Synthesis of A Cyclopropane Ring Fluorinated Pyrethroid Derivative

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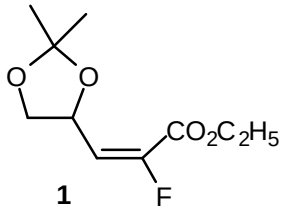
The synthesis of pyrethroids has received considerable attention because of their excellent activity against a wide range of insect pests and their non-persistence in the environment[1,2]. Our investigations into the development of fluorinated synthons led us to the synthesis of the first pyrethroid containing a fluorine atom in the cyclopropane ring. The results of the synthesis are described in this letter.

Previously we described the synthesis of ethyl 2-fluoro-(S)-4,5-dihydroxy-4,5-O-isopropylidene-(*E*)-2-pentenoate (**1**) and its conversion to a synthetically useful lactone[3]. Now we present the conversion of **1** to the ring-fluorinated ester component of deltamethrin (**6**), one of the most widely applied synthetic pyrethroids[1].



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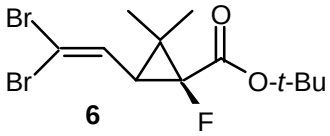

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The synthesis of **6** from **1** is shown in Scheme 1. Cyclopropanation of **1** follows methods developed by Corey, *et. al.* [4] and Krief, *et. al.* [5] The reaction requires excess t-butyllithium in order to achieve reasonable yields of cyclopropanation, but the ethyl ester function converts into a t-butylketone **2**. Removal of the ketal with aqueous Dowex 50W-X8 followed by periodate oxidation of the glycol **3** furnished the fluorocaronaldehydic ketone **4** in excellent overall yield. The dibromovinyation step followed smoothly from a procedure described by Topolski in which triethylamine is used as a base with

triphenylphosphine-carbon tetrabromide to provide **5** in 62 % yield[6]. The desired ester **6** was obtained in 70 % yield from **5** in a Baeyer-Villiger oxidation with trifluoroperacetic acid[7].

Detailed investigations into insecticidal activity are in progress. Preliminary results show significant activity for **6**.

Experimental

Nuclear magnetic resonance spectra were recorded on a Varian Unity plus 300 MHz NMR spectrometer. Proton spectra were recorded at 300 MHz and are referenced to tetramethylsilane (δ = 0.00 ppm). Carbon spectra were recorded at 75.46 MHz and are referenced to tetramethylsilane (δ = 0.00 ppm). Fluorine spectra were recorded at 282.3 MHz and are referenced to trifluoroacetic acid (δ = 0.00 ppm). The solvent used for spectroscopy was deuteriochloroform. All reagent solvents were dried before use. *Hazard.* α–Fluoroacid derivatives may be toxic.

1-Fluoro-2,2-dimethyl-3-(S)-(1,2-dihydroxyethanyl)-1,2-O-isopropylidene-(*E*)-cyclopropanyl t-Butyl Ketone (2).

tert- Butyllithium (1.7 M, 10 mL in hexanes) was added to a solution of diphenylisopropylsulfonium tetrafluoroborate (5.74 g, 15 mmol) in 100 mL of dry THF at - 78 ^{o}C. The mixture became orange in color and a solution of **1** (1.08 g, 5 mmol) in 10 mL of THF was added. The mixture was stirred at -78 ^{o}C for 6 hr and then allowed to warm to room temperature over 12 hr. The mixture was quenched with water (50 mL), extracted with ether and the ether was dried over sodium sulfate. After concentration and column chromatography (200-425 mesh, hexane/ethyl acetate, 19:1) compound **2** was obtained as a clear oil (0.62 g, 48 %). δ_H 1.03 (d, 2-CH_3, J = 2.1 Hz), 1.17 (s, t-butyl), 1.33 (s, 2-CH_3), 1.34, 1.42 (s, ketal CH_3), 1.47 (dd, J = 24, 9 Hz, H_3),3.58 (dd, J = 8.3, 6.5 Hz), 4.04 (dd, J = 8.3, 6.5), 4.46-4.38 (m); δ_C 14.42 , 20.90 , 25.50 (m), 26.94 , 31.21 , 41.9 (d, J = 9.4 Hz) , 44.36 (d, J = 4.7 Hz), 68.98 , 71.49 , 88.98 (J = 293.3 Hz), 108.98 ,

210.7 (d, J = 23.6 Hz)[8]; δ_F -106.8 (d, J = 23.1 Hz). Anal. Calcd for $C_{15}H_{25}FO_3$: C, 66.18; H, 9.19; F, 6.99. Found: C, 66.30; H, 9.16; F, 7. 12.

1-Fluoro-2,2-dimethyl-3-(S)-(1,2-dihydroxyehtanyl)-(*E*)-cyclopropyl t-Butyl Ketone (3).

A mixture of **2** (0.27 g, 1.0 mmol) in 5 mL of methanol, 1 mL of water and 50 mg of Dowex 50W-X8 was stirred at room temperature for 20 hr. Longer times caused lactone formation. After removal of the Dowex and concentration of the mixture, **3** (0.23 g, 97 %) was obtained in sufficient purity for conversion to **4**. δ_H 1.05 (d, J = 1.8 Hz), 1.15 (d, J = 1.5 Hz), 1.31 (d, J = 2.7 Hz), 1.42 (dd, J = 23.3, 10.1 Hz), 3.41 (m), 3.56 (dd, J = 11.1, 2.7), 4.15 (m): δ_F -105.9 (d, J = 26.0 Hz).

