Syntheses of *all*-(*Z*)-5,8,11,14,17-Eicosapentaenoic Acid and *all*-(*Z*)-4,7,10,13,16,19-Docosahexaenoic Acid from (*Z*)-1,1,6,6-Tetraisopropoxy-2-hexene

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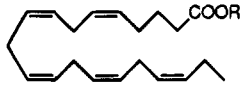
Received March 1, 1995

Polyunsaturated fatty acids (PUFAs) of the ω-3 family such as EPA (**1a**)[1] and DHA (**2a**)[1] are derived either from dietary α-linolenic acid (C18:3, ω-3) or directly from marine food.[2] EPA and DHA are correlated in preventing cardiovascular and inflammatory risks.[3] DHA, which is highly concentrated in structural lipids of the central nervous system and brain and particularly in the retina,[4] may act as a storable precursor of EPA through a retroconversion pathway.[5] Thus, the activity of EPA was established in the response of the eye to injury and inflammation,[6] in the inhibition of arachidonic acid metabolism and in the production of alternative bioactive products[7] such as TXA_3,[1] a very weak platelet aggregator, PGI_3,[1] a potent antiaggregator,[8] and LTB_5,[1] which may antagonize the proinflammatory action of LTB_4.[9] Although EPA and DHA play an important role in human metabolism, much research is still needed to gain more detailed knowledge on their metabolic effects by using pure or modified EPA and DHA. With this purpose in mind, we report herein two new and efficient stereoselective total syntheses of these PUFAs. Our approach uses, as a cornerstone reagent, the versatile C6 homologating agent **3**, easily obtained by oxidative dimerization of phosphonium salt **4**.[10]



1a: R = H, **EPA**
1b: R = Me

2a: R = H, **DHA**
2b: R = Me
2c: R = Et

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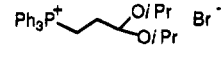

4

The first syntheses of EPA and DHA were described 30 years ago and involved sequential acetylenic homologations followed by selective hydrogenation of the polyyne systems.[11] Since acetylenic intermediates are difficult to handle and the main (*Z*) product of the partial reduction is generally contaminated with its (*E*) isomer, the Wittig reaction is a versatile alternative way to elaborate pure *all*-(*Z*) skipped polyenic skeletons of PUFAs.[12] Indeed, we have previously reported a stereoselective synthesis of EPA based on the development of a C6 phosphonium homologating agent obtained in 33% yield from 1-methoxy-1,4-cyclohexadiene[13] and, more recently, Taber[14] described a total synthesis of DHA ethyl ester (**2c**) using a related C9 1,4-dienic phosphonium salt homologating agent.

To further illustrate the synthetic potential of our approach, we have developed a new and efficient preparation of the symmetric C6 homologating agent **3**,[10] which allows a versatile access to different (*Z*)-skipped polyunsaturated precursors of PUFAs through a single Wittig reaction. The resulting (*Z*) 1,4-dienes (**15**, **19**) or 1,4,7-trienes (**7**, **8**) units can be used either as ylide or as carbonyl in a subsequent Wittig olefination leading stereoselectively to natural EPA and DHA (Scheme 1).

The (*Z*)-bis(diisopropylacetal) **3**[10] undergoes a monodeacetalization leading to a mixture of **3** and **5** in a 3:7 ratio (95%). This mixture was added to a THF solution of the ylide derived from (*Z*)-3-hexenyltriphenylphosphonium bromide (**6**)[15] and gives the *all*-(*Z*) trienic acetal **7** in 56% yield based on recovered **3**. Hydrolysis of the diisopropylacetal moiety under standard conditions[16] leads quantitatively to the pivotal intermediate of both syntheses, *all*-(*Z*) trienic aldehyde **8**. It is worth noting that under these conditions, no modification of the ethylenic skeleton occurs neither in the phosphonium salt **6** nor in the homologating agent **3**. The (*Z*) stereochemistry of all double bonds was checked by ^{13}C NMR (50.32 MHz) based on the chemical shift of allylic and bis allylic methylene. Indeed, it is known that the signals of allylic and bis allylic methylene are shifted downfield by *ca.* 5.3 ppm when the double bond is (*E*).[17] Without any purification, **8** is readily added to a THF solution of ylide derived from **9** to give in 60% yield methyl ester **1b** which upon saponification gives natural EPA (**1a**) (93%).[18,19] Although the preparation of the functionalized ethylenic phosphonium salt **9** has already been described,[20] our approach based on a Wittig olefination with the C3 homologating agent **4**[21] is competitive. Indeed, it involves

