Tetrahedron 65 (2009) 1967–1970

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Pd-catalyzed regio and stereocontrolled mono and bis-coupling reactions of 1-bromo-6-chlorohexa-1,3,5-triene: synthesis of a naturally occurring tetraenynone

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ARTICLE INFO

Article history:
Received 24 October 2008
Received in revised form 6 January 2009
Accepted 7 January 2009
Available online 14 January 2009

ABSTRACT

The synthesis of new 1,6-dihalogenohexatrienes is described. The chemoselectivity of pallado-catalyzed cross-coupling reaction is studied and a short synthesis, by Negishi and Sonogashira reactions, of a natural product is described.

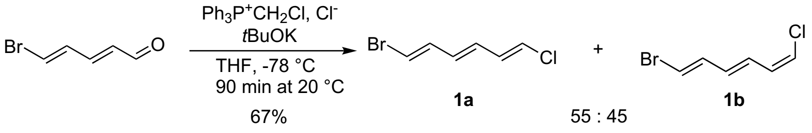
1. Introduction

Numerous natural products, with generally interesting biological properties, have in their structure a stereodefined polyenic conjugated chain.[1] For example, we can quote the large variety of all-*trans* heptatrienamides containing acetylenic linkages, isolated from plants of the Asteraceae family, and which have shown insecticidal and physiological properties;[2] *Scyphostatine*, extracted from the mycelium of *Dasyscyphus mollissimus*, which inhibits the activity of the enzyme sphingomylinase, is responsible of the formation of ceramides at the human ones[3] or *Ansatrienine A*, an antibiotic macrolide, which possess antibacterial, antifungal or antitumour activity.[4]

To synthesize polyenic systems, many strategies have been developed: for example, Wittig and Horner–Wadsworth–Emmons olefinations or Mac Murry olefination. However, the control of the stereochemistry of each formed double bond remains a challenge. One of the challenges today in this area is to design and develop new synthons allowing access to those trienic compounds with excellent stereoselectivity. In 1994, our team[5] has described the ω,ω′-dibromo-1,3,5-hexatriene. This reagent, by double Negishi cross-coupling reaction, has given product with retention configuration of every double bond. In 2003, Amat-Guerri and co-workers[6] have used reagents for preparing fluorescent transmembrane probes of lipid bilayers. Other 1,6-bis-stannylated systems have been developed by Brückner[7] and more recently hetero-bis-metalated by Coleman.[8]

During our work on the 1,6-dibromohexa-1,3,5-triene, we have shown that the monocoupling reactions on stereomer (*E*,*E*,*E*) were not selective and were accompanied by a significant quantity of dicoupled product.[9] To correct this lack of selectivity, we decided to develop a new non-symmetrical dihalogenated reagent having one atom of bromine and one atom of chlorine. This difference has allowed us to increase chemoselectivity, especially in pallado-catalyzed cross-coupling reaction.

After a study of these coupling reactions, we have developed a rapid synthesis of a natural compound, the (6*E*,8*E*,10*E*)-heptadeca-1,6,8,10-tetraen-4-yn-3-one, owning stimulating and diuretic properties. This compound is contained in several plants of the Ombellifer family as the common falcaire[10] (*falcaria vulgaris*) and several species of *seseli*.[11]



Scheme 1.

2. Results and discussion

2.1. Synthesis and reactivity of the 1-bromo-6-chlorohexatriene

1-Bromo-6-chlorohexa-1,3,5-triene **1** has been prepared according to a Wittig reaction with the (2*E*,4*E*)-5-bromopenta-2,4-dienal.[12] It was obtained as a mixture of 1*E*,3*E*,5*E* **1a** and 1*E*,3*E*,5*Z* **1b** stereomers in similar proportions with 67% yield (Scheme 1).

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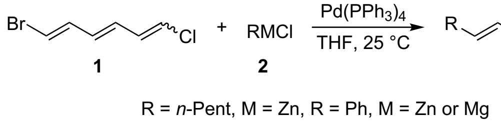
doi:10.1016/j.tet.2009.01.037



Scheme 2.

