A Versatile New Synthesis of Pyrethroid Acids

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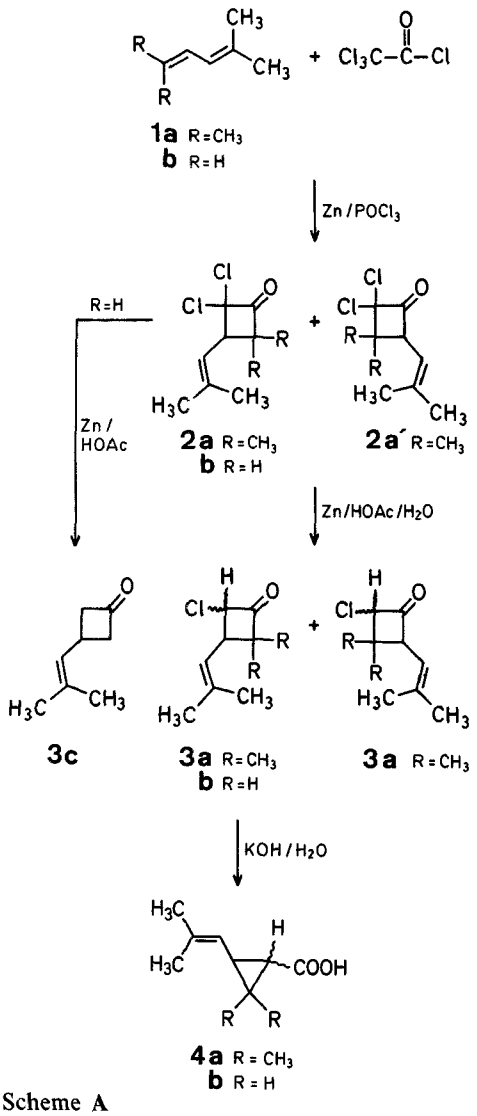
Chrysanthemic acid and certain analogues have been known for many years to be effective components of pyrethroid esters which are potent insecticides[1]. In this communication we describe a simple yet versatile synthesis of pyrethroid acids from conjugated dienes which we believe will offer an attractive alternative to existing pyrethroid acid syntheses. The procedure is based on the finding that α,α-dichloro-β-vinylcyclobutanones, readily available cycloaddition products from dichloroketene and conjugated dienes, will undergo a selective reductive removal of one chlorine atom. The resultant monochlorocyclobutanones undergo a facile Favorskii-type ring contraction to the pyrethroid acids.

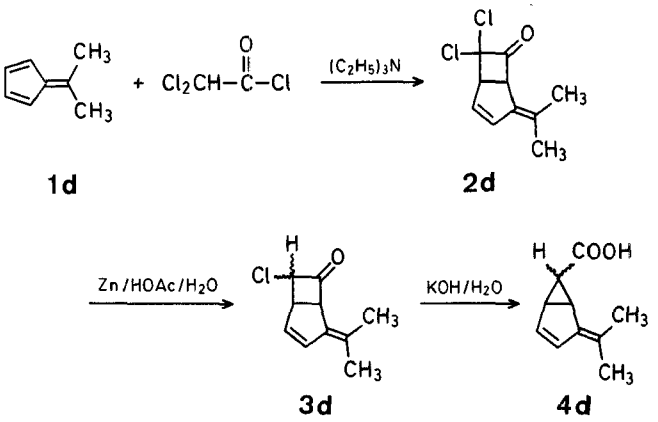
In our previous studies of dichloroketene/hindered olefin cycloadditions, we prepared the dichloroketene cycloadduct of 2,5-dimethyl-2,4-hexadiene (**2a** and **2a'**)[2]. This cycloaddition

product is now an important precursor to chrysanthemic acid **(4a)**. Dichloroketene[3] is generated *in situ* from trichloroacetyl chloride with zinc in ether containing phosphoryl chloride (a slight modification of existing literature procedure)[2,4] in the presence of the diene. Both regioisomers are obtained; 2,2-dichloro-4,4-dimethyl-3-(2-methylpropenyl)-cyclobutanone **(2a)** in 40% yield and 2,2-dichloro-3,3-dimethyl-4-(2-methylpropenyl)-cyclobutanone **(2a')** in 15% yield. A key step in the synthesis of chrysanthemic acid is the reductive removal of only one chlorine atom[4,5] in **2a** and **2a'** by treating the dichloro-cycloaddition product with one equivalent of zinc dust in acetic acid[6,7]. After 24 h at ambient temperature, a mixture of monochlorocyclobutanones **3a** and **3a'** is obtained in 82% yield. The structures of **3a** and **3a'** were determined by ^{1}H-N.M.R. and ^{13}C-N.M.R. spectrometry. The reduction step is not regiospecific and yields two stereomers for each regioisomer of the cycloadduct, thus accounting for the four signals for the carbon bearing the chlorine atom in the ^{13}C-N.M.R. spectrum. The Favorskii-type ring contraction reaction is a regiospecific reaction[8,9,10] and the four monochlorocyclobutanones yield *cis*- and *trans*-chrysanthemic acid **(4a)** in 73% yield. The isomeric chrysanthemic acids may be separated by crystallization from ethyl acetate[11].



