

Short Communication

Preparation of Two Aggression Controlling Substances in Bees

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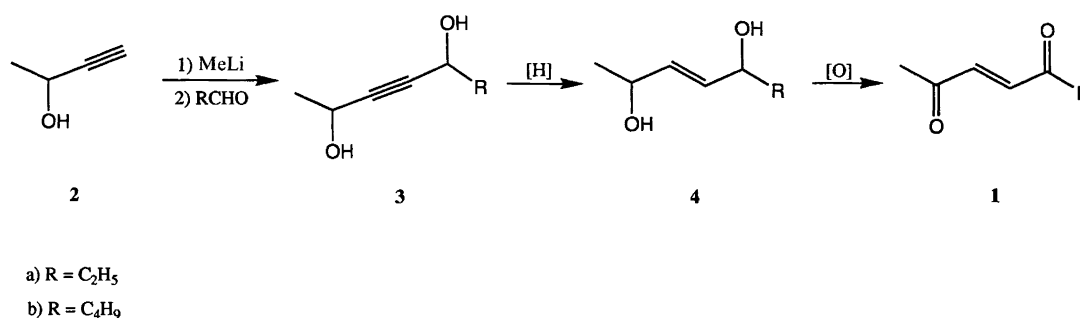
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Bees are probably the most socialised of insects. It is well known that they have a complex communication system involving chemical substances of which some have been identified.^{1,2} Several parasitic species towards the bees are known. Apparently the parasites have adopted part of the chemical communication system and developed it further to their own benefit. One of these parasites is the stingless fire bee *Trigona (Oxytrigona) taira*; this bee can actually enter the nest hive of the honey bee *Apis mellifera*, take any honey it needs and leave without being attacked and killed, as would happen to ordinary intruders.^{3–6} In fact, honey bees withdraw from the fire bee's track and those staying close seem to calm down. Two compounds have been isolated from the mandibular glands and identified as the active ones. They were found to be (*E*)-3-heptene-2,5-dione (**1a**) and (*E*)-3-nonene-2,5-dione (**1b**).^{3–5} To our surprise only a couple of syntheses exist for one or both of the compounds and these are low-yielding, multistep syntheses giving mixtures of products; in one case the isolation steps involved preparative GLC.^{3,7,8} We required larger quantities for biological studies of these structurally simple, but biologically interesting compounds and in the present paper their syntheses are reported.

Retrosynthetically the *E*-geometry of the double bond combined with the two conjugated carbonyl groups suggested the use of acetylenic chemistry. Moreover, with an intermediate acetylene both *E*- and *Z*-alkenes should be available for structure–activity studies. The preparation of both compounds followed the same general path and is presented in Scheme 1 in the case of the *E*-isomers.

A THF solution of the dianion of 3-butyn-2-ol (**2**) was formed either by the addition of one equivalent of lithium hydride followed by another equivalent of methyllithium or simply by addition of two equivalents of methyllithium. The reaction with propanal and pentanal gave practically quantitative yields of the corresponding acetylenic diols **3**. Owing to the water solubility of the diols they had to be thoroughly extracted to ensure full recovery from the aqueous phase. According to GLC and the NMR spectra the products consisted of diastereomeric mixtures in 60:40 and 55:45 ratios, respectively. Since the final products are non-chiral we proceeded with the oxidation step. Reduction with lithium aluminium hydride gave the olefinic diols **4** in near quantitative yield. Work-up was done according to a method in which the water was retained by the solid magnesium and aluminium salts. With



Scheme 1.

the usual aqueous work-up, the water solubility of **4** made tedious continuous extraction with ether a necessity for complete recovery of the product.

For the oxidation step we tried several of the ordinary chromium-based methods, i.e., Jones,⁹ Browns two-phase procedure¹⁰ and the pyridinium-based methods with PCC¹¹ and PDC.¹² In addition we attempted a Swern oxidation,¹³ as well as less common reagents such as $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$,¹⁴ $\text{K}_2\text{Cr}_2\text{O}_7$ -Adogen¹⁵ and BaMnO_4 in both benzene (preferred owing to a much faster reaction) and dichloromethane.¹⁶ However, with the exception of the last method none of them gave yields exceeding 70%. Apparently this was in part due to the water solubility of the products **1**, but we also suspect further oxidation of the conjugated 1,4-diketones to cause reduction in yields. With respect to BaMnO_4 ,¹⁶ the yield was optimized to 72%. However, a five- to seven-fold excess of reagent was needed and the reaction had to be carefully monitored due to further oxidation of **1**. Moreover, a tarry crude product and the price of the reagent made it less attractive for a multigram-scale preparation. We therefore looked for a milder and less expensive oxidising agent.

