Facile Synthesis of Racemic 3-Acetoxy-2,6-dimethyl-1,5-heptadiene, the Sex Pheromone of the Comstock Mealybug

Lars Skattebøl and Yngve Stenstrøm

Department of Chemistry, University of Oslo P.B. 1033, Blindern, N-0315 Oslo 3, Norway

Skattebøl, L. and Stenstrøm, Y., 1989. Facile Synthesis of Racemic 3-Acetoxy-2,6-dimethyl-1,5-heptadiene, the Sex Pheromone of the Comstock Mealybug. – Acta Chem. Scand. 43: 93–96.

A three step synthesis of 3-acetoxy-2,6-dimethyl-1,5-heptadiene is described. Starting from methyl chloroacetate and methyl acrylate, *trans*- and *cis*-dimethyl 1,2-cyclopropanedicarboxylate have been prepared. The isomers were treated with methyllithium or methylmagnesium iodide to give the corresponding diols in high yields. Heating the *trans* diol in a mixture of acetic acid and acetic anhydride at 80 °C gave the title compound in an overall yield of 50 % based on methyl chloroacetate. The corresponding *cis* diol gave, under the same conditions, 2,2,4,4-tetramethyl-3-oxabicyclo[3.1.0]hexane as the only product.

The comstock mealybug, *Pseudococcus comstocki* (Kuwana), is a worldwide pest of several stone and pome fruits. In 1980 two groups independently identified its sex pheromone as 3-acetoxy-2,6-dimethyl-1,5-heptadiene (**1**)[1,2] and the structure was confirmed by synthesis. The pheromone was found to have the *R* configuration, while its antipode was biologically inactive.[3] Several syntheses of the pheromone have since appeared, both of the racemic mixture[4,5] and of the enantiomers.[3,6] In all the syntheses the overall yields were either low (≤ 20 %) or involve difficult separations; none of them have provided more than a few hundred milligrams of the pheromone.

We now wish to report a short, efficient synthesis of the racemic pheromone that is adaptable to large-scale preparations.

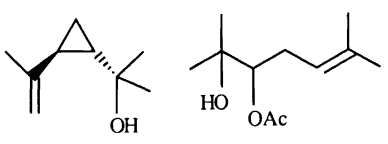
Results and discussion

The synthesis of compound **1** is outlined in Scheme 1. Dimethyl cyclopropane-1,2-dicarboxylate (**2**) was prepared from methyl acrylate and methyl chloroacetate essentially as described in the literature,[7] but with a greatly improved yield. The product was formed as a 60:40 mixture of *cis* and *trans* isomers, respectively. It became obvious from subsequent experiments that the *trans* isomer **2a** was required for conversion into the target molecule. This was easily achieved by heating the crude isomer mixture with sodium methoxide in methanol; almost complete equilibration to the thermodynamically more stable *trans* isomer took place. The yield of **2a** was 66 %. The reaction[8] of ethyl acrylate with ethyl diazoacetate afforded *trans*-diethyl cyclopropane-1,2-dicarboxylate as the only cyclic product, but the yield was only 25 %. In contrast, the addition of sulfoxonium methylide to maleic or fumaric ethyl esters is reported to give the cyclopropane derivatives in 78 and 80 % yields, respectively.[9]

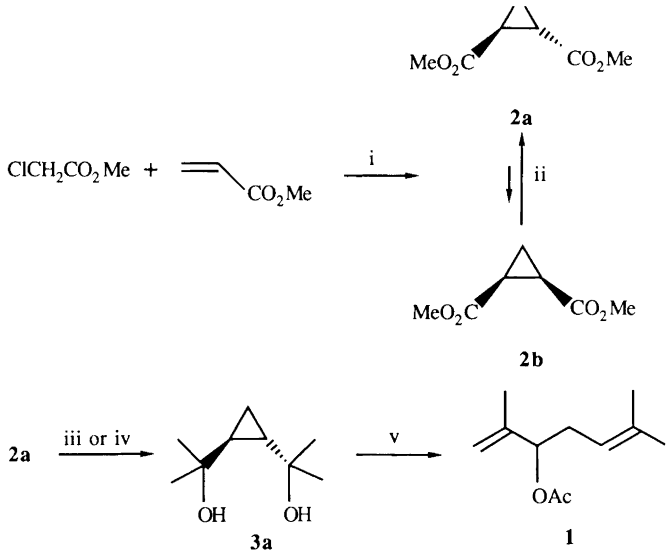
Reaction of the diester **2a** with methyllithium gave the corresponding crystalline diol **3a** in practically quantitative yield. The diol was also obtained from **2** and methylmagnesium iodide, but in lower yield.[10,11] From the mixture of isomeric diols, the pure *cis* diol **3b** was obtained by fractional crystallisation.