1-Fluoro-2,2-dimethyl-3-formyl-(*E*)-cyclopropyl t-Butyl Ketone (4).

A mixture containing **3** (0.27 g, 1.0 mmol), 5 mL of methylene chloride, sodium periodate (0.5g previously dissolved in 5 mL of water), and 5 mg of tetra-n-butylammonium bromide was allowed to stir at room temperature for 1.5 hr. The organic layer and one more methylene chloride extract were combined and dried over sodium sulfate, and then concentrated on a rotary evaporator. After chromatography on silica gel, **4** (0.19 g, 94%) was obtained as a clear colorless oil. δ_H 1.18 (s), 1.24 (d, J = 2.7 Hz), 1.34 (d, J = 2.1 Hz), 1.99 (dd, J = 21.4, 5.7 Hz), 9.56 (dd, J = 6.3, 6.1 Hz); δ_C 14.84, 20.12 (d, J = 10.9 Hz), 25.36, 33.74 43.85 (d, J = 4.4 Hz), 46.34 (d, J = 10.2 Hz), 93.27 (d, J = 250.8 Hz), 195.7, 208.6 (d, J = 22.5 Hz); δ_F -99.4 (d, J = 23 Hz). Anal. Calcd for $C_{10}H_{17}FO_2$: C, 66.0; H, 8.50; F, 9.50. Found: C, 65.88; H, 8.59; F, 9.24.

1-Fluoro-2,2-dimethyl-3-(2,2-dibromovinyl)-(*E*)-cyclopropanyl t-Butyl Ketone (5).

A solution of triphenylphosphine (2.6 g, 10.0 mmol) and carbon tetrabromide (1.66 g, 5 mmol) in anhydrous methylene chloride (25 mL) was heated at reflux for 1.5 hr and then cooled to O ^oC. Aldehyde 4 (0.094 g, 5.0 mmol) and 5 mL of anhydrous methylene

chloride was added dropwise and the mixture was stirred at 0 ^{o}C for 1 hr. Triethylamine (2.0 mL) was added and stirring was continued for 15 min. The organic layer was combined with two 50 mL methylene chloride extracts and dried over sodium sulfate. After concentration and column chromatography (silica gel, hexane/triethylamine, 19:1) two times, pure 5 (0.53 g, 62 %) was obtained as an oil. δ_H 1.04, (d, J + 2.1 Hz), 1.20 (s), 1.36 (d, J = 2.4 Hz), 2.12 (dd, J = 20.9, 8.3 Hz), 6.66 (dd, J = 8.3, 2.3 Hz); δ_C 15.15, 20.97. 25.59. 33.32. 42.27 (d, J = 13.1 Hz), 44.79 (d, J = 4.5 Hz), 89.87 (d, J = 245.3 Hz), 90.41, 131.6, 209.5 (d, J = 23.4 Hz); δ_F -104.7 (d, J = 21.7 Hz). Anal. Calcd for $C_{12}H_{17}Br_2FO$: C, 41.62; H, 4.91; F, 5.49. Found: C, 41.82; H, 4.99; F, 5.68.

1-Fluoro-2,2-dimethyl-3-(2,2-dibromovinyl)-(*E*)- cyclopropane Carboxylic Acid t-Butyl Ester (6).

A solution of peroxytrifluoroacetic acid was prepared by dropwise addition of trifluoroacetic anhydride (302.4 mg, 1.44 mmol) to a suspension of 90% hydrogen peroxide (32.8μL, 1.20 mmol) in cold methylene chloride (500 μL). This mixture was added over 20 min to a stirred suspension of dry, finely ground disodium hydrogen phosphate (520.1 mg, 3.66 mmol) in a mixture of methylene chloride (1 mL) and **5** (71.2 mg, 0.20 mmol). The solution boiled vigorously during the addition. The mixture was heated at reflux for 24 hr, and the insoluble salts were removed by filtration. The salts were washed with methylene chloride, and all methylene chloride solutions were combined. The organic solution was washed with 10% sodium bicarbonate and dried over sodium sulfate. Concentration gave a mixture containing 25 mg of **6** and 45 mg of **5** (estimated from NMR spectroscopy). Thin layer chromatography (silica gel) furnished a pure sample of **6** (19 mg, 70 % based on recovered **5**). δ_H 1.04, 1.36 (s, CH_3), 1.20 (s, t-butyl), 2.12 (dd, CH), 6.21 (d, vinyl); δ_C 15.1, 20.9 (CH_3), 25.6 (t-butyl), 40.0 (d, J = 12.3 Hz, cyclopropyl), 45.1 (d, J = 5.0 Hz cyclopropyl), 53.2 (t-butyl), 90.0 (d, J = 248.2 Hz, CF), 90.1 (vinyl-Br), 131.8 (vinyl), 208.1 (C=O, d, J = 24 Hz); δ_F -123.1 (d, J = 21 Hz). Anal. Calcd for $C_{12}H_{17}Br_2FO_2$: C, 37.78; H, 4.70; F, 5.25. Found: C, 37.77; H, 4.59; F, 5.04.

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