Preparative Scale Syntheses of Isomerically Pure (10*E*,12*E*,14*Z*)- and (10*E*,12*E*,14*E*)-Hexadeca-10,12,14-trienals, Sex Pheromone Components of *Manduca sexta*

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Abstract: Short, efficient syntheses yielding products of very high isomeric purity have been developed for (10*E*,12*E*,14*Z*)-hexadeca-10,12,14-trienal **1** and the (10*E*,12*E*,14*E*)-isomer **2**, the key pheromone components of the tobacco hornworm moth *Manduca sexta*. The penultimate (*EEZ*)-trienol, and aldehyde **1**, were freed from isomeric impurities by selective reaction of the impurities with tetracyanoethylene. (*EEE*)-Aldehyde **2** was prepared by Wittig reaction of (2*E*,4*E*)-hexa-2,4-dienyltriphenylphosphonium bromide with 10-acetoxydecanal, deprotection, selective crystallization of the (*EEE*)-trienol from the resulting mix of isomers, and oxidation. The yield of the (*EEE*)-trienol was increased further by iodine-catalyzed isomerization of the mix of isomers in the liquor, and further recrystallization.

Key words: (10*E*,12*E*,14*Z*)-hexadeca-10,12,14-trienal, (10*E*,12*E*,-14*E*)-hexadeca-10,12,14-trienal, tetracyanoethylene, Diels–Alder adduct, pheromone

The tobacco hornworm moth, *Manduca sexta* (Lepidoptera: Sphingidae), is a pest of tobacco and other solanaceous crops in the New World. It is also of importance to science because it has become the experimental animal of choice for studies of insect biochemistry, physiology, endocrinology, and olfaction on account of its relatively large size, fast growth rate, and ease of rearing.[1] However, the sex pheromone resisted identification for a number of years, in part due to the large number of possible pheromone components in female pheromone glands (12 saturated, and mono-, di-, and tri-unsaturated aldehydes), but principally due to the instability of one of the key components, (10*E*,12*E*,14*Z*)-hexadeca-10,12,14-trienal **1**, which was destroyed during preparative GC isolation attempts.[1] This compound, and the corresponding *EEE*-isomer **2**, were eventually isolated by reverse phase HPLC, and the bioactive pheromone blend was determined to consist of **1** in combination with (10*E*,12*Z*)-hexadeca-10,12-dienal.[1] In wind tunnel bioassays, the *EEE*-isomer was not attractive, and because of the ease of isomerization of **1**, its presence may be artifactual. Furthermore, the possible roles of the other aldehyde components in both inter- and intra-specific communication has not yet been resolved.[1]

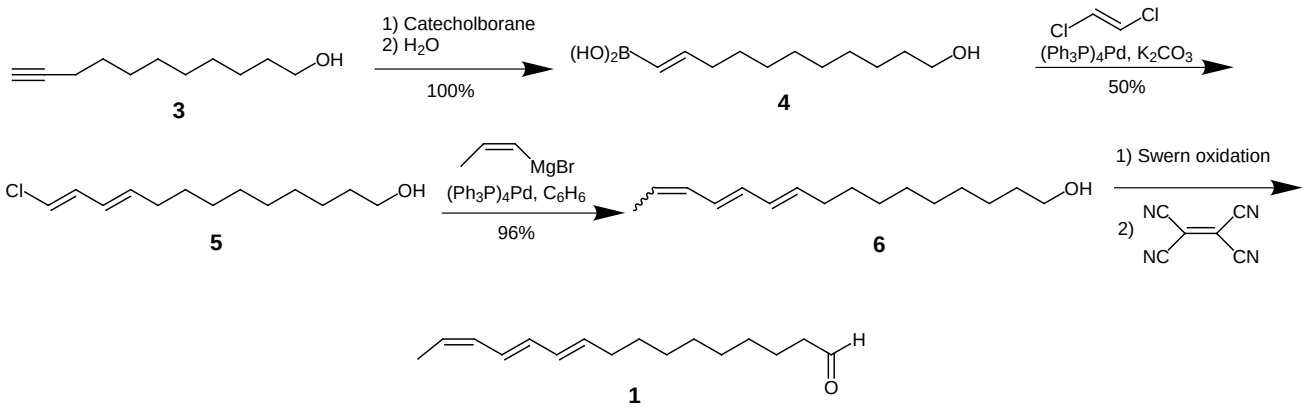
Isomeric and related impurities frequently exert dramatic effects on the behavioral responses of insect species to their pheromones, with well-documented cases of strong synergism or strong antagonism of responses at concentrations of less than 1% of the major component(s). Consequently, the chemical and isomeric purity of synthetic pheromone components is crucial, particularly when elucidating the roles of minor components in pheromone gland extracts. On paper, the syntheses of trienals **1** and **2** appear straightforward. In practice, synthesis of these labile compounds in very high purity and in significant quantities is not trivial. Two syntheses of **1** and **2** have been published,[2,3] but both produced small quantities of the target compounds heavily contaminated with isomeric impurities. A third synthesis of the analogous hexadecatrienyl alcohols has been reported, but the routes used were not stereoselective, and produced mixtures of isomers, which could only be separated on milligram scale by HPLC.[4]

