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Short Communication

A Practical Synthesis of Gossyplure, the Sex Pheromone of the Pink Bollworm Moth (*Pectinophora gossypiella*)

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The pink bollworm moth (*Pectinophora gossypiella*) is one of the most destructive pests to cotton growths in many parts of the world. The sex pheromone emitted by the female has been identified as a 1:1 mixture of (*Z*),(*Z*)-(*1a*) and (*Z*),(*E*)-7,11-hexadecadien-1-ol acetates (*1b*)[1]. The synthetic mixture with the trivial name gossyplure was found to be highly attractive to male moths in field tests,[1,2] and it has shown success in efforts to combat the pest using either trapping[3] or disruption methods.[4] The compounds *1a* and *1b* have been identified as sex pheromone components of other insect species as well.[5]

The presence in the mixture of the other stereoisomers of the diene *1* has an inhibitory effect.[6a] It therefore seems important to design a synthesis of gossyplure so as to avoid the formation of these isomers since, once formed, they are very difficult to remove from the product, at least on a practical scale. Several of the published syntheses of gossyplure[6] involve the possibility of having the product contaminated with the 7*E* stereoisomers. The synthesis reported by Anderson and Henrick[6f] is an exception; in their strategy one of the double bonds of 1,5-cyclooctadiene ends up as the 7*Z* double bond of *1a*. In the present work we want to report a similar approach which involves the transformation of (*Z*),(*E*),(*E*),1,5,9-cyclododecatriene (CDT) such that its *Z* double bond becomes the 7*Z* double bond of the gossyplure components. The steps in this synthesis are outlined in Scheme 1.

In an earlier paper[7] from our laboratory we described the convenient preparation of stereochemically pure methyl (*Z*)-12-oxo-8-dodecenoate(*2*) by oxidative ring opening of CDT. The Wittig reaction of *2* with pentyltriphenylphosphorane, carried out essentially as described by Anderson and Henrick,[6f] furnished an approximately 1:1 mixture of the (*Z*),(*Z*)- and (*Z*),(*E*)-C_{17} esters *3a* and *b*, respectively. The crude esters were hydrolyzed to the corresponding acids *4*. In the next step the chain was shortened by one carbon atom using the method of Konen *et al.*[8] An excess of lithium diisopropylamide in THF/HMPTA converted the acids *4* to the dianions which reacted with oxygen to give the crude α-hydroxyacids *5*. Subsequent oxidation with sodium metaperiodate afforded (*Z*),(*Z*)- and (*Z*),(*E*)-7,11-hexadecadienal (*6a,b*). We found it advantageous not to purify the products from each step of this sequence of reactions transforming the oxoester *2* into the aldehydes *6*; the overall yield of crude *6* was 85 %. The mixture of aldehydes was purified by short path distillation. The ratio between the isomers remained the same and no isomerization of the double bond had occurred in these reactions as shown by GLC and ^{1}H NMR spectra. Sodium borohydride reduction of *6* afforded the hexadienols *7* which were acetylated with acetyl chloride in pyridine to a liquid product purified by column chromatography. It was shown by GLC to consist essentially (>95 %) of a 48:52 mixture of two compounds which were identified as *1a* and *1b*, respectively, by comparing the spectral properties with those of authentic samples.[6g] The product contained none of the two unwanted stereoisomers.

The overall yield of gossyplure from the oxoester *2* was ~55 % which compares well with those of published syntheses. The advantage with the present synthesis is primarily the

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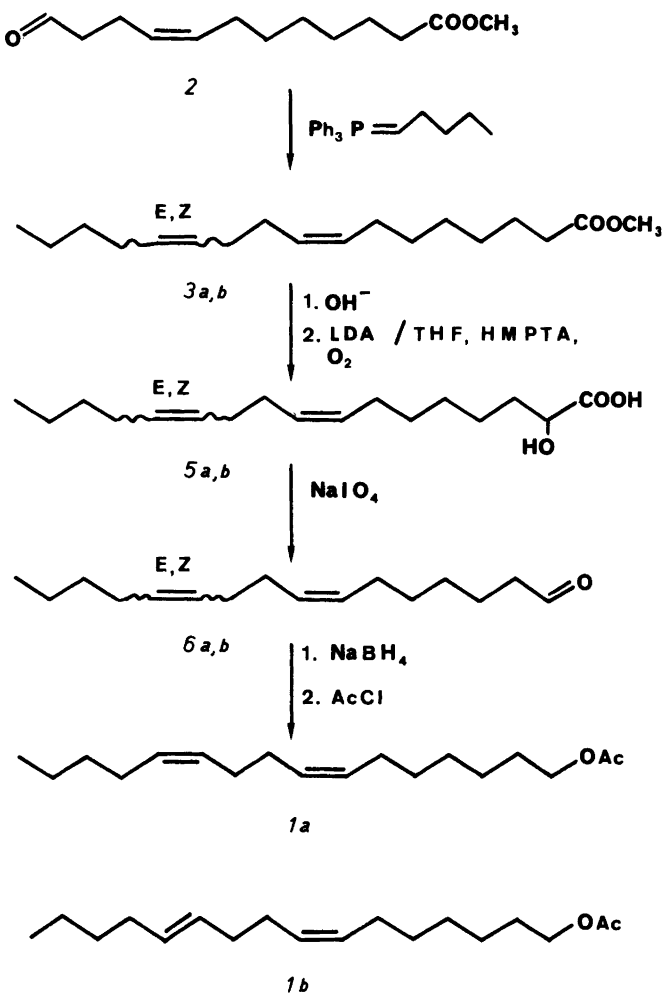