After separation by chromatography, they are purified by sublimation. To study the chemoselectivity of pallado-catalyzed cross-coupling reactions, depending on the nature of the halogen, 1-bromo-6-chlorohexa-1,3,5-triene **1** was involved in coupling reactions with an excess of pentyl- and phenylzinc chloride **2a** and **2b** or phenylmagnesium bromide **2c** (Scheme 2).

In all cases, we observed exclusively a monocoupling reaction on the bromide atom. We never observed any product resulting from a coupling reaction on the chlorine atom. These coupling reactions between bromochlorohexatrienes **1** and organozinc chlorides **2a**, **2b** and phenylmagnesium bromide (**2c**) are chemoselective and provide exclusively monocoupled products **3**, under friendly conditions, with acceptable yields. These coupling reactions occurred with a total retention of configuration whatever the starting isomer of **1** (for **3aa** and **3ab**: we observed by ^{1}H NMR the following values J_{1-2}=13.1 and 13.2 Hz and J_{5-6}=14.6 and 15.8 Hz; for **3ba** and **3bb**, similarly J_{1-2}=6.5 and 7.2 Hz and J_{5-6}=13.0 and 15.8 Hz, Table 1).

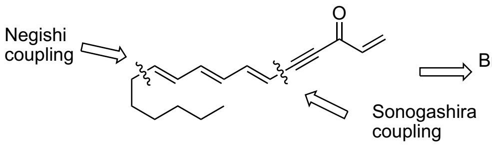
Table 1
Monocoupling reaction results from **1** and organometallic reagent via Scheme 2

Entry	1-Bromo-6-chlorohexatriene	Organometallic reagent	Single coupled product: yield[a] (%)	^{1}H NMR, *J* (Hz)
1	**1a**	**2a**: *n*-PentZnCl	**3aa**: 63	J_{1-2}=13.1; J_{5-6}=14.6
2	**1a**	**2b**: PhZnCl	**3ab**: 43	J_{1-2}=13.2; J_{3-4}=14.7; J_{5-6}=15.8
3	**1a**	**2c**: PhMgCl	**3ab**: 54	
4	**1b**	**2a**: *n*-PentZnCl	**3ba**: 45	J_{1-2}=6.5; J_{3-4}=15.1; J_{5-6}=13.0
5	**1b**	**2b**: PhZnCl	**3bb**: 54	J_{1-2}=7.2; J_{3-4}=15.1; J_{5-6}=15.8
6	**1b**	**2c**: PhMgCl	**3bb**: 62	

[a] Yield after purification.

2.2. Synthesis of a natural product

The originality of our synthesis lies in the introduction of the (*E*,*E*,*E*) trienic system in a one-step procedure, using the intermediate (1*E*,3*E*,5*E*)-1-bromo-6-chlorohexa-1,3,5-triene (**1a**), via chemoselective pallado-catalyzed coupling reactions. In the first step, the alkyl chain is introduced according to a selective monopallado-catalyzed coupling reaction (Negishi coupling reaction), on the bromine atom. Then, the acetylenic part is inserted on the chloro trienic system according to a Sonogashira coupling reaction (Scheme 3). To our knowledge, only one synthesis of compound **8** has been described in the literature. In 1966, Bohlmann and co-workers[10] have reported their synthesis, performed in five steps with an overall yield of 22%.



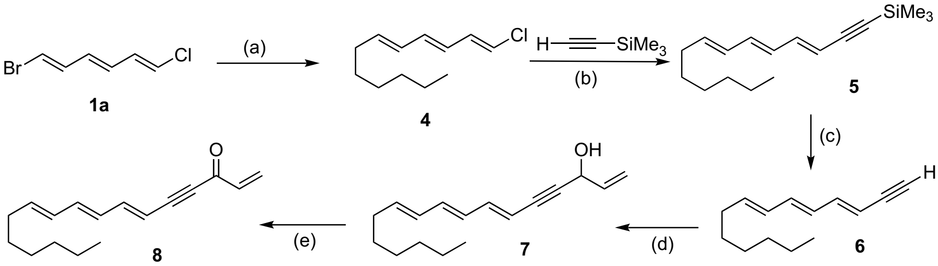
Scheme 3.