Our objective was to develop short, efficient syntheses of **1** and **2**, and of equal or greater importance, to develop straightforward preparative scale methods of attaining very high chemical and isomeric purity of the target compounds, to provide pure materials for further elaboration of the full pheromone blend of *M. sexta*. In developing syntheses of **1** and **2**, high stereochemical purity on a preparative scale could be obtained in two ways. First, highly stereoselective or stereospecific reactions, if available, could be used. Alternatively, one or more of the intermediates or the final products must be easily separable from all stereoisomeric and chemical contaminants. Both of these principles were used in the syntheses described below.

Synthesis of (10*E*,12*E*,14*Z*)-Hexadeca-10,12,14-trienal (1)

10-Undecyn-1-ol (**3)** was hydroborated with catecholborane, followed by hydrolysis of the adduct to produce *(E)*-11-hydroxy-1-undecenylboronic acid (**4)**[5] (Scheme 1). The key steps in assembling the remainder of the carbon skeleton were two sequential palladium-catalyzed cross-coupling reactions, first coupling **4** with *trans*-1,2-dichloroethylene to give the chlorodienol **5,** which was then coupled with *cis*-1-propenylmagnesium bromide.

The Suzuki cross-coupling reaction[6] between boronic acid **4** and *trans*-1,2-dichloroethylene proved more difficult than anticipated. Typical Suzuki reaction conditions with either aq Na_2CO_3[7] in 1,2-dimethoxyethane (DME) (entry 5, Table) or NaOEt[5] in benzene (entry 11) gave coupling product **5** in poor yield, with a major side product, 10-un-



Scheme 1

decen-1-ol, resulting from deboronation. Use of DME as solvent[8] or cosolvent did not completely suppress deboronation, but DME/EtOH solvent mixtures enhanced the yield of **5** (Table, compare entries 3−7), in part because the mixed solvent resulted in a homogeneous reaction mixture which appeared to favor the coupling reaction over deboronation. Among the bases tested, aq K_2CO_3 proved most efficacious (Table). Surprisingly, addition of a large excess of *trans*-1,2-dichloroethylene decreased the yield of **5** (Table, entries 1 vs. 2 and 3 vs. 4).

Coupling of chloride **5** with excess *cis*-1-propenylmagnesium bromide[9] proceeded smoothly in benzene at 0°C, affording triene alcohol **6** in excellent yield (96%), but contaminated with 6% of the corresponding *EEE*-isomer **3**. Compound **6** could be purified by repeated recrystallization, but it proved more expeditious and efficient to remove the unwanted *EEE*-isomer by selective Diels−Alder reaction with the powerful dienophile tetracyanoethylene (TCNE).[10] The sterically less hindered *EEE*-isomer reacted faster with TCNE at 0°C than the *EEZ*-isomer **6**, giving a mixture of the adducts **7a** or **7b** (Scheme 2) with unchanged **6**. Isomerically pure **6** was readily isolated from the mixture by flash chromatography on Florisil (chromatography on silica resulted in isomerization). The improvement in chemical and isomeric purity as compared to previous reports is indicated by the melting point (48−49ºC), 10−11ºC higher than previously reported (38ºC).[3]

