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A Convenient Conversion of Allethrolone into Pyrethrolone

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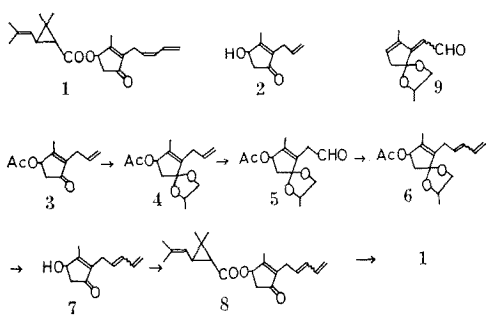
Pyrethrolone was synthesized in a practical manner from readily available allethrolone.

Pyrethrolone (**7**) is the alcohol component of pyrethrin I and pyrethrin II, the principal constituents of the naturally occurring insecticidal "pyrethrin" esters found in *Chrysanthemum cinerariaefolium*.[1] Although we have recently reported the conversion of readily available allethrolone (**2**) into several pyrethrolone derivatives, its practical use was limited by low yield in the Wittig condensation.[2] The defect seemed to be overcome by protection of the carbonyl group of **2**.[3] This paper describes the more efficient method for the preparation of pyrethrolone (**7**), establishing a simple synthetic route to (Z)-pyrethrin I (**1**, as the mixture of diastereoisomers).

Allethronyl acetate (**3**) reacted with propylene oxide in the presence of a catalytic amount of stannic chloride in carbon tetrachloride[3] to give an acetal (**4**) in 76% yield which is the key intermediate for this synthesis (Fig. 1). Attempted acetalization using ethylene glycol and mineral acid or transacetalization with butanone ethylene acetal was unsuccessful. An aldehyde (**5**) was obtained as an unstable liquid by ozonolysis of **4** followed by reduction with triphenylphosphine in methylene dichloride and used in the next step without further purification, since, with heat, acetic acid was easily eliminated from **5** to yield a conjugated aldehyde (**9**). The Wittig condensation between **5** and the ylide derived from allyl triphenylphosphonium bromide in tetrahydrofuran with *n*-butyllithium as a base gave a diene (**6**) in 47% yield containing the (E)- and the (Z)-isomers in a 1 : 1 ratio on GLC analysis. Each isomer of **6** was isolated by preparative GLC. The compound with the shorter retention time proved to be the (E)-isomer of **6**, as ascertained by its IR spectrum which has the absorption peak at 945 cm^{-1} (characteristic of trans-double bond). Hydrolysis of **6** in diluted sulfuric acid solution afforded a mixture of (E, Z)-isomeric pyrethrolones (**7**) in 66% yield which was unresolvable by GLC. The pyrethrolone was esterified with *d-trans*-chrysanthemic acid chloride[4] to give a mixture of (E, Z)-diastereoisomeric pyrethrins I (**8**) in 83% yield. The ratio of the (E)- and the (Z)-isomer was *ca.* 1 : 1 from the PMR spectrum of **8**, according to the fact that methylene protons of the pentadienyl group of the (E)-isomer exhibited a doublet signal centered at δ 3.00 while those of the (Z)-isomer exhibited the peaks centered at δ 3.10. Therefore, **8** was treated with tetracyanoethylene[5] in tetrahydrofuran at room temperature which selectively reacted with the (E)-isomer. Maleic anhydride and *p*-benzoquinone were less active as the dienophile for the complete removal of the (E)-isomer. Pure (Z)-pyrethrin I (**1**) was obtained in 41% overall yield from the diastereoisomeric mixture (**8**) after chromatographic purification. Thus, the purification yield of this isomer was 81%.



The spectral data of **1** were in good agreement with those of natural pyrethrin I.[6]

Thus, the defect of low yield in the Wittig condensation[2] was much improved by protection of the functional groups of **2**. Furthermore, because of easiness to remove the protecting groups of **6** this work would comprise to be a more convenient method for the preparation of the other natural pyrethrins.[7]

EXPERIMENTAL

Boiling points are uncorrected. PMR spectra were recorded on a JEOL (JNM-MH 100) spectrometer or on a Hitachi R-24A spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. UV spectra and IR spectra were measured with a Hitachi 124 spectrophotometer and with a JASCO IRA-1 spectrometer, respectively. Unless stated otherwise, mass spectra were measured with a Hitachi RMU-6L spectrometer at 70 eV. GLC analyses were performed on a Yanaco G-80 gas chromatograph. Preparative GLC was carried out on a Hitachi K-53 gas chromatograph.

