AN IMPROVED STEREOSPECIFIC SYNTHESIS OF *(Z,E)*-9,11,13-TETRADECATRIENAL.

SEX PHEROMONE COMPONENT OF *STENOMA CECROPIA*

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ABSTRACT: *(Z,E)-9,11,13-tetradecatrienal, a pheromone component of Stenoma cecropia, was prepared in 61% overall yield from 1-nonyne. The synthesis involved two palladium-catalyzed cross-couplings to afford a 1,3-dien-5-yne, which was reduced with disiamylborane to obtain the corresponding triene.*

Stenoma cecropia is an economically important defoliator of oil palm in Central and South America. Female pheromone glands of this insect contain *(Z,E)*-9, 11, 13- tetradecatrienal (**1**) and the corresponding acetate (**2**) that have been shown to be major pheromone components. The former has also been identified as a component of the sex pheromone of the carob moth, *Ectomyelosis ceratoniae* , a serious pest of fruit and nut crops.[2]

Tellier and Desconis reported a 10 step (16% overall yield) synthesis of **1**.[3] The major drawbacks of the synthesis are two palladium-catalyzed cross-coupling reactions used to build the triene. In the process an alkynylzinc bromide is coupled with excess *(E)/(Z)* 1,2-dibromoethylene under palladium catalysis to obtain 50 % of the corresponding *(E)*-1-bromo-1-en-3-yne. A second palladium cross-coupling between a bromoenyne and vinylzinc bromide afforded the 1,3-dien-5-yne (75% yield), the triple bond of which was stereoselectively reduced.

A much better aproach was developed by Millar,[2] wherein **1** was built by coupling 9-decyn-1-ol with *(E)*-1,2-dichloroethylene under palladium-catalysis (THF, $(Ph_3P)_2PdCl_2$, CuI, DIPA). The chloroenyne alcohol thus obtained was protected (THP, 84% from 9-decyn-1-ol) and coupled with vinyl magnesium bromide, under $(Ph_3P)_4Pd$ catalysis to obtain, after deprotection, the corresponding dienynol (79%). The triple bond of the latter was reduced using (HCl activated) zinc in 1-propanol/water. In the latter reaction a rearrangement by-product that formed, was removed by recrystallization of the *p*-nitrobenzoate. The synthesis yielded **1** in ~50% overall yield.

We report herein a modification of the synthetic strategy used by Millar, which allowed us to obtain **1** in 62% overall yield from 1-nonyne (**3**).

RESULTS AND DISCUSSION

The synthesis consists of two palladium-catalyzed cross-coupling reactions to produce a 1,3-*(E)*-dien-5-yne system, which was regio- and stereospecifically reduced to the corresponding triene with disiamylborane *(figure 1)*. The sequence utilized 2-decyn-1-ol (**4**), which was obtained in quantitative yield by low temperature reaction of 1-nonyne **3**, with *n*-BuLi and paraformaldehyde. Alcohol **4** was isomerized in 97 % to **5** by a zipper reaction.[4] The alcohol of **5** was protected (95%) as a *tert*-butyldimethylsilyl ether. This protecting group is very stable under subsequent conditions used to build the triene system and is easily removed, under non acidic conditions, without isomerization of the triene. Palladium cross-coupling of *trans*-1,2-dichloroethylene with alkyne **6** (but not with the alkynylzinc bromide as used by Tellier[3]) was performed according to the procedure of Ratovelomana and Linstrumelle,[5] using diethylamine instead of *n*-propylamine. Additionally we used $Pd(PPh_3)_4$ in benzene

rather than $Pd(PPh_3)_2Cl_2$ and THF as reported by Millar.[2] The cross-coupled product **7** was formed in quantitative yield and separated from the catalyst and triphenylphosphine oxide by cooling in pentane. Chloroenyne **7** thus obtained, was dissolved in benzene and reacted with vinylmagnesium bromide (1,5 equivalents) in THF under $Pd(PPh_3)_4$ to obtain 97% of the dienyne **8**.