(1) EPA: *all*-(*Z*) 5,8,11,14,17-eicosapentaenoic acid; DHA: *all*-(*Z*)-4,7,10,13,16,19-docosahexaenoic acid; TXA_3: thromboxane A3; PGI_3 prostaglandin I_3; LTB: leukotriene B.

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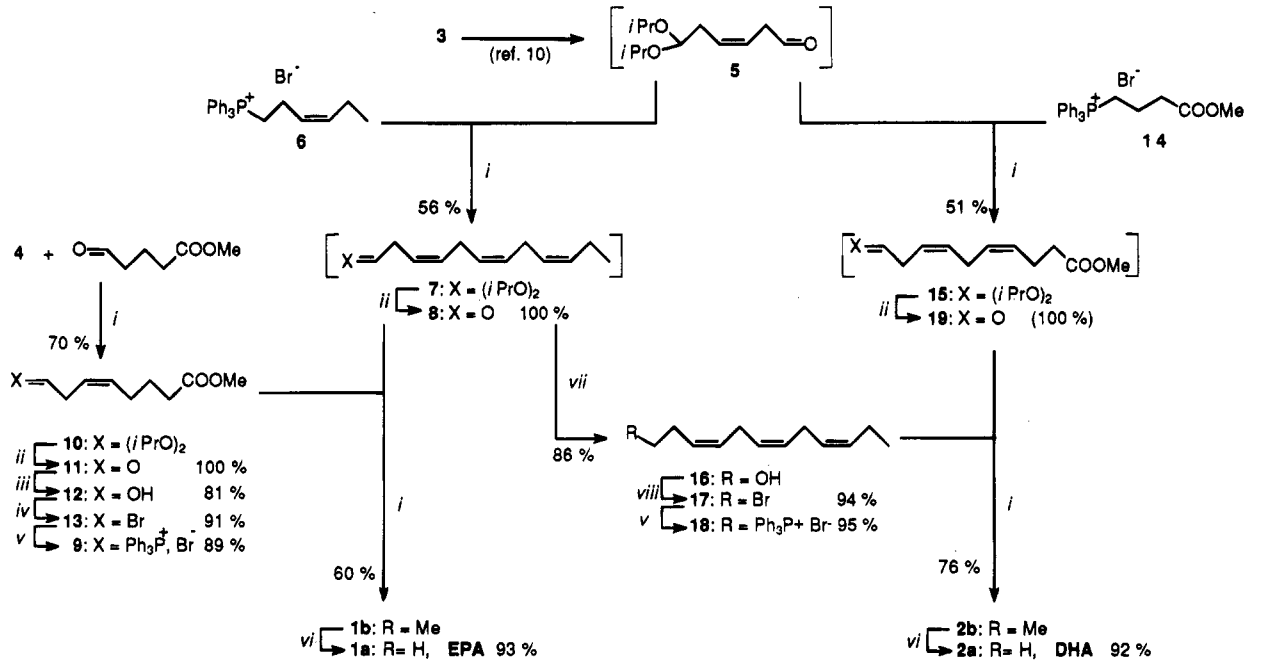
Scheme 1. C6 Homologation: Total Syntheses of EPA and DHA

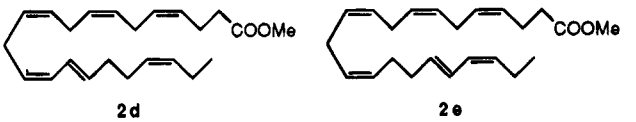


i: $NaN(SiMe_3)_2$; *ii*: THF, H+; *iii*: $NaBH_4$, EtOH; *iv*: Ph_3PBr_2, acetonitrile; *v*: Ph_3P, Δ; *vi*: LiOH, THF/H_2O; *vii*: $LiAlH_4$, THF, -70°C, *viii*: CBr_4,Ph_3P, CH_2Cl_2.

as the first two intermediates, acetal ester **10** (70%) and aldehyde ester **11** (100%), which are powerful synthetic tools.[22] Then, an easy reduction with $NaBH_4$ gives the known alcohol ester **12**,[23] while bromination and phosphorylation furnish the phosphonium salt **9**.

