Stereospecific Synthesis of (E,Z)- and (Z,Z)-Hexadeca-10,12-dienal. Sex Pheromone Components of *Diaphania hyalinata*

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Abstract: Isomeric (E,Z)- and (Z,Z)-hexadeca-10,12-dienal were prepared, stereospecifically, in 51% and 43% overall yields from dec-1-yne.

Key words: (*E*,*Z*)-hexadeca-10,12-dienal, (*Z*,*Z*)-hexadeca-10,12-dienal, dec-1-yne, stereospecific reaction

Diaphania hyalinata and Diaphania nitidalis are pyralid species that exhibit similar life cycles and habits. The former feeds upon the foliage of pumpkin and other cucurbits,² whereas the latter is particularly destructive to cantaloupe, cucumber and muskmelon.³ The damage caused make these crops unsuitable for marketing. The isomers (*E*,*Z*)-hexadeca-10,12-dienal (1) and (*Z*,*Z*)-hexadeca-10,12-dienal (2) were isolated, as minor components, from the extracts of ovipositors of female melonworm, *D. hyalinata*,² while trace amounts of 1 were found in extracts from pickleworm adults of *D. nitidalis*.³ These compounds, along with others, represent essential components of the sex pheromones of these species.

Previous syntheses of the (E,Z)-isomer 1 have involved Wittig condensation of butyltriphenylphosphorane with (*E*)-12-(2-tetrahydropyranyloxy)dodec-2-enal,⁴ followed by oxidation. The major drawback of this procedure is the generation of a mixture of E and Z isomers in the Wittig reaction. The (Z,Z)-isomer has been prepared by the Cadiot-Chodkiewicz coupling of pent-1-yne with undec-10yn-1-ol, followed by reduction of the triple bond with dicyclohexylborane to the corresponding dienol.² The alcohols (E,Z)- and (Z,Z)-hexadeca-10,12-dien-1-ol have been synthesized stereospecifically, by the palladium-catalyzed cross-coupling reaction between an hydroxyalkenylborane and the appropriate haloalkene in the presence of a base.⁵ The overall %yields reported for the syntheses of these alcohols, from undec-10-en-1-ol, are 41 and 27% respectively.⁵

In this paper we report stereospecific syntheses of the isomeric dienals 1 and 2 in 51 and 43% overall yields from dec-1-yne (3).

The syntheses utilized the common precursor *tert*-butyldimethylsilyl undec-10-ynyl ether (6) which was prepared from dec-1-yne (3) by coupling of its lithium acetylide with paraformaldehyde, at low temperature, to give undec-2-yn-1-ol (4) in 93% (Scheme 1). The latter was isomerized to undec-10-yn-1-ol (5) in 98% by a zipper reaction⁶ before protection of the alcohol of **5** as the *tert*-butyldimethylsilyl ether (92%). This protecting group is stable to subsequent conditions used to build the diene systems and is removed under nonacidic conditions without isomerization of the double bonds.

To transform acetylene 6 into envne 7 we used methodology developed by Negishi⁷ for the synthesis of *trans*enynes. Thus, we reacted 6 sequentially, with disiamylborane, pent-1-ynyllithium, iodine and sodium acetate. In our hands, the desired envne 7 was obtained in low yield and was contaminated with an unidentified product. A successful transformation of 6 into 7 was performed using Suzuki's⁸ stereospecific palladium cross-coupling of 1alkenylboranes with 1-alkynyl halides. Thus, acetylene 6 was treated with disiamylborane, sodium methoxide and 1-bromopent-1-yne under palladium catalysis, to produce (E)-envne 7 in 87%. Envne 7, was converted to the corresponding (E,Z)-diene 8, in 92%, by hydroboration with disiamylborane at low temperature (-20° C to 0° C) followed by protonolysis with acetic acid. GC analysis of the crude reaction mixture revealed that reduction yielded only one product. Diene 8 was treated with Bu₄NF in THF at 0°C to remove the protecting group. Silvl impurities were removed by Kugelrohr distillation and the residue filtered through a small pad of silica gel. The alcohol thus obtained was oxidized to 1, using Py_2CrO_3 , in 76% yield from 8. The ¹H NMR spectrum (400 MHz) indicated that this compound was obtained free from other stereoisomers (isomeric purity >99%) (Figure 1). The overall yield from dec-1-yne was 51%.

