.16−2.05 (m, 1H), 1.77−1.71 (m, 2H), 1.06 (s, 9H), 0.82 (t, 3H, *J* = 7.5 Hz, H_{10}), 0.18 (s, 9H); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ 146.5, 135.9, 135.8, 134.2, 134.1, 133.5, 129.8, 129.7 129.6, 127.6, 123.1, 123.0, 109.1, 103.7, 94.4, 73.0, 35.3, 27.0, 20.5, 19.3, 14.0, −0.1; HRMS (APPI-TOF) *m*/*z* 461.2690 $[M + H]^+$ calcd for $C_{29}H_{41}OSi_2$, found 461.2701.

*(5S,3E,7Z)-5-(tert-Butyldiphenylsilyloxy)deca-3,7-dien-1-yne (**7**).* To a solution of TMS-protected dienyne **6** (1.2 g, 2.7 mmol) in MeOH (25 mL) was added K_2CO_3 (46 mg, 0.33 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Water was added, and then the aqueous phase was extracted with CH_2Cl_2 and the combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The

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oily residue purified by flash chromatography on silica gel via gradient elution (98/2 hexanes−CH_2Cl_2 to 90/10 hexanes−CH_2Cl_2) to yield terminal (3*E*)-dienyne **7** as a yellow oil (950 mg, 95%). $[\alpha]^{21}_D$ −22 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.61 (m, 4H,), 7.45−7.34 (m, 6H), 6.21 (dd, 1H, *J* = 15.9, 5.4 Hz, H_4), 5.58 (dt, 1H, *J* = 15.9, 2.1 Hz, H_3), 5.61−5.34 (m, 1H, H_7), 5.21−5.15 (m, 1H, H_6), 4.21 (dtd, 1H, *J* = 8.4, 5.4, 2.1 Hz, H_5), 2.84 (d, 1H, *J* = 2.1 Hz, H_1), 2.25−2.09 (m, 2H, H_6), 1.80−1.73 (p, 2H, *J* = 7.5 Hz, H_9), 1.07 (s, 9H), 0.83 (t, 3H, *J* = 7.5 Hz, H_{10}); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 147.2, 135.9, 135.7, 134.3, 134.0, 133.5, 129.8, 129.6, 127.6, 123.0, 108.2, 82.1, 76.7, 73.0, 35.3, 27.0, 20.5, 19.3, 14.1; HRMS (APPI-TOF) *m*/*z* 389.2295 $[M + H]^+$ calcd for $C_{26}H_{33}OSi$, found 389.2295.

*Preparation of (3S,4E)-1,3-Di-tert-butylsilenyldioxy-5-iodopent-4-ene (**8**: C8−C12 Fragment).* (4*E*)-1,3-Di-*tert*-butylsilylene ketal **8** was prepared in four steps and 36% overall yield from commercially available (*S*)-1,2,4-butanetriol, as previously reported.[17a] ^{1}H NMR data were in full agreement with those reported in literature.[17a] $[\alpha]^{21}_D$ +6.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (dd, 1H, *J* = 14.2, 4.4 Hz, H_5), 6.37 (dd, 1H, *J* = 14.2, 1.5 Hz, H_4), 4.55 (tdd, 1H, *J* = 11.0, 4.2, 1.8 Hz, H_3), 4.12 (dd, 1H, *J* = 4.6, 2.6 Hz, H_1), 4.09 (d, 1H, *J* = 2.1 Hz, H_1), 1.91−1.79 (m, 1H, H_2), 1.76−1.65 (m, 1H, H_2), 1.02 (s, 9H), 1.00 (s, 9H); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 147.8, 76.2, 76.0, 63.8, 36.1, 27.3, 27.1, 19.9.

*Preparation of Phosphonium Iodide **15** (C1−C7 Fragment). (3-Carboxypropyl)triphenylphosphonium Bromide (**9**).* Phosphonium salt **9** was prepared as previously reported.[26] A flask was charged with γ-butyrolactone (5 g, 58 mmol) and triphenylphosphine hydrobromide (18.1 g, 52.7 mmol) and then preheated at 180−190 °C in a graphite bath under an argon atmosphere. After 10 min, all of the solids had melted, and the resulting liquid then became solid again. After 2 h at 180−190 °C, the mixture was cooled to room temperature and triturated with toluene. The solid was collected by filtration and washed with toluene. Upon drying under vacuum in the presence of phosphorus pentoxide, phosphonium salt **9** was recovered as a white powder (21.4 g, 94%). ^{1}H NMR data were consistent with those previously described:[26] ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (bs, 1H,), 7.91−7.74 (m, 15H), 3.58 (m, 2H), 2.49 (m, 2H), 1.70 (m, 2H).

