A Convenient Synthesis of Ethyl (±)-*cis,trans*-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate by the Wittig Reaction

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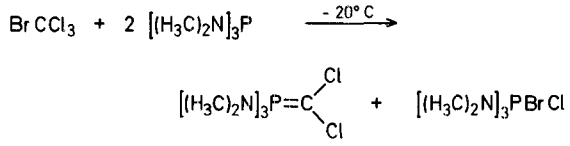
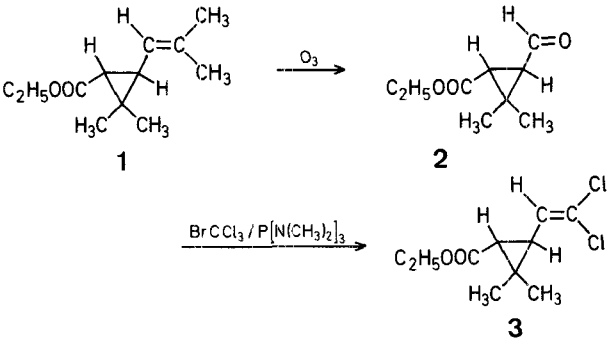
Interest in the synthetic utility of Wittig reactions for introducing a dichlorovinyl group[1] has increased since the potent insecticidal properties of permethrin [3-phenoxybenzyl (±)-*cis,trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate] were described by Elliott et al.[2]. A variety of synthetic pathways to the acid moiety of this pyrethroid from low-cost starting materials have recently been described by some pesticide manufacturers[3-7]. The Wittig reaction, performed on quite expensive cyclopropane aldehydes derived from chrysanthemic acids, has also been employed but for small-scale purposes. Initial approaches[8,9] to introducing the dichlorovinyl group involved the condensation of dichloromethylenetriphenylphosphorane with 2,2-dimethyl-3-formylcyclopropanecarboxylates (caronaldehydes). However, a number of difficulties have been reported with this Wittig reaction. Specifically, *t*-butyl-(1*R*-*trans*)-caronaldehyde in the presence of carbon tetrachloride and triphenylphosphine (60 °C, 7 h) gave the desired 3-(2,2-dichlorovinyl) ester in low yield. *t*-Butyl 3-dichloromethyl-2,2-dimethylcyclopropanecarboxylate (from the triphenylphosphine dichloride generated in the reaction) and another side product with a cleaved cyclopropane ring were also found[8]. Under conditions for radiosynthesis[9], methyl-(1*R*-*trans*)-caronaldehyde behaved similarly. The same work[8,9] also revealed that (1*R*-*cis*)-caronaldehydes gave insignificant yields of the desired Wittig products. Some improvements in this difficult conversion (again with carbon tetrachloride and triphenylphosphine) have recently been reported[10].

Salmond[11] has recently described a method for preparing 1,1-dichloro-1-alkenes from aldehydes using dichloromethylenetris[dimethylamino]-phosphorane (DTDP). This ylid was generated in dichloromethane solution by the interaction of bromotrichloromethane with hexamethylphosphorous triamide.

It was therefore of interest to investigate the reaction of caronaldehydes with DTDP and to assess its usefulness to pyrethroid synthesis. After comparing various procedures



(Table), we have found that the acid moiety of permethrin (as the ethyl ester 3) can readily be synthesized by a modification of Salmond's method. With the reaction conditions optimized, side-product formation was minimal and the Wittig product contained the same *cis-trans* isomer ratio as the starting caronaldehyde.



Ozonolysis of ethyl (±)-*cis,trans*-chrysanthemate (**1**) in dichloromethane solution gave ethyl-(±)-*cis,trans*-caronaldehyde[12] (**2**) in yields ranging from 75–80%. This procedure[13] compared favorably with other known methods for preparing caronaldehydes from chrysanthemates (ozonolysis in methanol[14] or acetic acid[15]; cleavage with osmium tetroxide/sodium periodate[10,16]). Integration of the ^{1}H-N.M.R. signals at $\delta = 9.8$ and 9.6 ppm (aldehyde protons[10,15]) showed 30% *cis*-**2** and 70% *trans*-**2**. An isomer ratio of 33% *cis* to 67% *trans* was found by analytical G.L.C.

