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Synthesis of (4*E*,6*Z*,10*Z*)-hexadeca-4,6,10-trien-1-ol and (4*E*,6*E*,10*Z*)-hexadeca-4,6,10-trien-1-ol, the pheromone components of cocoa pod borer moth *Conopomorpha cramerella*

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A concise and efficient synthesis of the pheromone components of the cocoa pod borer moth, namely (4*E*,6*Z*,10*Z*)-hexadeca-4,6,10-trien-1-ol and (4*E*,6*E*,10*Z*)-hexadeca-4,6,10-trien-1-ol, starting from commercially available materials, was reported. The overall yield was 30.4% and 27.4%, respectively. The stereoselective formation of (*E*,*Z*)- or (*E*,*E*)-conjugated double bond relied on Sonogashira coupling with (*E*)-5-bromopent-4-en-1-ol prepared from (*E*)-5-bromopent-4-enal and the stereoselective hydrogenation of the enyne, while the 10*Z*-double bond was formed by Wittig reaction from 4-hydroxybutanal and *n*-hexyltriphenylphosphonium bromide.

Introduction

(4*E*,6*Z*,10*Z*)-Hexadeca-4,6,10-trien-1-ol (**1a**), (4*E*,6*E*,10*Z*)-hexadeca-4,6,10-trien-1-ol (**2a**), and their acetates (**1b** and **2b**) are the pheromone components of cocoa pod borer moth (*Conopomorpha cramerella*, Lepidoptera: Gracillariidae) which is the most important pest damaging cocoa plantations in Southeast Asia.[1] The life cycle of the insect starts once the egg is laid on the pod surface of the cocoa plant (this cycle lasts for 2–7 days). Then, the larval stage is characterized by the formation of tunnels at the pod surface that reaches the sclerotic layer of the husk to reach food, causing scarification and sticking of the beans. Damage to the funicles of the pods results in beans that are deformed and under-sized, significantly reducing the quality and thus the value of the processed beans. Insect feeding in the pods also causes a change of the color of the beans into yellow or uneven and premature ripening, which do not match with the ripeness standards for harvesting.[2] Consequently, the production losses can exceed 50% of the crop.[1]

In 1986 Beevor *et al.* isolated and identified the pheromone components of the insect, and synthesized those compounds using a long and non-stereospecific route.[1] In 1992 Yen *et al.* reported a shorter synthesis for the pheromone components, in eight steps and with an overall yield of 32%.[3] Later, Pereira and Cabezas reported a new method for the synthesis of 1,5-diynes using the reaction of 1,3-dilithiopropyne with propargyl chlorides, and applied this new method to prepare **1a** with an overall yield of 51%.[4] Yet, the preparation of 1,5-diynes was complicated, and this compound could not be used as the starting material of isomer **2a**. The general utilization of insecticides is limited by their high cost, environmentally unfriendliness and the development of insecticide-resistance. Considerable efforts have been made for the development and evaluation of new integrated pest management techniques, such as the usage of pheromone compounds (Fig. 1).

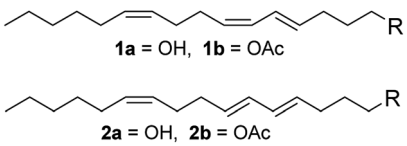

Fig. 1 Structure of the pheromone components of the cocoa pod borer moth *Conopomorpha cramerella*.

Previously, we reported the efficient syntheses of (5*Z*,7*E*)-dodecadien-1-ol, (7*Z*,11*Z*,13*E*)-hexadecatrienal, (8*E*,10*Z*)-tetradecadienal, and (9*Z*,11*E*)-hexadecadienal from (4*Z*,6*E*)-7-bromohepta-4,6-dienal (**3a**),[5] and developed an useful compound, namely (*E*)-5-bromopent-4-enal (**4a**).[5c] As a part of an ongoing investigation, we reported herein a concise and stereoselective synthesis of **1a** and **2a** from **4a**, which successfully overcame the major limitations of the previous strategies published.