*3-(tert-Butydimethylsilyloxy)propanal (**10**).* Aldehyde **10** was prepared in two steps in 83% overall yield from commercially available 1,3-propanediol as previously reported.[22] It was obtained as a crude liquid which was used in the next step without any further purification. ^{1}H NMR data were in full agreement with those reported in the literature:[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (bs, 1H), 3.90 (t, 2H, *J* = 6 Hz), 2.60 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H).

*Methyl (4Z)-7-(tert-Butyldimethylsilyloxy)hept-4-enoate (**12**).* A suspension of (3-carboxypropyl)triphenylphosphonium bromide (**9**) (2.8 g, 6.5 mmol) in dry THF (45 mL) was cooled under argon at −78 °C and treated with a solution of 1 M NaHMDS in THF (13 mL, 13 mmol). The mixture which turned yellow-orange was gradually warmed to 0 °C and stirred for 20 min at this temperature. After being cooled again to −78 °C, a solution of freshly prepared 3-(*tert*-butydimethylsilyloxy)propanal (**10**) (940 mg, 5 mmol) in THF (5 mL) was added dropwise to the orange ylide solution. The mixture was allowed to warm to 0 °C gradually and was stirred at that temperature for 2 h. The mixture was then quenched by addition of a saturated aqueous solution of NaH_2PO_4 and extracted by Et_2O. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The crude oil, which contains the desired *Z*-alcene **11** (1.1 g, 100% isomeric purity, ∼90% chemical purity) was dissolved in dry DMF (40 mL). MeI (0.95 mL, 15 mmol) was added followed by $KHCO_3$ (3 g, 30 mmol), and the resulting suspension was stirred at room temperature for 12 h. Water was added, and the aqueous phase was extracted with Et_2O. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The crude oil was purified by flash chromatography on silica gel (95/5 hexanes−EtOAc) to yield pure (*Z*)-ester **12** as an colorless oil (0.7 g, 51% from aldehyde **10**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (m, 2H), 3.67 (s, 3H), 3.61 (m, 2H), 2.36 (m, 4H), 2.28 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H).

*Methyl (4Z)-7-Hydroxyhept-4-enoate (**13**).* To an ice-cooled solution of ester **12** (2.9 g, 10.6 mmol) in dry THF (20 mL) was added TBAF (1 M solution in THF, 12 mL, 12 mmol). The reaction mixture was stirred for 1 h at room temperature before it was quenched by the addition of phosphate buffer (pH = 7). Brine and CH_2Cl_2 were added and the layers separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The oily residue was purified by flash chromatography on silica gel (80/20 hexanes-EtOAc) to yield hydroxyl ester **13** as a pale yellow oil (1.51 g, 90%).^{1}H NMR data were in full agreement with those reported in the literature:[17a,18,27] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58−5.40 (m, 2H), 3.69 (s, 3H), 3.60 (t, 2H, *J* = 6.0 Hz), 2.44−2.35 (m, 6H), 1.8 (bs, 1H).

*Methyl (4Z)-7-Iodohept-4-enoate (**14**).* Iodoester **14** was prepared as previously reported.[17a,18,27] To an ice-cooled solution of alcohol **13** (930 mg, 5.9 mmol) in dry CH_2Cl_2 (15 mL), protected against light with aluminum foil, were added while stirring, successively imidazole (1.2 g, 17.7 mmol), triphenylphosphine (2.3 g, 8.9 mmol), and iodine (2.25 g, 8.9 mmol). The mixture was stirred for 2 h and then diluted with CH_2Cl_2. The organic phase was successively washed with an saturated aqueous solution of $Na_2S_2O_3$ and a brine solution, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash chromatography on silica gel (90/10 hexanes−CH_2Cl_2) afforded iodide **14** (1.45 g, 92%) as a slightly yellow oil. ^{1}H NMR data were in full agreement with those reported in the literature:[17a,18,27] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53−5.43 (m, 1H), 5.41−5.30 (m, 1H), 3.65 (s, 3H), 3.14 (t, 2H, *J* = 7.1 Hz), 2.63 (q, 2H, *J* = 7.1 Hz), 2.32- 2.23 (m, 4H).