The isolated products from the Wittig reactions were identified as isomeric mixtures of ethyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (**3**) by comparison of ^{1}H-N.M.R. spectra with those reported[7,17] for (±)-*cis*-**3** and (±)-*trans*-**3**. Authentic samples of (±)-*cis*-**3** and (±)-*trans*-**3** were obtained by transesterifying permethrin with ethanol under the influence of potassium cyanide[18] followed by separation of the isomers by G.L.C. By G.L.C., T.L.C., and spectral evidence, samples of **3** from both routes were identical, except in the ratio of isomers.

In summary, the Wittig reaction employing DTDP provides a convenient, small-scale synthesis of the 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid moiety of synthetic pyrethroids. Possibilities also exist for introducing a labelled atom into the dichlorovinyl group and for preparing a required stereoisomer of permethrin from optically pure chrysanthemic acids now available from industry.

Ethyl-(±)-*cis,trans*-caronaldehyde (Ethyl 2,2-Dimethyl-3-formylcyclopropanecarboxylate) (2):

A solution of ethyl (±)-*cis,trans*-chrysanthemate (**1**; K and K 13933; 14.72 g, 75 mmol) in dichloromethane (300 ml) is ozonized according to a literature method[13]. The resulting mixture is flushed with nitrogen gas for 1 h and triphenylphosphine (18 g) is added. After the reaction mixture is at room temperature, it is concentrated on a rotary evaporator. The resulting white semi-solid is stirred with hexane, filtered, and the precipitate is washed well with ether. The combined filtrates are concentrated on the rotary evaporator and the crude product is distilled in vacuo; yield: 10.03 g (79%); b.p. 57–59 °C/0.2 torr (Ref.[21], b.p. 50–63 °C/0.08 torr for

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Table. Dichlorovinylation of Ethyl (±)-*cis,trans*-2,2-Dimethyl-3-formylcyclopropanecarboxylate (**2**) by Wittig Reactions

Quantity of reactants [mmol]					Reaction conditions	Solvent	Yield [%][a]	Ratio[b] *cis*-**3**/*trans*-**3**
2	CCl_4	$BrCCl_3$	$(C_6H_5)_3P$	$[(H_3C)_2N]_3P$				
6.8	8.2	—	13.6	—	0 °C/1 h, 60 °C/2 h[19]	—	31[c]	[d]
10.5	—	28	21	—	0 °C/4 h, 20 °C/18 h[4]	benzene	47[e]	[d]
5	—	5	—	11	−78 °C/4 h, 20 °C/16 h[11]	CH_2Cl_2	58[f]	30:70
5	—	5	—	11	−10 °C/70 h[11]	CH_2Cl_2	42[f]	28:72
5	7.5	—	—	16.5	−10 °C/3 h[20]	CH_2Cl_2	46[f]	49:51
5	—	7.5	—	16.5	−10 °C/3 h[11]	CH_2Cl_2	80[f]	34:66
5	—	10	—	22	−10 °C/20 h[11]	CH_2Cl_2	80[f]	32:68

[a] The yields are based on products isolated by column chromatography (silica gel with hexane as eluent).

[b] This ratio was determined by analytical G.L.C. (5% OV-210, 1.2 m, 110 °C) on samples from the silica gel column.

[c] A mixture was obtained after column chromatography (53% of **3**) which also contained ethyl 3-dichloromethyl-2,2-dimethylcyclopropanecarboxylate:
M.S. (70 eV) for $C_9H_{14}Cl_2O_2$ (Cl = 35): *m/e* (relative intensity) = 224 (M^+, 0.4), 189 (9), 179 (15), 151 (21), 148 (12), 141 (100).

[d] Could not be accurately determined because of interferences from side products.

[e] The yield of distilled product. G.L.C. analysis (5% OV-101, 1.2 m, 120 °C) showed **3** (54%) in addition to five side products.