An alternative synthesis of **3a** and **b** consists of the reduction of 2,5-dimethyl-3-hexyne-2,5-diol to the corresponding alkene followed by a Simmons–Smith cyclopropanation. Reduction of the acetylenic diol with $LiAlH_4$ gave the pure *trans* compound while catalytic hydrogenation with 5 % Pd–C in methanol in the presence of KOH[12] gave a 86:14 mixture of the *cis* and *trans* diols, respectively, according to ^1H NMR spectroscopy. Both compounds were obtained in excellent yields; however, the cyclopropanation reaction gave only poor to moderate yields and therefore this route was abandoned.

Isomers **3a** and **b** were treated separately with a mixture of acetic anhydride and acetic acid at about 80 °C. The *trans* compound gave, almost immediately, a product which was isolated by preparative GLC and identified as *trans*-2-(2-isopropenylcyclopropyl)-2-propanol (**4**).[10] Initially the amount of this compound increased at the expense of two other components; however, when all of the starting material had been consumed only traces of **4** were present and the product consisted essentially of an 11:1 mixture of two compounds. The major component was isolated in 74 %



4 5



i) NaOMe ii) NaOMe/MeOH/Δ iii) MeMgI/Et_2O

iv) MeLi/Et_2O v) HOAc/Ac_2O/70-80 °C

Scheme 1.

yield by fractional distillation and identified as the pheromone **1** by comparison of the spectral data with those of the literature.[1b,3] A pure sample of the minor component was obtained by preparative GLC and the spectral data were those expected for the alcohol **5**. The infrared spectrum revealed the hydroxy and the carbonyl absorptions at 3650 and 1725 cm^{-1}, respectively; the NMR spectra were also in agreement with the structure.

Identical treatment of the *cis* isomer **3b** resulted in rapid elimination of water with formation of the cyclic ether **6**[13] in quantitative yield (Scheme 2). The ether was stable under these conditions, but at higher temperatures it reacted further. After about 2 days at 130–140 °C, the ether was completely converted into several new products including **1**, which constituted 50 % of the mixture. The solution also became dark and a significant amount of a tarry residue was formed on distillation.

Acetic anhydride was essential for the success of the thermal reaction; heating **3a** in neat acetic acid resulted in a complex mixture which still contained >50 % **1**. Apparently, extended heating in the absence of acetic anhydride caused deterioration of the pheromone which was stable under similar conditions in the presence of acetic anhydride.

Heating the *trans* diol in the acetic acid–acetic anhydride mixture in the presence of a catalytic amount of *p*-toluenesulfonic acid gave rise to a complex product mixture of which **1** and **4** constituted only minor parts. The *cis* diol gave the bicyclic ether **6** as the only product under these conditions.

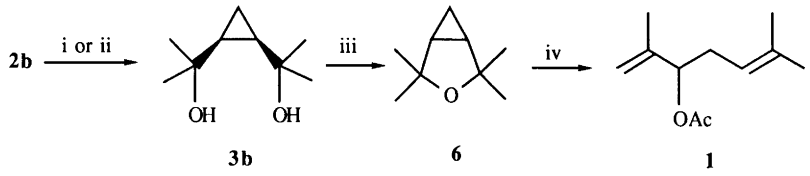
With boron trifluoride–diethyl ether complex under similar conditions, the diols afforded complex mixtures even at room temperature. The *trans* diol gave compounds **1**, **4** and **5** in a 2:1:1 ratio as the major products. Higher reaction temperatures resulted in polymeric material. The *cis* diol gave **1** as the major product, but only as 25 % of the total mixture, while **6** constituted less than 2 %.