Similarly, the synthesis of DHA based on the C6 homologation of the ylide prepared from **14**[24] was attempted. Addition of $NaN(SiMe_3)_2$ to a solution of **14** followed by low temperature addition of freshly prepared aldehyde **5** gives the (*Z,Z*)-1,4-dienic ester acetal **15** in 51% yield. This strategy shows its versatile feature since the next Wittig reaction, which completes the skeleton of DHA, can be run from synthons **7** and **15** by using them either as ylide or aldehyde and *vice-versa*.[25] Actually, acetal **7** was chosen as ylide, due to the better yields encountered during its preparation, and therefore it is converted into phosphonium salt **18** in 77% overall yield, through the pivotal aldehyde **8**. The (*Z*) trienic system remains unchanged during all these transformations. Hydrolysis of **15** into aldehyde **19** and addition to the ylide solution, prepared from **18** at 0 °C, lead, in very good yield (93%), to the unexpected mixture of DHA methyl ester **2b** and its conjugated isomers **2d** and **2e** resulting from the migration of a double bond in a 25:75 (**2b**:**2d**+**2e**) ratio.[26]

The 1,3-diene moiety is probably generated through an intramolecular process involving the migration of one of the double bonds during the ylide formation. This



2d **2e**

particular behavior is not observed with phosphonium salts bearing only two (*Z*) double bonds.[27] Fortunately, this isomerization pathway is largely temperature dependent: indeed a 88:12 (**2b**:**2d**+**2e**) ratio is observed at −40 °C while DHA methyl ester **2b** is the only isomer obtained, with 76% yield, at −80 °C. Finally, saponification with LiOH in THF furnishes natural DHA (**2a**) in 92% isolated yield.[19,28]

In conclusion, our new synthetic approach to high PUFAs by using the versatile C6 homologating agent **3** allows the stereoselective preparation of various powerful intermediates containing the *all*-(*Z*) 1,4- or 1,4,7-polyenic framework and bearing one or two modulable functions such as an ester, an acetal, an aldehyde, an alcohol, a bromide, or a phosphonium salt. Moreover, a judicious choice of the substrates and the adaptation of the experimental conditions required for the Wittig reactions enabled us to achieve new and efficient stereoselective syntheses of natural EPA and DHA. Finally, our results should be useful in future developments of new modified C6 homologating agents and hence should provide new entries to labeled or unnatural PUFAs which could be of great interest for biological studies.[2]

Experimental Section

For general experimental procedure see refs 16 or 10. Preparation of C6 homologating agent **3** and its conversion into aldehyde **5** are made according to ref 10. Preparation of compound **4** is performed according to ref 21.