Results and discussion

Compound **4a** was prepared by the tandem addition reaction of acrolein with acetylene using $Pd(OAc)_2$ as catalyst. Previously, Lu

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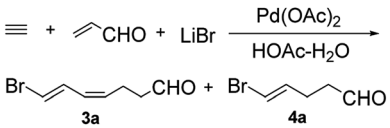
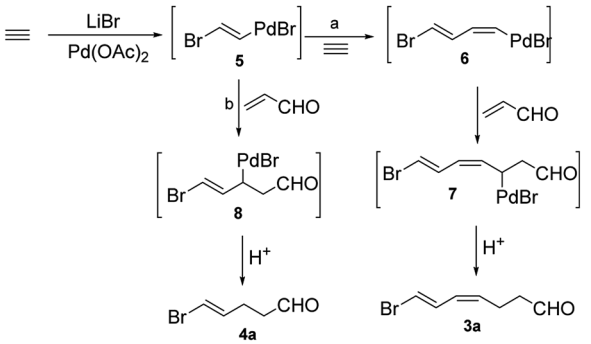


Scheme 1 Pd(II)-catalyzed coupling reaction of lithium bromide, acetylene, and acrolein.



Scheme 2 Possible mechanisms for Pd(II)-catalyzed coupling reaction of halide, acetylene, and acrolein.

et al. reported the preparation of **3a**.[6] By repeating the reported strategy, we found that the method was efficient only in small scale. In the large-scale preparations, **4a** was produced in considerable amount as a by-product. Based on this result, we optimized the experimental conditions to afford uniquely **4a** (Scheme 1).

We studied the effect of different reaction conditions on the ratio of **3a** and **4a**. The reaction time, reactant concentration and temperature were tested (Table 1). A high concentration of acrolein (a decrease of the quantity of HOAc and H_2O) did not increase the total conversion rate, but it resulted in a better selectivity of the reaction (Table 1, entries 1–3). Increasing the temperature resulted in a better selectivity of the reaction, but it decreased the total conversion rate (Table 1, entries 3–5), because acrolein and the two products were not stable at high temperature. When the reaction time was prolonged, significant improvements were observed in terms of conversion rate and selectivity (Table 1, entries 4, 6, and 7). Lower acetylene pressure allowed a better selectivity, but it did not affect strongly the total conversion rate (Table 1, entries 7–9). These results showed the same trend in both large-scale and small-scale preparation. Previously, Lu *et al.* explained the formation of **3a** (Scheme 2, path a).[6] First, transhalopalladation of acetylene lead to the (*E*)-vinylpalladium intermediate **5**, which was inserted by a second molecule of acetylene to form (*E*,*Z*)-dienylpalladium **6**. After the insertion of acrolein, (2-oxoalkyl) palladium intermediate **7** underwent protonolysis (path a) to afford **3a**. We suggest an explanation of the formation of **4a** based on the path a (Scheme 2, path b). (*E*)-Vinylpalladium intermediate **5** could react with acrolein to give (2-oxoalkyl) palladium intermediate **8**, which underwent protonolysis to afford **4a**. The crucial factors that decided which path to go were the acetylene pressure and the acrolein concentration. At a fixed acetylene pressure, a high acrolein concentration obviously increased the selectivity of the reaction.