Attempts to reduce the triple bond of **8**, with Zn (Cu/Ag) in aqueous methanol[6] gave only partial reaction. The triple bond of dienyne **8** was regio- and stereospecifically reduced with disiamylborane at low temperature (–18 to °0 C) to give, after 8 hours, the corresponding triene **9**. G.C analysis of the crude reaction mixture revealed reduction yielded only one product. This was treated with Bu_4NF in THF at 0 °C, to remove the protecting group without alkene isomerization. Silyl impurities present in the crude reaction mixture were removed by Kugelrohr distillation, and the residue was filtered through a small pad of silica gel. The alcohol thus obtained was oxidized to **1** using PDC in 75% yield from **8**. The ^{1}H-NMR and G.C. analysis showed that aldehyde **1** was obtained in high stereoisomeric purity. ^{1}H-NMR spectrum matched the reported data.[2]

This route allowed stereospecific generation of **1** in 62% yield from 1-nonyne. Formation of the haloenyne system *via* palladium cross coupling of 1,2-dihaloethylene is revealed as an efficient strategy. For this reaction, use of an alkyne with CuI and Et_2NH rather than the corresponding alkynylzinc halide[3], gives higher yields in the coupling. The use of disiamylborane to stereospecifically reduce the triple bond of dienyne **6** proved to be highly effective and the triene product was cleanly generated.