*(3Z)-(7-Carbomethoxyhept-3-enyl)triphenylphosphonium Iodide (**15**).* Phosphonium salt **15** was prepared as previously reported.[17a,18] To a solution of iodo ester **14** (973 mg, 3.6 mmol) in acetonitrile (20 mL) was added while stirring triphenylphosphine (1.14 g, 4.35 mmol). The mixture was heated under reflux and under argon for 10 h. After the mixture was cooled to room temperature, the solvent was evaporated under vacuum and the residue taken up with hexanes. To remove residual triphenylphosphine, the white suspension was vigorously stirred for 1 h and then filtered. The white solid was washed with hexanes and air-dried to yield the phosphonium salt **15** (1.8 g, 96%). This material was kept under vacuum and protected from light in a dryer containing phosphorus pentoxide as dehydrating agent. ^{1}H NMR data were in full agreement with those reported in the literature:[17a] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90−7.74 (m, 15H), 5.41 (m, 2H), 3.61 (m, 2H), 3.54 (s, 3H), 2.49 (m, 4H), 2.11 (m, 2H); ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6) δ 172.7, 134.9 (d, $^4J_{CP}$ = 2.8 Hz), 133.6 (d, $^3J_{CP}$ = 10.2 Hz), 130.2 (d, $^2J_{CP}$ = 11.6 Hz), 127.7, 127.5, 118.3 (d, $^1J_{CP}$ = 85 Hz), 51.3, 32.8, 22.2, 20.0 (d, $^1J_{CP}$ = 49.4 Hz), 19.7 (d, $^2J_{CP}$ = 3.1 Hz).

*Preparation of Conjugated-(4E,8E)-Trienyne **22**. (3S,10S,4E,8E,12Z)-10-(tert-Butyldiphenylsilyloxy)-1,3-((di-tert-butyl)silenyldioxy)pentadeca-4,8,12-trien-6-yne (**16**).* A solution of acetylenic compound **7** (950 mg, 2.45 mmol) in degassed benzene (5 mL) was added to a stirred mixture of vinyl iodide **8** (750 mg, 2.04 mmol), dichlorobis(triphenylphosphine)palladium(II) (172 mg, 0.2 mmol), and copper(I) iodide (91 mg, 0.48 mmol) in benzene (10 mL) under argon. (*i*-Pr)$_2$NH (15 mL) was added and the reaction mixture stirred at room temperature for 10 h. After this delay, the reaction mixture was filtered through a pad of Celite and washed with hexanes. The filtrate was concentrated and purified by flash chromatography on silica gel via gradient elution (99/1 hexanes−CH_2Cl_2 to 80/20 hexanes−CH_2Cl_2) to afford compound **16** as a pale brown oil (1.2 g, ∼100%). $[\alpha]^{21}_D$ −50 (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.61 (m, 4H), 7.44−7.33 (m, 6H), 6.12 (dd, 1H, *J* = 15.5, 4.1 Hz, H_4), 6.09 (dd, 1H, *J* = 15.7, 5.6 Hz, H_9), 5.95 (dd, 1H, *J* = 15.8, 1.5 Hz), 5.72 (dd, 1H, *J* = 15.8, 2.0 Hz), 5.38−5.34 (m, 1H, H_{13}), 5.22−5.16 (m, 1H, H_{12}), 4.66 (dtt, 1H, *J* = 11.0, 4.2, 1.5 Hz, H_3), 4.21 (dtd, 1H, *J* = 8.4, 5.4, 2.1 Hz, H_{10}), 4.13−4.08 (m, 2H, H_1), 2.24−2.20 (m, 1H), 2.18−2.10 (m, 1H), 1.88−1.67 (m,

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4H), 1.06, 1.03, and 1.00 (3s, 27H), 0.82 (t, 3H, J = 7.5 Hz, H_{15}); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ 145.0, 144.6, 135.9, 134.1, 134.0, 133.6, 129.7, 129.6, 127.5, 123.2, 109.3, 108.5, 88.7, 87.9, 73.4, 73.2, 64.0, 36.4, 35.5, 27.3, 27.1, 27.0, 20.5, 20.0, 19.3, 14.1; HRMS (APPI-TOF) m/z 629.3841 $[M + H]^+$ calcd for $C_{39}H_{57}O_3Si_2$, found 629.3843.

