Direct Preparation of (*Z*,*Z*)-1,4-Dienic Units with a New C6 Homologating Agent: Synthesis of α-Linolenic Acid

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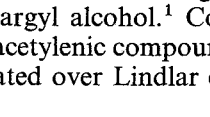
Received 14 October 1994; revised 10 November 1994

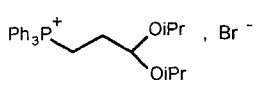
Syntheses of two C6 homologating agents **2a** and **2f** are described. These agents allow direct access to the (*Z*,*Z*)-1,4-diene unit **3**, a moiety present in a wide number of natural compounds. Compound **2a** is prepared in 40% overall yield by selective epoxidation of methoxycyclohexa-1,4-diene followed by oxidative ring cleavage and transacetalization. Compound **2f** is obtained in 90% yield by a one-step oxidative dimerization of phosphonium salt **1**. A short synthetic application of these two new C6 homologating agents to the synthesis of α-linolenic acid is described.

Several natural compounds contain in their skeleton the unsaturated (*Z*,*Z*)-1,4-dienic moiety which can be reproduced from 1 to 5 times. Particularly, such a pattern is present in polyunsaturated fatty acids (PUFA: n = 1 to 5), their metabolites (n = 1 to 3), and pheromones (n = 1, 2). Syntheses of these molecules are generally based on sequential C3 homologations to build up the 1,4-diene units. The first C3 homologating agent, due to Osbond, was propargyl alcohol.[1] Consecutive condensations led to polyacetylenic compounds, which were selectively hydrogenated over Lindlar catalyst into all *cis* polyenic systems.

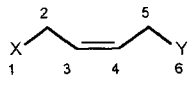


***Cis,cis* 1,4-diene unit**

Six years ago we described the preparation of an alternative C3 homologating agent, phosphonium salt **1**,[2] which enables the preparation of the 1,4-diene unit through two Wittig reactions via a (*Z*)-β,γ-ethylenic aldehyde. The synthetic potential of **1** was demonstrated by syntheses of arachidonic acid,[3] deuterated linoleic acid[4] and other biologically active compounds.[5] However, in connection with our interest in the synthesis of highly PUFA (n = 4 and 5),[6] we decided to prepare a C6 homologating agent **2** which would allow us to introduce in a versatile way the (*Z*,*Z*)-1,4-dienic unit through a single Wittig reaction.



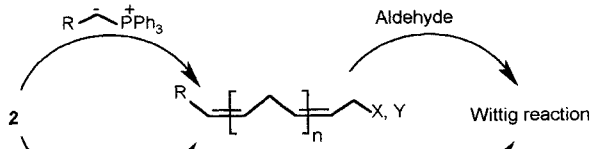
1



2

	X	Y
2a	COOMe	$CH(OMe)_2$
2b	COOMe	$CH(O\text{-}i\text{-}Pr)_2$
2c	CHO	$CH(OMe)_2$
2d	CHO	$CH(O\text{-}i\text{-}Pr)_2$
2e	COOMe	CH(OMe)(OiPr)
2f	$CH(O\text{-}i\text{-}Pr)_2$	$CH(O\text{-}i\text{-}Pr)_2$
2g	CHO	CHO

Depending on the strategy, compound **2** converted into either the aldehyde or the Wittig salt, will lead in one-step to the first 1,4-diene unit **3** (n = 1). This compound will bear a X or Y group able to react, in its turn, either as ylid or carbonyl group in a second Wittig reaction (Scheme 1).

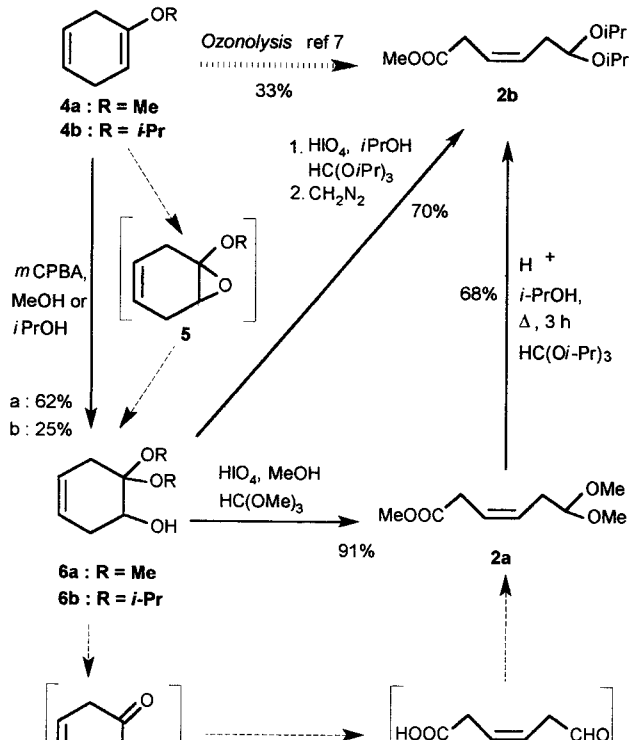


Scheme 1

We describe herein two syntheses of C6 homologating agent **2**. The first synthesis leads to compounds **2a** or **2b** (X = methoxycarbonyl, Y = dialkyl acetal) through an epoxidation and oxidative ring cleavage of **4**. The second gives symmetric compound **2f** [X = Y = $CH(OPr\text{-}i)_2$] through oxidative dimerization of phosphonium salt **1**. Finally, we describe an application to the total synthesis of α-linolenic acid **14b** (n = 2).