absence of the 7*E* isomers, but the low price for the starting material, CDT, is a positive feature as well.

Experimental. The NMR spectra were recorded on Varian EM 360 A, JNM FX 60 and Bruker WM-400 spectrometers. The mass spectra were obtained on a MM 7070 GLC/MS instrument.

*Methyl (Z),(Z)- and (Z),(E)-8,12-heptadecadienoate (*3a *and* 3b*).* To a suspension of dry pentyltriphenylphosphonium bromide (10.8 g, 26.15 mmol) in 120 ml of anhydrous ether under an N_2 atmosphere, butyllithium (17 ml, 1.6 M in hexane, 27 mmol) was added with stirring. After the mixture had been stirred for 30 min, the orange solution was cooled to −40 °C, and a solution of methyl (*Z*),12-oxo-8-dodecenoate (*2*) (3.92 g, 17.35 mmol) in 15 ml of ether was added dropwise. After stirring for 80 min at −40 °C, 100 ml of ethanol was added dropwise, and the solution was warmed to 25 °C and stirring continued for 1 h. The mixture was then poured into 300 ml of ether-hexane (3:1), and brine was added. The phases were separated and the aqueous layer extracted twice with hexane. The combined organic phases were washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was treated with light petroleum, left overnight at −10 °C, filtered and concentrated to give 5.10 g of crude *3*. GLC showed two major (95 %) components in a 48:52 ratio.

IR (film): 1730 (s), 980 (m), 720 (m) cm^{-1}. ^1H NMR (CCl_4, TMS): δ 0.88 (t, 3 H), 1.10–1.70 (m, 15 H), 1.70–2.40 (m, 10 H), 4.10 (q, 2 H), 5.35 (m, 4 H).

(Z),(Z)- and (Z),(E)-8,12-heptadecadienoic acids (4a *and* 4b). A solution of crude ester mixture *3* (5.10 g, 17.3 mmol) in 35 ml water and 10 ml methanol containing KOH (10 g, 179 mmol) was stirred at 65 °C for 4 h under N_2. The reaction mixture was diluted with 200 ml of water, and worked up in the usual way to give 4.52 g of crude acids *4*.

IR (film): 3400–2700 (m), 1710 (s), 980 (m), 720 (m), cm^{-1}. The acid mixture (0.1 g, 0.38 mmol), was dissolved in 2 ml of methanol containing 1 drop conc. H_2SO_4 and stirred at room temperature for 1 h. 10 % $NaHCO_3$ (aq.) was added, and the product was extracted with light petroleum. GLC showed the two corresponding methyl (*Z*),(*Z*)- and (*Z*),(*E*)-8,12-heptadecadienoates in a ratio of 48:52. IR (film): 1730 (s), 980 (m), 720 (m) cm^{-1}. ^1H NMR (CCl_4, TMS): δ 0.88 (t, 3 H), 1.12–1.75 (m, 12 H), 1.75–2.35 (M, 10 H), 3.55 (s, 3 H), 5.25 (m, 4 H). MS (EI, 70 eV): *m/z*: 280 M^+, 249, 152, 151, 109, 87, 74.

2-hydroxy-(Z),(Z)- and (Z),(E)-8,12-heptadecadienoic acids (5a *and* 5b). A solution of the crude acids *4* (4.42 g, 16.5 mmol) in 20 ml of dry THF was added at 0 °C under N_2 to LDA (40 mmol, from 26 ml of 1.55 M MeLi/Et_2O, dry diisopropylamin (5.75 ml, 40.6 mmol) and 100 ml of dry THF). After 15 min, HMPTA (CaH_2-dried, 7 ml, 39.8 mmol) was added and the mixture stirred at room temperature for 6 h. The mixture was cooled by means of an ice bath, and oxygen was bubbled in for 1 h. The mixture was then poured into 300 ml water, acidified and extracted with ether. The organic phase was washed with 1 % H_2SO_4 (aq.), brine, dried ($MgSO_4$) and concentrated to give 4.60 g of crude material. IR (film): 3400 (s), 3300–2700 (m), 1725 (s), 1050 (s), 980 (m), 720 (m) cm^{-1}. ^1H NMR (CCl_4, TMS): δ 0.88 (t, 3 H), 1.05–1.70 (m, 10 H), 1.70–2.25 (m, 10 H), 3.62 (m, 2 H), 5.25 (m, 4 H).