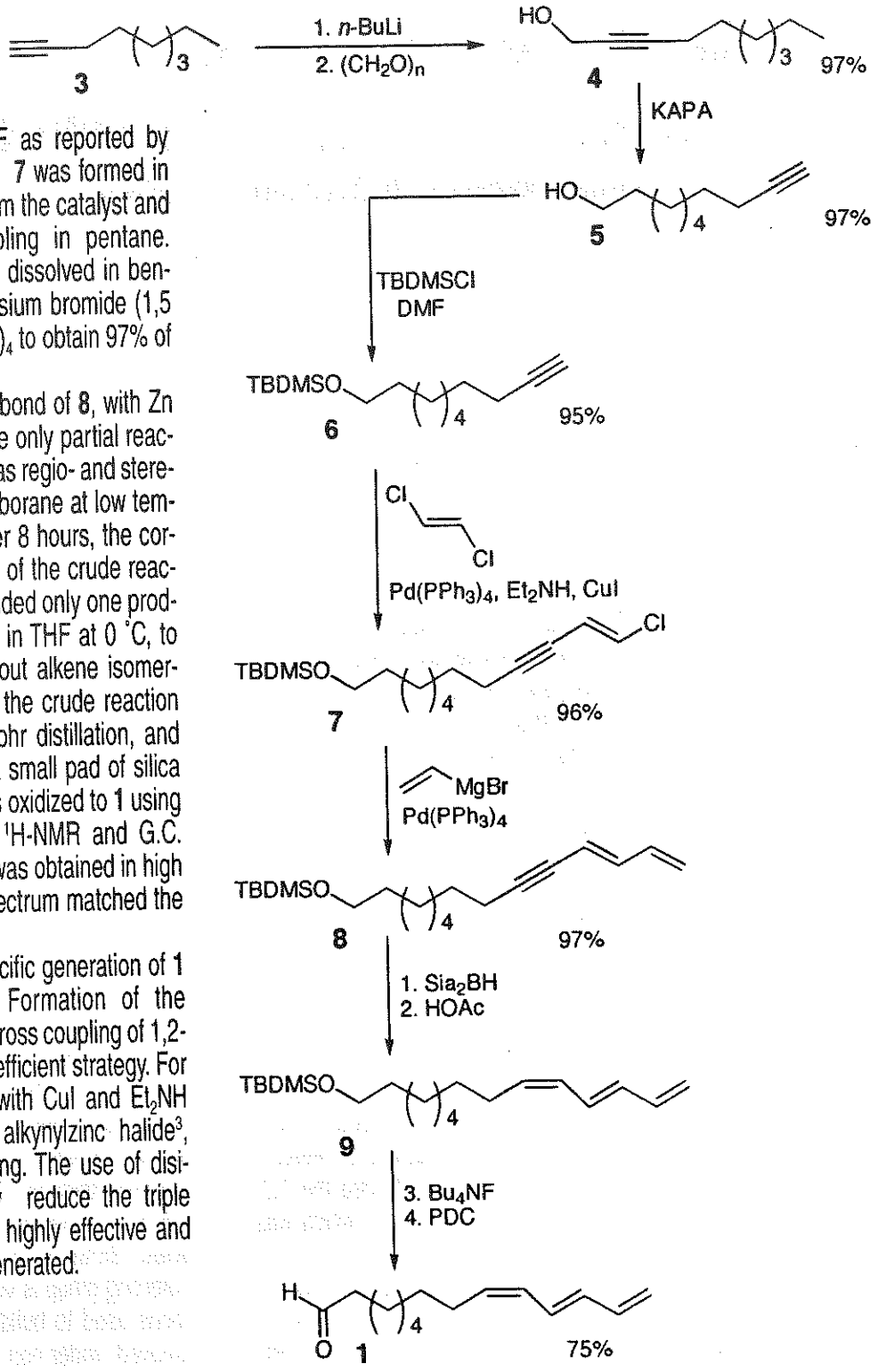

Figure 1

EXPERIMENTAL SECTION

All glassware and syringes were dried in an oven overnight at 140 °C and flushed with argon immediately prior to use. Transfers of liquids were performed with syringes equipped with stainless-steel needles. CrO_3, KH, TBDMSCl, CuI and $Pd(PPh_3)_4$ were weighted in a glove bag under nitrogen. *trans*-1,2-Dichloroethylene was purchased from Aldrich and dried over activated 3 Å molecular sieves. Reactions were carried out under positive pressure of argon. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker

AMX-400 spectrometer, operating at 400,13 MHz and 100,62 MHz, respectively. Gas chromatographic analyses were conducted on a Hewlett-Packard 5892 instrument equipped with a flame ionization detector and employing a fused silica capillary column (15m x 0,25 mm ID) with DB-1 liquid phase.

2-Decyn-1-ol (4): To a cold (-78 °C) THF solution (200 mL) of 1-nonyne (8,2 mL, 50 mmol) was added, over 15 min., a 2,45 M solution of *n*-BuLi in hexanes (20,4 mL, 50 mmol). After this time 1,65 g (55 mmol) of dry paraformaldehyde was added in one portion and the mixture warmed overnight to room temperature . The mixture was quenched by the addition of saturated aqueous NH_4Cl soln. and extracted with ether (2 X 100 mL). The extracts were dried over anhydrous $MgSO_4$ and the solvent evaporated *in vacuo*. The crude product was purified by Kugelrohr distillation to afford 7,46 g of product (97 % yield). [Chem. Abstr. No. 4117-14-0].

9-Decyn-1-ol (5): A ~20,7g portion of KH mineral oil suspension was succesively washed with dry THF (3 x 60 mL). Traces of solvent were removed under vacuum and the flask purged with argon. 1,3-Diaminopropane (260 mL) was added to the KH (11,67 g, 290 mmol) and stirred for 1 hour at room temperature. After this time 2-decyn-1-ol (**4**) was added (14,0 g, 90 mmol) and the resulting mixture stirred overnight under argon . The mixture was slowly added to ~200 g of ice and extracted with ether (4 x 200 mL), the extracts were washed with diluted HCl, brine and dried ($MgSO_4$). After evaporation of solvent *in vacuo*, 13,5 g of product (97%) was obtained. [Chem. Abstr. No. 17643-36-6].