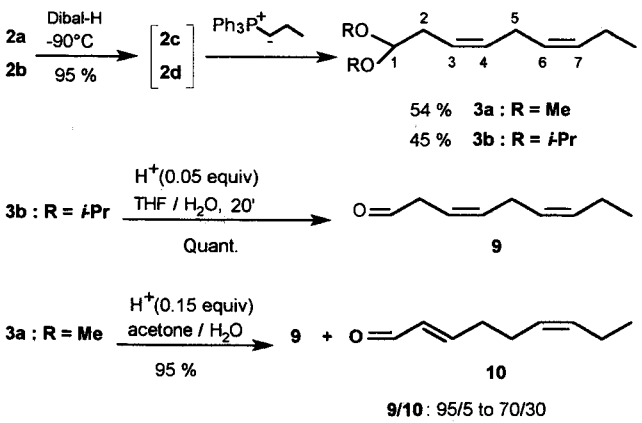
In a previous work directed towards the total synthesis of EPA,[7] the synthetic intermediate **2b** was obtained by direct ozonolysis of **4a** (Scheme 2); unfortunately, the low yield of the reaction (33%) combined with the presence of up to 10% of unseparable byproducts, arising from the cleavage of the second double bond,[8] prompted us to develop a more efficient methodology for the preparation of a new C6 homologating agent.

Epoxidation of **4a**[9] with *m*-chloroperbenzoic acid (MCPBA) occurs selectively on the most substituted double bond. Intermediate epoxy ether **5** (R = Me)[10] is directly solvolyzed under the reaction conditions by methanol giving, after flash chromatography, α-hydroxydimethyl acetal **6a** in 62% yield.[11] The next step is performed in anhydrous methanol with periodic acid dihydrate which first hydrolyzes the dimethyl acetal group providing unstable α-hydroxy ketone **7**.[12] Then, oxidative cleavage[13] leads to acid–aldehyde **8** which is acetalized and esterified by trimethyl orthoformate under the reaction conditions providing **2a** in 91% yield (Scheme 2). Similarly, **5b** obtained from **4b**[14] (25%) is transformed in 2 steps to **2b** in 70% yield.



Scheme 2

The first strategy developed for the stereoselective construction of (*Z*,*Z*)-1,4-diene unit **3** was based on the Wittig reaction[15] between aldehyde **2c** or **2d**, easily obtained by partial reduction of **2a** or **2b** with diisobutylaluminum hydride (DIBAH) in dichloromethane at low temperature,[16] and propylidenetriphenylphosphorane (Scheme 3). Hydrolysis of dienes **3** should give the corresponding dienal **9**, a powerful substrate for further Wittig condensations; however, hydrolysis of dimethyl acetal **3a** proceeds with partial migration of the double bond[17] leading to a mixture of **9** and **10**. The corresponding diisopropyl derivative **3b** gives pure aldehyde **9** (Scheme 3).

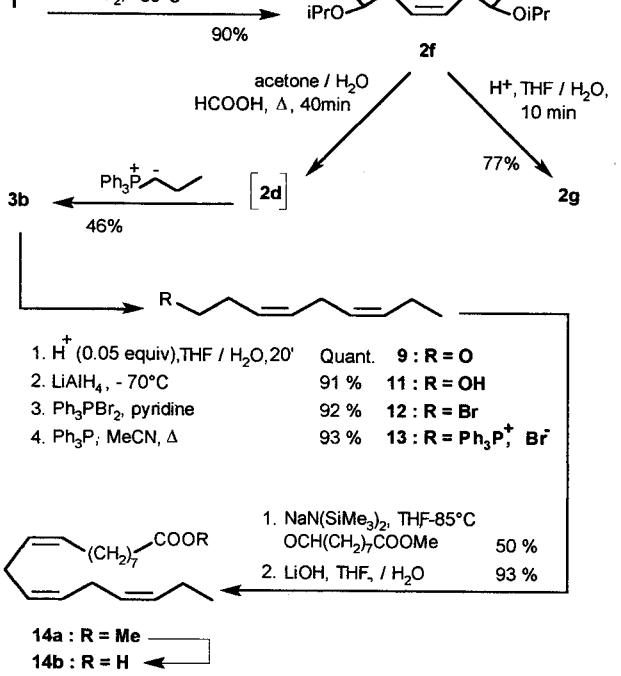


Scheme 3

Since the preparation of ester acetal **2b**, precursor of 1,4-dienic acetal **3b**, suffers from a low overall yield (17%), we chose to synthesize diisopropyl acetal **2b** through a transacetalization of acetal **2a**. This transformation, from a stable dimethyl acetal towards a labile diisopropyl acetal, takes place in isopropanol, on treatment with triisopropyl orthoformate and camphorsulfonic acid (Scheme 2). The equilibrium of the reaction is shifted towards **2b**, through mixed acetal **2e**, by distilling off the methanol formed over 3 hours.[18] A mixture of three acetals, **2b** (45%), **2a** (30%) and **2e** (7%), is obtained along with polycondensation products. Longer reaction times furnish lower yields of **2b**. Careful flash chromatography gives pure acetal **2b** in 68% overall yield based on recovered starting acetal **2a** and intermediate **2e**.[19] By this new procedure, the C6 homologating agent **2b** was prepared pure and free of byproducts.