[f] These samples were ~90% pure by G.L.C. Single bulb-to-bulb distillations gave **3** of greater than 98% purity.

(±)-*trans*-**2**); G.L.C. (5% OV-101, 1.2 m, oven temperature 120 °C) shows two peaks in a ratio of 67% to 33%.

I.R. (neat): $\nu = 1720\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 9.80$ (d, 0.3 H, —CHO of *cis* isomer, $J = 6$ Hz), 9.60 ppm (m, 0.7 H, —CHO of *trans* isomer).

Ethyl (±)-*cis,trans*-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (3); General Wittig Procedure (entry 6 in Table):
Under anhydrous conditions, a mechanically stirred solution of ethyl (±)-*cis,trans*-2,2-dimethyl-3-formylcyclopropanecarboxylate (**2**; 851 mg, 5 mmol) in dichloromethane (100 ml, distilled from phosphorus pentoxide) is cooled to −10 °C (argon atmosphere) and bromotrichloromethane (1.485 g, 7.5 mmol) is added. Hexamethylphosphorous triamide (3.0 g, 90% pure, 16.5 mmol) in dry dichloromethane (100 ml) is added by syringe during 30 min. After stirring the reaction mixture for 3 h, the mixture is allowed to approach room temperature and is poured into hexane (250 ml) and water (50 ml). The upper organic layer is washed with water (saturated with NaCl), 0.1 normal hydrochloric acid, again with water, then dried ($MgSO_4$), and concentrated. The residue is passed through a small column of silica gel (1.2 × 7 cm of silicAR cc-7) eluting with hexane (30 ml). The colorless hexane eluent is evaporated to give the product; yield: 953 mg (80%); b.p. 52–54 °C/0.1 torr (Ref.[17], b.p. 30–70 °C/0.5 torr for (±)-*cis,trans*-**3**); after distillation, G.L.C. analysis (5% OV-101, 1.2 m, 120 °C) shows one main component (98.5%) with a retention time of 9.1 min. Pure samples of *cis*-**3** (retention time 15 min) and *trans*-**3** (retention time 20 min) are collected by preparative G.L.C. (10% OV-210, 1.8 m, 100 °C).
$C_{10}H_{14}Cl_2O_2$ (237.1)

I.R. (neat): $\nu = 1725\ cm^{-1}$ (for both isomers).

M.S. (70 eV) for (±)-*cis*-**3** (Cl = 35): *m/e* (relative intensity) = 236 (M^+, 8), 201 (45), 191 (19), 173 (17), 163 (100).

^{1}H-N.M.R. for (±)-*cis*-**3** ($CDCl_3$): $\delta = 6.28$ (d, 1 H_{vinyl}, $J = 8$ Hz); 4.10 (q, 2 H, O—CH_2—CH_3, $J = 7$ Hz); 1.60–2.23 (m, 2 $H_{cyclopropyl}$); 1.27 [s, 6 H, $C(CH_3)_2$]; 1.27 ppm (t, 3 H, O—CH_2—CH_3, $J = 7$ Hz).

M.S. (70 eV) for (±)-*trans*-**3** (Cl = 35): *m/e* (relative intensity) = 236 (M^+, 3), 201 (27), 191 (17), 173 (11), 163 (100).

^{1}H-N.M.R. for (±)-*trans*-**3** ($CDCl_3$): $\delta = 5.62$ (d, 1 H_{vinyl}, $J = 8$ Hz); 4.13 (q, 2 H, O—CH_2—CH_3, $J = 7$ Hz); 2.23 (dd, 1 $H_{cyclopropyl}$, $J = 6$ Hz, 8 Hz); 1.58 (d, 1 $H_{cyclopropyl}$, $J = 6$ Hz); 1.29 (s, 3 H, H_3C—C—CH_3); 1.27 (t, 3 H, O—CH_2—CH_3, $J = 7$ Hz); 1.18 ppm (s, 3 H, H_3C—C—CH_3).

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