Synthesis of an \( M + 7 \) stable isotope of \( \gamma \)-cyhalothrin

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\( \gamma \)-Cyhalothrin is a single isomer, synthetic pyrethroid insecticide. This material was originally developed and marketed by Pytech Chemicals, a joint venture between Dow AgroSciences and Cheminova A/S. Cheminova A/S now wholly owns Pytech Chemical. As a part of registration studies, there was a need for a stable isotope of \( \gamma \)-cyhalothrin to serve as an internal standard. This paper will discuss the 11-step synthesis that was used to prepare an \( M + 7 \) stable isotope of \( \gamma \)-cyhalothrin by utilizing triethyl phosphonoacetate-\( \text{d}_2 \) and acetone-\( \text{d}_6 \) to incorporate deuterium into the molecule. In the end, the diastereomers were separated by preparative reverse-phase HPLC to give \( \gamma \)-cyhalothrin-\( \text{d}_7 \) in an overall yield of 6%.

**Keywords:** \( \gamma \)-cyhalothrin; \( \gamma \)-cyhalothrin-\( \text{d}_7 \); pyrethroid; insecticide; stable isotope

**Introduction**

Mass spectrometry is often used for the detection and/or quantitation of test materials in toxicology and metabolism studies. For quantitative analysis, an internal standard is required. One type of internal standard that can be used for this purpose is an analog of the test material that contains at least one or more stable isotopes (\( ^{13}\text{C}, \ ^{15}\text{N}, \ ^{2}\text{H} \) or \( ^{18}\text{O} \)). It is desirable to have the mass of the stable isotope standard at least three mass units higher than that of the test substance to aid the mass spectral analysis. During the course of registration studies of \( \gamma \)-cyhalothrin, a request was made for a stable isotope of this material with at least three mass units higher than the parent compound.

We believed that a single isomer of cyhalothrin could be prepared by using a route that was very similar to the route used to prepare carbon-14 labeled \( \gamma \)-cyhalothrin.\(^1\) This route would involve Horner–Wadsworth–Emmons olefination\(^2\) to transform acetone-\( \text{d}_6 \) into a deuterium labeled allylic alcohol, 1 (Scheme 1). The allylic alcohol could then be converted to a diazoester, 2, by coupling with a protected glycine derivative. The diazoester could then undergo intramolecular cyclopropanation to give the lactone, 3. Metal mediated \( \beta \)-elimination of the lactone would provide the desired cyclopropanecarboxylic acid, 4, having the Z-olefin geometry and cis cyclopropane stereochemistry found in \( \gamma \)-cyhalothrin.

We decided to incorporate deuterium into the 2-position of triethyl phosphonoacetate to avoid the proton scrambling. This would eventually lead to an \( M + 7 \) stable isotope of \( \gamma \)-cyhalothrin. This was readily accomplished by treating triethyl phosphonoacetate with a catalytic amount of potassium carbonate in deuterium oxide.\(^3\) Following distillation, triethyl phosphonoacetate-\( \text{d}_2 \) (6) was isolated in good yield and >98% deuterium incorporation (Scheme 2). Horner–Wadsworth–Emmons olefination of triethyl phosphonoacetate-\( \text{d}_2 \) and acetone-\( \text{d}_6 \) gave the ester, 7, in good yield. The ester was reduced to the allylic alcohol, 8, with the use of lithium aluminum hydride and then oxidized to the aldehyde, 9, with manganese oxide. Treatment of the aldehyde with 2,2-dichloro-1,1,1-trifluoroethane and potassium tert-butoxide at low temperature gave alcohol 10 in good yield.\(^4\) The alcohol was coupled with \( \text{t-Boc} \) protected glycine to give the glycinate ester, 11 in nearly quantitative yield. The protecting group was removed with dilute hydrochloric acid to give the amine hydrochloride salt, 12, which was then diazotized with sodium nitrite in the presence of sodium dihydrogenphosphate to give the diazoester, 13, in good overall yield.\(^5\)

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Next, the diazoester 13 was treated with the homogeneous copper cyclopropanation catalyst 6 in refluxing 1,2-dichloroethane to give the bicyclic lactone, 15, in good yield (Scheme 3). Zinc metal mediated β-elimination of the bicyclic lactone gave the racemic carboxylic acid 16, as a 90:10 mixture of Z/E olefin isomers. It has been shown previously that the isomer ratio can be increased to >98% Z by multiple recrystallizations from hexanes. However, recrystallization gave unacceptably low mass recovery.