However, this approach suffers from a moderate overall yield. In order to reach higher synthetic efficiency, we turned our attention to a more direct preparation of a new C6 homologating agent **2f** whose synthetic utility depends on efficient selective monodeacetalization leading to **2d**.

The preparation of symmetric compounds such as **2** [X = Y = CO_2Me, $CH(OMe)_2$, CHO] has been described in the literature;[20] however, a more direct preparation of the symmetric bis(acetal) **2f** would be the oxidative dimerization of phosphonium ylids described by Bestmann.[21] As expected, treatment of the phosphorane derived from **1** with oxygen at low temperature induces formation of **2f** in 90% isolated yield (Scheme 4). On large scale (over 10 g), isolation of **2f** can be done either by chromatography or distillation.



Scheme 4

Hydrolysis of **2f** under standard conditions,[4,5] led exclusively to bis(aldehyde) **2g** regardless of the reaction time; therefore we examined a variety of reaction parameters (e.g., solvents, water concentration, acid catalyst, temperature, time and workup) in order to accomplish selective monohydrolysis. Under optimum conditions, bis(acetal) **2f** was treated with water (20 equiv) and formic acid (2 equiv) in refluxing acetone, whereupon a mixture of **2f** and the monoacetal **2d** was obtained in a ratio of 3:7 in 95% yield. The crude mixture of **2f** and **2d** reacted with propylidenetriphenylphosphorane to give pure 1,4-diene **3b**.[22]

The stereochemistry of **3b** was established by NMR spectroscopy: selective irradiations allowed the attribution of a signal to each ethylenic proton (δ_{H3} 5.41, δ_{H4} 5.42, δ_{H6} 5.28 and δ_{H7} 5.35) and established the (*Z,Z*)-configuration of the double bonds ($J_{3,4} = 10.3$ Hz and $J_{6,7} = 10.6$ Hz); heteronuclear two dimensional experiments showed cross peaks allowing the attribution of a single signal to each ethylenic carbon atom (δ_{C3} 124.6, δ_{C4} 130.2, δ_{C6} 127.1, δ_{C7} 132.0). The ^{13}C NMR spectrum exhibited a single line for each ethylenic, allylic and bis(allylic) carbon atom.

To complete the synthesis of α-linolenic acid **(14b)**, *cis,cis*-1,4-dienic diisopropyl acetal **3b** was used to furnish phosphonium salt **13** in high yield without modification of the 1,4-dienic system. A second *cis*-stereoselective Wittig reaction with methyl 9-oxononanoate[23] followed by saponification led to α-linolenic acid **(14b)** (Scheme 4).

In summary, we have described an easy and convenient synthesis of the symmetric C6 homologating agent **2f** which can be selectively hydrolysed to (*Z*)-6,6-diisopropoxyhex-3-enal **(2d)** without isomerization of the double bond. A short synthesis of α-linolenic acid demonstrated the potential of **2d** for the stereoselective synthesis of the (*Z,Z*)-1,4-diene units of polyunsaturated fatty acids.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 or AMX 400 spectrometer at 200.13 or 400 MHz and 50.32 or 100.60 MHz respectively in $CDCl_3$ solutions. Chemical shifts are given in ppm relative to solvent (7.24 ppm ^{1}H; 77.1 ppm, ^{13}C). Coupling constants are given in Hz. Mass spectra were obtained on a Varian MAT 311 mass spectrometer. IR spectra were recorded on a Perkin-Elmer Model 298 or 1600 (FT) spectrophotometers. All reactions were carried out under a positive Ar atmosphere. All glassware was dried at 180°C and cooled in a desiccator under Ar atmosphere. THF was distilled over benzophenone/sodium and CH_2Cl_2 over P_2O_5 before being used. All reactions were monitored by TLC carried out on E. Merck 60F-254 silica gel plates. Microanalyses were performed with a CHN auto-analyzer Technicon.

Chemicals were purchased from Aldrich Chemical or Janssen Chimica. 3,3-(Diisopropoxy)propyltriphenylphosphonium bromide **(1)** was prepared as previously reported.[3] Satisfactory microanalyses were obtained for all new compounds: C ± 0.08, H ± 0.09.