1-(4-Methyl-1, 3-dioxolan-2-yl)-2-allyl-3-methyl-2-cyclopent-4-yl acetate (**4**)

To a stirred solution of allethronyl acetate (**3**, 100 g) and $SnCl_4$(25 g) in CCl_4(200 ml) was added propylene oxide (58 g) at 10~25°C. The reaction mixture was stirred at room temperature for 30 min, mixed with 10% $NaHCO_3$ solution (1 liter), filtered, evaporated and distilled to afforded the acetal (**4**, 100.5 g, 76.4%), bp 110~112°C (0.9 mmHg); n_D^{22} 1.4715; IR ν_{max} cm^{-1}: 2980, 2930, 2870, 1740, 1640, 1635, 1250, 1020; PMR δ 1.25 (3H, m, CH_3), 1.65 (3H, s, CH_3), 1.80~2.30 (2H, m), 2.00 (3H, s, AcO), 3.40~4.00 (3H, m), 4.94 (2H, m), 5.30~6.00 (1H, m); MS *m/e*: 250 (M^+); *Anal.* Found: C, 66.52; H, 7.60. Calcd. for $C_{14}H_{18}O_4$: C, 67.17; H, 7.26%.

1-(4-Methyl-1, 3-dioxolan-2-yl)-2-formylmethyl-3-methyl-2-cyclopent-4-yl acetate (**5**)

Ozonized oxygen was introduced to the acetal (**4**, 25 g) in CH_2Cl_2 (300 ml) at −50°C until **4** disappeared on TLC. The reaction mixture was treated with triphenylphosphine (28 g) and triturated with *n*-hexane–ether (300 ml, 2: 1, v/v), filtered and concentrated *in vacuo* to give 27.0 g of crude oil (**5**), IR ν_{max} cm^{-1}: 3060, 2970, 2920, 2720 (CHO), 1730, 1660, 1380, 1250, 1020; PMR δ 1.25 (3H, s, AcO), 2.50~2.80 (2H, m), 3.50 (1H, m), 4.20 (2H, m), 5.60 (1H, m), 9.50 (1H, m, CHO). This was employed for the next step without further purification.

1-(4-Methyl-1, 3-dioxolan-2-yl)-2-formylmethylidene-3-methylcyclopent-3-ene (**9**)

The crude **5** (10.2 g) was distilled *in vacuo* to yield 3.4 g (41%) of **9**, bp 120~122°C (0.8 mmHg); IR ν_{max} cm^{-1}: 1660, 1605, 1140, 1020, 890; PMR δ 1.18 (3H, m), 1.92 (3H, s, CH_3), 2.26 (2H, m), 3.60 (1H, m), 4.20 (2H, m), 5.86 (1H, m), 6.16 (1H, m), 10.08 (1H, m, CHO); MS *m/e*: 194 (M^+, loss of acetic acid from **3**).

1-(4-Methyl-1, 3-dioxolan-2-yl)-2-(penta-2, 4-dienyl)-3-methylcyclopent-2-en-4-yl acetate (**6**)