Access to hexylchlorotriene **4** is done according to a Negishi coupling reaction by a quick addition of an excess of organozinc reagent on bromochlorohexatriene **1a**, with a catalytic quantity of tetrakistriphenylphosphine palladium complex in THF at room temperature. Hexylchlorotriene **4** was obtained after purification by flash chromatography in 85% yield.

Sonogashira[13] coupling reaction of hexylchlorotriene **4** with the trimethylsilylacetylene, under Linstrumelle and Alami[14] conditions, gives compound **5** in 80% yield. Under classic conditions of deprotection (potassium carbonate in methanol), alkyne **6** is isolated. Then, alcohol **7**, precursor of the natural compound **8**, is obtained by condensation of lithium acetylide with acrolein. In the last step, the MnO_2 oxidation of alcohol **7** gives the natural product **8** (Scheme 4).

3. Conclusion

In this paper, we report the first synthesis of a new dihalogenated conjugated trienic system, 1-bromo-6-chlorotriene **1**. This reagent has been used in pallado-catalyzed cross-coupling reactions with organozinc or organomagnesium compounds and has shown a total chemoselectivity. In application, we have performed an original and rapid synthesis of a natural compound, the (6*E*,8*E*,10*E*)-heptadeca-1,6,8,10-tetraen-4-yn-3-one. The conjugated trienic system has been introduced in a one-step procedure and the chemoselectivity of the coupling reactions has permitted to introduce successively the alkyl and then the alkyne groups. This synthesis was realized in a five-step procedure, with an overall yield of 43%.



Scheme 4. (a) $C_6H_{13}ZnCl$, $Pd(PPh_3)_4$ (6%), THF, 30 min, rt, 85%; (b) $Pd(PhCN)_2Cl_2$ (6%), CuI (10%), piperidine, 80%; (c) K_2CO_3, MeOH, 90%; (d) BuLi (1 equiv), THF, 90 min, 0 °C at rt; addition of acrolein at −78 °C, 67%; (e) MnO_2, THF, 94%.

4. Experimental

4.1. General

Melting points were determined on a Reichert-Jung microscope apparatus. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 300 (300 MHz ^{1}H, 75 MHz ^{13}C) instrument. $CDCl_3$ or C_6D_6 was used as solvent. Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. The IR spectra were obtained as potassium bromide pellets with a Perkin Elmer Paragon 500 spectrometer. Absorption bands are given in cm^{-1}. Mass spectra were recorded with a Jeol JMS-AX500 spectrometer or an ATI Unicam Automass, under electron impact conditions (EI) at 70 eV ionizing potential, fitted (or not) with a GC-mass coupling.

4.2. 1-Bromo-6-chlorohexa-1,3,5-triene (1)

To a solution of chloromethyltriphenylphosphonium chloride (2.76 g, 10.00 mmol) in THF (50 mL) at −78 °C under an argon atmosphere was slowly added *t*-BuOK (1.24 g, 11.00 mmol) in THF (6 mL). After 1 h stirring at −78 °C, (2*E*,4*E*)-5-bromopentadienal (1.16 g, 7.20 mmol) in THF (6 mL) was slowly added. The mixture was stirred at room temperature for 1 h 30 min and the reaction mixture was quenched with a 5% aqueous solution of $NaHCO_3$ (20 mL). The organic layer was extracted with pentane and then dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation. The brown residue was washed with pentane (6×5 mL) to remove triphenylphosphine oxide and the crude product was further purified by silica gel column chromatography (pentane/Et_2O: 98/2) to give (0.93 g, 4.80 mmol) a mixture of two isomers **1a** and **1b** in the same ratio. Yield 67%.

The two isomers **1a** (1*E*,3*E*,5*E*) and **1b** (1*E*,3*E*,5*Z*) were separated by sublimation at 18 mmHg. Isomer **1b** (1*E*,3*E*,5*Z*) was sublimed at 35 °C, after that, isomer **1a** (1*E*,3*E*,5*E*) was sublimed at 45 °C.