2-Hydroxycyclohex-3-en-1-one Dimethyl Acetal (5a):
To a solution of 1-methoxycyclohexa-1,4-diene (3.3 g, 30 mmol) in MeOH (120 mL) at −10°C was added dropwise a solution of MCPBA (85%, 5.17 g, 30 mmol) in MeOH (20 mL). The mixture was stirred at 0°C for 1 h, then, at r.t. for an additional 1 h. A sat. aq $NaHCO_3$ solution (30 mL) was added. Extraction with CH_2Cl_2, (7 × 25 mL), drying ($MgSO_4$), concentraton in vacuo and flash chromatography (silica gel, 230–400 mesh, Et_2O/pentane, 1:10 to 1:2) gave pure **5a** as a colorless liquid (2.94 g, 62%); R_f 0.46 (silica gel, Et_2O).

^{1}H NMR (200.13 MHz): δ = 5.51 (2H, br s, CH=CH), 3.95–3.91 (1H, m, CHOH), 3.22 (3H, s, OCH_3), 3.17 (3H, s, OCH_3), 2.40–2.13 (4H, m, $2CH_2$).

^{13}C NMR (50.13 MHz): δ = 123.45 (d, 2C), 100.11 (s), 66.35 (d), 48.16 (q), 47.81 (q), 31.03 (t), 29.47 (t).

IR (Film): ν = 3460, 1660, 1220, 1050, 710 cm^{-1}.

2-Hydroxycyclo-3-hexen-1-one Diisopropyl Acetal **(5b)**: Starting with 1-isopropoxycyclohexa-1,4-diene (3 g, 21.7 mmol) the same procedure led, after flash chromatography, to pure acetal **5b** (1.16 g, 25%); R_f 0.45 (silica gel, Et_2O/pentane, 1:1).

^{1}H NMR (200.13 MHz): δ = 5.53–5.51 (2H, m, CH=CH), 4.18 [1H, sept, J = 6.2 Hz, C$\underline{H}$(CH$_3$)$_2$], 4.03 [1H, sept, J = 6.2 Hz, C$\underline{H}$(CH$_3$)$_2$], 3.79 (1H, m, CH), 2.40–2.06 (4H, m, 2CH), 1.21 (3H, d, J = 6.1 Hz, CH_3), 1.15 (3H, d, J = 6.1 Hz, CH_3), 1.13 (3H, d, J = 6.1 Hz, CH_3), 1.06 (3H, d, J = 6.1 Hz, CH_3).

^{13}C NMR (50.13 MHz): δ = 123.62 (d), 122.94 (d), 101.11 (s), 67.77 (d), 63.33 (d), 61.67 (d), 31.35 (t), 30.59 (t), 24.51 (q), 24.45 (q), 24.31 (q), 24.06 (q).

IR (Film): 3500, 1670, 1390, 1240, 1140, 1040, 640 cm^{-1}.

Methyl (*Z*)-6,6-Dimethoxyhex-3-enoate (2a):
To a solution of hydroxy acetal **5a** (4.74 g, 30 mmol) in MeOH (130 mL), at −10°C, was added dropwise a solution of $HIO_4 \cdot 2H_2O$ (8.20 g, 36 mmol) in MeOH (20 mL). Stirring was maintained at 0°C for 1 h, then at r.t. for 4 h. After addition of trimethyl orthoformate (9.83 mL, 90 mmol), the mixture was stirred overnight. Evaporation of solvents and flash chromatography (silica gel, 230–400 mesh, Et_2O/pentane 1:10 to 1:4) gave the pure acetal ester **2a** (5.13 g, 91%) as a colorless liquid; R_f 0.42 (silica gel, Et_2O/pentane, 1:1).

^{1}H NMR (200.13 MHz): δ = 5.69–5.48 (2H, m, CH=CH), 4.31 (1H, t, J = 5.7 Hz, CH), 3.61 (3H, s, CH_3), 3.25 (6H, s, $2CH_3$), 3.04 (2H, d, J = 6.5 Hz, CH_2CO_2Me), 2.33–2.27 [2H, br t, J = 5.7 Hz, $CH_2CH(OMe)_2$].

^{13}C NMR (50.13 MHz): δ = 171.91 (s), 129.08 (d), 123.34 (d), 103.68 (d), 52.92 (q, 2C), 51.88 (q), 32.76 (t), 31.09 (t).

IR (Film): ν = 1750, 1660, 1450, 1340, 720 cm^{-1}.

Methyl (*Z*)-6,6-Diisopropoxyhex-3-enoate (2b):
By Transacetalization of **2a**: In a 2-necked round-bottom flask fitted with a Vigreux column (length: 12 cm), was introduced the dimethyl acetal **2a** (0.91 g, 4.84 mmol), anhydr. isopropanol (30 mL), triisopropyl orthoformate (3.2 mL, 14.52 mmol) and camphorsulfonic acid (0.224 g, 0.97 mmol). The mixture was stirred and heated until a slow distillation of solvent took place (20 mL/h) while additional *i*-PrOH (10 mL) was added every 20 min for 2.5 h. After dilution with Et_2O (50 mL), washing with brine (2 × 15 mL) and concentration, the crude material was chromatographed (silica gel, 230–400 mesh, Et_2O/pentane 1:10) giving diisopropyl acetal ester **2b** (0.525 g, 45%), mixed acetal **2e** (0.077 g, 7%) and starting dimethyl acetal **2a** (0.273 g, 30%).

