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NEW STEREOSPECIFIC SYNTHESES OF (E,E,Z)- AND (E,E,E)-10,12,14-HEXADECATRIENAL SEX PHEROMONAL COMPONENTS OF MANDUCTA SEXTA

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Abstract: *New stereospecific syntheses of (E,E,Z)- and (E,E,E)-10,12,14-hexadecatrienal are described. The key steps are two sequential palladium-catalysed cross-coupling reactions between adequate organometallic reagents and (E)-1,2-dibromoethylene.*

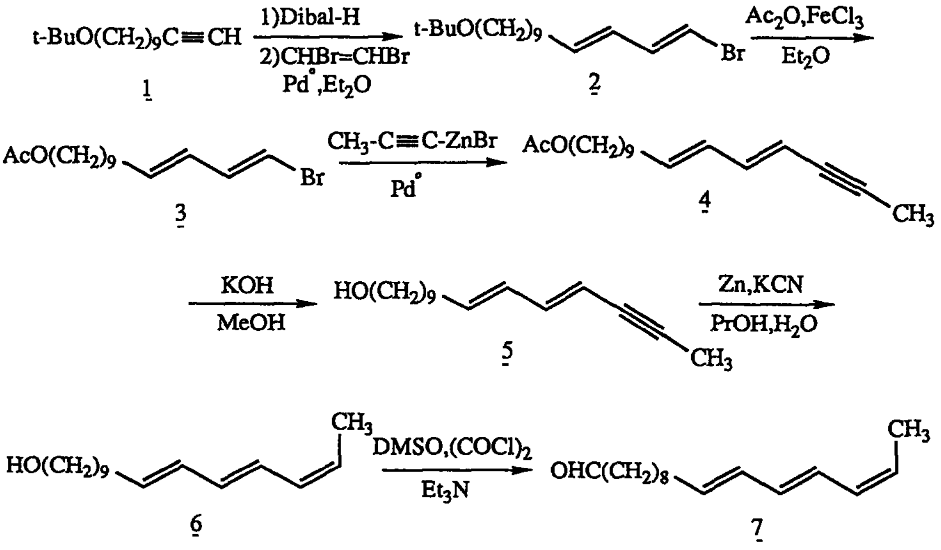
The tobacco hornworm moth, *Manducta sexta* (L.), (Lepidoptera, Sphingidae) occurs over the greater part of the United States, the West Indies, Mexico, Central America, and parts of South America. It is a common pest of tobacco in the United States and the larvae eat the leaves of a wide range of solanaceous plants including tomato, eggplant, Jerusalem cherry and potato *(1)*.

The female-produced sex pheromone of this species has recently been reported *(2)* as a blend of saturated and mono-, di- and triunsaturated C_{16} and C_{18} aldehydes. The triunsaturated components have been identified as the (E,E,Z)- and (E,E,E)-10,12,14-hexadecatrienal *(3)*. The (10E,12E,14Z) isomer has been described as the second essential component of this pheromonal blend.

The syntheses of the isomers (E,E,Z), (E,E,E) and (E,Z,E) of the 10,12,14-hexadecatrienal have recently been published by Doolittle *et al. (3)*.