We studied further the effect of different counter ions and reactants on the products distribution (Table 2). Br^- and Cl^- ions allowed satisfying total conversion rate and selectivity (Table 2, entries 1–3). In contrast, I^- ion resulted in poor total conversion rate and selectivity (Table 2, entry 4). The results indicated that a difference in the electron-deficiency of the alkenes could have a striking effect on the products distribution. The total conversion rate and the selectivity of the reaction were in agreement with the electrophilicity of the alkenes (enal or enone > acrolein dimethyl acetal > allyl bromide or allyl alcohol) (Table 2, entries 5–10). However, crotonaldehyde resulted in poor total conversion rate and selectivity, which probably resulted from the steric hindrance of the CH_3 group. The reaction with acrolein dimethyl acetal afforded a mixture, because acrolein dimethyl acetal and the products **3g** and **4g** were partially hydrolyzed by acetic acid. The reaction with allyl bromide gave **3h** and **4h** after 12 h reaction, as did the corresponding reaction with allyl alcohol resulting in **3j** and **4j**, but these chemicals were completely converted into **3i** and **4i** after 24 h reaction. These results could be explained by the fact that both Br and OH groups were good leaving groups, supporting a β-heteroatom elimination.[7]

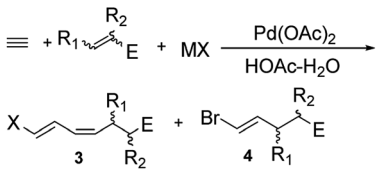
Both pheromone components of the cocoa pod borer moth were synthesized by an efficient and stereoselective route

Table 1 Optimization of Pd(II)-catalyzed coupling reaction of lithium bromide, acetylene, and acrolein[a]

					Yield (%)	
Entry	HOAc/H_2O (mol mol^{-1})	Reaction time (h)	Temp. (°C)	Acetylene pressure (atm)	**3a**	**4a**
1	4.5/3	24	5	1	16	15
2	3/2	24	5	1	18	21
3	1.5/1	24	5	1	3.2	35
4	1.5/1	24	25	1	1.0	38
5	1.5/1	24	45	1	0.8	31
6	1.5/1	48	25	1	1.2	59
7	1.5/1	72	25	1	1.3	73
8	1.5/1	72	25	0.8	0.5	70
9	1.5/1	72	25	1.2	3.3	73

[a] $Pd(OAc)_2$ (1 mmol), LiBr (1 mol), and acrolein (1.2 mol).

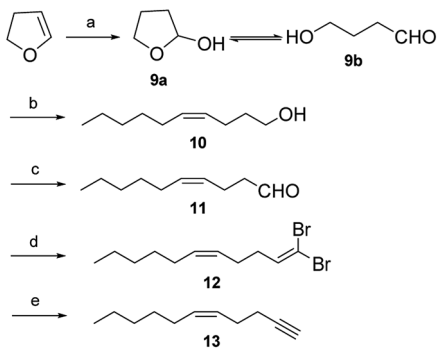
Table 2 Pd(II)-catalyzed coupling reaction of halides, acetylene, and electron-deficient alkenes[a]



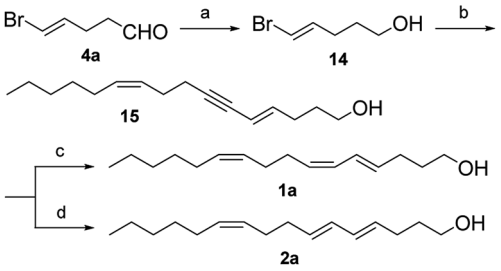
Entry	MX	R_1	R_2	*E*	Product (yield, %)	
1	n-Bu_4NBr	H	H	CHO	**3a** (2.6)	**4a** (71)
2	n-Bu_4NCl	H	H	CHO	**3b** (2.8)	**4b** (73)
3	LiCl	H	H	CHO	**3b** (0.9)	**4b** (69)
4	LiI	H	H	CHO	**3c** (2.2)	**4c** (25)
5	LiBr	H	H	$COCH_3$	**3d** (2.3)	**4d** (56)
6	LiBr	H	H	COC_2H_5	**3e** (2.4)	**4e** (65)
7	LiBr	H	CH_3	CHO	**3f** (1.1)	**4f** (68)
8	LiBr	H	H	$CH(OMe)_2$	**3a** (7.6)	**4a** (21)
					3g (6.8)	**4g** (19)
9	LiBr	H	H	CH_2Br	**3h** (traces)	**4h** (traces)
					3i (12)	**4i** (9.5)
10	LiBr	H	H	CH_2OH	**3j** (traces)	**4j** (traces)
					3i (15)	**4i** (12)
11	LiBr	CH_3	H	CHO	**3k** (8.3)	**4k** (14)

[a] $Pd(OAc)_2$ (1 mmol), halides (1 mol), and electron-deficient alkenes (1.2 mol), HOAc (1.5 mol), H_2O (1 mol), acetylene pressure (0.8 atm), 25 °C, 72 h.