Acetal **2b**: R_f 0.62 (silica gel, Et_2O/pentane, 1:1).

^{1}H NMR (400 MHz): δ = 5.66–5.54 (2H, m, CH=CH), 4.51 [1H, t, J = 5.5 Hz, C$\underline{H}$(OPr-*i*)$_2$], 3.81 (2H, sept, J = 6.2 Hz, 2C$\underline{H}$Me$_2$), 3.6 (3H, s, OCH_3), 3.08 (2H, d, J = 6.4 Hz, C$\underline{H}_2$CO$_2$Me), 2.31–2.28 [2H, br t, J = 5.5 Hz, C$\underline{H}_2$CH(OPr-*i*)$_2$], 1.15 [6H, d, J = 6.2 Hz, CH(C$\underline{H}_3$)$_2$], 1.10 [6H, d, J = 6.2 Hz, CH(C$\underline{H}_3$)$_2$].

^{13}C NMR (100.6 MHz): δ = 172.32 (s), 128.02 (d), 123.13 (d), 99.55 (d), 68.07 (d, 2C), 51.83 (q), 34.03 (t), 33.07 (d), 23.36 (q, 2C), 22.53 (q, 2C).

IR (Film): ν = 1750, 1652, 1260, 1130, 1040, 720 cm^{-1}.

Acetal **2e**: R_f 0.54 (silica gel, Et_2O/pentane, 1:1).

^{1}H NMR (200.13 MHz): δ = 5.74–5.50 (2H, m, CH=CH), 4.48 [1H, t, J = 5.7 Hz, C$\underline{H}$(OMe)(OPr-*i*)], 3.81 [1H, sept, J = 6.2 Hz, C$\underline{H}$Me$_2$], 3.66 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 3.11–3.09 (2H, br d, J = 6.0 Hz, C$\underline{H}_2$CO$_2$Me), 2.27–2.31 (2H, m, C$\underline{H}_2$CH), 1.18 (3H, d, J = 6.2 Hz, CH_3), 1.11 (3H, d, J = 6.2 Hz, CH_3).

^{13}C NMR (50.13 MHz): δ = 172.26 (s), 127.85 (d), 123.35 (d),

101.48 (d), 69.26 (d), 52.03 (q), 51.91 (q), 33.07 (t), 32.46 (t), 23.24 (q), 22.33 (q).

IR (Film): ν = 1750, 1660, 1440, 1390, 1360, 1340, 1170, 1130, 1040 cm^{-1}.

By oxidative cleavage of **5b**: To a solution of **5b** (2 g, 9.3 mmol) in anhydr. *i*-PrOH (45 mL) at −10 °C was added dropwise a solution of $HIO_4 \cdot 2H_2O$ (2.33 g, 10.23 mmol) 1.1 equiv) in *i*-PrOH (5 mL). After stirring at 0 °C for 1 h, triisopropyl orthoformate (6 mL, 27.9 mmol) was added. Then, precipitated iodic acid was filtered off and rinsed with isopropanol. The mixture was diluted with Et_2O, washed with 10% aq $Na_2S_2O_3$ solution, dried ($MgSO_4$) and concentrated. The crude material was diluted with Et_2O and esterified with diazomethane. After concentration, chromatography (silica gel 230–400 mesh, Et_2O/pentane 1:10) gave pure acetal **2a** (1.58 g, 70%).

(*Z*)-6,6-Dimethoxyhex-3-en-1-al (2c):

To a well stirred solution of acetal **2a** (0.4 g, 2.14 mmol) in CH_2Cl_2 (20 mL) at −90 °C was added dropwise DIBAH (1.5 M/toluene, 1.42 mL, 2.14 mmol). At −75 °C, the resulting white precipitate turned to a clear liquid and a solution of tartaric acid (0.642 g, 4.18 mmol) in absolute EtOH (2 mL) was added. At −30 °C a mixture of $Na_2SO_4 \cdot 10H_2O$/Celite (1:1) (4 g) was added and the suspension was allowed to warm up to r.t. Filtration through Celite, washing of alumina salts with Et_2O (3 × 20 mL), drying ($MgSO_4$) and concentration gave a crude material containing a light white precipitate. Filtration over Celite in a micropipette furnished a clear colorless liquid which was dried by azeotropic distillation with benzene and in vacuo for 3 h giving pure aldehyde **2c** (0.321 g, 95%); R_f 0.23 (silica gel,Et_2O/pentane, 1:1).

^{1}H NMR (200.13 MHz): δ = 9.36 (1H, t, J = 1.5 Hz, CHO), 5.6–5.57 (2H, m, CH=CH), 4.26 [1H, t, J = 5.6 Hz, C<u>H</u>(OMe)$_2$], 3.22 (6H, br s, $2CH_3$), 3.10 (2H, dd, J = 5.1, J = 1.5 Hz, C<u>H</u>$_2$CHO), 2.28–2.23 (2H, br t, J = 5.6 Hz, C<u>H</u>$_2$CH).