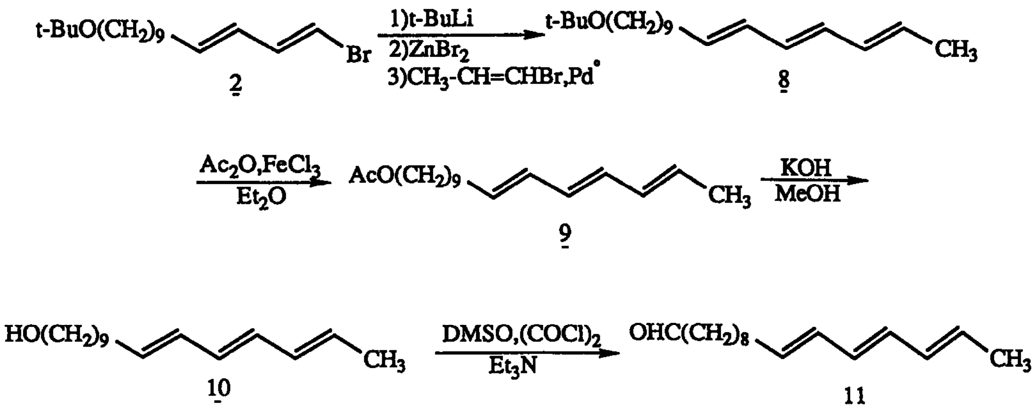
In this publication is reported new syntheses of the two trienic pheromonal components of *Manducta sexta* in which the conjugated double bonds are introduced with a high degree of stereochemical control. In previous publications *(4,5)*, we have described efficient routes to synthesize functionalized terminal-conjugated trienic compounds by means of two sequential palladium-catalyzed cross-coupling reactions. Herein, the same approach has been chosen. A first coupling between a molar excess of commercially available (Z)/(E)-1,2-dibromoethylene and adequate alkenylalanes led to (E,E)-1-bromo-1,3-diene derivatives with a high stereoisomeric purity; (E)-1,2-dibromoethylene reacting preferencially, when it is in blend with the (Z) stereoisomer *(4,6)*. The intermediate bromodienes were then coupled with the appropriate alkenyl synthons to afford the corresponding conjugated (E,E,E) or (E,E,Z) trienes.

In all our syntheses, the alcohols were first protected as t-butyl ether because in two recent publications, Alexakis *et al. (7)* have pointed out the great advantages of this protective group. Preparation and reactivity of ω-t-butoxy Grignard reagents are exactly the same as non-functionalized ones and ω-t-butoxyalkynes undergo smooth hydroalumination with diisobutylaluminium hydride in contrast with the other classical protective groups.



Synthesis of the (E,E,Z)-10,12,14-hexadecatrienal 7

The (E)-alkenylalane (1 eq.), available *via* hydroalumination *(8)* of the t-butoxyalkyne 1 *(9)*, was added dropwise at r.t. to a solution of (Z)/(E) (60/40)-1,2-dibromoethylene (5 eq.) and $Pd(PPh_3)_4$ (0.02 eq.) in Et_2O (16 h, r.t.) *(5)* to afford the (E,E)-bromodiene 2 in 50% yield and with isomeric purity more than 99%. The t-butyl ether of 2 was easily cleaved into the corresponding acetate 3 with Ac_2O and $FeCl_3$ in Et_2O (92% yield) without isomerisation *(7)*. The treatment of 3 (1 eq.) with the propynylzinc bromide (5 eq.), generated *in situ* from propyne, under palladium-catalyzed conditions (0.02 eq.) (12 h, r.t.) led to (E,E)-10,12-hexadecadien-14-yn-1-yl acetate 4 with 73% yield (96% isomeric purity). The saponification with KOH gave the corresponding alcohol 5 which was crystallized from pentane leaving most non polar impurities in the mother liquor (68% yield and 98% isomeric purity). The triple bond of 5 was stereospecifically semi-hydrogenated according to Morris *(10)* (Zn, KCN, $PrOH/H_2O$, 24 h, r.t., 90% yield) to furnish (E,E,Z)-10,12,14-hexadecatrienol 6 which was recrystallized from pentane to give a white solid (mp. 38°C, 87% yield, 96% steric purity). The synthesis was completed by an oxydation of the alcohol 6 to the aldehyde 7. Initially PDC (pyridinium dichromate) in CH_2Cl_2 was used, however it was found that the oxidation proceeded more cleanly and in better yield (72%) by using Swern oxidation conditions *(11)* (oxalyl chloride, DMSO and then Et_3N, -60°C to 20°C) (96% isomeric purity). The trienes (10E,12E,14Z) were configurationnaly unstable as they isomerized partly on storage to the undesired (E,E,E) isomer.



Synthesis of the (E,E,E)-10,12,14-hexadecatrienal 11

The (E,E)-bromodiene 2 (1 eq.) was treated with t-BuLi (2 eq.) (THF/Et_2O (60/40), -120°C to -90°C) *(12)*, followed by a solution of $ZnBr_2$ (THF, -90°C to r.t.) to give the (E,E)-dienylzinc bromide which was coupled with available commercially (Z/E) (75/25)-1-bromo-1-propene (10 eq.) in presence of a palladium catalysis (12 h, r.t.), to afford the (E,E,E)-trienic compound 8 with 52% yield and 95% of isomeric purity; (E)-1-bromopropene reacting preferentially when it is in blend with the (Z) stereoisomer *(13)*. The t-butyl ether of 8 was cleaved into the corresponding acetate 9 (65% yield). The saponification with KOH led to the alcohol 10 which was recrystallized from pentane to give a white solid (mp. 42°C, 88% yield). The latter was oxidized according to Swern's procedure to afford the (E,E,E)-10,12,14-hexadecatrienal 11 (73% yield). The trienes 9, 10, and 11 were obtained with isomeric purity of 95%.