(Z),(Z)- and (Z),(E)-7,11-hexadecadienal (6a *and* 6b). A solution of *5* (4.60 g, 16.3 mmol) and $NaIO_4$ (5.1 g, 24 mmol) in 70 ml of acetone–acetic acid–water (4:2:1) was stirred at 45 °C for 20 h. The mixture was poured into 200 ml of water and the product was extracted with ether. The organic phase was washed with sat. $NaHCO_3$, dried ($MgSO_4$) and evaporated to give 3.6 g of a slightly brown coloured crude product. A portion was distilled at 100 °C (0.001 mmHg) to give 0.8 g of a >95 % pure 48:52 mixture of the aldehydes *6a* and *6b*. IR (film): 2720 (m), 1730 (s), 980 (m), 720 (m) cm^{-1}. ^1H NMR (CCl_4, TMS): δ 0.88 (t, 3 H), 1.02–1.67 (m, 12 H), 1.67–2.25 (m, 8 H), 5.32 (m, 4 H), 9.65 (s, 1 H). MS (EI, 70 eV) *m/z*: 236 M^+, 218, 149, 109, 97, 67, 57, 55, 49.

(Z),(Z)- and (Z),(E)-7,11-hexadecadien-ol (7a *and* 7b). To a stirred solution of the aldehydes *6* (0.8 g, 3.3 mmol) in 30 ml methanol was added 0.1 ml water containing $NaBH_4$ (0.14 g, 3.8 mmol) and NaOH(0.04 g, 1 mmol). After 20 h at room temperature under N_2, the reaction mixture was diluted with 150 ml ether and poured into 100 ml water. Solid NaCl was added and the aqueous layer was extracted with ether. The organic phase was washed with 1 % HCl (aq.) 5 % $NaHCO_3$ (aq.), brine, dried ($MgSO_4$) and evaporated to give 0.85 g of crude material. GLC showed the product to be >96 % pure. IR (film): 3400 (s), 1050 (s), 980 (m), 720 (m) cm^{-1}. ^1H NMR (CCl_4,TMS): δ 0.91 (t, 3 H), 1.08–1.72 (m, 12 H), 1.72–2.55 (m, 8 H), 3.55 (s and t, 3 H), 5.25 (m, 4 H). MS (EI, 70 eV) *m/z*: 238 M^+, 123, 110, 97, 82, 81, 55, 54, 41.

(Z),(Z)- and (Z),(E)-7,11-hexadecadienyl acetate (1a *and* 1b). To a solution of the alcohols *7* (0.85 g, 3.3 mmol) in 15 ml dry pyridine at 0 °C under N_2, was added freshly distilled acetyl chloride (0.32 g, 4 mmol). After stirring at 0 °C for 10 min, sufficient ice water was added to dissolve the pyridine–hydrochloride complex, and the product was extracted with ether. The organic phase was washed with 1 % HCl (aq), 5 % $HaHCO_3$ (aq.), brine, dried ($MgSO_4$) and concentrated to give 0.9 g of crude material. Column chromatography (silica–light petroleum) gave 0.6 g (65 % yield from *6*) of a 48:52 mixture of *1a* and *1b*. IR (film): 1740 (s), 1360 (m), 1240 (s), 1050 (m), 980 (m), 720 (m) cm^{-1}. ^1H NMR (CCl_4, TMS): δ 0.88 (t, 3 H), 1.08–1.72 (m, 12 H), 1.72–2.25 (m, 8 H), 1.92 (s, 3 H), 3.95 (t, 2 H), 5.25 (m, 4 H). ^{13}C NMR (50.3 MHz, $CDCl_3$) *1a*: 13.97, 20.97, 22.35, 25.86, 26.97, 27.15, 27.44, 28.62, 28.90, 29.58, 31.94, 64.58, 129.09, 129.37, 130.03, 130.33, 171.07. *1b*: 13.97, 20.97, 22.20, 25.86, 27.15, 27.44, 28.62, 28.90, 29.58, 31.78, 32.28, 32.72, 64.58, 129.37, 129.62, 129.87, 130.76, 171.07.

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