Mechanistically it seems reasonable that **4** is initially formed from **3a** and subsequently converted into the acetate **1** by nucleophilic attack of the acetate ion on the cyclopropane ring. This reaction probably involves the formation of the cyclopropylmethyl cation as an intermediate. Oda and coworkers[10,11,13] have investigated the acid-catalysed dehydration of both neat **3a** and **b**. The quantitative formation of **6** from the *cis* compound is consistent with our results. The *trans* isomer gave several products including the alcohol **4**. A methanolic solution of **3a** under similar conditions gave 3-methoxy-2,6-dimethyl-1,5-heptadiene, an analogue of **1**, together with a number of other compounds.

In conclusion, the reported sequence of reactions represents a convenient synthesis of the comstock mealybug sex pheromone. From inexpensive starting materials an overall yield of 50 % in three steps is achieved, and the synthesis is adaptable to large-scale preparations.

Experimental

General. The instruments employed have been described elsewhere.[14] GLC analyses were performed on a 25 m SP 2100 capillary column. For preparative work a 10 % SP 2100 packed column was used.



i) MeMgI/Et_2O ii) MeLi/Et_2O iii) HOAc/Ac_2O/70-80 °C iv) HOAc/Ac_2O/130-140 °C

Scheme 2.

trans-*Dimethyl 1,2-cyclopropanedicarboxylate* (**2a**). The compound was prepared according to the literature[7] by slowly adding 14.15 g (0.26 mol) NaOMe, with stirring, to a mixture of 27.14 g (0.25 mol) methyl chloroacetate and 48.51 g (0.56 mol) methyl acrylate. After the addition the reaction mixture was stirred for a further 16 h at room temperature. According to GLC and spectral data **2a** and **2b** were formed as the major products in a 40:60 ratio. The volatile constituents, consisting mainly of unchanged methyl acrylate and methyl 3-methoxypropanoate, were evaporated and 100 ml 2 M NaOMe in methanol were added to the residue. The mixture was heated at 75–80 °C for 14 h when, according to GLC, the ratio of **2a**:**2b** was >99:1. After most of the methanol had been evaporated, ether and sufficient water to dissolve the precipitated NaCl were added to the residue. The organic phase was separated and the water phase was extracted several times with ether. The collected extracts were washed with brine, dried ($MgSO_4$) and distilled to give 26.1 g (66 %; lit.,[7] 45 %) of **2a**, b.p. 84–85 °C/9 mmHg (lit.,[7] 115–117 °C/10 mmHg). IR (film): 3020 (w), 1730 (s) cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 1.35 (dd, J_1 6, J_2 8 Hz, 2 H), 2.05 (dd, J_1 6, J_2 8 Hz, 2 H), 3.62 (s, 6 H).

trans-*α,α,α',α'-Tetramethylcyclopropane-1,2-diyldimethanol* (**3a**). To a mixture of 10.34 g (65.3 mmol) **2a** in 200 ml ether were added dropwise, with stirring, 170 ml of 1.65 M (280.5 mmol) methyllithium in ether. After the addition the mixture was stirred for a further 2 h. Sufficient water was then added to dissolve the precipitated salts. The water phase was extracted several times with ether. The collected ether extracts were washed with brine, dried ($MgSO_4$) and evaporated to give 10.5 g (100 %) of **3a** as a viscous liquid which crystallised when allowed to stand. The crude product was found pure enough for further reaction. A portion was recrystallised from CCl_4 to give pure **3a**, m.p. 69–70 °C (lit.,[15] 70–72 °C). IR (CCl_4): 3600 (m), 3350 (m), 3060 (w) cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 0.42 (d, *J* 6.5 Hz, 2 H), 0.90 (d, *J* 6.5 Hz, 2 H), 1.02 (s, 6 H), 1.23 (s, 6 H), 3.23 (s, 2 H).