We were subsequently able to show the four stereoisomers of 16 that could be separated by preparative normal-phase HPLC. With this result in hand, the crude deuterium labeled carboxylic acid 16 was coupled with the optically active cyanohydrin 17 to give a high yield of 18 as a mixture of four stereoisomers (Scheme 4). This mixture was subjected to preparative normal-phase HPLC using hexanes and ethyl acetate as the eluent. Although this method failed to cleanly separate all four isomers, it was able to provide the desired product, γ-cyhalothrin-d-f (18), in >97% purity.

**Experimental**

Triethyl phosphonoacetate, deuterium oxide, and acetone-d6 were purchased from Aldrich. N-t-Boc-glycine was purchased from Advanced

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**Scheme 1.** Synthetic strategy for synthesis of a stable isotope of γ-cyhalothrin from acetone-d6.

**Scheme 2.** (a) 3 mol-% K2CO3, D2O; (b) NaH, acetone-d6, Et2O; (c) LiAlH4, Et2O, 0°C; (d) MnO2, CH2Cl2; (e) Cl2CHCF3, t-BuOK, –17°C; (f) N-t-Boc-glycine, disopropylcarbodiimide, cat. DMAP, toluene; (g) 4 M HCl, 1,4-dioxane; (h) 6 M NaNO2, sodium dihydrogenocitrate, H2O, CH2Br2.

**Scheme 3.** (a) 1,2-Dichloroethane, reflux; (b) Zn(0), methanol, reflux.

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ChemTech and 2,2-dichloro-1,1,1-trifluoroethane was purchased from Matrix Scientific. (S)-3-Hydroxy-3-phenoxymethyleneneacetonitrile, 17, was obtained from Cheminova. Nuclear magnetic resonance spectra were recorded on a Varian Gemini spectrometer (300 or 600 MHz). Chemical shifts are given as δ values with reference to tetramethylsiline as internal standard. Infrared spectra were recorded using a Digilabs FTS-40 spectrometer. Mass spectra were obtained using either a Hewlett-Packard HP-5985 gas chromatography (GC)/mass spectrometry (MS) or a Micromass ZMD single quadrupole liquid chromatography/MS.

Triethyl phosphono[2,2-2H2]acetate (6)

To a mixture of triethyl phosphonoacetate (30.0 mL, 150 mmol) and deuterium oxide (12.0 mL, 675 mmol) under N2 at room temperature was added potassium carbonate (622 mg, 4.50 mmol). The solution was stirred, and concentrated in vacuo. The crude product was purified by bulb-to-bulb distillation (90–100°C, 35–45 mmHg) to give 9.80 g of the desired product as a colorless liquid (80% yield). 1H NMR (300 MHz, CDCl3) δ 4.14 (q, J = 7.0 Hz, 2H), 1.27 (t, 3H, J = 3.0 Hz), 1.31 (bs, 1H); MS (EI) 135 (M+), 107, 90 (base), 62; IR (neat) 3328 (br), 2924, 2228, 2196, 1651, 1422, 1266, 1018, 984 cm−1.

Ethyl 3-methylbut-2-enoate-d6 (7)

A solution of triethyl phosphonoacetate-d6 6 (21.0 g, 93.0 mmol) in 20 mL anhydrous ether was added dropwise via an addition funnel to a suspension of sodium hydride (4.08 g, 102 mmol, 1.10 equiv, 60% dispersion in mineral oil, washed with 2 × 10 mL hexanes) in 80 mL anhydrous ether under N2 at room temperature. The reaction mixture was stirred 1 hour at room temperature then cooled to 0°C at which time acetone-d6 (8.2 mL, 112 mmol, 1.2 equiv) was added dropwise via syringe. Upon completion of the addition, the reaction was allowed to warm at room temperature. The reaction was stirred for 1 hour at room temperature then quenched with water (50 mL). The layers were separated and the organic phase was washed with water (2 × 50 mL) then brine (50 mL). The combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo. The resulting liquid was purified by bulb-to-bulb distillation (90–100°C, 35–45 mmHg) to give 4.59 g of the desired product as a colorless liquid (78% yield). 1H NMR (300 MHz, CDCl3) δ 4.14 (q, J = 3.0 Hz, 2H), 1.27 (t, 3H, J = 3.5 Hz); MS (EI) 135 (M+), 107, 90 (base), 62; IR (neat) 2983, 1714, 1632, 1229, 1107, 1049 cm−1.