Scheme **A**

The general utility of this synthetic sequence for pyrethroid acids has been demonstrated by employing several other conjugated dienes and the corresponding pyrethroid acids were obtained in yields comparable to that of chrysanthemic acid. The utilization of 4-methyl-1,3-pentadiene **(1b)** is also illustrated in Scheme **A**. To demonstrate that **2b** was 2,2-dichloro-3-(2-methylpropenyl)-cyclobutanone, both chlorine atoms were reductively removed with zinc/acetic acid to yield 3-(2-methylpropenyl)-cyclobutanone, **(3c)**. 6,6-Dimethylfulvene **(1d)** has also been utilized in this synthesis as illustrated in Scheme **B**. The alternate method of generating dichloroketene from dichloroacetyl chloride with triethylamine was used in this *in situ* cycloaddition to provide the cycloaddition product in 89% yield.



Scheme **B**

The advantages of this three-step reaction sequence are that the reagents are readily available, the procedure is simple and requires only mild conditions, and the reaction can be performed with a wide variety of conjugated dienes. This method should compete quite favorably with existing procedures in the literature in terms of simplicity and availability of starting compounds for a broad range of pyrethroid acids[12].

2,2-Dichloro-4,4-dimethyl-3-(2-methylpropenyl)-cyclobutanone (2a) and 2,2-Dichloro-3,3-dimethyl-4-(2-methylpropenyl)-cyclobutanone (2a'):
A solution of freshly distilled trichloroacetyl chloride (25 mmol) and phosphoryl chloride (25 mmol) in anhydrous ether (250 ml) is added over a 10 h period to a stirring mixture of 2,5-dimethyl-2,4-hexadiene (**1a**; 0.1 mol) and activated zinc (1.64 g, 25 mmol) in ether (250 ml) at ambient temperature. After the addition is complete, the mixture is stirred for an additional 12 h. The excess zinc is removed by filtration and the solution concentrated to about 50 ml and then stirred with pentane (100 ml). The solution is decanted from the zinc chloride etherate and washed with water (200 ml) and a saturated solution of sodium hydrogen carbonate (100 ml). The solvent is removed under reduced pressure and the residue vacuum distilled at 55–58 °C/0.2 torr to give the product; yield: 3.1 g (55%); the ratio of **2a/2a'** = 3 as evidenced by the ^{1}H-N.M.R. The I.R. and ^{1}H-N.M.R. data are identical with reported values[2].

^{13}C-N.M.R. ($CDCl_3$): δ = 201.3 (s); 195.0 (s); 140.0 (s); 116.1 (d); 113.6 (d); 91.7 (s); 87.6 (s); 63.3 (d); 60.4 (s); 56.1 (d); 46.0 (s); 25.9 (q); 25.5 (q); 24.9 (q); 23.6 (q); 21.7 (q); 20.1 (q); 18.9 (q); 18.6 ppm (q).

2-Chloro-4,4-dimethyl-3-(2-methylpropenyl)-cyclobutanone (3a) and 2-Chloro-3,3-dimethyl-4-(2-methylpropenyl)-cyclobutanone (3a'):
The mixture of **2a** and **2a'** (4.0 g, 18 mmol) in acetic acid (50 ml) and water (5 ml) is added in portions to zinc dust (18 mmol) over a 1 h period and then the mixture is stirred for 24 h at ambient temperature. Ether (150 ml) is added to the mixture and the mixture washed with water (500 ml) and sodium hydrogen carbonate solution (200 ml). The ether solution is dried with anhydrous magnesium sulfate, the solvent removed under reduced pressure, and the residue vacuum distilled to give a mixture of **3a** and **3a'**; yield: 2.8 g (82%); b.p. 58–60 °C/0.1 torr.

I.R. (film): ν = 1780 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.0–1.6 (m, 6H); 1.6–1.9 (m, 6H); 3.0 (m, 1H); 3.8 (d, 1H, J = 6.0 Hz); 4.7 (dd, 1H, J = 6.0 Hz, 1.2 Hz, —CHCl); 5.3 ppm (d, 2H, J = 8.0 Hz).