*(3S,10S,4E,8E,12Z)-Pentadeca-4,8,12-trien-6-yne-1,3,10-triol (**17**).* To an ice-cooled solution of (4*E*,8*E*)-trienyne **16** (1.2 g, 2 mmol) in THF (20 mL) was added TBAF (1 M in THF, 9 mL, 9 mmol). After being stirred for 10 min, the reaction mixture was then warmed to room temperature and stirred for an additional 2 h. After this time, it was partitioned between Et_2O and water, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated. Purification of the residue by flash chromatography on silica gel (60/40 hexanes−acetone) afforded triol **17** (360 mg, 72%) as a light yellow oil: $[\alpha]^{21}_D$ −32 (c 0.18, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.16 (dd, 1H, J = 15.8, 5.8 Hz, H_4), 6.15 (dd, 1H, J = 15.7, 5.4 Hz, H_9), 5.90 (d, 1H, J = 15.8 Hz), 5.87 (d, 1H, J = 15.8 Hz), 5.66−5.56 (dt, 1H, J = 10.5, 7.5 Hz, H_{13}), 5.36−5.32 (dt, 1H, J = 10.8, 6.9 Hz, H_{12}), 4.48 (dt, 1H, J = 7.7, 4.5 Hz, H_{10}), 4.21 (q, 1H, J = 5.8 Hz, H_3), 3.93−3.81 (m, 2H, H_1), 2.60 (bs, 1H, OH), 2.32 (t, 2H, J = 6.9 Hz, H_{11}), 2.06 (p, 2H, J = 7.4 Hz, H_{14}), 1.92−1.72 (m, 2H, H_2), 1.60 (bs, 2H, OH), 0.97 (t, 3H, J = 7.5 Hz, H_{15}); $^{13}C\{^1H\}$ NMR (100.6 MHz, MeOH-d_4) δ 146.8, 146.4, 134.9, 125.1, 110.6, 110.4, 88.9, 88.8, 72.7, 70.0, 59.6, 40.5, 35.8, 21.6, 14.5; HRMS (ESI-TOF) m/z 249.1485 $[M + H]^+$ calcd for $C_{15}H_{21}O_3$, found 249.1481.

*(3S,10S,4E,8E,12Z)-1-O-(Triphenylmethyl)pentadeca-4,8,12-trien-6-yne-1,3,10-triol (**18**).* To an ice-cooled solution of triol **17** (360 mg, 1.44 mmol), Et_3N (0.9 mL, 6.2 mmol), and DMAP (5 mg) in CH_2Cl_2 (100 mL) was added chlorotriphenylmethane (691 mg, 2.48 mmol). The reaction mixture was then warmed to room temperature and stirred for an additional 2 h. After this time, it was partitioned between Et_2O and water, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. Crude material (∼800 mg) was used directly in the next step without any purification. A pure sample of monoprotected triol **18** was obtained by flash chromatography (80/20 hexanes/EtOAc) and used for characterization: $[\alpha]^{21}_D$ −8.8 (c 0.28, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.42 (m, 5H), 7.41−7.22 (m, 10H), 6.14 (dd, 1H, J = 15.7, 5.6 Hz), 6.05 (dd, 1H, J = 15.7, 5.3 Hz), 5.85 (dd, 1H, J = 15.8, 1.8 Hz), 5.82 (dd, 1H, J = 15.8, 1.8 Hz), 5.63−5.57 (m, 1H), 5.37−5.31 (m, 1H), 4.42−4.39 (m, 1H, H_{10}), 4.25−4.06 (m, 1H, H_3), 3.37−3.33 (m, 1H, H_1), 3.01−3.32 (m, 1H, H_1), 2.96 (d, 1H, J = 4.0 Hz, OH), 2.20−2.24 (m, 1H), 2.33 (dd, 2H, J = 7.1, 6.4 Hz, H_{10}), 2.07 (p, 2H, J = 7.4 Hz, H_{14}), 1.90−1.76 (m, 2H, H_2), 1.67 (d, 1H, J = 4.3 Hz, OH), 0.97 (t, 3H, J = 7.6 Hz, H_{15}); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ 144.9, 144.5, 143.6, 135.8, 128.5, 128.3, 127.9, 127.1, 123.1, 110.0, 109.6, 88.3, 87.9, 87.4, 71.5, 71.1, 61.6, 36.3, 34.9, 20.7, 14.1; no molecular ion obtained by ESI, APPI, or APCI mass spectrometry.