3-Methylbut-2-en-1-ol-d7 (8)

Lithium aluminum hydride (2.66 g, 70.0 mmol) was placed in a flame-dried, three-neck, round-bottom flask under N2 along with 45 mL anhydrous diethyl ether and cooled to −78°C. 3-Methyl-2-butenolic acid ethyl ester 7 (9.50 g, 70.0 mmol) was added dropwise via an addition funnel. After 1 hour of stirring at −78°C, the reaction was warmed to 0°C and quenched by the dropwise addition of saturated NH4Cl. The layers were separated and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic phases were washed with water (2 × 60 mL) then brine (50 mL). The organic phase was dried over MgSO4, filtered, and concentrated in vacuo. The resulting liquid was purified by bulb-to-bulb distillation (80–100°C, 35–45 mmHg) to give 4.59 g of the desired product as a colorless liquid (70% yield). 1H NMR (300 MHz, CDCl3) δ 4.11 (d, 2H, J = 3.0), 1.31 (bs, 1H); MS (EI) 93 (M+), 75 (base), 56; IR (neat) 3328 (br), 2924, 2228, 2196, 1651, 1422, 1266, 1018, 984 cm−1.

Scheme 4. (a) Diisopropylcarbodiimide, cat. DMAP, toluene; (b) preparative normal-phase HPLC.
3-Methylbut-2-enal-\textit{d}_7 (9)

Manganese dioxide (21.3 g, 245 mmol, 5 equiv.) was added to 3-methyl-2-butenol-\textit{d}_8 (4.59 g, 49.0 mmol) in 100 mL methylene chloride at room temperature. The reaction mixture was stirred for reflux for 20 hours then cooled at room temperature and filtered over Celite, washing with methylene chloride. The crude material was purified by bulb-to-bulb distillation (75–90 °C, 35–45 mmHg) to give 3.43 g of the desired product as a colorless liquid (75% yield).\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) ð 9.53 (t, 1H, J = 4.5); MS (EI) 91 (M\textsuperscript{+}), 75, 62, 58; IR (neat) 3442, 2923, 1781, 1449, 1273, 1234, 1128, 1018, 913 cm\textsuperscript{-1}.

2,2-Dichloro-1,1,1-trifluoro-5-methylhex-4-en-3-ol-\textit{d}_7 (10)

A solution of potassium tert-butoxide (2.47 g, 22.0 mmol) in 40 mL anhydrous THF was added dropwise via an addition funnel to a solution of 3-methyl-2-butenal-\textit{d}_9 (1.80 g, 20.0 mmol) and 2,2-dichloro-1,1,1-trifluoroethane (2.10 mL, 20.0 mmol) in 40 mL THF under N\textsubscript{2} at ~78 °C. The reaction was stirred for 2 hours at ~78 °C then quenched by the dropwise addition of saturated NH\textsubscript{4}Cl, maintaining an internal temperature less than ~50 °C. The resultant mixture was allowed to warm to ~30 °C then poured onto saturated NH\textsubscript{4}Cl, maintaining an internal temperature less than ~50 °C. The combined organic phases were washed with water (2 × 60 mL) then brine (60 mL). The organic layers were dried over MgSO\textsubscript{4}, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography (15% EtOAc/Hexanes) to give 0.28 g of the desired product as a pale yellow liquid (67% yield).\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) ð 4.84 (d, 1H, J = 3.0), 2.16 (d, 1H, J = 4.5); MS (EI) 242 (M+), 226, 151, 132, 92 (base); IR (neat) 3390 (br), 1651, 1389, 1257, 1193, 1049, 846 cm\textsuperscript{-1}.

1-(1,1-Dichloro-2,2,2-trifluoroethyl)-3-methylbut-2-enyl N-(tert-butoxycarbonyl)glycinate-\textit{d}_7 (11)

N-t-Boc glycine (1.23 g, 7.0 mmol), 2,2-dichloro-1,1,1-trifluoro-5-methyl-hex-3-ol-\textit{d}_10 (1.70 g, 7.0 mmol) and a catalytic amount of 4-fluorophenyl methyl chloroformate (0.50 mL, 3.20 mmol) in 25 mL methanol was heated to reflux under N\textsubscript{2}. After stirring for 4 hours at room temperature, the reaction mixture was filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography to give 1.53 g of the desired product as a yellow solid (78% yield).\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) ð 4.62 (s, 1H), 4.84 (d, 1H, J = 4.5); MS (EI) 226 (M+), 204, 167, 147, 132, 104, 85, 73, 57; IR (KBr pellet) 3125, 2979, 1702, 1449, 1273, 1234, 1128, 1018, 913 cm\textsuperscript{-1}.