^{13}C NMR (50.13 MHz): δ = 198.90 (d), 128.47 (d), 120.76 (d), 103.46 (d), 52.01 (q, 2C), 42.23 (t), 31.17 (t).

IR (Film): ν = 2820, 2720, 1730, 1560, 1440, 1190, 730 cm^{-1}.

(*Z*)-1,1,6,6-Tetraisopropoxyhex-3-ene (2f):

To a suspension of phosphonium salt **1**[2] (25.15 g, 50 mmol), in THF (350 mL) at 0 °C, was added $NaN(SiMe_3)_2$ (1 M/THF, 50 mL, 50 mmol). The dark orange solution was stirred for 2 h at r.t. and cooled to −80 °C. Oxygen was bubbled slowly for 0.5 h at −80 °C then the temperature was allowed to warm up to r.t. Hydrolysis with sat. aq NH_4Cl solution (50 mL) at 0 °C, dilution of mineral salts with H_2O, extraction with Et_2O (3 × 150 mL), washing of organic layers with aq NaCl solution (50 mL) and brine (50 mL), drying ($MgSO_4$) and concentration gave a crude material. Dilution with CH_2Cl_2, filtration over silica gel (70–230 mesh) with Et_2O/pentane (1:10) to eliminate Ph_3PO furnished a liquid. Flash chromatography (silica gel, 230–400 mesh, Et_2O/pentane: 1:10) gave pure bis(acetal) **2f** (7.11 g, 22.5 mmol, 90%). In some cases, to avoid chromatography, the crude product was distilled (25 g scale); bp 130 °C/5 mbar; R_f 0.63 (silica gel, Et_2O/pentane, 1:1).

^{1}H NMR (200.13 MHz): δ = 5.47 (2H, br t, J = 5.1 Hz, CH=CH), 4.51 (2H, t, J = 5.6 Hz, 2CH), 3.83 (4H, sept, J = 6.2 Hz, $4CHMe_2$), 2.32 (4H, dd, J = 5.1 Hz, 5.6, $2CH_2$), 1.16 (12H, d, J = 6.2 Hz, $4CH_3$), 1.11 (12H, d, J = 6.2 Hz, $4CH_3$).

^{13}C NMR (50.13 MHz): δ = 128.18 (d, 2C), 99.64 (d, 2C), 67.48 (d, 4C), 33.72 (t, 2C), 23.03 (q, 4C), 22.24 (q, 4C).

IR (Film): ν = 1610, 1590, 1470, 1130, 1030, 720 cm^{-1}.

(*Z*)-6,6-Diisopropoxyhex-3-en-1-al (2d):

Reduction of **2b**: The same procedure used for the preparation of **2c**, was used starting from ester acetal **2b** (0.662 g, 2.71 mmol), CH_2Cl_2 (27 mL) and DIBAH (2.71 mmol). Aldehyde acetal **2d** (0.55 g, 95%) was used directly in the Wittig reaction.

Monodeacetalization of **2f**: A mixture of bis(acetal) **2f** (1.07 g, 3.38 mmol), formic acid (0.310 g, 6.76 mmol), H_2O (1.2 mL, 67 mmol) in acetone (17 mL) was refluxed for about 40 min or until the formation of bis(aldehyde) **2g** was observed by TLC. Dilution with Et_2O/pentane (1:1, 70 mL), and cooling of the resultant well stirred solution at −50 °C allowed the precipitation of polar products (like formic acid and small amount of bis(aldehyde) **2g** (0 to 5%)) which were filtered off through cotton (cooled with liquid N_2) and rinsed with Et_2O/pentane (1:1, 2 × 20 mL). The resultant solution was allowed to warm up to r.t., dried ($MgSO_4$), filtered and concentrated. The yellow pale liquid was filtered through silica gel (230–400 mesh) in a micropipette and distilled in a Kugelrohr apparatus (bp 110–150 °C/2 mbar) giving a colorless liquid which was directly used in the Wittig reaction; R_f 0.5 (silica gel, Et_2O/pentane, 1:1).

^{1}H NMR (200.13 MHz): δ = 9.42 (1H, t, J = 1.5 Hz, CHO), 5.67–5.57 (2H, m, CH=CH), 4.51 [1H, t, J = 5.3 Hz, C<u>H</u>(OPr-*i*)$_2$], 3.80 (2H, sept, J = 6.1 Hz, $2CHMe_2$), 3.19 (2H, dd, J = 6.6, 1.5 Hz, C<u>H</u>$_2$CHO), 2.32–2.26 (2H, br t, J = 5.8 Hz, CH_2), 1.16 (6H, d, 6.1 Hz, $2CH_3$), 1.11 (6H, d, J = 6.1 Hz, $2CH_3$).

^{13}C NMR (50.13 MHz): δ = 199.70 (d), 129.75 (d), 120.66 (d), 99.46 (d), 66.24 (d, 2C), 42.64 (t), 34.35 (t), 23.37 (q, 2C), 22.55 (q, 2C).

IR (film): ν = 2720, 1730, 1610, 1460, 1380, 1230, 1120, 1030, 720 cm^{-1}.