*(3S,10S,4E,8E,12Z)-3,10-Bis(tert-Butyldiphenylsilyloxy)-1-O-(triphenylmethyl)pentadeca-4,8,12-trien-6-yne-1,3,10-triol (**19**).* A solution of crude monoprotected triol **18** (∼ 800 mg, 1.44 mmol), imidazole (476 mg, 7 mmol), and DMAP (10 mg) in CH_2Cl_2 (5 mL) was cooled to 0 °C, and chloro-*tert*-butyldiphenylsilane (0.92 mL, 3.5 mmol) was added. The reaction was stirred for 10 h at room temperature. After this time, the reaction mixture was diluted with CH_2Cl_2, washed with a 10% aqueous HCl solution and then brine, and finally dried over Na_2SO_4. Filtration, concentration, and purification of the residue by flash chromatography on silica gel via gradient elution (99/1 hexanes−CH_2Cl_2 to 95/5 hexanes−CH_2Cl_2) afforded tris-protected triol **19** (1.15 g, 80% from triol **17**) as a viscous oil: $[\alpha]^{21}_D$ −57 (c 0.18, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.52 (m, 8H), 7.44−6.99 (m, 27H), 6.05 (dd, 1H, J = 15.7, 5.6 Hz), 5.97 (dd, 1H, J = 15.8, 6.4 Hz), 5.68 (d, 1H, J = 15.8 Hz), 5.46 (d, 1H, J = 16.3 Hz), 5.39−5.30 (m, 1H), 5.26−5.17 (m, 1H), 4.40 (q, 1H, J = 5.6 Hz), 4.23−4.19 (m, 1H), 3.02−2.95 (m, 2H, H_1), 2.23−2.03 (m, 2H), 1.80−1.70 (m, 2H), 1.70−1.49 (m, 2H), 1.07 (s, 9H), 1.00 (s, 9H), 0.84 (t, 3H, J = 7.6 Hz, H_{15}); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ 144.8, 144.7, 144.2, 135.9, 135.8, 135.7, 134.1, 134.0, 133.6, 128.7, 129.6, 129.5, 128.6, 127.7, 127.5, 127.4, 127.3, 126.8, 123.2, 109.6, 109.4, 88.1, 88.2, 86.4, 73.2, 71.6, 59.8, 38.0, 35.5, 27.0, 26.9, 20.5, 19.3, 19.2, 14.1; HRMS (APPI-TOF) m/z 968.5014 $[M]^+$ calcd for $C_{66}H_{72}O_3Si_2$, found 968.5045.

*(3S,10S,4E,8E,12Z)-3,10-Bis(tert-butyldiphenylsilyloxy)-pentadeca-4,8,12-trien-6-yn-1-ol (**20**).* A solution of tris-protected diol **19** (1.15 g, 1.17 mmol) in CH_2Cl_2 (10 mL) and MeOH (10 mL) was cooled to 0 °C, and camphor-10-sulfonic acid (200 mg, 0.87 mmol) was added in portions. The mixture was stirred at 0−5 °C for 30 min and then warmed to room temperature. After being stirred for 2 h at this temperature, the reaction was neutralized with a saturated aqueous solution of $NaHCO_3$. MeOH was evaporated, and the residue extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash chromatography on silica gel via gradient elution (99/1 hexanes−EtOAc to 80/20 hexanes−EtOAc afforded bis-protected triol **20** (700 mg, 80%) as a viscous oil: $[\alpha]^{21}_D$ −96 (c 0.24, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.62 (m 8H,), 7.44−7.35 (m, 12H), 6.10 (dd, 1H, J = 15.5 Hz, 6.0 Hz, H_4), 6.06 (dd 1H,, J = 16.2, 6.5 Hz, H_9), 5.71 (dd, 1H, J = 15.8, 1.5 Hz), 5.65 (dd, 1H, J = 15.8, 1.5 Hz), 5.39−5.30 (m, 1H, H_{13}), 5.22−5.16 (m, 1H, H_{12}), 4.46 (qd, 1H, J = 4.9, 1.5 Hz, H_3), 4.21 (dtd,1H, J = 7.0, 5.0, 1.5 Hz, H_{10}), 3.74−3.66 (m, 1H, H_1), 3.63−3.57 (m, 1H, H_1), 3.49 (d, 1H, J = 5.6 Hz, OH), 2.25−2.04 (m, 2H), 1.80−1.72 (m, 2H), 1.70−1.60 (m, 2H), 1.08 (s, 9H), 1.07 (s, 9H), 0.83 (t, 3H, J = 7.5 Hz, H_{15}); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ 145.2, 144.1, 135.9, 135.8, 134.1, 134.0, 133.6, 133.5, 133.1, 129.9, 129.8, 129.7, 127.7, 127.6, 127.5, 123.2, 110.1, 109.3, 88.7, 87.7, 73.2, 72.1, 59.2, 35.4, 30.3, 27.1, 27.0, 19.3, 19.2, 14.1; molecule apolar, no ion detected by ESI or APCI mass spectrometry.