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(24) Prepared in two steps from butyrolactone according to Franke, I.; Binder, M. *Helv. Chim. Acta* **1980**, *63*, 2508.
(25) Aldehyde ester **19** has been reduced with $NaBH_4$ into the corresponding alcohol in good yield, without isomerization or migration of the double bonds.
(26) Compounds **2d** and **2e** exhibit, in ^1H NMR, the characteristic signals of a 1,3-dienic moiety: (δ) 6.32 (1H, dd, J = 14.9; 11.0 Hz), 5.93 (1H, br t, J = 11.0 Hz), 5.72−5.58 (1H, br quint, J = 7.0 Hz).
(27) See ref 10. Formation of ylide of [(*Z,Z*)-3,6-nonadien-1-yl]-triphenylphosphonium bromide at 0 °C for 2 h does not lead to a 1,3-diene Wittig product.
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(Z)-3-Hexenyltriphenylphosphonium Bromide (6). To a solution of (Z)-3-hexenol (5.47 g, 54 mmol, 1 equiv) and pyridine (7 mL, 71 mmol, 1.6 equiv) in acetonitrile (110 mL) was added, at 0°C in several portions, Ph_3PBr_2 (30 g, 71 mmol, 1.3 equiv). The reaction was checked by TLC (disapearance of alcohol). The reaction mixture was added to ether/pentane 1/1 (400 mL), and then filtered through a short pad of silica gel. Slow distillation of solvents gave the crude 1-bromo-3-hexene which was diluted in acetonitrile (60 mL) with Ph_3P (17.6 g, 108 mmol, 2 equiv) and refluxed for 24 h. After concentration, the crude material was chromatographed (silica gel 70–230 mesh, ether/pentane = 1/1, ether, CH_2Cl_2/MeOH = 20/1) giving pure white crystalline salt **6** (16.06 g, 70%): R_f = 0.18 (CH_2CL_2/MeOH = 20/1), mp = 162 °C. ^1H NMR δ 7.80–7.52 (15H, m, m), 5.43–5.24 (2H, m), 3.76–3.62 (2H, m), 2.43–2.26 (2H, m), 1.80–1.65 (2H, br quint, J = 7.2 Hz), 0.74 (3H, t, J = 7.5 Hz). ^{13}C NMR δ 134.97 (3C, d, J = 3.5 Hz), 133.97 (1C), 133.38 (6C, d, J = 11.3 Hz), 130.62 (6C, d, J = 12.9 Hz), 125.06 (1C, d, J = 14.3 Hz), 117.81 (3C, d, J = 85.8 Hz), 22.79 (1C, d, J = 47.7 Hz), 20.25 (1C), 19.94 (1C, d, J = 4.0 Hz), 13.69 (1C). ^{31}P NMR δ 23.25 (s).

(Z,Z,Z)-1,1-Diisopropoxydodeca-3,6,9-triene (7). To a suspension of 3-hexenyltriphenylphosphonium bromide (**6**) (5 g, 11.76 mmol, 1.1 equiv) in THF (130 mL) was added, at −10 °C, 1 M THF solution of sodium bis(trimethylsilyl)amide (10.5 mL, 10.5 mmol, 0.98 equiv). The orange solution of ylide was stirred at rt while homologating agent **3** (3.38 g, 10.68 mmol, 1 equiv) underwent the monodeacetalization.[10] The ylide solution was cooled at −90 °C, and aldehyde **5** was added. After hydrolysis with saturated NH_4Cl and classical workup, flash chromatography (silica gel 230–400 mesh, ether/pentane = 1/100 to 1/1) gave unreacted **3** (0.368 g, 1.16 mmol) and the pure trienic acetal **7** (1,49 g, 56% based on recovered **3**) as a colorless oil: R_f = 0.77 (ether/pentane = 1/4). ^1H NMR δ 5.44–5.24 (6H, m), 4.52 (1H, t, J = 5.6 Hz), 3.83 (2H, sept, J = 6.1 Hz), 2.82–2.74 (4H, m), 2.37–2.32 (2H, br t, J = 5.6 Hz), 2.11–1.97 (2H, br quint, J = 7.3 Hz), 1.16 (6H, d, J = 6.1 Hz), 1.11 (6H, d, J = 6.1 Hz), 0.94 (3H, t, J = 7.4 Hz). ^{13}C NMR δ 131.99 (1C), 130.91 (1C), 128.50 (1C), 127.91 (1C), 127.05 (1C), 124.79 (1C), 99.89 (1C), 67.63 (2C), 33.79 (1C), 25.89 (1C), 25.55 (1C), 23.37 (2C), 22.54 (2C), 20.56 (1C), 14.27 (1C). IR (film) ν 1650, 1470, 1380, 1340, 1180, 1130, 1030, 700 cm^{-1}.