(Schemes 3 and 4). Preparation of the key intermediate **13** involved the following five steps. Hydration of 2,3-dihydrofuran in wet acid according to our improved method based on the literature[8] to afforded 4-hydroxybutanal (**9b**) in 84% yield. Construction of the 10*Z*-double bond relied on Wittig reaction. To ensure the *cis* selectivity of the Wittig olefination, potassium bis(trimethylsilyl) amide was selected as the base. The ylide was prepared from *n*-hexyltriphenylphosphonium bromide by treatment with potassium bis(trimethylsilyl) amide in dry THF at −78 °C. Subsequently, the ylide reacted with aldehyde **9b** to afford enol **10** in 78% yield and with 98% isomeric purity (GC).[9]



Scheme 3 Synthetic route of key intermediate **13**. Reagents and conditions: (a) HCl/H_2O, rt, 5 h; (b) *n*-hexyltriphenylphosphonium bromide, $KN[Si(Me)_3]_2$, THF, −78 °C, 12 h; (c) PCC/Celite, CH_2Cl_2, rt, 5 h; (d) PPh_3, CBr_4, CH_2Cl_2, 0 °C, rt, 12 h; (e) *n*-BuLi, THF, −50 °C, 2 h.



Scheme 4 Synthetic route of the target compounds. Reagents and conditions: (a) $NaBH_4$, CH_3OH, 0 °C, 3 h; (b) alkyne **7**, $Pd(PPh_3)_4$, CuI, Et_2NH, rt, 12 h; (c) Zn, 1,2-dibromoethane, LiBr, CuBr, EtOH, reflux, 4 h; (d) $LiAlH_4$, diglyme, reflux, 24 h.

Enal **11** was prepared by oxidation of enol **10** using pyridinium chlorochromate in dichloromethane in 86% yield.[9b] The aldehydic carbonyl group was converted into the carbon–carbon triple bond *via* the standard Corey–Fuchs protocol. Enal **11** reacted with carbon tetrabromide and triphenylphosphine in dichloromethane to afford dibromoolefin **12** in 87% yield.[10] Subsequently, dibromoolefin **12** was converted cleanly and rapidly into enyne **13** in 91% yield by treatment with 2 equivalents of *n*-butyllithium followed by aqueous work-up.[10]

On the other hand, reduction of enal **4a** to enol **14** was achieved in 86% yield by treatment with an excess of sodium borohydride in methanol, without affecting the double bonds. The Sonogashira coupling of enol **14** with enyne **13** using $Pd(PPh_3)_4$ as catalyst in dry diethylamine at room temperature gave enynol **15** in 83% yield.[11] The Sonogashira coupling maintained the excellent isomeric purity owing to the moderate conditions used. Enynol **15** was hydrogenated using Zn to form trienol **1a** in 82% yield and with a high isomeric purity (>98%, GC).[12] The reduction of enynol **15** with $LiAlH_4$ provided the corresponding trienol **2a** in 74% yield and with a high isomeric purity (>98%, GC).[13]