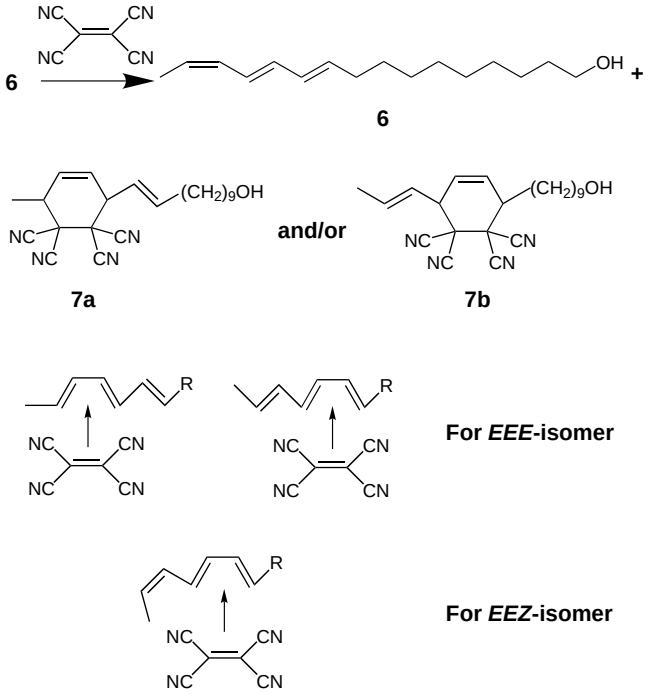
Because the conjugated trienes were sensitive to acid, heat, and electrophilic attack, oxidation of **6** to the corresponding aldehyde **1** proved problematic. It had been re-

Table Cross-coupling Reaction of Boronic Acid **4** with *trans*-1,2-Dichloroethylene[a]

Entry	Base	Molar ratio dichloride:**4**	Solvent	Conditions	Ratio of Products[b] **5**:10-undecenol	
1	aq K_2CO_3	2:1	DME/EtOH	45°C, 22 h	64	3
2	aq K_2CO_3	5:1	DME/EtOH	45°C, 15 h	45	2
3	aq Na_2CO_3	2:1	DME/EtOH	45°C, 20 h	50	10
4	aq Na_2CO_3	5:1	DME/EtOH	45°C, 15 h	35	7
5	aq Na_2CO_3	2:1	DME	45°C, 15 h	22	8
6	aq Na_2CO_3	2:1	EtOH	45°C, 15 h	13	9
7	aq Na_2CO_3	2:1	THF	45°C, 20 h	15	6
8	aq $NaHCO_3$	2:1	DME/EtOH	45°C, 20 h	20	10
9	aq KOH	2:1	DME	45°C, 5 h	10	30
10	NaOH, EtOH	2:1	DME/EtOH	25°C, 15 h	9	31
11	NaOEt, EtOH	3:1	C_6H_6	45°C, 4 h	17	4
12	KOBu^t, ^{t}BuOH	2:1	DME/EtOH	45°C, 23 h	16	25
13	KOBu^t, ^{t}BuOH	2:1	DME	45°C, 23 h	10	32
14	$KN(TMS)_2$	2:1	DME/EtOH	25°C, 20 h	0	4
15	DBU	2:1	DME/EtOH	45°C, 16 h	5	4
16	Ag_2O	4:1	THF	25°C, 15 h	13	3

[a]Typical procedure, e.g., entry 3:*trans*-1,2-dichloroethylene (2 mmol) was added under Ar to a soln of $(Ph_3P)_4Pd$ (6 mol%) in DME (5 mL) and the mixture was stirred for 30 min at r.t. Compound **4** (1 mmol) in EtOH (2 mL) and 2M aq Na_2CO_3 (1 mL) were added sequentially, and the mixture was heated at 45ºC with vigourous stirring for 20 h. After concentration, the residue was diluted with H_2O and extracted with hexane. The hexane layer was washed with brine and dried (Na_2SO_4).
[b]Determined by GC. Semiquantitative comparisons of yields between entries were obtained by comparison of the peak areas of products with those of triphenylphosphine from the catalyst.

ported that oxidizing agents such as PCC and PDC resulted in degradation,[2] and even the relatively mild Dess−Martin periodinane reagent[11] caused variable and uncontrollable isomerization.[2] In our hands, Swern oxidation[12-14] (oxalyl chloride and DMSO in CH_2Cl_2) with a careful, cold workup gave a good yield of **1**, albeit with a small amount of isomerization (3%). Substituting THF for CH_2Cl_2 as the solvent[15] decreased isomerization (<1%), but the reaction did not go to completion.