Synthesis of (Z,Z)-hexadeca-10,12-dienal (2) involved the palladium cross-coupling of acetylene 6, with (Z)-1-iodopent-1-ene (10) prepared by the cis-addition of Gilman cuprate 9 to acetylene followed by quenching with iodine (Scheme 2). GC analysis of the cross-coupling reaction mixture evidenced the formation of only one product and total consumption of reagents 6 and 10. ¹H NMR analysis corroborated the stereochemistry of the (Z)-enyne 11, which was obtained with an isomeric purity of 96% (75% isolated yield). The (Z)-enyne 11, was stereospecifically reduced to the (Z,Z)-diene 12, by hydroboration with disiamylborane followed by protonolysis (94% yield). Diene 12 was deprotected with Bu₄NF and oxidized with Py_2CrO_3 to yield dienal 2 in 72% yield from 12. The overall yield from dec-1-yne was 43%. ¹H NMR spectrum showed that dienal 2 was obtained without contamination with other stereoisomers and with an isomeric purity higher than 99% (Figure 2).



Obtention of a highly pure synthetic sample of 1, allowed observation in the ¹H NMR spectrum of long range constant couplings (⁴J) for olefinic hydrogen H_{11} (Figure 1). Thus, H₁₁ shows a multiplicity of a doublet, doublet, doublet, of triplets (dddt) (or ddtd) as a result of couplings with $H_{10}({}^{3}J), H_{12}({}^{3}J), H_{9}({}^{4}J), and H_{13}({}^{4}J)$ with coupling constants of 15, 11, 1.5 and 1.5 Hz respectively. This signal had been previously reported⁵ with a multiplicity of a doublet of doublets (dd), because in the earlier spectrum long range coupling $({}^{4}J)$ was not observed. Likewise, the ${}^{1}H$ NMR spectrum (400 MHz) of dienal 2 (and its precursor 12) showed a complex pattern for olefinic hydrogens H_{10} , H_{13} (Figure 2, $\delta = 5.43$) and H_{11} , H_{12} (Figure 2, $\delta = 6.25$), as a result of ${}^{3}J$, and probably ${}^{4}J$, coupling. These signals were previously reported,⁵ for the corresponding dienols as a doublet of doublets (dd) for both H_{10} and H_{13} , and a doublet (d) for H_{11} and H_{13} .

Glassware and syringes were dried overnight in an oven at 140 °C and flushed with argon immediately prior to use. Transfers of liquids were performed with syringes equipped with stainless-steel needles. CrO₃, KH, TBDMSCl, CuI and Pd(PPh₃)₄ were weighed in a glove bag under N₂. Reactions were carried out under positive pressure of argon. THF was refluxed and freshly distilled from K/ benzophenone ketyl under argon. ¹H and ¹³C NMR spectra were recorded on a Bruker AMX-400 spectrometer, operating at 400.13 MHz and 100.62 MHz respectively. GC analyses were conducted on a Hewlett–Packard 5892 instrument equipped with a flame ionization detector.

Undec-2-yn-1-ol (4)