Conclusions

In conclusion, preparation of (*E*)-5-bromopent-4-enal (**4a**) was optimized. (4*E*,6*Z*,10*Z*)-Hexadeca-4,6,10-trien-1-ol (**1a**) and (4*E*,6*E*,10*Z*)-hexadeca-4,6,10-trien-1-ol (**2a**) were prepared stereoselectively in 8 steps starting from commercially available materials with an overall yield of 30.4% and 27.4%, respectively. The stereoselective formation of (*E*,*Z*)- or (*E*,*E*)-conjugated double bond relied on the Sonogashira coupling with (*E*)-5-bromopent-4-en-1-ol (**14**) prepared from **4a** and stereoselective hydrogenation of (*Z*)-undec-5-en-1-yne (**13**), while the 10*Z*-double bond was formed by the Wittig reaction of 4-hydroxybutanal and *n*-hexyltriphenylphosphonium bromide. (*E*)-5-Bromopent-4-enal (**4a**) may be used in biologically active natural products including insect pheromones.

Experimental

General

All reagents used in reactions were obtained commercially in China. All anhydrous solvents were dried and purified by

standard techniques just before use. All nonaqueous reactions were performed under an inert atmosphere (nitrogen) with rigid exclusion of moisture from reagents, and all reaction vessels were oven dried. ^{1}H NMR spectra were recorded on Bruker-Ascend 400 spectrometer at 400 MHz. Chemical shifts are reported in parts per million (ppm) relative to TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet), coupling constants, and integration. ^{13}C NMR were recorded on Bruker-Ascend 400 spectrometer at 100 MHz. Chemical shifts are reported in parts per million measured relative to TMS. In preparation of (*E*)-5-bromopent-4-enal (**4a**), some reaction conditions may be different from those cited in the text (small scale) since they have been chosen for large scale reactions.

(*E*)-5-Bromopent-4-enal (4a)

Acetylene (passed through concentrated sulfuric acid) was tardily passed through a mixture of $Pd(OAc)_2$ (1122 mg, 5 mmol), LiBr (261 g, 3 mol), and acrolein (168 g, 3 mol) in HOAc (500 mL) and H_2O (100 mL) at room temperature for 72 h. The reaction mixture was poured into a saturated aqueous solution of Na_2CO_3 and then extracted with CH_2Cl_2 (500 mL × 3). The extract was washed with water, dried over Na_2SO_4, and then concentrated by evaporation. The residue was purified through a silica gel column (eluent: 20 : 1 petroleum ether/ethyl acetate) to afford enal **4a** as a colorless oil (337 g, 69%, isomeric purity > 99%, GC). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 9.76 (s, 1H, CHO), 6.15–6.12 (m, 2H, CH=CH), 2.55–2.50 (m, 2H, CH_2), 2.44 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 202.1, 131.5, 130.8, 42.9, 21.3; EI-MS (*m*/*z*): 164/162 (M^+), 121/119, 108/106, 95/93, 83, 65, 55.

4-Hydroxybutanal (9b)

After adding concentrated hydrochloric acid (2.0 g, 20 mmol) and H_2O (10.8 g, 0.6 mol) to CH_2Cl_2 (600 mL), 2,3-dihydrofuran (28 g, 0.4 mol) was added to the mixture. The resulting mixture was stirred for 5 h at room temperature, neutralized with Na_2CO_3, dried over Na_2SO_4, and then concentrated to afford 4-hydroxybutanal (**9b**) as a colorless oil (29.6 g, 84%). The product was directly used for the Wittig reaction without further purification. Tetrahydrofuran-2-ol (**9a**): ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 5.55–5.50 (m, 1H, CHOH), 3.95–3.81 (m, 2H, OCH_2), 2.09–2.01 (m, 1H, CH_2), 2.0–1.8 (m, 3H, CH_2CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 100.3/98.6, 67.6/67.4, 33.5/32.6, 23.8. 4-Hydroxybutanal (**9b**): ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 9.75 (s, 1H, CHO), 3.70–3.64 (m, 2H, CH_2OH), 2.51–2.48 (m, 2H, CH_2CHO), 2.0–1.8 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 203.0, 66.4, 41.4, 23.0; EI-MS (*m*/*z*): 87.0 ($M^+ - 1$), 71.1.