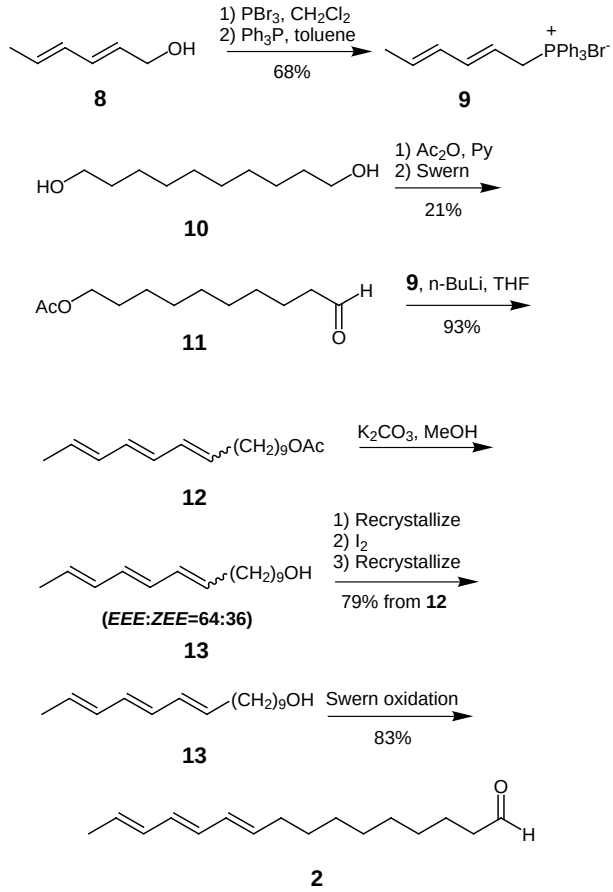


Scheme 2

However, as with alcohol **6**, treatment of crude aldehyde **1** with TCNE selectively removed the unwanted *EEE*-isomer. After Florisil chromatography, **1** was obtained in 32% overall yield from **3**, with isomeric purity > 99%. It was difficult to determine the isomeric purity more accurately because of slight isomerization (~1.5%) of **1** during GC analysis, even with injector temperatures of 200 ºC. Also, pure **1** was quite unstable, and polymerized to a white solid at −20°C, either as the pure material or in hexane solution with 2,6-di-*tert*-butyl-4-methylphenol (BHT) stabilizer, over the course of a few days to weeks. Consequently, the purified material was stored as a dilute solution in frozen cyclohexane at −70ºC.

Synthesis of (10*E*,12*E*,14*E*)-Hexadeca-10,12,14-trienal (2)

The synthesis of **2** was designed to take advantage of the crystallinity of a logical precursor, the corresponding alcohol **13**, and of the ease with which other stereoisomers could be isomerized to the *EEE* configuration. Retrosynthetic analysis of **2** revealed a convenient disconnection between carbons 10 and 11. Thus, (2*E*,4*E*)-hexa-2,4-dien-1-ol (sorbic alcohol) (**8**) was brominated with phosphorus tribromide at −10 °C,[16] then treated with triphenylphosphine in toluene at room temperature to afford (2*E*,4*E*)-hexa-2,4-dienyltriphenylphosphonium bromide (**9**) in 68% yield (Scheme 3). Wittig reaction of **9** with aldehyde **11** (prepared from 1,10-decanediol (**10**) in 2 steps) gave 10,12,14-hexadecatrienyl acetates **12** in 93% yield (*EEE*:*ZEE*-isomer, 64:36).



Scheme 3

The acetates **12** were hydrolyzed to crude alcohols **13** with anhydrous potassium carbonate in methanol, and the ratio of *EEE*- to *ZEE*-isomers at this point remained unchanged. Pure (10*E*,12*E*,14*E*)-hexadeca-10,12,14-trienol (**13**) was readily obtained by recrystallization of the trienol mixture from 5% Et_2O in hexane (isolated yield 55%), with the remaining mother liquor being enriched in the *ZEE*-isomer (84%). The mixed isomers in the liquor were isomerized to a mixture rich in *EEE*-**13** (71%) by addition of a catalytic amount of iodine and exposure to light.[2] Recrystallization yielded a second portion of *EEE*-**13** (24%), for a combined yield of 79%. Finally, Swern oxidation gave **2** in 83% yield after recrystallization, with no detectable isomerization during oxidation and purifica-

tion. Overall yield of **2** from **8** was 41%. The NMR spectra of **2** closely matched those previously reported.[2]

In summary, short and efficient syntheses yielding aldehydes **1** and **2** in high isomeric purity have been developed. These syntheses, and the key purification steps, are amenable to scaling up to multigram quantities. Furthermore, the route developed for **1** should also be applicable to stereoselective syntheses of the *EZZ*- and *EZE*-isomers by substitution of *cis*-1,2-dichloroethylene and *trans*-propenylmagnesium bromide synthons into the appropriate steps.