*(3S,10S,4E,8E,12Z)-3,10-Bis(tert-butyldiphenylsilyloxy)-pentadeca-4,8,12-trien-6-ynal (**21**).* Dess−Martin periodinane (18 mg, 0.041 mmol) was added to an ice-cooled solution of alcohol **20** (20 mg, 0.027 mmol) in CH_2Cl_2 (2 mL). The solution was warmed to room temperature and stirred for 2 h. The reaction was quenched by adding a solution of $Na_2S_2O_3$ containing some Et_3N (0.1 mL). The mixture was vigorously stirred for 30 min to destroy any excess of oxidizing reagent. Solid Na_2SO_4 was added and the mixture filtered through a pad of deactivated silica gel. Elution with 99/1 pentane−Et_2O yielded aldehyde **21** (16 mg, 80%) as a pale yellow oil: $[\alpha]^{21}_D$ −105 (c 0.1, acetone); ^1H NMR (400 MHz, $CDCl_3$) δ 9.64 (t, 1H, J = 2.3 Hz, H_1), 7.69−7.61 (m, 8H) 7.44−7.35 (m, 12H,), 6.12 (dd, 1H, J = 15.8, 5.8 Hz) 6.10 (d, 1H, J = 15.7 Hz), 5.76 (dd, 1H, J = 15.8, 1.5 Hz), 5.70 (d, 1H, J = 15.8, 1.5 Hz), 5.38−5.33 (m, 1H), 5.21−5.16 (m, 1H), 4.69 (m, 1H), 4.21 (m, 1H), 2.47 (ddd, 1H, J = 7.6, 5.0, 2.1 Hz, H_2), 2.22−2.10 (m, 2H), 1.78−1.72 (m, 2H), 1.07 (s, 18H), 0.83 (t, 3H, J = 7.5 Hz, H_{15}); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ 200.5, 145.4, 142.9, 135.9, 135.8, 134.1, 134.0, 132.9, 130.0, 129.9, 129.7, 129.6, 127.8, 127.7, 127.5, 110.8, 109.2, 89.4, 87.3, 73.2, 69.2, 55.1, 50.6, 35.6, 35.4, 30.9, 27.0, 26.9, 20.5, 19.4, 14.0; molecule apolar and unstable, no ion detected by ESI or APCI mass spectrometry.

*Methyl (10S,17S,4Z,7Z,11E,15E,19Z)-10,17-Bis(tert-butyldiphenylsilyloxy)docosa-4,7,11,15,19-penten-13-ynoate (**22**).* Prior to starting the reaction, phosphonium salt **15** was coevaporated twice with toluene. A flamed dried flask was charged with phosphonium salt **15** (647 mg, 1.2 mmol), THF (6 mL), and HMPA (0.6 mL) under argon. The mixture was cooled to −78 °C. A solution of NaHMDS (1 M in THF, 1 mL, 1 mmol) was added dropwise and the mixture stirred for 1 h at −78 °C. The color of the reaction mixture changed during this period, passing from dark-yellowish to dark orange. Freshly prepared aldehyde **21** (445 mg, 0.58 mmol) in THF (1 mL) was added and the cooling bath replaced by an ice bath. The mixture was slowly warmed to 0−5 °C with further stirring for 1 h and then quenched with an aqueous solution of saturated NaH_2PO_4. The resulting solution was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash chromatography on deactivated silica gel (98/2 pentane−Et_2O) afforded ester (7*Z*)-**22**

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(372 mg, 75%) as a pale yellow oil: $[\alpha]^{21}_{D}$ −68 (*c* 0.19, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, 2H, *J* = 6.6 Hz), 7.63 (d, 2H, *J* = 7.1 Hz), 7.57−7.26 (m, 16H), 6.09 (dd, 1H, *J* = 15.8, 6.1 Hz), 6.08 (dd, 1H, *J* = 14.2, 6.0 Hz), 5.73 (d, 1H, *J* = 15.8 Hz), 5.72 (d, 1H, *J* = 15.8 Hz), 5.69−5.16 (m, 6H, H_4, H_5, H_7, H_8, H_{19}, H_{20}), 4.27−4.19 (m, 2H, H_{10}, H_{17}), 3.66 (s, 3H, CO_2CH_3), 2.56 (t, 2H, *J* = 5.7 Hz, H_6), 2.35−2.30 (m, 4H, H_2, H_3), 2.30−2.08 (m, 4H, H_9, H_{18}), 1.76 (p, 2H, *J* = 7.4 Hz, H_{21}), 1.07 (s, 18H), 0.83 (t, 3H, *J* = 7.4 Hz, H_{22}); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 173.4, 144.9, 144.6, 135.9, 135.9, 134.1, 133.7, 133.6, 130.0, 129.8, 129.7, 129.6, 129.2, 127.7, 127.5, 124.6, 123.3, 109.7, 109.5, 88.3, 88.1, 73.2, 73.1, 51.5, 35.6, 35.5, 34.0, 27.0, 26.9, 22.7, 20.5, 19.3, 14.0; molecule apolar, no ion detected by ESI or APCI mass spectrometry.