(*Z*)-Dec-4-en-1-ol (10)

Potassium bis(trimethylsiyl)amide (300 mL, 0.3 mol, 1 M in THF) was added dropwise over 30 min to a suspension of *n*-hexylphosphonium bromide (128 g, 0.3 mol) in dry THF (600 mL) at 0 °C under nitrogen. The resulting orange solution was further stirred for 1 h at 0 °C and then cooled to −78 °C. A solution of aldehyde **9b** (17.6 g, 0.2 mol) in dry THF (200 mL) was added dropwise to the above mixture over 1 h, maintaining the temperature below −70 °C. The resulting yellow solution was allowed to slowly warm up to room temperature over a period of 10 h. Then the reaction mixture was quenched with a saturated solution of NH_4Cl. After the complete evaporation of THF, the reaction mixture was extracted with EtOAc (300 mL × 3). The extract was washed with H_2O and brine, dried over Na_2SO_4, and then concentrated. The residue was purified through a silica gel column (eluent: 10 : 1 petroleum ether/ethyl acetate) to afford enol **10** as a colorless oil (24.3 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 5.45–5.37 (m, 2H, *Z*–CH=CH), 3.67 (t, J = 6.42 Hz, 2H, CH_2OH), 2.14 (m, 2H, =$CHCH_2$), 2.06 (m, 2H, =$CHCH_2$), 1.65 (m, 2H, CH_2), 1.40–1.29 (m, 6H, –CH_2–), 0.91 (t, 3H, J = 7.5 Hz, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 131.2, 129.2, 62.9, 33.0, 32.2, 30.1, 27.6, 24.0, 23.1, 14.5.

(*Z*)-Dec-4-enal (11)

Enol **10** (15.6 g, 0.1 mol) was stirred at room temperature for 5 h with a slurry of pyridinium chlorochromate (32.3 g, 0.15 mol) and Celite (32.3 g) in CH_2Cl_2 (200 mL). The mixture was then diluted with CH_2Cl_2 and filtered through Celite. The filter cake was washed with CH_2Cl_2 (200 mL × 2). The extract was washed with water, dried over Na_2SO_4, and then concentrated. The residue was purified through a silica-gel column (eluent: 25 : 1 petroleum ether/ethyl acetate) to afford enal **11** as a colorless oil (13.3 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 9.79, 5.46 (m, 1H, *Z*–CH=CH), 5.35 (m, 1H, *Z*–CH=CH), 2.51 (m, 2H, CH_2CHO), 2.39 (m, 2H, CH_2CH_2CHO), 2.06 (m, 2H, =$CHCH_2$–), 1.40–1.29 (m, 6H, –CH_2–), 0.91 (t, 3H, J = 7.5 Hz, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 202.7, 132.1, 127.4, 44.2, 31.9, 29.6, 27.6, 23.0, 20.5, 14.5.

(*Z*)-1,1-Dibromoundeca-1,5-diene (12)

A solution of enal **11** (10.8 g, 80 mmol) in CH_2Cl_2 (240 mL) was cooled to 0 °C and triphenylphosphine (63 g, 240 mmol) was added to the reaction mixture. A solution of carbon tetrabromide (39.8 g, 120 mmol) in CH_2Cl_2 (120 mL) was added dropwise, then the reaction mixture was allowed to warm up slowly to room temperature, and stirred overnight. After removal of CH_2Cl_2 by evaporation, petroleum ether (200 mL × 2) was added to precipitate triphenylphosphine oxide. The mixture was filtered and the solvent was removed. The residue was purified through a silica gel column (eluent: petroleum ether) to afford diene **12** (21.6 g, 87%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 6.44 (t, J = 6.83 Hz, 1H, CH=CBr_2), 5.49 (m, 1H, *Z*–CH=CH), 5.37 (m, 1H, *Z*–CH=CH), 2.23–2.19 (m, 4H, =CH–CH_2CH_2–CH=), 2.06 (m, 2H, =$CHCH_2$–), 1.43–1.32 (m, 6H, –CH_2–), 0.92 (t, 3H, J = 7.5 Hz, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 138.6, 132.1, 127.9, 89.32, 33.5, 31.9, 29.9, 27.6, 25.9, 23.0, 14.5.