4.2.1. Isomer *1a* (1E,3E,5E)

Yield after sublimation: 38%, white solid. Mp 90 °C. ^{1}H NMR (C_6D_6): δ 5.39 (dd, 2H, J_{3-4}=13.2 Hz and J_{3-2}=J_{4-5}=9.8 Hz, H^3 and H^4), 5.71 (d, 1H, J_{6-5}=13.2 Hz, H^6), 5.83 (d, 1H, J_{1-2}=13.2 Hz, H^1), 6.10 (dd, 1H, J_{5-6}=13.2 Hz and J_{5-4}=9.8 Hz, H^5), 6.38 (dd, 1H, J_{2-1}=13.2 Hz and J_{2-3}=9.8 Hz, H^2). ^{13}C NMR (C_6D_6): δ 110.2 (C^1), 122.3 (C^6), 129.2 (C^3), 130.4 (C^4), 133.4 (C^5), 137.3 (C^2). IR: 1597, 980, 742 cm^{-1}. MS (EI) *m*/*z*: 192–194–196 ($M^{+\bullet}$, 32%, 44%, 12%), 157–159 ($M^{+\bullet}$−Cl, 9%, 9%), 113–115 ($M^{+\bullet}$−Br, 41%, 14%), 77 ($C_6H_6^{+\bullet}$, 100%). Anal. Calcd for C_6H_6BrCl (191.93): C 37.25, H 3.13; found: C 37.26, H 3.02.

4.2.2. Isomer *1b* (1E,3E,5E)

Yield after sublimation: 30%, white solid. Mp 40 °C. ^{1}H NMR ($CDCl_3$): δ 6.04 (d, 1H, J_{6-5}=7.2 Hz, H^6), 6.20 (m, 2H, H^3 and H^5), 6.35 (d, 1H, J_{1-2}=13.5 Hz, H^1), 6.57 (dd, 1H, J_{4-3}=13.2 Hz and J_{4-5}=9.8 Hz, H^4), 6.75 (dd, 1H, J_{2-1}=13.2 Hz and J_{2-3}=9.8 Hz, H^2). ^{13}C NMR (C_6D_6): δ 111.3 (C^1), 120.5 (C^6), 126.9 (C^4), 129.5 (C^5), 132.7 (C^3), 137.7 (C^2). IR: 1597, 980, 742 cm^{-1}. MS (EI) *m*/*z*: 192–194–196 ($M^{+\bullet}$, 32%, 44%, 12%), 157–159 ($M^{+\bullet}$–Cl, 9%, 9%), 113–115 ($M^{+\bullet}$–Br, 41%, 14%), 77 ($C_6H_6^{+\bullet}$, 100%). Anal. Calcd for C_6H_6BrCl (191.93): C 37.25, H 3.13; found: C 37.28, H 3.06.

4.3. Preparation of alkylzinc chloride solution

To a stirred solution of zinc dichloride (1.5 equiv) in anhydrous THF was slowly added at 0 °C a 2 M THF solution of alkylmagnesium bromide. The resulting white mixture was stirred for 2 h at room temperature to give a 0.5 M solution of alkylzinc chloride **2**.

4.4. Coupling reaction

To a solution of triene **1** (400.00 mg, 2.07 mmol) and $Pd(PPh_3)_4$ (143.00 mg, 0.12 mmol) in anhydrous THF (10 mL) under an argon atmosphere was added the alkylzinc chloride **2** solution previously prepared. The resulting mixture was stirred for 30 min at 25 °C and then with a solution of $NaHCO_3$ (5%) and extracted three times with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, pentane) to give chlorotriene **3** (349.00 mg, 1.75 mmol).

4.4.1. (1E,3E,5E)-1-Chloroundeca-1,3,5-triene (*3aa*)

^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J*=7.0 Hz, H^{11}), 1.20 at 1.50 (m, 6H, H^{10}, H^9, H^8), 2.05 (dt, 2H, J_{7-6}=6.8 Hz and J_{7-8}=7.1 Hz, H^7), 5.74 (dt, 1H, J_{6-5}=15.1 Hz and J_{6-7}=6.8 Hz, H^6), 6.01 (m, 2H, H^3 and H^4), 6.11 (d, 1H, J_{1-2}=13.5 Hz, H^1), 6.18 (dd, 1H, J_{5-6}=14.6 Hz and J_{5-4}=9.6 Hz, H^5), 6.33 (dd, 1H, J_{2-3}=10.5 Hz and J_{2-1}=13.1 Hz, H^2).