7-Preparation of Methyl Ester ***24*** *and PDX (****2****). Methyl (10S,17S,4Z,7Z,11E,15E,19Z)-10,17-Dihydroxydocosa-4,7,11,15,19-pentene-13-ynoate (****23****).* Pentaenyne **22** (372 mg, 0.438 mmol) was treated with TBAF (1 M solution in THF, 5 mL), and the reaction mixture was then stirred at room temperature for 2 h. After this time, it was partitioned between EtOAc and an aqueous solution of saturated NaH_2PO_4, and the layers were separated. The organic layer was successively washed with water and brine solutions, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash chromatography on deactivated silica gel via gradient elution (95/5 pentane−Et_2O to 75/25 pentane−Et_2O) afforded diol **23** (140 mg, 80%) as a light yellow oil: $[\alpha]^{21}_{D}$ +17 (*c* 0.2, MeOH); ^{1}H NMR (400 MHz, MeOH-d_4) δ 6.08 (dd, 1H, *J* = 15.6, 3.4 Hz), 6.06 (dd, 1H, *J* = 15.5, 3.5 Hz), 5.79 (dd, 1H, *J* = 15.8, 1.7 Hz), 5.78 (dd, 1H, *J* = 15.8, 1.5 Hz), 5.52−5.32 (m, 6H, H_4, H_5, H_7, H_8, H_{19}, H_{20}), 4.16−4.02 (m, 2H, H_{10}, H_{17}), 3.65 (s, 3H, CO_2CH_3), 2.83 (bt, 2H, *J* = 5.5 Hz, H_6), 2.38−2.36 (m, 4H, H2, H3), 2.35−2.27 (m, 4H, H_9, H_{18}), 2.05 (m, 2H, H_{21}), 0.96 (t, 3H, *J* = 7.6 Hz, H_{22}); ^{13}C{^{1}H} NMR (100.6 MHz, MeOH-d_4) δ 175.3, 146.4, 146.3, 136.3, 135.0, 131.2, 130.9, 130.2, 129.9, 129.8, 129.0, 126.5, 126.2, 125.6, 125.1, 110.7, 110.6, 88.9, 88.8, 72.6, 72.5, 52.1, 36.0, 35.9, 34.8, 30.9, 28.9, 26.7, 23.8, 21.6, 14.5; MS (APCI neg) *m*/*z* (intensity) 371 [M − H] (25), 353 [M − H − H_2O] (25), 335 [M − H − 2H_2O] (100). HPLC analysis; mobile phase MeOH−H_2O from 70:30 to 85:15 (15 min) and 100:0 (5 min), flow (1.0 mL/min), UV detector at 265 nm, t_R = 13.5 min, 96% purity.

Methyl (10S,17S,4Z,7Z,11E,13Z,15E,19Z)-10,17-Dihydroxydocosa-4,7,11,13,15,19-hexenoate, ***(24****: PDX-methyl Ester).* A 10 mL Schlenk tube was charged with freshly prepared activated Zn(Cu/Ag)[23,24] (20% suspension in a 1:1 mixture of MeOH−H_2O, 6.5 mL). Argon was bubbled through the mixture, and then TMSCl (100 μL) was added. A solution of conjugated alkyne **23** (35 mg, 0.094 mmol) in MeOH (4 mL) was added 5 min later, and the black suspension was purged again for 5 min and then the tube was sealed. After vigorous stirring at room temperature for 16 h in the dark, the black slurry was filtered through a pad of Celite and thoroughly washed with Et_2O. The solvents were evaporated under vacuum in the dark and without heating. The residue was purified by flash chromatography on deactivated silica gel via gradient elution (95/5 pentane−Et_2O to 70/30 pentane−Et_2O) giving PDX-methyl ester **24** (18 mg, 51%) as a pale yellow oil. This material was found to decompose at room temperature when exposed to light and air (allylic oxidation); thus, it was kept in a vial protected from light under argon at −80 °C: $[\alpha]^{21}_{D}$ +6 (c 0.02, MeOH); ^{1}H NMR (400 MHz, MeOH-d_4) δ 6.78−6.66 (m, 2H, H_{12}, H_{15}), 5.96 (dt, 2H, *J* = 10.2, 8.5 Hz, H_{13}, H_{14}), 5.74 (dd, 1H, *J* = 15.1, 6.4 Hz, H_{11} or H_{16}), 5.70 (dd, 1H, *J* = 15.1, 6.4 Hz, H_{11} or H_{16}), 5.52−5.32 (m, 6H, H_4, H_5, H_7, H_8, H_{19}, H_{20}), 4.16−4.02 (m, 2H, H_{10}, H_{17}), 3.65 (s, 3H, CO_2CH_3), 2.82 (bt, 2H, *J* = 5.7 Hz, H_6), 2.38−2.26 (m, 8H, H_2, H_3, H_9, H_{18}), 2.05 (p, 2H, *J* = 7.6 Hz, H_{21}), 0.96 (t, 3H, *J* = 7.6 Hz, H_{22}); ^{13}C{^{1}H} NMR (100.6 MHz, MeOH-d_4) δ 173.9, 137.7, 136.6, 134.6, 133.2, 130.0, 129.5, 129.2, 128.9, 128.6, 128.5, 127.5, 125.4, 125.2, 125.1, 125.0, 124.5, 124.0, 71.7, 71.6, 50.6, 34.9, 34.8, 33.4, 28.1,25.2, 22.4, 20.2, 13.1; MS (APCI pos) *m*/*z* (intensity) 375 [M + H] (5), 357 [M + H − H_2O] (100), 339 [M + H − 2H_2O] (100). HPLC analysis; mobile phase MeOH-H_2O from 70:30 to 85:15 (15 min) and 100:0 (5 min), flow (1.0 mL/min), UV detector at 270 nm, t_R = 15.8 min, 93% purity.