(Z,Z,Z)-Dodeca-3,6,9-trienal (8). By using the standard conditions of hydrolysis,[16] trienic acetal **7** (0.153 g, 0.54 mmol, 1 equiv) yielded quantitatively pure **8**: R_f = 0.23 (ether/pentane = 1/4). ^1H NMR δ 9.65 (1H, t, J = 1.9 Hz), 5.74–5.21 (6H, m), 3.22–3.18 (2H, dd, J = 6.5 Hz, 1.8 Hz), 2.83–2.75 (4H, br q, J = 5.8 Hz), 2.12–1.98 (2H, br quint, J = 7.2 Hz), 0.95 (3H, t, J = 7.5 Hz). ^{13}C NMR δ 199.39 (1C), 133.20 (1C), 132.20 (1C), 129.20 (1C), 126.86 (1C), 126.75 (1C), 118.64 (1C), 42.49 (1C), 25.96 (1C), 25.56 (1C), 20.59 (1C), 14.29 (1C). IR (film) ν 2721, 1726, 1651, 730 cm^{-1}.

(Z)-8,8-Diisopropoxyoct-5-enoic Acid Methyl Ester (10). The procedure described in ref 16, with phosphonium salt **4** (3.9 g, 7.78 mmol, 1.5 equiv) and 5-oxopentanoic acid methyl ester (0.675 g, 5.19 mmol, 1 equiv), led after workup to acetal ester **10** (0.988 g, 70%): R_f = 0.65 (ether/pentane = 1/1) as a colorless oil. ^1H NMR δ 5.45–5.36 (2H, m), 4.48 (1H, t, J = 5.6 Hz), 3.80 (2H, sept, J = 6.1 Hz), 3.61 (3H, s), 2.35–2.22 (4H, m), 2.08–2.00 (2H, br q, J = 7.2 Hz), 1.71–1.61 (2H, br quint, J = 7.3 Hz), 1.12 (6H, d, J = 6.1 Hz), 1.07 (6H, d, J = 6.1 Hz). ^{13}C NMR δ 174.11 (1C), 130.61 (1C), 125.50 (1C), 99.84 (1C), 67.85 (2C), 51.47 (1C), 33.75 (1C), 33.45 (1C), 26.61 (1C), 24.71 (1C), 23.55 (2C), 22.27 (2C). IR (film) ν 1740, 1650, 1440, 1380, 1360, 1030, 740 cm^{-1}.

(Z)-8-Oxooct-5-enoic Acid Methyl Ester (11). Standard conditions for hydrolysis[16] of acetal ester **10** (0.938 g, 3.44 mmol, 1 equiv) led to aldehyde ester **11** as a colorless oil without further purification. ^1H NMR δ 9.63 (1H, t, J = 1.8 Hz), 5.61–5.58 (2H, m), 3.63 (3H, s), 3.18–3.14 (2H, br d, J = 4.75 Hz), 2.28 (2H, t, J = 7.3 Hz), 2.10–2.00 (2H, br q, J = 6.8 Hz), 1.75–1.63 (2H, br quint, J = 7.3 Hz). ^{13}C NMR δ 199.53 (1C), 173.50 (1C), 133.93 (1C), 119.36 (1C), 51.60 (1C), 42.51 (1C), 33.27 (1C), 26.90 (1C), 24.44 (1C). IR (film) ν 2950, 1733, 1439, 1163, 1034 cm^{-1}.

(Z)-8-Hydroxyoct-5-enoic Acid Methyl Ester (12). A solution of aldehyde ester **11** in 95% ethanol (7 mL) was added, at 0 °C, to a solution of $NaBH_4$ (0.13 g, 3.42 mmol, 1 equiv) in 95% ethanol (7 mL). After stirring for 5 min at 0 °C and 5 min at rt, a solution of 2 M HCl was slowly added until pH 1. Extraction with ether and flash chromatography (silica gel 230–400 mesh, ether/pentane = 1/4 to ether) gave the pure alcohol ester **12** (0.481 g, 81%) as a colorless oil: R_f = 0.25 (ether/pentane = 1/1). Spectra data are in accord with the literature.[23] Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.75; H, 9.37.

