Note

A Convenient Synthesis of 4-Hydroxy-3-methyl-2-(2-propynyl)-cyclopent-2-enone, an Alcohol Moiety of a Synthetic Pyrethroid Having Strong Killing and Knockdown Activity

Noritada MATSUO, Fumio FUJITA, Osamu MAGARA, Hiroko YAMAZAKI, Koichi AKETA, Toshio NISHIOKA and Nobushige ITAYA

Institute for Biological Science, Sumitomo Chemical Co. Ltd., Takatsukasa, Takarazuka, Hyogo 665, Japan

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Gersdorff *et al.*[1] reported that 2-propynylrethrin (**I**) [2-methyl-4-oxo-3-(2-propynyl)cyclopent-2-enyl (±)-*cis*, *trans*-chrysanthemate] with a triple bond instead of a double bond in the side chain of allethrin (**III**) is only 64% as toxic as **III** to houseflies. However, our experiments[2] proved that **I** has over 1.5 times the killing activity of **III** and over twice the knockdown activity of **III** against both houseflies and mosquitoes. Although there are a few patents[3a,c] including the syntheses of 4-hydroxy-3-methyl-2-(2-propynyl)cyclopent-2-enone (**II**), an alcohol moiety of **I**, no example has been disclosed. Only one patent[3b] including the synthesis of **II** was recorded, but it was a multistage method (8 steps) and the product (**II**) with this procedure was contaminated with the regio-isomer of a hydroxy group. These facts prompted us to search for a more covenient method to prepare the alcohol (**II**). Herein we describe a simple and efficient synthesis of **II** starting from dimethyl 3-oxoglutarate (**V**).

According to Bavley *et al.*,[4] dimethyl-2-allyl-3-oxoglutarate (**VI**) was transformed to the diketone (**VIII**), the key intermediate of allethrolone (**IV**), as shown in Fig. 2. However, the yield of **VIII** from the diester (**VI**) was very low (26%). We assumed that the low yield was due to nonregioselective decarboxylation of the diester (**VI**) and that the key 3-oxo-6-heptenoate anion (**VII**) was obtained in the minor part. When we applied this route to the synthesis of the diketone (**XI**), the key intermediate of **II**, the 2-propynyl diester (**IX**) was surprisingly transformed to **XI** in an over 80% yield. The more with-drawing effect of the 2-propynyl group might cause the preferential regioselective decarboxylation at the C-4 carbon atom to give the desired 3-oxo-6-heptynoate anion (**X**), which coupled with methylglyoxal to give the diketone (**XI**) in a high yield. Treatment of **XI** in aqueous sodium hydroxide solution gave the desired alcohol (**II**) in a 62% yield. Furthermore, at the first step [(**V**)→(**IX**)], we found that the addition of a catalytic amount of lithium iodide had a favorable influence on both the yield (71%) of the mono-alkylation and the reaction time (4 hr). In the absence of lithium iodide, the yield of **IX** was 44% in 20 hr.*1

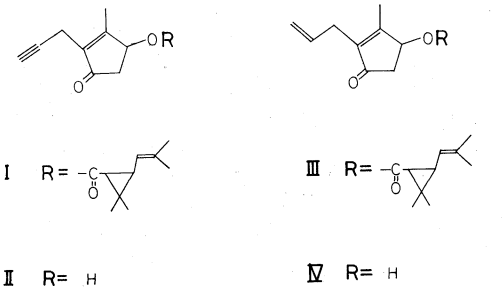

FIG. 1. Structures of Allethrin, 2-Propynylrethrin and Their Alcohol Moieties.

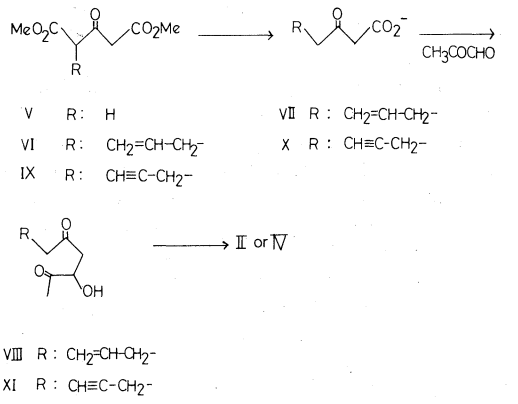

FIG. 2. Syntheses of Rethrolones.

In conclusion, these findings have proved this route to be a practical one for the synthesis of the alcohol (**II**).

EXPERIMENTAL

All bps were uncorrected. IR spectra refer to films. NMR spectra were recorded at 60 MHz in $CDCl_3$ with TMS as an internal standard unless otherwise stated. All compounds described here were racemates.