cis-*α, α, α', α'-Tetramethylcyclopropane-1,2-diyldimethanol* (**3b**). The stereoisomeric mixture of diesters **2** (19.30 g, 0.122 mol) was treated with a 50 % excess of methylmagnesium iodide as previously described.[10,11] Usual work up gave 19.52 g (100 %) of crude diols **3a** and **b** in a 40:60 ratio. Trituration of this mixture with hexane gave 6.85 g (35 %) of the *cis* isomer as white crystals, m.p. 86–87 °C (lit.,[13] 85.5–87 °C). IR (CCl_4): 3600 (w), 3220 (s), 3060 (w) cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 0.3–1.0 (m, 4 H), 1.31 (s, 6 H), 1.42 (s, 6 H), 5.60 (s, 2 H).

3-Acetoxy-2,6-dimethyl-1,5-heptadiene (**1**). A solution of 7.94 g (50.2 mmol) of crude **2a** in 42 g acetic anhydride and 17 g acetic acid was heated at 80–85 °C for 3 h while being monitored by GLC. The alcohol **4** was formed initially and a sample was obtained by preparative GLC. After 3 h all of the diol had been consumed resulting in a mixture consisting of two major products in a 92:8 ratio. Evaporation of the solvent through a small column followed by fractional distillation of the residue gave 6.67 g (74 %) of **1**, b.p. 80–82 °C/9 mmHg (lit.,[2b] 68–70 °C/15 mmHg). The IR spectrum was in accordance with the literature.[2b] ^1H NMR (300 MHz,$CDCl_3$): δ 1.62 (s, 3 H), 1.69 (s, 3 H), 1.73 (s, 3 H), 2.05 (s, 3 H), 2.25–2.45 (m, 2 H), 4.88 (br s, 1 H), 4.94 (br s, 1 H), 5.04 (br t, *J* 7.1 Hz, 1 H), 5.15 (t, *J* 6.7 Hz, 1 H). ^{13}C NMR (75 MHz,$CDCl_3$): δ 17.73 (CH_3), 18.19 (CH_3), 21.01 (CH_3), 25.58 (CH_3), 31.43 (CH_2), 76.90 (CH), 112.51 (CH_2), 118.85 (CH), 134.10 (C), 142.92 (C), 170.10 (C=O) ppm.

trans-*2-(2-Isopropenylcyclopropyl)propan-2-ol* (**4**):[10] IR ($CDCl_3$): 3590 (s), 3470 (w), 3060 (m), 1630 (m) cm^{-1}. ^1H NMR (300 MHz,$CDCl_3$): δ 0.61–0.71 (m, 2 H), 0.99–1.05 (m, 1 H), 1.23 (s, 6 H), 1.40 (ddd, J_1 5.1, J_2 5.4, J_3 5.6 Hz, 1 H), 1.68 (s, 3 H), 1.75 (br s, 1 H), 4.67 (br s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.15 (CH_2), 20.93 (CH_3), 21.13 (CH), 2859 (CH_3), 28.88 (CH_3), 30.70 (CH), 69.29 (C–O), 107.88 (=CH_2), 145.85 (=C) ppm.

An analytical sample of the minor component was isolated by preparative GLC and characterised as *3-acetoxy-2,6-dimethylhept-5-en-2-ol* (**5**): IR ($CDCl_3$): 3650 (w), 3060 (w), 1725 (s) cm^{-1}. ^1H NMR (300 MHz,$CDCl_3$): δ 1.22 (s, 6 H), 1.62 (s, 3 H), 1.68 (s, 3 H), 1.75 (br s, 1 H), 2.07 (s, 3 H), 2.31 (t, *J* 7 Hz, 2 H), 4.82 (t, *J* 7 Hz, 1 H), 5.08 (t, *J* 7 Hz, 1 H). ^{13}C NMR (75 MHz,$CDCl_3$): δ 17.81 (CH_3), 21.01 (CH_3), 25.16 (CH_3), 25.76 (CH_3), 26.61 (CH_3), 28.43 (CH_2), 72.30 (COH), 79.66 (CHOAc), 119.90 (=CH), 134.14 (=C), 170.95 (C=O) ppm.