The stereoisomeric purity of all the mentioned products was evaluated by gas chromatographic analysis on capillary columns *(14)*.

The stereochemistry of the double bonds has been ascertained by NMR spectral properties *(15)*. ^1H NMR and mass spectra of these trienic aldehydes are identical to those previously published *(3)*.

In conclusion, this route allowed us to prepare products of very high stereoisomeric purity, with excellent overall yields and in few steps from readily available starting materials. Moreover, in this publication, it has been shown that (E,E)-bromodienes were efficient precursors of stereoselective syntheses of conjugated (E,E,E) or (E,E,Z) trienes.

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(14) The stereoisomeric purity of the products was evaluated by gas chromatograhic analysis which were performed on a model 2900 Carlc Erba instrument equipped with fused silica capillary polar column (25m WCOT FFAP 0.32 id, H_2 carrier gas flow 25ml/mn, 1.2b)

(15) All NMR spectra were recorded in $CDCl_3$ on a Varian VXR 300 ($CDCl_3$; δ ppm), J (Hz).

^1H NMR : 4,5: Data of the double bond system of 4 and 5 are the same: 5.42 (dq) H^{13}, 5.71 (dt) H^{10}, 6.02 (dd) H^{11}, 6.44 (dd) H^{12}; JH^9/H^{10}=6.95, JH^{10}/H^{11}=15.2, JH^{11}/H^{12}=10.8, JH^{12}/H^{13}=15.6, JH^{13}/CH_3=2.2.

4: 4.04 (t) CH_2O; 5: 2.15 (s) OH, 3.6 (t) CH_2O.

6,7: Data of the double bond system: 5.41 (dq) H^{15}, 5.64 (dt) H^{10}, 5.96 (ddq) H^{14}, 6.05 (ddt) H^{11}, 6.11 (dd) H^{12}, 6.36 (dd) H^{13}; JH^{14}/H^{15}=10.7, $JH^{15}/CH3$=7.2, $JH^{14}/CH3$=1.7, JH^{13}/H^{14}=11.3, JH^{12}/H^{13}=14.15, JH^{11}/H^{12}=10.6, JH^{10}/H^{11}=14.4, JH^9/H^{10}=7.1, JH^9/H^{11}=1.8.

6: 1.83 (s) OH, 3.57 (t) CH_2O; 7: 9.70 (t) CHO.

8,9,10,11: Data of the double bond system: 5.4-5.74 (m) H^{10} and H^{15}, 5.8-6.1 (m) H^{11}, H^{12}, H^{13} and H^{14}.

8: 3.27 (t) CH_2O; 9: 3.99 (t) CH_2O; 10: 2.92 (s) OH, 3.54 (t) CH_2O; 11: 9.70 (t) CHO.

^{13}C NMR :

4:	170.5	142.3	138.3	131.0	110.3	88.6	80.0		64.6	4.9
5:		142.1	138.2	130.7	110.1	88.3	79.8		63.7	4.9
6:		136.1	133.6	131.4	130.4	126.6	126.5		63.5	13.7
7:	204.0	135.9	133.5	131.5	130.4	126.5	126.5		44.3	13.7
8:		135.3	132.8	131.6	131.5	131.3	129.4	72.9	62.1	18.6
9:	172.1	135.1	132.7	131.6	131.5	131.4	129.4		65.1	18.5
10:		135.1	132.7	131.6	131.5	131.3	129.4		63.1	18.5
11:	204.0	135.2	132.7	131.6	131.45	131.3	129.5		44.3	18.6

Mass spectra were obtained by using a Nermag R10X10:

7: m/z: 278 (M^+,11%), 79 (100%). 11: m/z: 278 (M^+,15%), 79 (100%).