Alcohol **5** was transformed into silyl ether **6** according to the procedure of Corey and Venkateswarlu.[7]

(11*E*)-12 Chloro-dodec-11-en-9-ynyl *tert*-butyl dimethyl silyl ether (7): To a dry benzene (25 mL) solution of $Pd(PPh_3)_4$ (0,87 g, 0,75 mmol) was added *trans*-1,2-dichloroethylene (7,27 g, 75 mmol) and the solution stirred under argon for 30 min at room temperature. Acetylene **6** (4,0 g, 15 mmol) dissolved in diethylamine (10 mL), was added followed by the addittion of CuI[8] (0,143 g, 0,75 mmol) (an exothermic reaction occurred). The resulting mixture was stirred overnight under argon. The reaction mixture was poured into water (~75 mL), the organic phase separated, and the aqueous layer extracted with ether (2 x 75 mL). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. After concentration *in vacuo*, the resulting oil was dissolved in pentane and cooled in the fridge overnight before filtration to remove the catalyst and an impurity (presumably triphenylphosphine oxide). The solution was filtered through a small pad of silica gel, and the filtrate was concentrated *in vacuo* to give **7** as an oil (4.83 g.), 98% pure by G.C. analysis (96% yield); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0,05 (s, 6H); 0,90 (s, 9 H); 1,20-1,42 (m, 8H); 1,45-1,60 (m, 4H); 2,28 (td, 2H, J = 7,0, 2,4 Hz); 3,59 (t, 2H, J = 6,6 Hz); 5,90 (dt, 1H, J = 13,5; 2,4 Hz); 6,42 (d, 1H, J = 13,5); ^{13}C-NMR ($CDCl_3$, 100,6 MHz) δ-5,3; 18,3; 19,4; 2,6; 26,0; 28,4; 28,8; 29,1; 29,3; 32,8; 63,3; 75,7; 93,4; 114,3; 128,6; ^{1}H-NMR spectrum was in agreement with the data reported for the corresponding deprotected alcohol.[2]

11*(E)*,13-Tetradecadien-9-ynyl *tert*-butyldimethylsilyl ether (8) A 100 mL round bottom flask, containing vinyl chloride **7** (4,1 g, 98% pure, 12,2 mmol), was evacuated with a vacuum pump and purged with argon and the process repeated three times. $Pd(PPh_3)_4$ (0,70 g, 0,60 mmol) was added, the mixture dissolved in dry benzene (25 mL) and stirred at room temperature, under argon, for 30 minutes. After this time a 1 M THF solution of vinyl magnesium bromide (18,3 mL, 18,3 mmol) was added dropwise over 15 minutes (an exothermic reaction occurred) and the resulting mixture was stirred overnight. The crude reaction mixture was poured into water (100 mL) and the organic phase separated. The aqueous phase was extracted with ether (3 x 75 mL) and the combined extracts were dried ($MgSO_4$). After evaporation of the solvents *in vacuo*, the residue was dissolved in pentane and the product filtered from the precipitate through a small pad of silica gel. After evaporation of the solvent 3,91 g of product was obtained, GC analysis showed that the product was 97% pure (97% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0,05 (s, 6H), 0,87 (s, 9 H), 1,22-1,42 (m, 8H), 1,45-1,60 (m, 4H); 2,31 (dt, 2H, J = 2,2; 7,0 Hz); 3,59 (t, 2H,

J =6,6 Hz); 5,12 (ddd, 1H, J = 10,0; 0,7; 0,7 Hz); 5,24 (ddd, 1H, J = 16,8; 0,7; 0,7 Hz); 5,61 (dtd, 1H, J = 15,4; 2,2; 0,6 Hz); 6,34 (dddd, 1H, J = 16,8; 10,8; 10,0; 0,6 Hz); 6,50 (dddd, 1H, J = 15,4; 10,8; 0,7; 0,7 Hz); ^{13}C-NMR (100,6 MHz, $CDCl_3$) δ-5,3; 17,9; 19,6; 25,6; 25,8; 26,0; 28,8; 29,1; 29,3; 32,9; 63,3; 79,6; 93,5; 112,7; 118,4; 136,4; 140,9; ^{1}H-NMR spectrum was in agreement with the data reported for the corresponding deprotected alcohol.[2]