(*Z*)-Undec-5-en-1-yne (13)

A solution of diene **12** (15.5 g, 50 mmol) in dry THF (200 mL) was cooled to −70 °C under nitrogen. After a solution of *n*-BuLi (44 mL, 110 mmol, 2.5 M solution in hexane) was slowly added to

the reaction mixture, the mixture was stirred at −70 °C for 2 h and then allowed to warm up to room temperature. The reaction mixture was quenched with a saturated solution of NH_4Cl, and the organic phase was washed with brine, dried over Na_2SO_4, and then concentrated. The residue was purified through a silica gel column (eluent: petroleum ether) to afford enyne **13** as a colorless oil (6.83 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 5.53–5.42 (m, 2H, *Z*–CH=CH), 2.34–2.25 (m, 4H, =CH–CH_2CH_2–C≡), 2.08 (m, 2H, =CHCH_2–), 2.00 (s, 1H, ≡CH), 1.41–1.30 (m, 6H, –CH_2–), 0.93 (t, 3H, J = 7.5 Hz, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 132.1, 127.8, 84.6, 68.7, 31.9, 29.8, 27.7, 26.8, 23.0, 19.3, 14.5.

(*E*)-5-Bromopent-4-en-1-ol (14)

A solution of enal **4a** (16.3 g, 100 mmol) and sodium borohydride (2.27 g, 60 mmol) in methanol (500 mL) was stirred for 3 h at 0 °C. The reaction mixture was quenched with diluted HCl followed by evaporation of methanol. The reaction mixture was then extracted with EtOAc (100 mL × 2). The extract was washed with water and brine, dried over Na_2SO_4, and then concentrated. The residue was purified through a silica-gel column (eluent: 8 : 1 petroleum ether/ethyl acetate) to afford enol **14** as a colorless oil (14.2 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 9.76 (s, 1H, CHO), 6.15–6.12 (m, 2H, CH=CH), 2.55–2.50 (m, 2H, CH_2), 2.44 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 202.1, 131.5, 130.8, 42.9, 21.3.

(4*E*,10*Z*)-Hexadeca-4,10-dien-6-yn-1-ol (15)

A solution enol **14** (3.3 g, 20 mmol) and enyne **13** (3.0 g, 20 mmol) in dry diethylamine (40 mL) was degassed with a stream of nitrogen for 20 min. After subsequent addition of $Pd(PPh_3)_4$ (1155 mg, 1 mmol) and CuI (209 mg, 1.1 mmol), the reaction mixture was degassed for an additional 10 min. The reaction mixture was stirred overnight and filtered through Celite. The filter cake was washed with CH_2Cl_2 (50 mL × 2). After concentration of the combined organic phase, the residue was purified through a silica-gel column (eluent: 10 : 1 petroleum ether/ethyl acetate) to afford enynol **15** as a colorless oil (3.89 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 6.07 (td, 1H, J = 7.05 Hz, J = 16.0 Hz, CH=CH–CH_2), 5.51 (d, 1H, J = 16.0 Hz, ≡CH=CH), 5.48–5.40 (m, 2H, *Z*–CH=CH), 3.66 (t, 2H, J = 6.4 Hz), 2.34–2.27 (m, 4H, =CH–CH_2CH_2–C≡), 2.22–2.17 (m, 2H, CH_2), 2.08–2.03 (m, 2H, CH_2), 1.70–1.61 (m, 2H, CH_2), 1.40–1.31 (m, 6H, –CH_2–), 0.91 (t, 3H, J = 7.4 Hz, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 142.8, 131.9, 128.1, 110.9, 89.0, 79.5, 62.5, 32.1, 31.9, 29.8, 29.6, 27.7, 27.1, 23.0, 20.2, 14.5.