(Z)-8-Bromooct-5-enoic Acid Methyl Ester (13). By using the procedure previously described,[29] alcohol ester **12** (0.347 g, 2.01 mmol) led to bromide ester **13** (0.431 g, 91%): R_f = 0.56 (ether/pentane = 1/1) as a colorless oil. ^1H NMR δ 5.53–5.33 (2H, m), 3.63 (3H, s), 3.32 (2H, t, J = 7.0 Hz), 2.61–2.51 (2H, br q, J = 6.7 Hz), 2.28 (2H, t, J = 7.3 Hz), 2.10–2.00 (2H, br q, J = 7 Hz), 1.73–1.58 (2H, br quint, J = 7.3 Hz). ^{13}C NMR δ 173.15 (1C), 131.68 (1C), 127.06 (1C), 51.57 (1C), 33.38 (1C), 32.49 (1C), 30.77 (1C), 26.72 (1C), 24.65 (1C). IR (film) ν 2949, 1737, 1437, 1210 cm^{-1}.

(Z)-(8-Methoxy-8-oxo-3-octenyl)triphenylphosphonium Bromide (9). Procedure used for the preparation of **6**, started from bromide **13** (0.431 g, 1.83 mmol) and led to white crystalline phosphonium salt **9** (0.810 g, 89%) after flash chromatography (silica gel, 70–230 mesh, ether/pentane = 1/1, ether, CH_2Cl_2/MeOH = 20/1 to 5/1): R_f = 0.21 (CH_2Cl_2/MeOH = 10/1). ^1H NMR δ 7.77–7.57 (15H, m), 5.57–5.17 (2H, m), 3.71–3.57 (2H, m), 3.46 (3H, s), 2.39–2.13 (2H, m), 2.08 (2H, t, J = 7.2 Hz), 1.79–1.68 (2H, br q, J = 7.2 Hz), 1.52–1.41 (2H, br quint, J = 7.0 Hz). ^{13}C NMR δ 173.62 (1C), 134.99 (3C, d, J = 3.1 Hz), 133.43 (6C, d, J = 10.4 Hz), 130.99 (1C), 130.37 (6C, d, J = 10.4 Hz), 126.91 (1C, d, J = 15.0 Hz), 117.79 (3C, d, J = 86.2 Hz), 51.29 (1C), 32.96 (1C), 26.24 (1C), 24.17 (1C), 22.67 (1C, d, J = 48.3 Hz), 20.08 (1C, d, J = 3.7 Hz).

***all*-(Z)-Eicosa-5,8,11,14,17-pentaenoic Acid; EPA (1b).** To a suspension of phosphonium salt **8** (0.465 g, 0.93 mmol, 1.7 equiv) in THF (10 mL) was added at −10 °C, a 1 M THF solution of sodium bis(trimethylsilyl)amide (0.88 mL, 0.88 mmol). The ylide solution was stirred at rt for 1 h and then cooled at −90 °C before **7** was added. Hydrolysis and classical workup, followed by flash chromatography (silica gel 230–400 mesh, ether/pentane = 1/4), gave pure EPA methyl ester (**1b**) (0.102 g, 60%). Saponification[16] led to EPA (**1a**) (0.09 g, 93%): R_f = 0.17 (ether/pentane = 1/4) as a pale yellow oil. ^1H and ^{13}C NMR identical to ref 13. IR (film) ν 3000, 2690, 1610, 1430, 1270, 1240, 720 cm^{-1}. HRMS Calcd for $C_{20}H_{30}O_2$ 302.2246. Found 302.2261.

(Z,Z)-10,10-Diisopropoxydeca-4,7-dienoic Acid Methyl Ester (15). The same procedure used for the preparation of **7** and starting from (4-methoxy-4-oxobutyl)triphenylphosphonium bromide (**14**)[24] (1.6 g, 3.61 mmol, 1.6 equiv), sodium bis(trimethylsilyl)amide (3.42 mL, 3.42 mmol), and C6 homologating agent **3** (0.711 g, 2.25 mmol, 1 equiv) led to unreacted **3** (0.15 g, 0.48 mmol) and pure acetal ester **15** (0.269 g, 51% based on recovered **3**) as a colorless oil: R_f = 0.68 (ether/pentane = 1/1). ^1H NMR δ 5.42–5.34 (4H, m), 4.52 (1H, t, J = 5.6 Hz), 3.84 (2H, sept, J = 6.1 Hz), 3.64 (3H, s), 2.81–2.75 (2H, br t, J = 5.0 Hz), 2.34–2.31 (6H, m), 1.15 (6H, d, J = 6.1 Hz), 1.10 (6H, d, J = 6.1 Hz). ^{13}C NMR δ 173.50 (1C), 129.69 (1C), 129.31 (1C), 127.76 (1C), 124.66 (1C), 99.62 (1C), 67.64 (2C), 51.49 (1C), 33.97 (1C), 33.75 (1C), 25.79 (1C), 22.73 (1C), 23.30 (2C), 22.49 (2C). IR (film) ν 1750, 1650, 1440, 1390, 1270, 1130, 1030, 730 cm^{-1}. Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.44; H, 10.16.