To a cold (-78°C) THF solution (200 mL) of dec-1-yne (9.0 mL, 50 mmol) was added, over 15 min, 2.45 M BuLi in hexanes (20.4 mL, 50 mmol), and the resulting solution stirred for 30 min. After this time dry paraformaldehyde (1.65 g, 55 mmol) was added in one portion and the mixture warmed overnight to r.t. The mixture was quenched by addition of sat. NH₄Cl and extracted with Et₂O (2 × 100 mL). Et₂O extracts were dried (MgSO₄) and the solvent evaporated in vacuo. Kugelrohr distillation (90–92°C/0.9 Torr) gave 7.85 g of product (93% yield). [Chem. Abstr. Reg. No. 34683-71]. ¹H NMR (400 MHz, CDCl₃): $\delta = 0.88$ (t, 3H, J = 7.0 Hz), 1.22–1.30 (m, 8H), 1.32–1.40 (m, 2H), 1.45–1.54 (tt, 2H, J = 7.0, 7.0 Hz), 1.58 (s, 1H), 2.20 (tt, 2H, J = 7.0, 2.5 Hz), 4.24 (t, 2H, J = 2.5 Hz). ¹³C NMR (100 MHz, CDCl₃): $\delta = 14.0$, 18.7, 22.6, 28.6, 28.9, 29.1, 29.1, 31.8, 51.4, 78.3, 86.7.

Undec-10-yn-1-ol (5)

KH mineral oil suspension (ca. 7.6 g) was successively washed with anhyd THF (3×30 mL) under argon. Traces of solvent were removed under vacuum and the flask purged with argon. Propane-1,3diamine (80 mL) was added to the KH (3.50 g, 87 mmol) and stirred for 1 h at r.t. After this time undec-2-yn-1-ol (**4**) was added (4.34 g, 25.8 mmol) and the resulting mixture stirred overnight under argon. The mixture was slowly added to ~100 g of ice and extracted with Et₂O (4×100 mL), the extracts were washed with dil HCl, brine and dried (MgSO₄). Evaporation of solvent in vacuo gave 4.24 g of product (98%). [Chem. Abstr. Reg. No. 2774-84-7].

¹H NMR (400 MHz, CDCl₃): δ = 1.23–1.43 (m, 11H), 1.46–1.60 (m, 4H), 1.92 (t, 1H, *J* = 2.5 Hz), 2.17 (td, 2H, *J* = 7.5, 2.5 Hz), 3.62 (t, 2H, *J* = 7.0 Hz).

 ^{13}C NMR (100 MHz, CDCl₃): $\delta = 18.4, 25.7, 28.5, 28.7, 29.0, 29.3, 29.4, 32.8, 63.0, 68.0, 84.7.$

The spectroscopic characteristics matched the reported data.⁵

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Figure 1 Olefinic region of the ¹H NMR (400 MHz) spectrum of (*E*,*Z*)-hexadeca-10,12-dienal (1).

H₁₁, H₁₂





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Alcohol **5** was transformed into silyl ether **6** according to the procedure of Corey and Venkateswarlu.⁹

tert-Butyldimethylsilyl (E)-Hexadeca-10-en-12-ynyl Ether (7)

To a dry round-bottom flask, maintained at -10 °C under argon, was added 1 M BH₃ THF solution (3.9 mL, 3.9 mmol) followed by the dropwise addition of 2 M 2-methylbut-2-ene in THF (3.9 mL, 7.8 mmol), and the resulting mixture stirred at 0 °C, under argon, for 2 h. After this time, a THF solution (3 mL) of acetylene **6** (1.0 g, 3.55 mmol) was added and the mixture stirred at °C for 3 h. Dry NaOMe (0.22 g, 4.13 mmol) was then added and the reaction stirred for an additional hour. After this time the solvent was removed under vacuum, the system purged with argon and the vinylborate thus obtained, dissolved in benzene (5 mL).

In a different flask, equipped with a reflux condenser were dissolved 1-bromopent-1-yne (0.52 g, 3.55 mmol) and Pd(PPh₃)₄ (0.100 g, 0.08 mmol) in benzene (6 mL). The resulting solution was stirred at r.t. for 30 min. To this solution was added, under argon, the borate solution previously prepared and the mixture refluxed for 3 h. The residual organoborane was oxidized [3 M NaOH (0.5 mL) and 30% H₂O₂ (0.5 mL)] for 1 h at r.t. The mixture was extracted with Et₂O, dried (MgSO₄) and the solvent evaporated in vacuo. The residue was dissolved in pentane and filtered through a pad of Florisil, and eluted with Et₂O/hexane 5:95. Evaporation of solvent in vacuo, gave 1.08 g of product (87%).