(*Z*)-Hex-3-ene-1,6-dial (2g):

Hydrolysis of bis(acetal) **2f** (0.155 g, 0.49 mmol) according to the standard procedure[4,5] gave bis(aldehyde) **2g** (0.43 g, 0.38 mmol) in 77% yield only, because of its water solubility; R_f 0.12 (silica, Et_2O/pentane, 1:1).

^{1}H NMR (200.13 MHz): δ = 9.36 (2H, s, 2CHO), 5.83 (2H, br t, J = 4.6 Hz, CH=CH), 3.18 (4H, d, J = 4.3 Hz, $2CH_2$).

^{13}C NMR (50.13 MHz): δ = 196.82 (d, 2C), 123.44 (d, 2C), 42.38 (t, 2C).

(*Z,Z*)-Nona-3,6-dien-1-al Diisopropyl Acetal (3b):

To a suspension of propyltriphenylphosphonium bromide (2.92 g, 6.76 mmol) in THF, at 0 °C, was added $NaN(SiMe_3)_2$ (1 M/THF, 6.08 mL, 6.08 mmol). Stirring was maintained for 3 h at r.t., while bis (acetal) **2f** (1.07 g, 3.38 mmol) underwent monodeacetalization (see above). The orange suspension was cooled at −90 °C and aldehyde **2d** was added diluted in THF (3 mL). After classical work-up,[4,5] flash chromatography gave starting **2f** (0.185 g) and 1,4-diene **3b** (0.210 g, 47% based on recovered starting material). Starting from ester acetal **2b**, selective reduction (see above) and Wittig condensation led to **3b** in 45% yield; R_f 0.59 (silica gel, Et_2O/pentane, 1:4).

^{1}H NMR (400 MHz): δ = 5.46–5.26 (4H, m, 2CH=CH), 4.52 [1H, t, J = 5.6 Hz, C<u>H</u>(OPr-*i*)$_2$], 3.84 (2H, sept, J = 6.2 Hz, $2CHMe_2$), 2.79–2.73 [2H, br t, J = 5.8 Hz, C<u>H</u>$_2$(CH=CH)$_2$], 2.37–2.31 [2H, br t, J = 5.7 Hz, C<u>H</u>$_2$CH(OPr-*i*)$_2$], 2.10–1.96 (2H, br quint, J = 7.5 Hz, C<u>H</u>$_2$Me), 1.16 [6H, d, J = 6.2 Hz, CH(C<u>H</u>$_3$)$_2$], 1.11 [6H, d, J = 6.2 Hz, CH(C<u>H</u>$_3$)$_2$], 0.94 (3H, t, J = 7.5 Hz, CH_2C<u>H</u>$_3$).

^{13}C NMR (100.60 MHz): δ = 131.99 (d), 130.24 (d), 127.07 (d), 124.60 (d), 99.96 (d), 67.66 (d, 2C), 33.79 (t), 25.63 (d), 23.39 (q, 2C), 22.57 (q, 2C), 20.56 (t), 14.29 (q).

IR (Film): ν = 1660, 1460, 1380, 1180, 1130, 1030, 740 cm^{-1}.

(Z,Z)-3,6-Nona-3,6-dien-1-al **(9)**: By using the classical procedure for the hydrolysis of diisopropyl acetal,[4,5] 1,4-diene **3b** (1.03 g, 4.3 mmol) yielded quantitatively **9** (0.593 g) which was used directly for reduction; R_f 0.2 (silica gel, Et_2O/pentane, 1:4).

^{1}H NMR (200.13 MHz): δ = 9.64 (1H, br s, CHO), 5.73–5.19 (4H, m, 2CH=CH), 3.21–3.17 (2H, br d, J = 6.6 Hz, C<u>H</u>$_2$CHO), 2.79–2.72 [2H, br t, J = 6.7 Hz, C<u>H</u>$_2$(CH=CH)$_2$], 2.10–1.96 (2H, br quint, J = 7.3 Hz, C<u>H</u>$_2$Me), 0.94 (3H, t, J = 7.4 Hz, CH_2C<u>H</u>$_3$).

^{13}C NMR (50.13 MHz): δ = 199.44 (d), 133.48 (d), 132.60 (d), 125.94 (d), 118.36 (d), 42.45 (t), 25.83 (t), 20.56 (t), 14.16 (q).

IR (Film): ν = 2728, 1729, 1650, 730 cm^{-1}.

(*Z,Z*)-Nona-3,6-dien-1-ol (11):

The crude aldehyde **9** (0.593 g) diluted in THF (20 mL) was added dropwise, at −70 °C, to a suspension of $LiAlH_4$ (0.227 g, 5.98 mmol) in THF (100 mL). The mixture was allowed to warm

up to −20 °C and was hydrolyzed with H_2O (3 mL), then 2N HCl was added until pH 1. Saturation with solid NaCl, extraction with Et_2O (3 × 50 mL), drying ($MgSO_4$) and flash chromatography (silica gel, 230–400 mesh, Et_2O/pentane, 1:4) led to pure alcohol **11** (0.547 g, 91%): R_f 0.28 (silica gel, Et_2O/pentane, 1:1).