^{13}C-N.M.R. ($CDCl_3$): δ = 210.7 (s); 205.5 (s); 138.2 (s); 136.6 (s); 119.5 (d); 117.9 (d); 114.8 (d); 114.1 (d), 69.6 (d, —CHCl); 68.7 (d, —CHCl); 65.7 (d, —CHCl); 64.7 (d, —CHCl); 63.1–18.3 ppm (overlapped).

cis- and _trans_-Chrysanthemic Acids (4a):

A mixture of **3a** and **3a'** (2.0 g) is treated with potassium hydroxide (2 equiv) in water (50 ml) at ambient temperature for 24 h. The solution is then washed with chloroform (100 ml) to remove unreacted cyclobutanone and/or nonacidic products. The aqueous solution is then acidified with 2 normal hydrochloric acid and extracted with chloroform (200 ml), dried with anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue is vacuum distilled to give *cis*- and *trans*-chrysanthemic acids; yield: 1.3 g (73%); b.p. 95–96 °C/0.25 torr or 138–139 °C/10 torr; *trans/cis* ratio = 3.

The *trans*-acid is crystallized from ethyl acetate at −10 °C (2 days), washed with petroleum ether, and recrystallized from ethyl acetate, m.p. 54 °C. The filtrate is cooled to −78 °C to yield the *cis*-acid; m.p. 115–116 °C (the m.p. and ^{1}H-N.M.R. data of *cis*- and *trans*-chrysanthemic acids are identical with those in the literature[13]).

^{13}C-N.M.R. ($CDCl_3$): *cis*-acid: δ = 177.8 (s); 134.9 (s); 117.9 (d); 33.2 (d); 31.2 (d); 28.8 (q); 27.2 (s); 25.6 (q); 18.2 (q); 14.7 ppm (q).

^{13}C-N.M.R. ($CDCl_3$): *trans*-acid: δ = 178.9 (s); 135.7 (s); 120.7 (d); 34.6 (d); 33.4 (d); 29.5 (s); 25.6 (q); 22.1 (q); 20.3 (q); 18.3 ppm (q).

2,2-Dichloro-3-(2-methylpropenyl)-cyclobutanone (2b):

Prepared as described for **2a** using trichloroacetyl chloride (5.6 ml, 50 mmol), 4-methyl-1,3-pentadiene (**1b**; 5 g, 60 mmol), phosphoryl chloride (4.6 ml, 50 mmol), zinc (5 g, 78 mmol), and ether (500 ml); yield: 6.8 g (71%); b.p. 65–67 °C/0.2 torr.

I.R. (film): ν = 1800 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.8 (dd, 3H, J = 1.4 Hz, 0.5 Hz); 1.9 (dd, 3H, J = 1.32 Hz, 0.5 Hz); 2.9–3.9 (m, 3H); 5.2 ppm (d, 1H, J = 7.9 Hz).

^{13}C-N.M.R. ($CDCl_3$): δ = 192.7 (s); 139.5 (s); 120.5 (d); 90.1 (s); 65.1 (q); 62.6 (d); 48.7 (q); 44.3 ppm (q).

2-Chloro-3-(2-methylpropenyl)-cyclobutanone (3b):

Prepared as described for **3a** using **2b** (5 g, 26 mmol); zinc (1.7 g), acetic acid (50 ml), water (5 ml) for 20 h at ambient temperature; yield: 3.2 g (79%); b.p. 52–54 °C/0.1 torr.

I.R. (film): ν = 1790 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.75 (d, 3H, J = 0.5 Hz); 1.85 (d, 3H, J = 0.5 Hz); 2.6–3.7 (m, 3H, *endo*- and *exo*-); 4.6 (m, 1H); 5.2 ppm (m, 1H).

^{13}C-N.M.R. ($CDCl_3$): (*endo*- and *exo*-): δ = 199.7 (s); 198.1 (s); 136.5 (s); 136.4 (s); 124.1 (d); 121.0 (d); 67.1 (d); 65.2 (d); 50.0 (t); 48.9 (t); 35.5 (d); 29.5 (d); 25.3 (q); 25.2 (q); 18.1 ppm (q).

3-(2-Methylpropenyl)-cyclobutanone (3c):

Prepared from **2b** (10 mmol), zinc (6 g, 10 mmol), acetic acid (30 ml), water (2 ml) for 80 h at ambient temperature; yield: 1.2 g (90%); b.p. 42 °C/3.5 torr.

I.R. (film): ν = 1775 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.65 (d, 3H, J = 0.5 Hz); 1.7 (d, 3H, J = 0.5 Hz); 2.6–3.4 (m, 5H); 5.2 ppm (d, 1H, J = 6.3 Hz).

^{13}C-N.M.R. ($CDCl_3$): δ = 2.5.6 (s); 132.4 (s); 128.0 (d); 53.7 (t); 24.8 (q); 21.9 (d); 17.5 ppm (q).

