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Research Article

Synthesis of (*S*)-cyano(3-phenoxyphenyl)methyl (1*R*,3*R*)-3-((1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate-1-^{14}C

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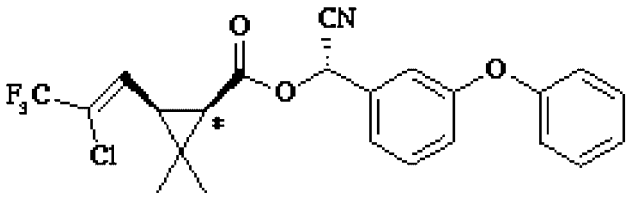
Abstract: γ-Cyhalothrin (**1a**), (*S*)-cyano(3-phenoxyphenyl)methyl (1*R*,3*R*)-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate, is a single-isomer, synthetic pyrethroid insecticide marketed by Pytech Chemicals GmbH, a joint venture between Dow AgroSciences and Cheminova A/S. As a part of the registration process there was a need to incorporate a carbon-14 label into the cyclopropyl ring of this molecule. A high yielding radiochemical synthesis of γ-cyhalothrin was developed from readily available carbon-14 labeled *N*-*t*-Boc protected glycine. This seven step synthesis, followed by a preparative normal phase HPLC separation of diastereomers, provided 21.8 mCi of γ-cyhalothrin-1-^{14}C (**1b**) with >98% radiochemical purity. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: γ-cyhalothrin; carbon-14; radiochemical synthesis; (*S*)-cyano(3-phenoxyphenyl)methyl (1*R*,3*R*)-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate-1-^{14}C

Introduction

γ-Cyhalothrin (**1a**) is the most active of the 16 possible isomers of cyhalothrin for the control of insects.[1] As such it is effective at lower use rates with less environmental impact compared to previous generation pyrethroids. To register this single isomer active ingredient a variety of metabolism and environmental fate studies needed to be conducted. These studies required that a carbon-14 label be incorporated into the cyclopropyl ring of this molecule. Therefore, a route was required that would incorporate a radiotracer in the cyclopropyl ring. This route needed to use a relatively inexpensive starting material and to provide all intermediates and the final product in high chemical yield and purity. This paper will discuss the route selection and radiochemical synthesis of cyclopropyl carbon-14 labeled γ-cyhalothrin (**1b**).



Results and discussion

Carbon-14 labeled glycine hydrochloride has previously been used in the synthesis of labeled pyrethroids.[2] However, this route relied on an intermolecular cyclopropanation reaction that led to predominately the trans geometrical isomer of the cyclopropane ring. An alternative synthesis that was proposed for incorporating carbon-14 into the cyclopropane ring of γ-cyhalothrin would start with *N*-*t*-Boc glycine-2-^{14}C (**2**, relatively cheap and commercially available) and rely on an intramolecular cyclopropanation reaction (Scheme 1). The resultant

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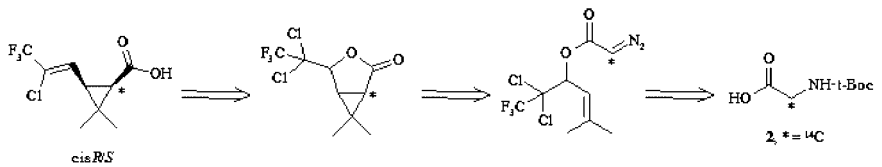
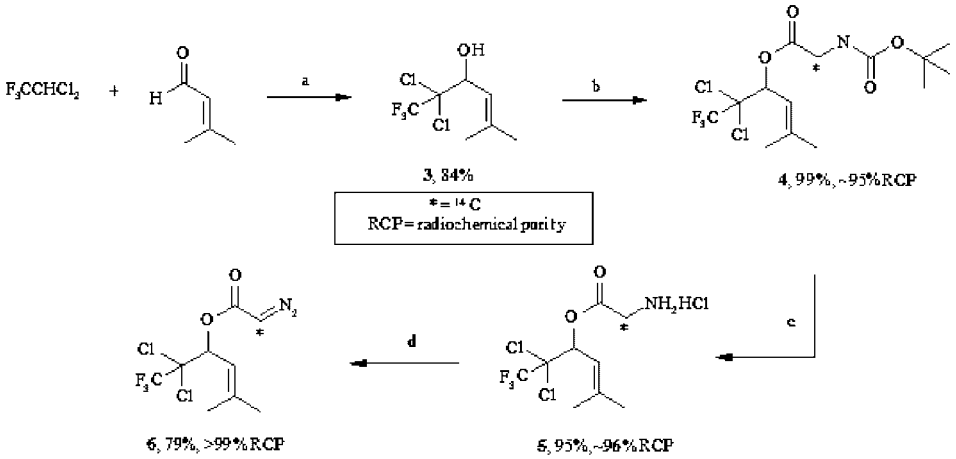