¹H NMR (400 MHz, CDCl₃): $\delta = 0.05$ (s, 6H), 0.90 (s, 9H), 0.97 (t, 3H, J = 7.0 Hz), 1.25–1.40 (m, 12H), 1.45–1.58 (m, 4H), 2.0 (br td, 2H, J = 7.0, 7.0 Hz), 2.25 (td, 2H, J = 7.0, 1.7 Hz), 3.58 (t, 2H, J = 6.7 Hz), 5.45 (dt, 1H, J = 15.0, 1.7 Hz), 6.05 (dt, 1H, J = 15.0, 7.0 Hz).

¹³C NMR (100 MHz, CDCl₃): δ = -5.2, 13.5, 18.7, 21.4, 22.3, 25.8, 26.0, 28.9, 29.1, 29.4, 29.6, 32.9, 63.3, 79.6, 88.6, 109.9, 143.3.

The NMR spectra are in agreement with previously reported data.¹⁰

tert-Butyldimethylsilyl (E,Z)-Hexadeca-10,12-dienyl Ether (8)

A THF solution (3 mL) of enyne 7 (1.06 g, 3.0 mmol) was added via cannula, under argon, to a disiamylborane solution (4.2 mmol) (prepared as described above and cooled to -20 °C). The resulting solution was allowed to warm to 0 °C over 5 h. HOAc was added to the cold solution (0 °C) and the mixture stirred overnight. After oxidation of the remnant borane, as above, the solution was extracted with Et₂O and the organic phase dried (MgSO₄). Evaporation of the solvent gave 0.97 g of product (92%).

¹H NMR (400 MHz, CDCl₃): $\delta = 0.05$ (s, 6H), 0.87 (s, 9H), 0.92 (t, 3H, J = 7.0 Hz), 1.20–1.32 (m, 12H), 1.34–1.55 (m, 4H), 2.08 (td, 2H, J = 7.0, 7.5 Hz), 2.14 (tdd, 2H, J = 7.0, 7.0, 1.5 Hz), 3.59 (t, 2H, J = 6.75 Hz), 5.30 (br dt, 1H, J = 11.0, 7.5 Hz), 5.65 (dt, 1H, J = 15.0, 7.0 Hz), 5.95 (br dd, 1H, J = 11.0, 11.0 Hz), 6.29 (ddtd, 1H, J = 15.0, 11.0, 1.5, 1.5 Hz).

¹³C NMR (100 MHz, CDCl₃): δ = -5.2, 13.7, 18.7, 22.9, 25.8, 26.0, 29.2, 29.4, 29.6, 29.8, 32.8, 32.9, 63.3, 125.7, 128.9, 129.8, 134.6.

The NMR spectra are in agreement with the reported data.5

(E,Z)-Hexadeca-10,12-dienal (1)

The crude diene **8**, obtained in the previous reaction, was dissolved in THF (~7 mL), cooled to 0°C and 1 M Bu₄NF in THF (9.0 mL) added dropwise. The resulting solution was stirred for 4 h and worked-up according to standard procedures. The silyl impurities present in the crude mixture were removed by Kugelrohr distillation. The residue was filtered through a pad of silica gel and eluted with mixtures pentane/Et₂O. The oil obtained after evaporation of solvent in vacuo (assumed to be ~2.7 mmol) was dissolved (CH₂Cl₂), added in one portion to PDC (20 mmol) in CH₂Cl₂¹¹ and stirred at r.t. for 1 h. The mixture was diluted with Et₂O and filtered through a small pad of Florisil. Concentration in vacuo gave 0.5 g of 1 (76% from 8). [Chem. Abstr. Reg. No. 69977-23-7].