2,2,4,4-Tetramethyl-3-oxabicyclo[3.1.0]hexane (**6**). A mixture of 982 mg (6.2 mmol) **3b** in 5.0 g acetic anhydride and

1.9 g acetic acid was heated at about 80 °C for 1 h. According to GLC analysis the diol was converted quantitatively into the bicyclic ether (**6**). An analytical sample was isolated by preparative GLC. The IR spectrum was in accordance with the literature.[13] ^{1}H NMR (60 MHz,CCl_4): δ 0.33 (t, *J* 6 Hz, 2 H), 1.10 (s, 6 H), 1.30 (s, 6 H), 1.40 (t, *J* 6 Hz, 2 H).

Thermal reaction of **6**. When a solution of **6** in the acetic acid–acetic anhydride mixture was heated to 130–140 °C, a slow reaction took place. After approximately 2 days most of **6** had been consumed to give a complex mixture. Three of the products constituting 50, 5 and 4 % of the total mixture were identified as **1**, **4** and **5**, respectively, from GLC retention times. Distillation gave 358 mg (32 % based on **3b**) of **1** and left a significant amount of a dark, tarry material.

References

1. (a) Bierl-Leonhardt, B. A., Moreno, D. S., Schwarz, M., Forster, H. S., Plimmer, J. R. and DeVilbiss, E. D. *Life Sci. 27* (1980) 399; (b) Bierl-Leonhardt, B. A., Moreno, D. S., Schwarz, M., Forster, H. S., Plimmer, J. R. and DeVilbiss, E. D. *J. Chem. Ecol. 8* (1982) 689.
2. (a) Negishi, T., Uchida, M., Tamaki, Y., Mori, K., Ishiwatari, T., Asano, S. and Nakagawa, K. *Appl. Entomol. Zool. 15* (1980) 328; (b) Uchida, M., Nakagawa, K., Negishi, T., Asano, S. and Mori, K. *Agric. Biol. Chem. 45* (1981) 369.
3. Mori, K. and Ueda, H. *Tetrahedron 37* (1981) 2581.
4. Baeckstrøm, P., Bjørkling, F., Høgberg, H.-E. and Norin, T. *Acta. Chem. Scand., Ser. B 38* (1984) 779.
5. Fall, Y., van Bac, N. and Langlois, Y. *Tetrahedron Lett. 27* (1986) 3611.
6. Nakagawa, N. and Mori, K. *Agric. Biol. Chem. 48* (1984) 2799.
7. McCoy, L. L. *J. Am. Chem. Soc. 80* (1958) 6568.
8. Wiberg, K. B., Barnes, R. K. and Albin, J. *J. Am. Chem. Soc. 79* (1957) 4994.
9. Landor, S. R., Landor, P. D. and Kalli, M. *J. Chem. Soc., Perkin Trans. 1* (1983) 2921.
10. Shono, T., Yoshimura, T. and Oda, R. *J. Org. Chem. 32* (1967) 1088.
11. Shono, T., Yoshimura, T. and Oda, R. *Tetrahedron 24* (1968) 729.
12. Tedeschi, R. T. *J. Org. Chem. 27* (1962) 2398.
13. Shono, T., Oku, A., Morikawa, T., Kimura, M. and Oda, R. *Bull. Chem. Soc. Jpn. 38* (1965) 940.
14. Fjeldskaar, I. R., Rongved, P. and Skattebøl, L. *Acta Chem. Scand., Ser. B 41* (1987) 477.
15. Olah, G. A., Grant, J. L., Spear, R. J., Bollinger, J. M., Serianz, A. and Sipos, G. *J. Am. Chem. Soc. 98* (1976) 2501.

Received July 17, 1988.