4.4.2. (1Z,3E,5E)-1-Chloroundeca-1,3,5-triene (*3ba*)

^{1}H NMR (C_6D_6) δ 0.80 (t, 3H, *J*=7.0 Hz, H^{11}), 1.07 at 1.30 (m, 6H, H^{10}, H^9, H^8), 1.83 (dt, 2H, J_{7-6}=6.8 Hz and J_{7-8}=7.1 Hz, H^7), 5.52 (d, 1H, J_{1-2}=6.5 Hz, H^1), 5.52 (dt, 1H, J_{6-5}=13.0 Hz and J_{6-7}=6.8 Hz, H^6), 5.87 (m, 2H, H^2 and H^5), 6.03 (dd, 1H, J_{3-2}=10.1 Hz and J_{3-4}=15.1 Hz, H^3), 6.56 (dd, 1H, J_{4-3}=14.7 Hz and J_{4-5}=10.5 Hz, H^4). ^{13}C NMR (C_6D_6): δ 14.4 (C^{11}), 23.0 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 33.2 (CH_2), 117.7 (CH), 124.2 (CH), 130.4 (CH), 130.9 (CH), 136.8 (CH), 137.9 (CH). MS (EI) *m*/*z*: 184–186 ($M^{+\bullet}$, 22%, 8%), 91 (84%), 77 ($C_6H_5^{+\bullet}$, 100%).

4.4.3. (1E,3E,5E)-1-Chloro-6-phenylhexa-1,3,5-triene (*3ab*)

^{1}H NMR (C_6D_6) δ 5.89 (dd, 1H, *J*=10.2 and 15.8 Hz, H^5), 5.93 (d, 1H, J_{1-2}=13.2 Hz, H^1), 6.10 (dd, 1H, J_{4-3}=14.7 Hz and J_{4-5}=10.2 Hz, H^4), 6.45 (d, 1H, J_{6-5}=15.8 Hz, H^6), 6.53 (dd, 1H, J_{2-1}=13.2 Hz and J_{2-3}=10.9 Hz, H^2), 6.67 (dd, 1H, J_{3-2}=10.9 Hz and J_{3-4}=14.7 Hz, H^3), 7.13 at 7.36 (m, 5H, H^{arom}). ^{13}C NMR ($CDCl_3$): δ 121.3 (CHCl), 126.9, 128.3, 128.8, 129.0, 129.1, 129.2, 134.2, 134.3, 137.5 (C). MS (EI) *m*/*z*: 190–192 ($M^{+\bullet}$, 48%, 17%), 155 ($M^{+\bullet}$−Cl, 100%), 115 (28%), 91 (32%), 77 ($C_6H_5^{+\bullet}$, 45%).

4.4.4. (1Z,3E,5E)-1-Chloro-6-phenylhexa-1,3,5-triene (*3bb*)

^{1}H NMR (C_6D_6) δ 5.90 (d, 1H, J_{1-2}=7.2 Hz, H^1), 6.25 (dd, 1H, J_{2-1}=7.2 Hz and J_{2-3}=10.9 Hz, H^2), 6.44 (dd, 1H, J_{4-3}=15.1 Hz and J_{4-5}=10.9 Hz, H^4), 6.36 (d, 1H, J_{6-5}=15.8 Hz, H^6), 6.87 (dd, 1H, J_{5-4}=10.9 Hz and J_{5-6}=15.8 Hz, H^5), 7.03 (dd, 1H, J_{3-2}=10.9 Hz and J_{3-4}=15.1 Hz, H^3), 7.27 at 7.49 (m, 5H, H^{arom}). MS (EI) *m*/*z*: 190–192 ($M^{+\bullet}$, 25%, 9%), 155 ($M^{+\bullet}$−Cl, 100%), 115 (32%), 91 (45%), 77 ($C_6H_5^{+\bullet}$, 56%).