¹H NMR (400 MHz, CDCl₃): $\delta = 0.90$ (t, 3H, J = 7.0 Hz), 1.20–1.48 (m, 12H), 1.55–1.65 (m, 2H), 2.08 (td, 2H, J = 7.0, 7.5 Hz), 2.14 (tdd, 2H, J = 7.0, 7.0, 1.5 Hz), 2.41 (td, 2H, J = 7.0, 1.5 Hz), 5.30 (br dt, 1H, J = 11.0, 7.5 Hz), 5.65 (dt, 1H, J = 15.0, 7.0 Hz), 5.95 (br dd, 1H, J = 11.0, 11.0 Hz), 6.29 (ddtd, 1H, J = 15.0, 11.0, 1.5, 1.5 Hz), 9.75 (t, 1H, J = 1.5 Hz).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 13.7, 22.1, 22.9, 29.2, 29.3, 29.4, 29.8, 32.8, 43.9, 125.8, 128.8, 129.9, 134.5, 202.7.

MS: *m/z* (%) = 236 (M⁺, 11), 109 (13), 95 (25), 81 (61), 67 (100), 55 (26), 41 (40).

The NMR spectra are in agreement with the reported data.5

(Z)-1-Iodopent-1-ene (10)

Propyllithium, prepared from 1-bromopropane and lithium according to Brandsma¹² was titrated according to the method of Watson and Easthman.¹³

Gilman cuprate, 9, was prepared from propyllithium and CuI. Its addition to acetylene was performed according to standard procedures.¹⁴

¹H NMR (400 MHz, CDCl₃): δ = 0.95 (t, 3H, *J* = 7.0 Hz), 1.46 (qt, 2H, *J* = 7.0, 7.0 Hz), 2.12 (m, 2H), 6.13–6.20 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 13.6, 21.3, 36.7, 82.2, 141.2.

The NMR spectra are in agreement with the reported data.¹⁰

tert-Butyldimethylsilyl (Z)-Hexadec-12-en-10-ynyl Ether (11)

Enyne 11 was prepared, in 75% isolated yield, by the palladium cross-coupling reaction between 1-iodopent-1-ene (10) and acetylene 6, according to Ratovelama and Linstrumelle.¹⁵

¹H NMR (400 MHz, CDCl₃): $\delta = 0.05$ (s, 6H), 0.88 (s, 9H), 0.92 (t, 3H, J = 7.0 Hz), 1.25–1.60 (m, 16H), 2.26 (tdd, 2H, J = 7.5, 7.5, 1.0 Hz), 2.33 (td, 2H, J = 8.0, 2.0 Hz), 3.59 (t, 2H, J = 6.5 Hz), 5.44 (m, 1H), 5.81 (dt, 1H, J = 11.0, 7.5 Hz).

¹³C NMR (100 MHz, CDCl₃): δ = -5.3, 13.7, 18.4, 19.5, 22.2, 26.0, 28.8, 28.9, 29.1, 29.4, 29.5, 32.1, 32.9, 63.3, 77.5, 94.4, 109.6, 142.2.

The NMR are in agreement with the previously reported data.¹⁰

(*Z*,*Z*)-Hexadeca-10,12-dienal (2)

Diene 12, was treated with Bu_4NF and PDC as described above for 1. [Chem. Abstr. Reg. No. 96348-46-8].

¹H NMR (400 MHz, CDCl₃): $\delta = 0.90$ (t, 3H, J = 7.0 Hz), 1.20–1.50 (m, 12H), 1.60 (m, 2H), 2.15 (m, 4H), 2.41 (td, 2H, J = 7.0, 1.5 Hz), 5.43 (m, 2H), 6.25 (m, 2H), 9.75 (t, 1H, J = 1.5 Hz).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 13.7, 22.1, 22.8, 27.4, 29.1, 29.3, 29.5, 29.6, 43.9, 123.7, 123.8, 131.8, 131.9, 202.6.

MS: *m/z* (%) = 236 (M⁺, 5), 109 (15), 95 (30), 81 (69), 67 (100), 54 (22).

The NMR spectra are in agreement with previously reported data.⁵

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