Mps are not corrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a General Electric QE-300 instrument. Electron impact mass spectra (70 eV) were recorded with a HP 5970 mass selective detector interfaced to an HP 5890 GC fitted with a DB-5 column (20m × 0.25mm i.d.). Routine GC analyses were carried out on a HP 5890 GC fitted with a DB-5 column (20m × 0.32mm i.d.), and an injector temperature of 200 ºC to minimize isomerizations. THF was purified by distillation from sodium/benzophenone ketyl under Ar. Solvents for flash chromatography (hexane and EtOAc), were distilled prior to use. All other solvents and reagents were used as received. Unless otherwise specified, flash chromatography was carried out using Florisil (100−200 mesh, Acros Organics) because the weak acidity of silica gel resulted in extensive isomerization of triene compounds. Moisture- and air-sensitive reactions were carried out in oven-dried glassware under Ar. Unless otherwise stated, extracts were dried over anhyd Na_2SO_4 and concentrated by rotary evaporation under reduced pressure. NMR spectra of trienes were taken in DMSO-d_6 rather than $CDCl_3$ to avoid acid-catalyzed isomerization.

(1*E*)-11-Hydroxy-1-undecenylboronic Acid (4)

Boronic acid **4** was prepared by modification of a reported procedure.[5] Catecholborane (14.8 mL, 116 mmol; Lancaster) was added dropwise to 10-undecyn-1-ol (**3**) (9.8 g, 58 mmol) in anhyd THF (20 mL) at r.t. After the evolution of H_2 ceased, the mixture was heated at 75 °C for 15 h. H_2O (350 mL) was added to the cooled reaction mixture, and the mixture was stirred at r.t. for 4 h. The resulting white slurry was cooled in an ice-bath and filtered, rinsing the solid with ice-cold H_2O (3×50 mL). The solids were re-suspended in H_2O (100 mL), cooled to 0 °C again and filtered off. The sticky white boronic acid **4** (12.4 g, 100%) was dried under aspirator vacuum, and used without further purification.

(10*E*,12*E*)-13-Chlorotrideca-10,12-dien-1-ol (5)

A three-necked flask charged with $(Ph_3P)_4Pd$ (2.08 g, 1.8 mmol) and anhyd DME (120 mL) was flushed with Ar, and *trans*-1,2-dichloroethylene (4.62 mL, 60 mmol) was introduced by syringe. After stirring at r.t. for 30 min, a solution of boronic acid **4** (6.44 g, 30 mmol) in EtOH (60 mL) and 2M aq K_2CO_3 (30 mL) were added sequentially. Heating at 45−50 °C with vigorous stirring for 22 h resulted in a dark brown solution and a sticky white sludge on the bottom of the flask. After concentration of the liquid portion by rotary evaporation, the black residue was diluted with H_2O (100 mL), extracted with hexane (600 mL), and the hexane extract was washed with brine (2×100 mL), dried and concentrated. The crude product was purified by flash chromatography (10% EtOAc in hexane) to afford **5** (3.46 g, 50% yield) as a viscous oil. Recrystallization from hexane (150 mL) at −20ºC gave a white solid, mp: 36.0−37.5 °C.

^{1}H NMR ($CDCl_3$): δ = 1.28−1.58 (m, 14H), 2.06 (dt, 2H, *J* = 6.9, 6.8 Hz), 3.64 (t, 2H, *J* = 6.5 Hz), 5.70 (dt, 1H, *J* = 15.1, 6.9 Hz), 5.97 (dd, 1H, *J* = 15.1, 10.6 Hz), 6.07 (d, 1H, *J* = 13.1 Hz), 6.41 (dd, 1H, *J* = 13.1, 10.6 Hz).

^{13}C NMR ($CDCl_3$): δ = 25.74, 29.03, 29.13, 29.40, 29.53, 32.63, 32.80, 63.08 (2×C), 118.22, 126.04, 133.88, 136.31.

MS: *m/z* 194 (M−HCl, 12), 135 (3), 114 (10), 101 (12), 90 (33), 88 (100), 79 (45), 67 (42), 65 (64), 55 (50), 41 (75).

(10*E*,12*E*,14*Z*)-Hexadeca-10,12,14-trien-1-ol (6)

1,2-Dibromoethane (10 drops, approx. 0.4 mL) was added to a mixture of Mg powder (50 mesh, 1.92 g, 80 mmol; Aldrich) in anhyd THF (25 mL) to initiate the Grignard reaction. This was followed by dropwise addition (**Caution**: vigorously exothermic!) of a solution of 97% *cis*-1-bromopropene (4.84 g, 40 mmol; Aldrich) in THF (15 mL) at a rate sufficient to maintain gentle refluxing (**Caution**: commercial batches of *cis*-1-bromopropene varied in isomeric purity. Purity was checked easily by GC, programming from 15 ºC). After the addition was complete, the mixture was heated at 48−50 °C for 1 h to assure completion of the reaction.