Dimethyl 2-(2-propynyl)-3-oxoglutarate (**IX**). To the $Mg(OMe)_2$ solution [prepared from Mg (5.2 g) and MeOH (150 ml)] was added dimethyl 3-oxoglutarate (25 g), and the mixture was kept at 60°C for 1.5 hr. LiI (1.9 g) and 2-

*1 Except for the 2-propynyl group, the yield of monoalkylation is high in the absence of lithium iodide. See Y. Muramoto, K. Oishi, I. Ichimoto and H. Ueda, *Nippon Nôgeikagaku Kaishi*, **47**, 201 (1973).

propynyl chloride (11.2 g) were added and the mixture was kept at 60°C for 4 hr. After removal of MeOH, ice, dil.HCl and NaCl were added. The mixture was extracted with ethyl acetate, and the extract was dried over $MgSO_4$, concentrated and distilled to give 26.1 g of an oil. This oil contained 83% of **IX** as judged by GLC analysis (71% yield), bp 90~101°C (0.2 mmHg); n_D^{24} 1.4650; IR ν_{max} cm^{-1}: 3270, 2105, 1735, 1436, 1400, 1326, 1260, 1160, 1095, 1015, 838; NMR: 2.06 (1H, t, J=2.5 Hz), 2.75 (2H, dd, J=2.5, 8.0 Hz), 3.70 (2H, s), 3.72 (3H, s), 3.76 (3H, s), 3.93 (1H, t, J=8.0 Hz); GLC (column, 5%SE30, 1.0 m × 3 mm i.d. at 120°C; carrier gas, N_2 1.0 kg/cm^2): t_R; 10.5 min.

3-Hydroxy-8-nonyne-2,5-dione (**XI**). The dimethyl ester (**IX**, 10 g) was added to an 11% NaOH aqueous solution (38.2 g) at −5~−10°C and the mixture was stirred at 30°C for 5 hr. After pH adjustment (pH 3.9) with H_2SO_4 at 5°C, the mixture was stirred at 5°C overnight. To the mixture, $NaHCO_3$ (0.44 g), $Na_2S_2O_4$ (0.88 g) and toluene (33 ml) were added. The mixture was warmed to 36°C and 20.8% methylglyoxal (17.8 g, 0.05 mol) was added over 2 hr under N_2 and then the mixture was kept at 36°C for 16 hr. The organic layer was separated and the aqueous layer was saturated with NaCl followed by extraction with ethyl acetate. The combined organic layers were concentrated *in vacuo* to give the diketone (**XI**, 6.9 g) as an oil (purity: 90% by GLC, 80% yield); n_D^{23} 1.4584; IR ν_{max} cm^{-1}: 3450, 3280, 2110, 1715, 1705, 1400, 1380, 1240, 1155, 1095, 1015; NMR: 2.03 (1H, t, J=2.5 Hz), 2.26 (3H, s), 2.43 (2H, m), 2.77 (2H, broad t), 2.90 (1H, dd, J=17 Hz), 2.95 (1H, dd, J=4, 17 Hz), 3.45 (1H, broad s), 4.41 (1H, dd, J=4, 6 Hz).

4-Hydroxy-3-methyl-2-(2-propynyl)cyclopent-2-enone (**II**). The diketone (**XI**, 25.0 g) was added to a mixture of 10% NaOH aqueous solution (237 g) and toluene (100 ml) with vigorous stirring over 2.5 hr at −3~−1°C, and the stirring was continued for 2.5 hr. After acidification with 35% HCl solution at 0°C, the mixture was saturated with NaCl. The toluene layer was separated and the aqueous layer was extracted with ethyl acetate. The combined layers were concentrated and distilled to give 12.5 g of **II** (62% yield), bp 100~110°C (0.1 mmHg); n_D^{23}=1.5275; IR ν_{max} cm^{-1}: 3400, 3280, 2120, 1700, 1647, 1420, 1382, 1342, 1315, 1280, 1215, 1195, 1145, 1095, 1053, 1015, 940; NMR: 2.00 (1H, t, J=2.5 Hz), 2.22 (3H, s), 2.1, 2.4 (1H, dd, J=3, 18 Hz), 2.65, 2.95 (1H, dd, J=6, 18 Hz), 3.06 (2H, d, J=2.5 Hz), 3.95 (1H, broad s, –OH), 4.69 (1H, m); GLC (column, 5%SE30, 1.0 m × 3 mm i.d. at 120°C; carrier gas, N_2 0.6 kg/cm^2): t_R, 8.8 min. There are no phyisical data of **II** in the references. To confirm the structure, **II** (130 mg) in MeOH (5 ml) was hydrogenated over Lindlar catalyst (23 mg) at 20°C to obtain allethrolone (**IV**, 101 mg) which was found to be identical with authentic allethrolone by comparisons of IR and NMR.

REFERENCES

1) W. A. Gersdorff and P. G. Piquett, *J. Econ. Entomol.*, **54**, 1250 (1961).
2) M. Hirano *et al.*, unpublished results.
3) a) M. S. Schechter and F. B. LaForge, US Patent 2574500 (1951) [*C.A.*, **46**, 5078h (1952)] and 2661374 (1953) [*C.A.*, **49**, 1788e (1955)]. The claims in these patents include the synthesis of the alcohol (**II**) from 5-hexyn-2-one, but no example was disclosed. Our experiments proved that the total yield of **II** from ethyl acetoacetate *via* 5-hexyn-2-one was below 5% in 5 steps.
b) R. W. Kierstead and R. A. Lemahieu, US Patent 3715400 (1973); [*C.A.*, **78**, 147438t (1973)].
c) M. Matsui, J. Katsube, H. Shimomura and S. Kitamura, Japanese Patent Kokai 7705736 (1977) [*C.A.*, **87**, 5495 (1977)].
4) A. Bavley and E. C. Schreiber, US Patent, 2768967 (1956) [*C.A.*, **51**, 7407f (1957)].