4.4.5. (1E,3E,5E)-1-Chlorododeca-1,3,5-triene (*4*)

Yield: 85%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, *J*=6.5 Hz, H^{12}), 1.16 at 1.41 (m, 8H, H^{11}, H^{10}, H^9, H^8), 2.09 (q, 2H, J_{7-8}=J_{7-6}=6.9 Hz, H^7), 5.69 (dt, 1H, J_{6-5}=15.5 Hz and J_{6-7}=6.8 Hz, H^6), 5.95 (m, 2H, H^3, H^4), 6.05 (d, 1H, J_{1-2}=13.2 Hz, H^1), 6.11 (dd, 1H, J_{5-6}=15.1 Hz and J_{5-4}=10.2 Hz, H^5), 6.37 (dd, 1H, J_{2-1}=13.2 Hz and J_{2-3}=10.9 Hz, H^2). ^{13}C NMR ($CDCl_3$): δ 14.5 (C^{12}), 23.0 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 32.1 (CH_2), 33.3 (CH_2), 119.8 (CH), 126.3 (CH), 130.1 (CH), 134.3 (CH), 134.4 (CH), 137.6 (CH). IR: 2956, 2852, 1686, 1462, 1377, 990, 754 cm^{-1}. MS (EI) *m*/*z*: 198–200 ($M^{+\bullet}$, 54%, 18%), 114–116 ($M^{+\bullet}$−C_6H_{13}, 12%, 4%), 91 (69%), 77 ($C_6H_6^{+\bullet}$, 100%). Anal. Calcd for $C_{12}H_{19}Cl$ (198.12): C 72.52, H 9.57; found: C 72.47, H 9.28.

4.4.6. Trimethyl-(3E,5E,7E)-tetradeca-3,5,7-trien-1-ynylsilane (*5*)

To a stirred solution of chlorotriene **4** (154.90 mg, 0.78 mmol), $PdCl_2(PhCN)_2$ (17.90 mg, 0.05 mmol) and CuI (14.85 mg, 0.08 mmol) in piperidine (2 mL) under an argon atmosphere was slowly added, at room temperature trimethylsilylacetylene

(92.00 mg, 0.93 mmol) in piperidine (1 mL). The resulting black mixture was stirred for 4 h at room temperature and the reaction mixture was treated with a saturated aqueous solution of NH_4Cl.

The aqueous layer was extracted with ether (3×10 mL). The combined organic layers were washed successively with aqueous HCl (0.2 M, 15 mL), $NaHCO_3$ (10 mL) and H_2O (2×10 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, pentane) to give pure compound **5** (163.80 mg, 0.62 mmol).

Yield: 80%, yellow oil. ^1H NMR ($CDCl_3$): δ 0.18 (9H, s, CH_3), 0.86 (3H, t, J_{14-13}=6.5 Hz, H^{14}), 1.18 at 1.24 (8H, m, H^{13}, H^{12}, H^{11}, H^{10}), 2.09 (2H, q, J_{9-10}=J_{9-8}=6.9 Hz, H^9), 5.55 (d, 1H, J_{3-4}=15.5 Hz, H^3), 5.78 (dt, 1H, J_{8-7}=15.2 Hz and J_{8-9}=6.7 Hz, H^8), 5.98 at 6.16 (m, 2H, H^5, H^6), 6.26 (dd, 1H, J_{7-8}=14.7 Hz and J_{7-6}=10.0 Hz, H^7), 6.62 (dd, 1H, J_{4-3}=15.5 Hz and J_{4-5}=10.4 Hz, H^4). ^{13}C NMR ($CDCl_3$): δ 0.5 ($SiCH_3$), 14.6 (CH_3), 22.5 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 31.6 (CH_2), 32.8 (C^9), 97.8 (C^1), 105.5 (C^2), 110.3 (C^3), 129.9 (C^4), 130.6 (C^5), 136.5 (C^6), 138.7 (C^7), 143.6 (C^8). IR: 2958, 2926, 2854, 2114, 1250, 994, 844 cm^{-1}. MS (EI) *m*/*z*: 260 ($M^{+\bullet}$, 15%), 245 ($M^{+\bullet}-CH_3$), 73 ($Si(CH_3)_3^+$, 100%). Anal. Calcd for $C_{17}H_{28}Si$ (260.20): C 78.38, H 10.83; found: C 78.63, H 10.68.