(4*E*,6*Z*,10*Z*)-Hexadeca-4,6,10-trien-1-ol (1a)

A mixture of Zn powder (13.8 g, 200 mmol) and 1,2-dibromoethane (1.88 g, 10 mmol) in ethanol (20 mL) was heated until a vigorous reaction occurred. The mixture was again treated with 1,2-dibromoethane (1.88 g, 10 mmol) and refluxed for 10 min. The mixture was then cooled to 50 °C followed by addition of a mixture of LiBr (4.34 g, 50 mmol) and CuBr (2.87 g, 20 mmol) in THF (10 mL) within 3 min. After addition of a solution of enynol **15** (1172 mg, 5 mmol) in THF (10 mL), the reaction mixture was refluxed for 4 h and then quenched with a saturated solution of NH_4Cl. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified through a silica-gel column (eluent: 8 : 1 petroleum ether/ethyl acetate) to afford trienol **1a** as a colorless oil (981 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 6.30 (ddd, 1H, J = 15.0, 11.0, 1.0 Hz, CH=CH), 5.95 (dd, 1H, J = 11.0, 10.7 Hz, CH=CH), 5.62 (dt, 1H, J = 15.0, 7.5 Hz, CH=CH), 5.26–5.43 (m, 3H, CH=CH), 3.61 (t, 2H, J = 6.5 Hz, CH_2OH), 2.19 (m, 4H, =CH–CH_2CH_2–C=), 2.14 (m, 2H, CH_2), 2.05 (m, 2H, CH_2), 1.66 (m, 2H, CH_2), 1.18–1.40 (m, 6H, –CH_2–), 0.90 (t, 3H, J = 7.3 Hz, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 134.5, 131.5, 129.9, 129.2, 128.9, 126.4, 62.8, 32.5, 31.8, 29.7, 29.5, 27.9, 27.5, 27.2, 23.0, 14.4.

(4*E*,6*E*,10*Z*)-Hexadeca-4,6,10-trien-1-ol (2a)

Lithium tetrahydroaluminate (950 mg, 25 mmol) was added in portions to an ice-cooled mixture of dry diglyme (12 mL) and THF (1.5 mL) under nitrogen atmosphere. When the vigorous foaming had subsided, the solution of enynol **15** (1172 mg, 5 mmol) in diglyme (3 mL) was added to the thick slurry. Following the initial foaming, the reaction mixture was heated at 117–121 °C for 24 h. The mixture was cooled to 0 °C and petroleum ether (100 mL) was added followed by a cautious and dropwise addition of water (2 mL). Then, 20% (w/w) NaOH solution (1.6 mL) and H_2O (8 mL) were added to the reaction mixture. The mixture was stirred for 15 min to allow the precipitate to granulate, then the petroleum ether layer was decanted, and the solid residue was rinsed with petroleum ether (50 mL × 3). The combined organic phases were washed with water and brine, dried over Na_2SO_4, and then concentrated. The residue was purified through a silica-gel column (eluent: 8 : 1 petroleum ether/ethyl acetate) to afford trienol **2a** as a colorless oil (875 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 5.98–6.07 (m, 2H, *E*–CH=CH), 5.53–5.63 (m, 2H, *E*–CH=CH), 5.45–5.37 (m, 2H, *Z*–CH=CH), 3.60 (t, 2H, J = 6.5 Hz, CH_2OH), 2.21 (m, 4H, =CH–CH_2CH_2–C=), 2.15 (m, 2H, CH_2), 2.04 (m, 2H, CH_2), 1.66 (m, 2H, CH_2), 1.18–1.40 (m, 6H, –CH_2–), 0.90 (t, 3H, J = 7.3 Hz, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 132.3, 131.7, 131.5, 130.2, 129.3, 126.7, 62.7, 32.8, 32.1, 31.6, 29.6, 29.4, 27.7, 27.3, 23.0, 14.3.

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