(Z,Z,Z)-Dodeca-3,6,9-trien-1-ol (11). The trienic acetal **7** (2.87 g, 10.25 mmol, 1 equiv) was hydrolyzed under the standard conditions into aldehyde **8** which was diluted in THF (20 mL) and added, at −70 °C, to a suspension of lithium aluminum hydride (0.389 g, 10.25 mmol, 1 equiv) in THF (80 mL). Workup as described in ref 10 and flash chromatography (silica gel, 230–400 mesh, ether/pentane = 1/4) furnished the pure trienic alcohol **16** (1.59 g, 86%) as a colorless oil: R_f = 0.34 (ether/pentane = 1/1). ^1H NMR δ 5.58–5.21 (6H, m), 3.62 (2H, t, J = 6.5 Hz), 2.85–2.74 (4H, m), 2.37–2.27 (2H, br q, J = 6.5 Hz), 2.11–1.97 (2H, br quint, J = 7.3 Hz), 0.94 (3H, t, J = 7.5 Hz). ^{13}C NMR δ 131.93 (1C), 130.64 (1C), 128.54 (1C), 127.67 (1C), 126.66 (1C), 125.60 (1C), 61.96 (1C), 30.67 (1C), 25.62 (1C), 25.43 (1C), 20.46 (1C), 14.16 (1C). IR (film) ν 3640, 1650, 1470, 1385, 720 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18; found: C, 79.92; H, 11.16.

(29) Sandri, J.; Viala, J. *Synth. Commun.* **1992**, 2945.

(Z,Z,Z)-1-Bromododeca-3,6,9-triene (17). To a solution (under argon) of alcohol **16** (1.36 g, 7.55 mmol, 1 equiv) and tetrabromomethane (3.58 g, 10.78 mmol, 1.42 equiv) in CH_2Cl_2 (10 mL) was added, at 0 °C, a solution of Ph_3P (3.1 g, 11.83 mmol, 1.56 equiv) in CH_2Cl_2 (6 mL). After 15 min at 0 °C and 1 h at rt, the reaction was completed. Addition to ether/pentane 1/1 (200 mL), filtration over a short pad of silica gel, concentration, and flash chromatography (silica gel 70−230 mesh, ether/pentane = 1/100 to 1/10) gave the pure bromide **17** (1.73 g, 94%) as a colorless oil: R_f = 0.79 (ether/pentane = 1/1). ^{1}H NMR δ 5.49−5.21 (6H, m), 3.30 (2H, t, J = 7.1 Hz), 2.80−2.70 (4H, m), 2.63−2.53 (2H, br q, J = 6.9 Hz), 2.09−1.94 (2H, br quint, J = 7.3 Hz), 0.91 (3H, t, J = 7.5 Hz). ^{13}C NMR δ 132.07 (1C), 130.91 (1C), 128.83 (1C), 127.42 (1C), 126.88 (1C), 126.29 (1C), 32.29 (1C), 30.80 (1C), 25.79 (1C), 25.56 (1C), 20.58 (1C), 14.29 (1C). IR ν (film) 3040, 1665, 690 cm^{-1}.