*4.4.7. (3E,5E,7E)-Tetradeca-3,5,7-trien-1-yne (**6**)*[15]

To a solution of trienyne silane **5** (163.80 mg, 0.63 mmol) in degassed MeOH (2 mL) and under an argon atmosphere was added K_2CO_3 (100.00 mg, 0.69 mmol). The reaction mixture was stirred at room temperature for 4 h. Diethylether was added and the organic layer washed with water (2×5 mL), dried over $MgSO_4$ and the solvent was removed under vacuum. The crude product was purified by column chromatography (SiO_2, pentane) to give pure compound **6** (106.60 mg, 0.56 mmol).

Yield: 90%, yellow oil. ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, J_{14-13}=6.5 Hz, H^{14}), 1.18 at 1.24 (m, 8H, H^{13}, H^{12}, H^{11}, H^{10}), 2.09 (q, 2H, J_{9-10}=J_{9-8}=6.9 Hz, H^9), 3.03 (d, 1H, J_{1-3}=2.2 Hz, H^1), 5.51 (dd, 1H, J_{3-4}=15.4 Hz and J_{3-1}=2.2 Hz, H^3), 5.80 (dt, 1H, J_{8-7}=15.0 Hz and J_{8-9}=6.9 Hz, H^8), 6.05 (dd, 1H, J_{6-5}=14.6 Hz and J_{6-7}=10.0 Hz, H^6), 6.12 (dd, 1H, J_{5-6}=14.6 Hz and J_{5-4}=10.6 Hz, H^5), 6.28 (dd, 1H, J_{7-8}=15.0 Hz and J_{7-6}=10.0 Hz, H^7), 6.66 (dd, 1H, J_{4-3}=15.4 Hz and J_{4-5}=10.0 Hz, H^4). ^{13}C NMR ($CDCl_3$): δ 14.2 (C^{14}), 22.7, 29.0, 29.2, 31.8 (C^{10}, C^{11}, C^{12}, C^{13}), 33.1 (C^9), 79.8 (C^2), 83.5 (C^1), 108.7 (C^3), 129.1 (C^6), 130.0 (C^5), 136.4 (C^7), 138.5 (C^8), 143.7 (C^4). IR: 3308, 3018–2926–2854, 2092, 1458, 1376, 992 cm^{-1}. MS (EI) *m*/*z*: 188 ($M^{+\bullet}$, 80%), 117 (69%), 103 ($M^{+\bullet}-C_6H_{13}$, 100%), 77 ($C_6H_6^+$, 80%). Anal. Calcd for $C_{14}H_{20}$ (188.16): C 89.28, H 10.71; found: C 89.48, H 10.75.

*4.4.8. (6E,8E,10E)-Heptadeca-1,6,8,10-tetraen-4-yn-3-ol (**7**)*

To a solution of trienyne **6** (181.00 mg, 0.96 mmol) in THF (5 mL) and under an argon atmosphere at 0 °C, 2.5 M *n*-BuLi (0.38 mL, 0.96 mmol) was added dropwise at this temperature, and the mixture was stirred for 1 h at room temperature. Then the solution was cooled at −78 °C and acrolein (43.00 mg, 0.76 mmol) in THF (3 mL) was added dropwise at this temperature. The reaction mixture was stirred for 1 h at room temperature, quenched with 10 mL of NH_4Cl and was extracted with diethyl ether. The organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The crude product was purified by column chromatography (SiO_2, pentane) to give pure compound **7** (157.50 mg, 0.64 mmol).