A mixture of **5** (2.31 g, 10 mmol) and $(Ph_3P)_4Pd$ (0.58 g, 0.5 mmol) in anhyd benzene (60 mL) was stirred at r.t. for 30 min, then cooled to 0 °C. The freshly prepared *cis*-1-propenylmagnesium bromide was added dropwise by syringe to the resulting suspension, and the mixture was stirred at 0 °C for 2 h. The reaction was quenched with ice-cold dilute aq NH_4Cl (150 mL) and the resulting mixture was extracted with hexane (600 mL). The organic extract was washed with H_2O (2×80 mL) and brine (80 mL), dried, and concentrated. Flash chromatography (30% Et_2O in hexane) followed by recrystallization from 5% Et_2O in hexane (120 mL) at 5 ºC afforded **6** (2.26 g, 96% yield) as white needles, contaminated by 6% of the *EEE*-isomer. To remove the *EEE*-isomer, TCNE (0.019 g, 0.15 mmol) was added to a solution of **6** (0.35 g, 1.5 mmol) in Et_2O (5 mL) at 0°C, and stirred for 30 min at 0 ºC. After removal of the solvent at r.t., the residue was purified by flash chromatography followed by recrystallization from hexane (10 mL) at 5 ºC to give pure **6** as white crystals (0.32 g; mp: 48−49 °C (Lit.[3] 38 °C)) with no detectable isomeric or other impurities.

^{1}H NMR (DMSO-d_6): δ = 1.21−1.36 (m, 14H), 1.68 (dd, 3H, *J* = 7.2, 1.1 Hz), 2.03 (dt, 2H, *J* = 7.0, 6.9 Hz), 3.33 (dt, 2H, *J* = 6.2, 5.3 Hz), 4.28 (t, 1H, *J* = 5.3 Hz, OH), 5.42 (dq, 1H, *J* = 10.6, 7.2 Hz), 5.68 (dt, 1H, *J* = 14.2, 7.1 Hz), 5.94−6.19 (m, 3H), 6.40 (m, 1H).

^{13}C NMR (DMSO-d_6): δ = 13.72, 25.94, 29.04, 29.18, 29.29, 29.38, 29.49, 32.61, 32.99, 61.15, 126.04, 126.26, 129.99, 131.06, 133.11, 135.26.

MS: *m/z* 236 (M^+, 30), 150 (2), 135 (4), 121 (5), 107 (20), 93 (49), 79 (100), 67 (10), 55 (11), 41 (30).

(*E*10,*E*12,*Z*14)-Hexadeca-10,12,14-trienal (1)

DMSO (1.1 mL, 15.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of oxalyl chloride (0.7 mL, 8.1 mmol) in CH_2Cl_2 (60 mL) at −78 °C. After stirring at −78 ºC for 5 min, impure alcohol **6** (1.3 g, 5.5 mmol) in CH_2Cl_2 (30 mL) was added dropwise. The mixture was stirred at −78 °C for 20 min, Et_3N (4.6 mL, 32.9 mmol) was then added dropwise, the mixture was stirred a further 5 min, and then allowed to warm to 0 °C. Ice-cold sat. $NaHCO_3$ (50 mL) was added and the resulting mixture was extracted with ice-cold hexane (300 mL). The hexane extract was washed with ice-cold brine (2×50 mL), and dried. GC analysis indicated that the oxidation was complete, but that there was about 9% of *EEE*-trienal **2** in the mixture. The solvent was removed by rotary evaporation below 20 °C, and the residue was dissolved in Et_2O (20 mL) and cooled to 0 °C. TCNE (0.10 g, 0.78 mmol) was added, and the mixture was stirred at 0 °C for 30 min, monitoring by GC. The undesired *EEE*-isomer was completely removed, although the GC chromatogram still showed 1.5% of the *EEE*-isomer because of thermally induced isomerization of the *EEZ*-isomer during the GC run. This small amount of isomerization during analysis was confirmed by adding

another 15 mg of TCNE, and stirring for 20 min, after which the ratio of *EEE*- to *EEZ*-isomers in the GC trace remained unchanged, although the absolute amount of both was decreased. After concentration, the crude product was purified by flash chromatography (8% Et_2O in hexane) to furnish aldehyde **1** (0.88 g, 68% yield) as an almost colorless liquid.