(Z,Z,Z)-Dodeca-3,6,9-trienyltriphenylphosphonium Bromide (18). The procedure described in ref 10 starting from bromide **17** (1.7 g, 6.99 mmol, 1 equiv) and Ph_3P (3.66 g, 13.9 mmol, 2 equiv) led to pure phosphonium salt **18** (3.35 g, 95%) after flash chromatography (silicagel 70−230 mesh, ether/pentane = 1/1 to ether, and then MeOH/CH_2Cl_2 = 1/20 to 1/5) as a viscous colorless oil: R_f = 0.35 (MeOH/CH_2Cl_2 = 1/20). ^{1}H NMR δ 7.82−7.37 (15H, m), 5.59−5.08 (6H, m), 3.84−3.70 (2H, m), 2.57−2.30 (6H, m), 1.98−1.84 (2H, br quint, J = 7.2 Hz), 0.84 (3H, t, J = 7.5 Hz). ^{13}C NMR δ 134.46 (3C, d, J = 3.3 Hz), 132.84 (6C, d, J = 10.3 Hz), 131.33 (1C), 129.84 (6C, d, J = 12.7 Hz), 129.45 (1C), 128.11 (1C), 126.22 (1C), 125.86 (1C), 125.80 (1C, d, J = 15.0 Hz), 117.18 (3C, d, J = 86.0 Hz), 24.74 (1C), 24.66 (1C), 22.08, (1C, d, J = 48.7 Hz), 19.72 (1C), 19.59, (1C, d, J = 4.0 Hz), 13.50, (1C). ^{31}P NMR δ 23.19.

(Z,Z)-10-Oxodeca-4,7-dienoic Acid Methyl Ester (19). Hydrolysis of ester acetal **15** (0.22 g, 0.74 mmol, 1 equiv) led to aldehyde ester **19** without further purification and was used directly in the next Wittig step. ^{1}H NMR δ 9.64 (1H, t, J = 1.8 Hz), 5.71−5.32 (4H, m), 3.64 (3H, s), 3.22−3.18 (2H, br d, J = 6 Hz), 2.81−2.75 (3H, br t, J = 5.6 Hz), 2.35−3.34 (4H, br s). ^{13}C NMR δ 199.42 (1C), 173.49 (1C), 132.96 (1C), 128.50 (1C), 128.27 (1C), 118.74 (1C), 51.58 (1C), 42.46 (1C), 33.83 (1C), 25.90 (1C), 22.78 (1C). IR (film) ν 2725, 1735, 1655, 1436, 730 cm^{-1}.

***all*-(Z)-Docosa-4,7,10,13,16,19-hexaenoic Acid; DHA (2a).** Phosphonium salt **18** (0.932 g, 1.85 mmol, 2.5 equiv) was thoroughly dried four times under *vacuo* by azeotropic distillation of anhydrous benzene (5 mL) and then diluted in THF (8 mL). After cooling at −80 °C, a 1 M THF solution of sodium bis(trimethylsilyl)amide (1.75 mL, 1.75 mmol, 2.36 equiv) was added and stirred for 1 h at −80 °C. To this ylide solution was added aldehyde ester **19** diluted in THF (1 mL). Classical workup and flash chromatography (silica gel, 230−400 mesh, ether/pentane = 1/10) gave pure DHA methyl ester (**2b**) (0.192 g, 76%): R_f = 0.56 (silica, ether/pentane = 1/4). Saponification[16] led to DHA **2a** (0.169 g, 92%) as a colorless oil: R_f = 0.55 (ether). ^{1}H NMR δ 5.44−5.26 (12H, m), 2.85−2.76 (10H, m), 2.40−2.38 (4H, m), 2.12−1.98 (2H, br quint, J = 7.4 Hz), 0.95 (3H, t, J = 7.5 Hz). ^{13}C NMR δ 179.56 (1C), 132.11 (1C), 129.64 (1C), 128.64 (1C), 128.37 (1C), 128.34 (1C), 128.31 (1C), 128.15 (2C), 128.04 (1C), 127.94 (2C), 127.03 (1C), 34.06 (1C), 25.69 (5C), 22.54 (1C), 20.63 (1C), 14.36 (1C). IR (film) 3013, 1711, 1650, 1430, 1279, 730 cm^{-1}. Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.43; H, 9.83.

Supporting Information Available: ^{1}H (with assignments) and ^{13}C NMR spectra of compounds **1a**, **2a**, **7−13** and **15 −19** (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO950403V