9*(Z)*,11*(E)*,13-Tetradecatrienyl *tert*-butydimethylsilyl ether (9): To a dry round bottom flask, maintained at –10 °C under argon, was added a 1 M BH_3·THF solution (13,5 mL, 13,5 mmol) folllowed by the dropwise addition of a 2 M 2-methyl-2-butene THF solution (13,5 mL, 27 mmol), and the resulting mixture stirred at 0 °C, under argon, for 2 hours. After this time, the external temperature was lowered to -18 °C and 2,9 g (9,0 mmol) of the dienyne **8**, dissolved in THF, was added *via* canula. The resulting solution was warmed from -18 to 0 °C in 6 hours. Acetic acid was added to the cold solution (0 °C) and the mixture stirred overnight. The crude reaction was poured into water (~50 mL), extracted with ether (3 x 75 mL) and the solvent evaporated *in vacuo*. The residue obtained was dissolved in THF (~10 mL), cooled in ice and a 3 M NaOH solution (2 mL) added, followed by the addition of 30% H_2O_2 (2 mL) and the mixture stirred at this temperature for 1 hour. The crude was partitioned in water/ether, the ethereal extracts were washed with brine, dried ($MgSO_4$) and the solvent evaporated. GC analysis of the crude obtained showed complete reduction of the triple bond and no apparent isomerization of the double bonds. The crude product obtained was used in the next step without further purification; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0,05 (s, 6H), 0,90 (s, 9H), 1,22-1,42 (m, 8H), 1,45-1,55 (m, 4H), 2,18 (m, 2H), 3,59 (t, 2H, J = 6,6 Hz), 5,07 (br. d, 1H, J = 10,2 Hz), 5,20 (br. d, 1H, J = 16,8 Hz), 5,47 (dt, 1H, J = 10,7; 7,7 Hz), 6,00 (dd, 1H, J = 10,7; 10,7 Hz), 6,20 (dd, 1H, J = 14,9, 10,7 Hz), 6,40 (ddd, 1H, J = 16,8; 10,7; 10,2 Hz), 6,48 (dd, 1H, J = 14,9; 10,7 Hz). ^{1}H-NMR spectrum was in agreement with the data reported for the corresponding deprotected alcohol.[2]

9*(Z)*,11*(E)*,13-Tetradecatrienal (1): Crude trienyl silyl ether **9**, obtained in the previous reaction, was dissolved in THF (~15 mL), cooled to 0 °C and a 1 M THF solution of Bu_4NF added. The resulting solution was stirred for 4 hours and worked-up according to standard procedures. The silyl impurities present in the crude reaction mixture were removed by Kugelrohr distillation (50-60 °C, 1 mm Hg). The residue was filtered through a pad of silica gel and eluted with mixtures pentane-ether, and the combined fractions were concentrated *in vacuo*. The oil obtained (assumed to be 8-9 mmol) was dissolved (CH_2Cl_2) and added in one portion to a PDC (54 mmol) dichloromethane solution and stirred at room temperature for 1 h. The reaction mixture was diluted with ether and filtered through a small pad of Florisil. After concentration *in vacuo* 1,39 g of **1** was obtained (75% from **8**); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1,31-1,40 (m, 8H), 1,55-1,65 (m, 2H), 2,15-2,24 (m, 2H), 2,42 (td, 2H, J = 7,3, 1,8 Hz), 5,07 (br. d, 1H, J =10,2 Hz); 5,20 (br. d, 1H, J =16,8 Hz); 5,46 (dt, 1H, J= 10,7; 7,7 Hz); 6,00 (dd, 1H, J = 10,7; 10,7 Hz), 6,20 (dd, 1H, J = 14,9; 10,7 Hz); 6,40 (ddd, 1H, J = 16,8; 10,7; 10,2 Hz), 6,48 (dd, 1H, J = 14,9; 10,7 Hz), 9,76 (t, 1H, J = 1,8 Hz); ^{13}C-NMR (100,6 MHz, $CDCl_3$) δ 22,1; 27,8; 29,0; 29,1; 29,2; 29,5; 43,9; 116,8; 128,5; 128,8; 133,0; 133,3; 137,2; 202,6; The ^{1}H-NMR spectrum matched the reported data for **1**.[2]

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References and Notes

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