^{1}H NMR (DMSO-d_6): δ = 1.21−1.47 (m, 12H), 1.69 (dd, 3H, *J* = 7.2, 1.1 Hz), 2.03 (dt, 2H, J = 7.0, 6.9 Hz), 2.37 (dt, 2H, *J* = 7.2, 1.3 Hz), 5.42 (dq, 1H, *J* = 10.6, 7.2 Hz), 5.67 (dt, 1H, *J* = 14.2, 7.1 Hz), 5.93−6.19 (m, 3H), 6.40 (m, 1H), 9.62 (t, 1H, *J* = 1.3 Hz).

^{13}C NMR (DMSO-d_6): δ= 13.70, 21.94, 28.98 (2×C), 29.15 (2×C), 29.21, 32.61, 43.42, 126.03, 126.25, 129.99, 131.06, 133.09, 135.23, 203.89.

MS: *m/z* 234 (M^+, 8), 148 (1), 135 (1), 121 (5), 107 (15), 93 (35), 79 (100), 67 (10), 55 (10), 41 (40).

(2*E*,4*E*)-Hexa-2,4-dienyltriphenylphosphonium Bromide (9)

Bromide **9** was prepared from (2*E*,4*E*)-hexa-2,4-dien-1-ol (**8**) (10 g, 102 mmol; Aldrich) by the reported procedure,[16] with the workup procedure modified as follows. After the reaction was quenched with ice-cold sat. $NaHCO_3$ (30 mL) at −10 °C, the resulting mixture was extracted with pentane (350 mL), and the organic phase was washed with brine (2×50 mL), and dried. After removal of the pentane and CH_2Cl_2 by rotary evaporation at r.t., the crude bromide (~ 16 g) was transferred to a wide-mouth brown glass bottle containing triphenylphosphine (28 g, 107 mmol) and anhyd toluene (160 mL). The mixture was kept at r.t. for 3 d, and the resulting crystalline product was collected by suction filtration, rinsing the solids with a small amount of toluene. After pumping under vacuum (0.01 mm Hg) at r.t. for 6 h to remove traces of toluene, 29 g of the crystalline phosphonium salt **9** were obtained (68% from **8**); mp: 158–160 °C.

^{1}H NMR ($CDCl_3$): δ = 1.65 (br d, 3H, *J* = 7.1 Hz), 4.66 (dd, 2H, *J* = 7.5; J_{P-H} = 15.3 Hz), 5.27 (dq, 1H, *J* = 14.7, 7.1 Hz), 5.63 (m, 1H), 5.88 (dd, 1H, *J* = 14.7, 10.6 Hz), 6.31 (ddd, 1H, *J* = 15.2, 10.2; J_{P-H} = 5.1 Hz), 7.56–7.95 (m, 15H).

10-Acetoxydecanal (11)

1,10-Decanediol (**10**) (34.8 g, 200 mmol) was dissolved in a mixture of THF (250 mL), pyridine (17 mL, 210 mmol) and dimethylaminopyridine (0.5 g) at r.t. over 3 h. The homogeneous solution was cooled to 0 °C, and Ac_2O (18.9 mL, 200 mmol) was added dropwise over 45 min with a syringe pump. The resulting white suspension was stirred at 0 °C for 1 h and at r.t. for a further 19 h. After concentration, the mixture was partitioned between hexane (250 mL) and 1M HCl (250 mL). The aqueous phase was extracted again with hexane (3×100 mL), the combined organic phase was washed with 1M HCl (100 mL) and brine (2×100 mL), dried, and concentrated. Silica gel flash chromatography (35% EtOAc in hexanes) gave a moderate yield of 10-acetoxydecanol (11.7 g), which was oxidized to 10-acetoxydecanal (**11**) using the standard Swern oxidation procedure,[12] giving **11** (9.1 g) as a viscous oil after silica gel flash chromatography (25% EtOAc in hexane). The yield was not optimized in either of the two steps.

^{1}H NMR ($CDCl_3$): δ = 1.28−1.67 (m, 14H), 2.05 (s, 3H), 2.42 (dt, 2H, *J* = 7.3, 1.5 Hz), 4.05 (t, 2H, *J* = 6.7 Hz), 9.76 (t, 1H, *J* = 1.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 20.97, 22.01, 25.84, 28.55, 29.08, 29.12, 29.22 (2×C), 43.85, 64.95, 173.20, 202.85.

MS: *m/z* 171 ($M-CH_3CO$, 2), 136 (1), 126 (2), 111 (15), 97 (5), 83 (7), 69 (32), 55 (30), 43 (100), 41 (25).