For NMR data, see Ref. 7.

IR (Film): ν = 3350, 3040, 1650, 1050, 730 cm^{-1}.

HRMS for $C_9H_{16}O$ calc. 140.12011, found 140.1209.

(Z,Z)-1-Bromonona-3,6-diene **(12)**: Prepared according to our previously reported procedure;[24] alcohol **11** (1.19 g, 8.5 mmol) led to pure bromide **12** (1.58 g, 92%): R_f 0.76 (silica gel, Et_2O/pentane, 1:1).

For NMR data, see Ref. 24.

IR (Film): ν = 3040, 1660, 680 cm^{-1}.

[(Z,Z)-Nona-3,6-dien-1-yl]triphenylphosphonium Bromide (13):
A solution of bromide **12** (1.5 g, 7.4 mmol) and PPh_3 (3.9 g, 14.8 mmol) in MeCN (7.5 mL) was saturated in argon by flushing 3 times with Ar in vacuo and refluxed for 24 h. Filtration of the mixture over silica gel (70–230 mesh) with solvents free of oxygen (Et_2O/pentane, 1:1, Et_2O, then MeOH/CH_2Cl_2, 1:20 to 1:5) led to phosphonium salt **13** (3.15 g, 92%); R_f 0.62 (silica gel, MeOH/CH_2Cl_2, 1:20).

^1H NMR (200.13 MHz): δ = 7.85–7.60 (15 H, m, arom), 5.59–5.00 (4 H, m, 2CH=CH), 3.85–3.71 (2 H, m, CH_2P), 2.51–2.08 (4 H, m, $2CH_2$), 1.89–1.74 (2 H, quint, J = 7.4 Hz, $C\underline{H}_2\underline{C}H_3$), 0.81 (3 H, t, J = 7.5 Hz, $CH_2\underline{C}\underline{H}_3$).

^{13}C NMR (50.13 MHz): δ = 135.13 (3 C, dd, J = 3.5 Hz), 133.66 (6 C, dd, J = 10 Hz), 132.35 (d), 130.54 (6 C, dd, J = 12.7 Hz), 130.42 (d), 126.30 (1 C, dd, J = 14.3 Hz), 126.10 (d), 118.11 ((3 C, ds, J = 86 Hz), 25.45 (t), 22.96 (1 C, dt, J = 49.7 Hz), 20.49 (t), 20.36 (1 C, dt, J = 4 Hz), 14.14 (q).

^{31}P NMR δ (100 MHz): δ = 22.61 (s).

α-Linolenic Acid (14b):
Phosphonium salt **13** (0.985 g, 2.11 mmol) was dried 3 times by azeotropic distillation with anhydr. benzene (10 mL) and diluted with THF (35 mL). $NaN(SiMe_3)_2$ (1 M/THF, 2 mL, 2 mmol) was added at 0 °C and the dark orange mixture was stirred for 2 hours at r.t. After cooling to −95 °C, a solution of methyl 9-oxononanoate[23] in THF (3 mL) was added. Classical workup and chromatography (silica gel, 230–400 mesh, Et_2O/pentane, 1:50 to 1:4) gave pure methyl α-linolenate (0.292 g, 50%);[25] R_f 0.56 (silica gel, Et_2O/pentane, 1:4).

To a solution of methyl α-linolenate (0.205 g, 0.7 mmol) in THF (4.6 mL), was added LiOH (0.5 M/H_2O, 2.8 mL) in H_2O at 0 °C. After stirring at r.t. for 18 h, the mixture was acidified to pH 1 by addition of 2N HCl and saturated with solid NaCl. Extraction with Et_2O (4 × 20 mL), drying ($MgSO_4$), concentration and chromatography (silica gel, 230–400 mesh, Et_2O/pentane, 1:4 to Et_2O, and MeOH/Et_2O, 1:20) gave pure α-linolenic acid (0.180 g, 93%): R_f 0.50 (silica gel, Et_2O).

^1H NMR (200.13 MHz): δ = 5.43–5.25 (6 H, m, 3CH=CH), 2.80–2.75 (4 H, br t, J = 5.6 Hz, $2CH_2$ bisallylic), 2.31 (2 H, t, J = 7.3 Hz, CH_2CO_2H), 2.12–1.98 (4 H, m, $2CH_2$ allylic), 1.63–1.57 (2 H, m, $CH_2CH_2CO_2H$), 1.28 (8 H, br s, $4CH_2$), 0.94 (3 H, t, J = 7.5 Hz, CH_3).

^{13}C NMR (50.13 MHz): δ = 179.92 (s), 131.99 (d), 130.28 (d), 128.32 (d), 128.28 (d), 127.78 (d), 127.15 (d), 34.14 (t), 29.62 (t), 29.20 (t), 29.11 (t, 2 C), 27.24 (t), 25.65 (t), 25.55 (t), 24.72 (t), 20.57 (t), 14.26 (q).

IR (Film): ν = 2940, 1709, 1650, 1412 cm^{-1}.

The authors gratefully acknowledge Dr. J.M. Pons and Dr. J. Rodriguez for helpful discussions.

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