It is well known that manganese dioxide can oxidise allylic alcohols.^{17,18} However, the method has several disadvantages making it less attractive especially on a larger scale, namely, (1) low reproducibility, (2) a large excess of the reagent is needed (10–20 molar equivalents is common) and (3) the finely divided reagent makes everything black and messy. Recently some Japanese workers¹⁹ have shown commercially available electrolytically precipitated manganese dioxide to be a promising oxidising reagent especially with respect to reproducibility. The examples in their paper were all on a small scale. When we tried the reagent we also found it to work quite satisfactorily on a small scale (< 100 mg), although even here a ten-fold excess of the reagent was needed; however, on a multigram scale an even larger excess, 18–25 equivalents, was necessary. We found it advantageous to add the manganese dioxide in smaller portions; when all was added at once the reaction slowed down and stopped after 50–60% conversion, no matter how large the excess was. We tried several solvents; the reaction went fastest when dichloromethane was used; pentane, benzene and diethyl ether could be used as well, but the reaction time needed for full conversion increased approximately five, four and two times, respectively. Increasing the temperature did not increase the reaction rate significantly; even in refluxing benzene the reaction was slower than in dichloromethane. Despite the drawback of the large excess of the oxidising agent needed, the method was found superior for three reasons: (1) the reproducibility was very good, (2) high yields were achieved and (3) the work-up procedure was very simple with filtration, evaporation and distillation and no aqueous phases were involved. Comparison of the spectroscopic data of **1** with those in the literature confirmed the structure.^{3,7,8}

In conclusion the preparation is a simple, large-scale

procedure giving the biologically interesting target molecules in 73–76% overall yields.

Biological testing of the compounds on both bees and wasps is under way and the results will be published in due course.²⁰

Experimental

General. The NMR spectra were recorded on a JEOL JNM-GX270 instrument. Me_4Si was used as the internal standard and CDCl_3 as the solvent in both the ^1H NMR and ^{13}C NMR spectra. Analytical GLC was performed on a 25 m OV 17 capillary column.

3-Heptyne-2,5-diol (3a). A solution of 5.01 g (71.5 mmol) 3-butyn-2-ol in 100 ml dry THF was cooled to -50°C after which 62.5 ml 2.29 M (143 mmol) methylolithium in ether were added dropwise over ca. 20 min. The solution was stirred for approximately 20 min and 4.15 g (71.5 mmol) propanal were added dropwise. After being stirred for 1 h at this temperature, the mixture was stirred overnight at 0°C and then poured into 100 ml saturated $\text{NH}_4\text{Cl}(\text{aq})$ precooled to 0°C . Saturation with NaCl , followed by extraction with ether (6 \times 60 ml), drying (MgSO_4) and evaporation gave 9.2 g (100% crude yield) of **3a**, as a 3:2 mixture of diastereomers according to GLC and confirmed by the NMR spectra where slightly overlapping signals were seen. For the major isomer: ^1H NMR (270 MHz): δ 0.91 (t, J 7.4 Hz, 3 H), 1.36 (d, J 6.4 Hz, 3 H), 1.5–1.7 (m, 2 H), 4.10 (br s, 2 H), 4.24 (q, J 6.4 Hz, 1 H), 4.45 (t, J 6.3 Hz, 1 H). ^{13}C NMR (66.5 MHz): δ 9.63 (CH_3 , C7), 24.31 (CH_3 , C1), 30.83 (CH_2 , C6), 58.12 (CH, C2), 63.58 (CH, C5), 85.04 (C, C3), 87.05 (C, C4). The crude product was used in the next step without further purification.

3-Nonyne-2,5-diol (3b) was prepared in the same manner to give a quantitative yield of a 55:45 mixture of diastereomers according to GLC and confirmed by the NMR spectra. ^1H NMR (270 MHz): δ 0.92 (t, J 7.4 Hz, 3 H), 1.3–1.5 (m, 4 H), 1.43 (d, J 6.4 Hz, 3 H), 1.60–1.75 (m, 2 H), 3.20 (br s, 2 H), 4.37 (q, J 6.4 Hz, 1 H), 4.57 (t, J 6.3 Hz, 1 H). ^{13}C NMR (66.5 MHz): δ 14.01 (CH_3 , C9), 22.37 (CH_3 , C1), 24.24, 27.33, 37.37 (3 \times CH_2 , C6, C7, C8), 58.21 (CH, C2), 62.36 (CH, C5), 85.15 (C, C3), 86.71 (C, C4).

(E)-3-Heptene-2,5-diol (4a). To a stirred solution of 4.36 g (115 mmol) LiAlH_4 in 150 ml dry ether was added a solution of 7.37 g (57.5 mmol) **3a** dropwise over 45 min while the temperature of the solution was kept at room temperature. The reaction was then refluxed for 30 min while being monitored by TLC. The reaction was stopped by the successive addition of 4.4 ml water, 4.4 ml 15% NaOH and 13.1 ml water. Filtering, washing with ether and evaporation yielded 7.02 g (94%) of **4a** sufficiently pure for the next reaction. ^1H NMR (270 MHz): δ 0.91

(t, J 4.7 Hz, 3 H), 1.27 (d, J 6.2 Hz, 3 H), 1.4–1.6 (m, 2 H), 2.9–3.2 (br s, 2 H), 3.9–4.1 (m, 1 H), 4.2–4.4 (m, 1 H), 5.6–5.8 (m, 2 H). ^{13}C NMR (66.5 MHz): δ 9.79 (CH_3 , C7), 23.33 (CH_3 , C1), 29.99 (CH_2 , C6), 68.26 (CH, C2), 73.76 (CH, C5), 132.15, 134.81 ($2 \times$ CH, C3, C4).