Yield: 80%, yellow solid. ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, J=6.5 Hz, H^{17}), 1.18 at 1.24 (m, 8H, H^{16}, H^{15}, H^{14}, H^{13}), 2.09 (q, 2H, J_{12-13}=J_{12-11}=6.9 Hz, H^{12}), 2.65 (1H, OH), 5.00 (d, 1H, J_{3-2}=3.4 Hz, H^3), 5.15 (d, 1H, $J_{1'-2}$=10.2 Hz, $H^{1'}$), 5.44 (d, 1H, J_{1-2}=17.0 Hz, H^1), 5.56 (d, 1H, J_{6-7}=15.5 Hz, H^6), 5.80 (dt, 1H, J_{11-10}=15.1 Hz and J_{11-12}=6.8 Hz, H^{11}), 5.95 (ddd, 1H, J_{2-1}=17.0 Hz, $J_{2-1'}$=10.2 Hz and J_{2-3}=3.4 Hz, H^2), 6.02 (dd, 1H, J_{10-11}=15.5 Hz and J_{10-9}=10.2 Hz, H^{10}), 6.12 (dd, 1H, J_{8-9}=15.5 Hz and J_{8-7}=10.9 Hz, H^8), 6.26 (dd, 1H, J_{9-8}=15.5 Hz and J_{9-10}=10.2 Hz, H^9), 6.60 (dd, 1H, J_{7-6}=15.5 Hz and J_{7-8}=10.9 Hz, H^7). ^{13}C NMR ($CDCl_3$): δ 14.3(C^{17}), 22.8, 27.1, 29.1, 29.3, 31.9 (C^{16}, C^{15}, C^{14}, C^{13}), 33.2 (C^{12}), 63.8 (C^3), 86.1 (C^4), 90.6 (C^5), 109.2 (C^6), 114.8 ($C^{1,1'}$), 129.3 (C^{10}), 130.2 (C^8), 136.2 (C^9), 137.2 (C^2), 138.4 (C^{11}), 142.9 (C^7). IR: 3620, 2210, 1640, 1615, 1405 cm^{-1}. MS (EI) *m*/*z*: 244 ($M^{+\bullet}$, 20%), 226 ($M^{+\bullet}-H_2O$, 100%), 163 ($M^{+\bullet}-C_5H_5O$, 40%), 85 ($C_6H_{13}^+$, 60%). Anal. Calcd for $C_{17}H_{24}O$ (244.18): C 83.55, H 9.90; found: C 83.60, H 9.54.

*4.4.9. (6E,8E,10E)-Heptadeca-1,6,8,10-tetraen-4-yn-3-one (**8**)*

A solution of alcohol **7** (125.00 mg, 0.51 mmol) and MnO_2 (436.00 mg, 5.10 mmol) in THF (8 mL) under argon was stirred overnight. The reaction mixture was filtered on Celite and the solvent was removed under vacuum. The crude product was purified by column chromatography (SiO_2, pentane) to give pure compound **8** (116 mg, 0.48 mmol).

Yield: 94%, yellow oil. ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, J_{17-16}=6.5 Hz, H^{17}), 1.18 at 1.24 (m, 8H, H^{16}, H^{15}, H^{14}, H^{13}), 2.09 (q, 2H, J_{12-13}=J_{12-11}=6.9 Hz, H^{12}), 5.65 (d, 1H, J_{6-7}=15.5 Hz, H^6), 5.86 (dt, 1H, J_{11-10}=15.5 Hz and J_{11-12}=10.2 Hz, H^{11}), 6.14 (3H, m, H^8, H^{10}, H^2), 6.45 (3H, m, H9, H^1, $H^{1'}$), 6.90 (dd, 1H, J_{7-6}=15.5 Hz and J_{7-8}=10.1 Hz, H^7). ^{13}C NMR ($CDCl_3$): δ 14.5 (C^{17}), 22.9, 29.3, 29.4, 32.1 (C^{13}, C^{14}, C^{15}, C^{16}), 33.5 (C^{12}), 89.3 (C^5), 93.4 (C^4), 106.9 (C^6), 129.1 (C^{10}), 130.3 (C^8), 133.1 (C^1), 138.4 (C^2), 139.9 (C^9), 141.3 (C^{11}), 149.1 (C^7), 179.1 (C^3). IR: 2270, 1648, 1400, 995, 940 cm^{-1}. MS (EI) *m*/*z*: 242 ($M^{+\bullet}$, 40%), 214 ($M^{+\bullet}-CO$, 100%), 187 ($M^{+\bullet}-C_3H_3O$, 40%), 85 ($C_6H_{13}^+$, 60%). Anal. Calcd for $C_{17}H_{22}O$ (242.17): C 84.24, H 9.15; found: C 84.35, H 9.30.

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