3-[(12Z)-2-Chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylic acid-\textit{d}_7 (16)

A mixture of bicyclic lactone 15 (2.10 g, 7.40 mmol) and zinc dust (382 mg, 5.89 mmol) in 25 mL methanol was heated to reflux under N\textsubscript{2}. After 8 hours, additional zinc dust was added (250 mg, 3.82 mmol), and the reaction mixture was stirred overnight at reflux (~16 hours). GC analysis indicated that the starting material remained, so a third portion of zinc dust (250 mg, 3.82 mmol) was added. After 1 hour stirring at reflux, GC analysis indicated that the starting material had been consumed. The reaction mixture was filtered over Celite, washing with methanol, then concentrated in vacuo. The residual oil was stirred with 0.5 M HCl (20 mL) and CH\textsubscript{2}Cl\textsubscript{2} (20 mL). The phases were separated, and the aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 20 mL). The combined CH\textsubscript{2}Cl\textsubscript{2} extracts were dried over MgSO\textsubscript{4}, filtered, and concentrated in vacuo to give 1.64 g (89% crude yield) of the desired product as an off-white solid.\textsuperscript{1}H NMR showed an approximately 90/10 \(Z/S\) isomer ratio.\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) ð 10.68 (bs, 1H), 6.85 (s, 1H, Z isomer), 6.57 (s, 1H, E isomer), 1.98 (s, 1H); \textsuperscript{3}H NMR (CD\textsubscript{2}OD) ð 2.15 (br, 1D), 1.25 (br, 6D); MS (EI) 283 (M\textsuperscript{+}), 248, 204, 167, 147, 132 (base), 104, 85, 73, 57; IR (KBr pellet) 2323, 1731, 1257, 1204, 1078, 1041, 1022, 942, 888, 845, 752, 718 cm\textsuperscript{-1}.

(S)-Cyano(3-phenoxypyphenyl)methyl (1R,3R)-3-[(12Z)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylate-\textit{d}_7 ([\(\gamma\)-cyhalothrin-\textit{d}]-18

To a solution of carboxylic acid 16 (~90/10 Z/E, 800 mg, 3.20 mmol), (S)-\(\alpha\)-hydroxy-3-phenoxynbenzenecarboxonitrile 17 (722 mg, 3.20 mmol) and a catalytic amount of 4-N,N-dimethylaminopyridine (3 mg) in 12 mL toluene under N\textsubscript{2} at 0 °C was added 1,3-disopropylcarbodiimide (0.50 mL, 3.20 mmol) dropwise via syringe. Upon completion of addition,
the reaction mixture was allowed to warm at room temperature. After stirring for 1 hour, the reaction mixture was filtered over Celite, washing with toluene, and concentrated in vacuo to give 1.79 g of a yellow oil. After purification of the crude material by flash column chromatography (4% EtOAc/Hexanes), the fractions containing the desired product were combined and concentrated in vacuo to give 1.41 g of a colorless oil. A stock solution of the purified product in hexanes was prepared with a concentration of 100 mg/mL. Approximately 1.5 mL of this stock solution was loaded onto a preparative HPLC (approximately 150 mg/run). Ten consecutive preparative HPLC runs gave 428 mg of the desired diastereomer 18 as a white solid (Lot-1). This reaction was repeated on 918 mg of the carboxylic acid (16) to give an additional 449 mg of 18 (Lot-2). Lots 1 and 2 of 18 were combined to give a total of 877 mg of g-cyhalothrin-d7 (62% yield based on 1:1 mixture of diastereomers and 90/10 E/Z olefin isomer mixture of starting material). The 1H NMR, mass spectra, HPLC retention time and UV spectrum of g-cyhalothrin-d7 matched an unlabeled standard of g-cyhalothrin.

Conclusion

An M+7 stable isotope of g-cyhalothrin was prepared utilizing relatively inexpensive triethyl phosphonoacetate-d2 and acetone-d6 as starting materials. This 11-step synthesis, which included a preparative normal-phase HPLC separation of isomers, gave the desired target in an overall yield of 6%. In the end, 877 mg of g-cyhalothrin-d7 was prepared with a chemical purity of >97%. The stable isotope of g-cyhalothrin was obtained in sufficient quantity and isotopic purity to be used in method development studies related to the registration of this molecule.

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Conflict of Interest

The authors did not report any conflict of interest.

References