(*E*)-Non-3-ene-2,5-diol (**4b**) was made in the same manner to give a 95% yield on a similar scale. ^1H NMR (270 MHz): δ 0.90 (t, J 4.7 Hz, 3 H), 1.24 (d, J 6.2 Hz, 3 H), 1.2–1.6 (m, 6 H), 2.5–3.0 (br s, 2 H), 4.0–4.1 (m, 1 H), 4.3–4.4 (m, 1 H), 5.6–5.8 (m, 2 H). ^{13}C NMR (66.5 MHz): δ 14.04 (CH_3 , C9), 22.61 (CH_3 , C1), 23.06, 27.65, 36.80 ($3 \times$ CH_2 , C6, C7, C8), 67.65 (CH, C2), 72.40 (CH, C5), 133.08, 134.42 ($2 \times$ CH, C3, C4).

(*E*)-Hept-3-ene-2,5-dione (**1a**). To a solution of 6.80 g (52.2 mmol) **4a** in 150 ml CH_2Cl_2 , were added 170 g (1.96 mol; 18.5 equivalents) MnO_2 ²¹ in small portions over 2–3 h. The reaction was monitored by TLC. An intermediate compound was formed first. Probably this was a hydroxy ketone since it disappeared when the reaction went to completion. When all was converted, the mixture was filtered through Celite, evaporated and distilled to give 5.14 g (78%), b.p. 90–93°C/16 mmHg. Spectroscopic data were in accord with those given in the literature.^{3,7,8}

(*E*)-Non-3-ene-2,5-dione (**1b**) was made in the same manner to give an 80% yield, b.p. 89–91°C/13 mmHg. Spectroscopic data were in accord with those given in the literature.³

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References

- Free, J. B. *J. Apicult. Res.* 27 (1988) 227.
- Moritz, R. F. A. and Crewe, R. M. *Apidologie* 22 (1991) 205.
- Bian, Z., Fales, H. M., Blum, M. S., Jones, T. H., Rinderer, T. E. and Howard, D. F. *J. Chem. Ecol.* 10 (1984) 451.
- Roubik, D. W., Smith, B. H. and Carlson, R. G. *J. Chem. Ecol.* 13 (1987) 1079.
- Rinderer, T. E., Blum, M. S., Fales, H. M., Bian, Z., Jones, T. H., Buco, S. M., Lancaster, V. A., Danka, R. G. and Howard, D. F. *J. Chem. Ecol.* 14 (1988) 495.
- Wittmann, D., Radtke, R., Zeil, J., Lübke, G. and Francke, W. *J. Chem. Ecol.* 16 (1990) 631.
- Severin, T. and König, D. *Chem. Ber.* 107 (1974) 1499.
- Andersen, S. H., Das, N. B., Jørgensen, R. D., Kjeldsen, G., Knudsen, J. S., Sharma, S. C. and Torssell, K. B. G. *Acta Chem. Scand., Ser. B* 36 (1982) 1.
- Bowers, A., Halsall, T. G., Jones, E. R. H. and Lemm, A. J. *J. Chem. Soc.* (1953) 2548.
- Brown, H. C., Craig, C. P. and Lin, K. T. *J. Org. Chem.* 36 (1971) 387.
- Corey, E. J. and Suggs, J. W. *Tetrahedron Lett.* (1975) 2647.
- Corey, E. J. and Schmidt, G. *Tetrahedron Lett.* (1979) 399.
- Omura, K. and Swern, D. *Tetrahedron* 34 (1978) 1651.
- Kanemoto, S., Tomioka, T., Oshima, K. and Nozaki, H. *Bull. Chem. Soc. Jpn.* 59 (1986) 105.
- Firouzabadi, H. and Mostafavipoor, Z. *Bull. Chem. Soc. Jpn.* 56 (1983) 914.
- Hutchins, R. O., Natale, N. R. and Cook, W. J. *Tetrahedron Lett.* (1977) 4167.
- Evans, R. M. *Q. Rev. Chem. Soc.* 13 (1959) 61.
- Stork, G. and Tomasz, M. *J. Am. Chem. Soc.* 86 (1964) 471.
- Tsuboi, S., Ishii, N., Sakai, T., Tari, I. and Utaka, M. *Bull. Chem. Soc. Jpn.* 63 (1990) 1888.
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