*(10S,17S,4Z,7Z,11E,13Z,15E,19Z)-10,17-Dihydroxydocosa-4,7,-11,13,15,19-hexenoic Acid (****2****: PDX).* PDX-methyl ester (**24**) (10 mg, 0.026 mmol) was dissolved in a 2:2:1 mixture of THF−MeOH−H_2O (0.5 mL), and the solution was degassed with argon. After being cooled at 5 °C, solid LiOH (34 mg, 0.8 mmol) was added, and the mixture was degassed again. After 3 h of stirring at 5 °C, the reaction was neutralized with an aqueous solution of saturated NaH_2PO_4, followed by an extraction with Et_2O. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated under vacuum without any heating. The residue was purified by flash chromatography on deactivated silica gel via gradient elution (95/5 hexanes−acetone to 70:30 hexanes−acetone) to give PDX (**2**) (7.4 mg, 77%) as a pale yellow oil. PDX (**2**) was known to be sensitive when exposed to light and air. A concentrated solution of PDX (**2**) in MeOH was found to decompose quickly thus it was kept in dilute EtOH solution (0.01%) in a vial protected from light under argon at −80 °C: ^{1}H NMR (400 MHz, MeOH-d_4) δ 6.75−6.69 (m, 2H, H_{12}, H_{15}), 5.97 (dt, 2H, *J* = 10.1, 8.1 Hz, H_{13}, H_{14}), 5.74 (dd, 1H, *J* = 15.3, 6.4 Hz, H_{11} or H_{16}), 5.71 (dd, 1H, *J* = 15.0, 6.4 Hz, H_{11} or H_{16}), 5.50−5.32 (m, 6H, H_4, H_5, H_7, H_8, H_{19}, H_{20}), 4.20−4.15 (m, 2H, H_{10}, H_{17}), 2.83 (bt, 2H, *J* = 5.4 Hz, H_6), 2.39−2.12 (m, 8H, H_2, H_3, H_9, H_{18}), 2.07 (p, 2H, *J* = 7.4 Hz, H_{21}), 0.95 (t, 3H, *J* = 7.5 Hz, H_{22}); ^{13}C{^{1}H} NMR (100.6 MHz, MeOH-d_4) δ 136.7, 136.6, 135.7, 133.3, 130.0, 129.5, 128.7, 128.5, 127.8, 125.1, 125.0, 124.7, 124.0, 71.7, 71.6, 34.9, 34.8, 33.6, 29 4, 25.3, 22.5, 20.2, 13.1; MS (APCI neg) *m*/*z* (intensity) 359 [M − H] (100), 341 [M − H − H_2O] (16). HPLC analysis, mobile phase MeOH−H_2O from 70:30 to 85:15 (30 min) and 100:0 (5 min), flow (1.0 mL/min), UV detector at 266 nm, t_R = 13.49 min, 96% purity. LC−MS/MS analysis for comparison assay with natural material (for the analytical procedures see ref 12a), t_R = 14.20 min for PDX (**2**) from the Cayman Chemical Company, t_R = 14.21 min for synthetic PDX (**2**); UV−vis (MeOH) λ_{max} 269 nm (shoulders at 258 and 280 nm).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01973.

NMR spectra of **3**, **5**−**8**, **12**, **13**, **15**-**23**, PDX-methyl ester (**24**), and PDX (**2**); HPLC chromatograms of PDX-methyl ester (**24**) and PDX (**2**); UV−vis absorption spectrum of PDX (**2**) (PDF)

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Notes

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