2-(2-Methylpropenyl)-cyclopropanecarboxylic Acid (4b):

Prepared as described for **4a** using **3b** (2 g, 12 mmol); potassium hydroxide (1.6 g, 30 mmol), and water (50 ml) for 24 h at ambient temperature; yield: 1.2 g (75%); b.p. 85–86 °C/0.1 torr; *trans/cis* ratio = 10.

$C_8H_{12}O_2$	calc.	C 68.54	H 8.63
(140.2)	found	68.23	8.69

I.R. (film): ν = 1680 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 0.9 (m, 1H); 1.35 (m, 2H); 1.4 (dd, 3H, J = 1.5 Hz, 0.5 Hz); 1.48 (dd, 3H, J = 1.5 Hz, 0.5 Hz); 2.06 (m, 1H); 4.6 (dd, 1H, J = 8.9 Hz, 1.2 Hz); 12.3 ppm (br. s, 1H).

^{13}C-N.M.R. ($CDCl_3$): δ = (*trans*-acid): 180.1 (s); 134.0 (s); 124.0 (d); 24.9 (q); 22.3 (d); 21.5 (d); 17.8 (q); 16.3 ppm (q); (*cis*-acid): 178.7 (s); 134.0 (s); 120.7 (d); 20.8 overlapped with 20.3 overlapped with 14.5 ppm (the *cis*- and *trans*-acids were not separated).

7,7-Dichloro-4-isopropylidenebicyclo[3.2.0]hept-2-en-6-one (2d):

A solution of dichloroacetyl chloride (13.8 g, 93 mmol) in hexane (10 ml) is added dropwise to a warm (40 °C) solution of 6,6-dimethylfulvene (**1d**; 10 g, 94 mmol) and triethylamine (9.5 g, 94 mmol) in hexane (500 ml) during a 5 h period. The amine salt is removed by filtration and the filtrate washed with water. The solvent is removed under reduced pressure and the residue vacuum distilled to give **2d**; yield: 18.2 g (89%); b.p. 94 °C/0.25 torr or 100 °C/0.7 torr (Ref.[14], b.p. 100 °C/0.7 torr).

I.R. (film): ν = 1802 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.8 (s, 6H); 4.1 (m, 1H); 4.7 (m, 1H); 5.9 (m, 1H); 6.5 ppm (dd, 1H, J = 8.0 Hz, 2.0 Hz).

^{13}C-N.M.R. ($CDCl_3$): δ = 193.9 (s); 136.2 (d); 133.4 (s); 129.7 (s); 129.4 (d); 87.7 (s); 62.3 (d); 58.1 (d); 21.9 (q); 20.8 ppm (q).

7-Chloro-4-isopropylidenebicyclo[3.2.0]hept-2-en-6-one (3d):

Prepared as described for **3a** using **2d** (10 g, 46 mmol), zinc (3.0 g, 46 mmol), acetic acid (100 ml), and water (10 ml) for 24 h at ambient temperature; yield: 6.8 g (82%); m.p. 63 °C (recrystallized from petroleum ether); Ref.[14], m.p. 63 °C.

I.R. (film): ν = 1780 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.8 (s, 6H); 3.95 (m, 1H); 4.4 (m, 1H); 5.0 (dd, 1H, J = 10 Hz, 4.8 Hz); 5.9 (m, 1H); 6.1 ppm (dd, 1H, J = 6.0 Hz, 0.5 Hz).

^{13}C-N.M.R. ($CDCl_3$): δ = 201.9 (s); 135.7 (d); 135.1 (s); 129.9 (d); 127.4 (s); 64.4 (d); 63.1 (d); 44.3 (d); 21.7 (q); 20.6 ppm (q).

4-Isopropylidenebicyclo[3.1.0]hex-2-en-6-carboxylic Acid (4d):

Prepared as described for **4a** using **3d** (5 g, 27 mmol), potassium hydroxide (4.0 g, 70 mmol), and water (100 ml) for 24 h at ambient temperature; yield: 4.1 g (68%); m.p. 135–137 °C (recrystallized from hexane/benzene).

$C_{11}H_{12}O_2$	calc.	C 73.17	H 7.31
(176.2)	found	73.09	7.45

I.R. (film): ν = 1680 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.9 (s, 6H); 2.0 (d, 1H, J = 3.0 Hz); 2.65 (dd, 2H, J = 9.6 Hz, 1.2 Hz); 5.8 (m, 1H); 6.15 ppm (dd, 1H, J = 7.5 Hz, 1.2 Hz).

^{13}C-N.M.R. ($CDCl_3$): δ = 169.5 (s); 137.1 (s); 130.2 (d); 126.7 (s); 30.1 (d); 29.6 (d); 25.1 (d); 21.6 (q); 20.8 ppm (q).

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