Hexadeca-10,12,14-trienyl Acetates 12

A mixture of phosphonium salt **9** (21.5g, 51 mmol) and THF (120 mL) was cooled to −30 °C with a dry ice-acetone bath, BuLi (2.5M in hexanes, 20.4 mL, 51 mmol) was added dropwise, and the mixture was stirred at −30 ºC for 1 h. Aldehyde **11** (9.0 g, 42 mmol) in THF (50 mL) was then added dropwise. After the addition was complete, the mixture was warmed to r.t. over 1 h, then quenched with ice-water (250 mL), and extracted with hexane (800 mL). The hexane extract was washed with H_2O (2×100 mL) and brine (2×100 mL), dried, and concentrated. Flash chromatography (10% Et_2O in hexanes) of the residue gave acetates **12** (8.9g, 76% yield based on **11,** *EEE*: *ZEE*, 64:36 by GC), followed by alcohols **13** (1.7g, 17% yield).

(*E*10,*E*12,*E*14)-Hexadeca-10,12,14-trien-1-ol (13)

Anhyd K_2CO_3 (4.8g, 34.8 mmol) was added in portions to an ice-cold solution of the acetates **12** (8.8 g, 31.6 mmol) in MeOH (50 mL), the mixture was stirred at r.t. for 1 h, then quenched with ice-cold H_2O (40 mL). The mixture was extracted with hexane (400 mL), and the hexane phase was washed with brine (2×50 mL), dried, and concentrated. The ratio of *EEE*- to *ZEE*-isomers was unchanged by GC analysis. After concentration at r.t., the residue was purified by flash chromatography (20% Et_2O in hexanes) to afford the mixed trienols **13** (7.1g, 95% yield) as a white solid. Recrystallization from 5% Et_2O in hexane (400 mL) at 5 ºC gave pure *EEE*-trienol **13** (4.1 g, 55% yield) as colorless needles, mp: 73−74 °C (Lit.[2] 71−72.5 °C; Lit.[3] 42 °C).

^{1}H NMR ($CDCl_3$): δ = 1.27−1.58 (m, 14H), 1.76 (d, 3H, *J* = 6.5 Hz), 2.07 (dt, 2H, *J* = 7.0 Hz), 3.63 (t, 2H, *J* = 6.6 Hz), 5.63−5.69 (m, 2H), 6.00−6.07 (m, 4H).

^{13}C NMR ($CDCl_3$): δ = 18.25, 25.72, 29.15, 29.34, 29.40 (2×C), 29.52, 32.79 (2×C), 63.07, 128.74, 130.40, 130.61, 130.68, 131.78, 134.46.

MS: *m/z* 236 (M^+, 50), 149 (2), 135 (2), 121 (6), 107 (35), 93 (55), 79 (100), 67 (10), 55 (10), 41 (42).

The mother liquor containing 84% of the *ZEE*-isomer was evaporated to dryness, the residue was dissolved in 1:1 hexane-Et_2O (1 L) containing a few crystals I_2 (~ 5 mg), and kept in laboratory light for 10 min. The solution was washed with sat. $Na_2S_2O_3$ (30 mL) and brine (2×100 mL), and dried. GC analysis showed that the *EEE*-isomer now constituted 71% of the mixture. After concentration and recrystallization as before, a further 1.8g (24%) of pure *EEE*-**13** was obtained.

(*E*10,*E*12,*E*14)-Hexadeca-10,12,14-trienal (2)

Employing the same Swern oxidation procedure used for **1**, *EEE*-alcohol **13** (5.5 g, 23.3 mmol) was oxidized to aldehyde **2**. Recrystallization from hexane at −20 °C gave **2** (4.5g, 83%) as white crystals, mp: 43−44 °C. Previously, this compound had only been reported as a liquid.[2,3]

^{1}H NMR ($CDCl_3$): δ = 1.29−1.64 (m, 12H), 1.76 (d, 3H, *J* = 6.5 Hz), 2.07 (dt, 2H, *J* = 7.0 Hz), 2.41 (dt, 2H, *J* = 7.3, 1.8 Hz), 5.62−5.70 (m, 2H), 5.99−6.09 (m, 4H), 9.76 (t, 1H, *J* = 1.8 Hz).

^{13}C NMR ($CDCl_3$): δ = 18.26, 22.06, 29.07, 29.13, 29.25, 29.29 (2×C), 32.76, 43.90, 128.78, 130.45, 130.57, 130.72, 131.77, 134.36, 202.94.

MS: *m/z* 234 (M^+, 10), 148 (1), 135 (1), 121 (2), 107 (15), 93 (20), 79 (100), 67 (10), 55 (12), 41 (30).

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