A solution of *n*-BuLi in *n*-hexane (1.5 M, 70 ml) was jnjected to a stirred suspension of allyl triphenylphosphonium bromide (57.5 g) in THF (400 ml) at 20°C under argon atmosphere. The crude aldehyde (**5**, 26.0 g) in THF (50 ml) was injected to the red solution of the ylide at 10~20°C. The reaction mixture was stirred at room temperature for 2 hr, triturated with *n*-hexane (600 ml), filtered, washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil (15.3 g) was chromatographed over Al_2O_3 (activity II, 150 g, *n*-hexane) to give 13.7 g (47.5%) of the diene (**6**), n_D^{21} 1.5080. GLC analysis (3% SE-30, 3 mm *i. d.* × 2.5 m at 180°C, N_2 = 1.0 kg/cm^2) showed two peaks in a 1: 1 ratio. Then, a part of **6** was submitted to preparative GLC. (3% SE-30, 20 mm *i. d.* × 2 m at 160°C, N_2 = 1.0 kg/cm^2); (E)-isomer of **6**; t_R, 12 min; n_D^{21} 1.5065; UV λ_{max}^{EtOH} nm(ε): 228 (29300); IR ν_{max} cm^{-1}: 3080, 2970, 2930, 2860, 1735, 1645, 1595, 1430, 1375, 1345, 1300, 1245, 1200, 1130, 1090, 1040, 1000, 965, 945 (*trans*), 895, 870, 810, 770, 720, 695; PMR δ 1.22 (3H, m, CH_3), 1.64 (3H, s, CH_3), 1.84 (1H, dd, J=4 and 14 Hz), 2.04 (3H, s, CH_3), 2.48 (1H, dd, J=4 and 14 Hz), 2.84 (2H, d, J=6Hz), 3.40 (1H, m), 4.12 (2H, m), 4.98 (2H, m), 5.44 (1H, m), 5.64 (1H, m), 5.94~6.40 (2H, m); MS *m/e*: 278 (M^+), 218 (M^+–AcOH, base peak). (Z)-isomer of **6**; t_R, 14 min; n_D^{21} 1.5085; UV λ_{max}^{EtOH} nm (ε): 228 (22500); IR ν_{max} cm^{-1}: 3080, 2970, 2930, 2860, 1735, 1640, 1590, 1430, 1375, 1345, 1300, 1245, 1200, 1130, 1090, 1040, 1020, 1000, 965, 900, 870, 810, 770, 720, 695; PMR δ 1.22 (3H, m, CH_3), 1.64 (3H, s, CH_3), 1.84 (1H, dd, J=4 and 14 Hz), 2.04 (3H, s, CH_3), 2.56 (1H, dd, J=4 and 14 Hz), 2.96 (2H, d, J=6Hz), 3.40 (1H, m), 4.12 (3H, m), 5.04~5.40 (3H, m), 5.44 (1H, m), 6.00 (1H, m), 6.56~6.94 (1H, m); MS *m/e*: 278 (M^+, base peak).

(E, Z)-*Pyrethrolone* (**7**)

A mixture of **6** (13.6 g), 8% H_2SO_4 (100 ml) and acetone (200 ml) was kept at room temperature for 7 days. The yellow solution was neutalized with $NaHCO_3$ and extracted with ether (100 ml × 3). The ether extracts were combined, washed with water, dried over $MgSO_4$ and concentrated to give 5.8 g (66%) of **7**, n_D^{22} 1.5420; IR ν_{max} cm^{-1}; 3400 (OH), 1700 (C=O), 1640 (C=C);

PMR 2.08 (3H, s, CH_3), 2.20 (1H, m), 2.80 (1H, m), 3.00 (2H, d, J=6Hz), 3.15 (1H, s, OH), 4.50 (1H, m), 5.20 (3H, m), 6.00, 6.70 (2H, m); MS *m/e*; 178 (M^+).

(Z)-Pyrethrin I (**1**)

To a solution of (E, Z)-pyrethrolone (3.0 g) and pyridine (1.4 g) in benzene (20 ml) was added dropwise *d-trans*-chrysanthemic acid chloride (3.5 g) at 10~15°C. The reaction mixture was stirred at room temperature for 2 hr, washed with dil. HCl, water, dil. $NaHCO_3$ and water, successively. The benzene layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was chromatographed over silica gel (60 g, *n*-hexane) to give 4.6 g (83%) of **8**, n_D^{21} 1.5205. The PMR spectrum of **8** showed the presence of the (E)- and the (Z)-isomers in a 1:1 ratio as described above. Then, **8** (1.2 g) was treated with tetracyanoethylene (0.37 g) in THF (25 ml) at room temperature for 1 day. THF was removed *in vacuo* and the residue was chromatographed on a Florisil column(30 g, *n*-hexane: ethyl acetate=1:1, v/v) to give 0.49 g (purification yield: 81%) of **1**, n_D^{22} 1.5220 (lit.[7] n_D^{25} 1.5179); IR ν_{max} cm^{-1}: 1725, 1660, 1590, 1160, 995, 905; PMR δ 1.15 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.40 (1H, d, J=6Hz), 1.70 (6H, s, CH_3), 2.05 (3H, s, CH_3), 2.10~2.40 (2H, m), 2.80 (1H, m), 3.10 (2H, d, J=6Hz), 4.85 (1H, d, J=8Hz), 5.00~5.43 (3H, m), 5.75 (1H, d, J=6Hz), 6.00 (1H, t, J=10Hz), 6.40~7.12 (1H, m); MS *m/e*: 328 (M^+).

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