Scheme 1 Retrosynthetic route to required cyclopropanecarboxylic acid.



Scheme 2 (a) *t*-BuO$^-$Na$^+$, THF, −78°C; (b) *N*-*t*-Boc-glycine-2-^{14}C (2), *N*,*N*′-diisopropylcarbodiimide, toluene, cat. DMAP; (c) 4 M HCl, 1,4-dioxane; (d) 6 M $NaNO_2$, sodium dihydrogencitrate, H_2O, CH_2Br_2.

bicyclic lactone could then be transformed into the desired cyclopropanecarboxylic acid having a *Z*-olefin and *cis* stereochemistry about the ring via metal mediated β-elimination of the lactone. This route would provide only the desired cis stereochemistry about the cyclopropane ring. Similar chemistry has been used in our labs for the preparation of a deuterium labeled sample of cyhalothrin (unpublished work) and is documented in the literature for pyrethroid syntheses that did not bear a C-14 label.[3] This proposed route was verified and optimized on unlabeled material to ensure maximum recovery of radioactivity when the labeled material was used.

The first step in the synthesis of carbon-14 labeled γ-cyhalothrin was the preparation of allylic alcohol **3**, which was to be coupled with glycine derivative **2**. This was accomplished by reacting 3-methyl-2-butenal with 2,2-dichloro-1,1,1-trifluoroethane in the presence of sodium *t*-butoxide (Scheme 2).[4] This resulted in a high yield of the desired alcohol, 3, after distillation. Commercially available *N*-*t*-Boc-glycine-2-^{14}C (**2**) was then coupled with the allylic alcohol **3** with the aid of *N*,*N*′-diisopropylcarbodiimide to give the ester, **4**, in high yield and radiochemical purity. The *t*-Boc group of **4** was removed with dilute HCl in 1,4-dioxane to give a near quantitative yield of the amine hydrochloride salt, **5**. Treatment of the amine salt with sodium nitrite in a water/dibromomethane mixture, buffered at pH 3 with sodium dihydrogencitrate, gave a decent yield of the diazoester, **6**, in high radiochemical purity following column chromatography.[5]

Next, the intramolecular cyclopropanation of **6** was explored. The conditions that gave the highest yield of the bicyclic lactone **8**, with fewest side products, used a homogeneous copper catalyst **7**[6] in refluxing 1,2-dichloroethane (Scheme 3). Formation of the carbon-14 labeled *cis*-cyclopropanecarboxylic acid **9** from **8** was accomplished by refluxing the bicyclic lactone in methanol in the presence of zinc metal. While the literature describes the use of platinum on carbon in the presence of hydrogen gas to effect this transformation in high yield and selectivity (>97% *Z*),[7] we found the use of zinc metal in refluxing methanol to be more reproducible, giving higher overall yields with shorter reaction times. This resulted in a high yield of the carboxylic acid, which was obtained as a 90/10 mixture of *Z*/*E* isomers, as determined by HPLC analysis. The crude carboxylic acid was recrystallized four times from hexanes to give a moderate yield of

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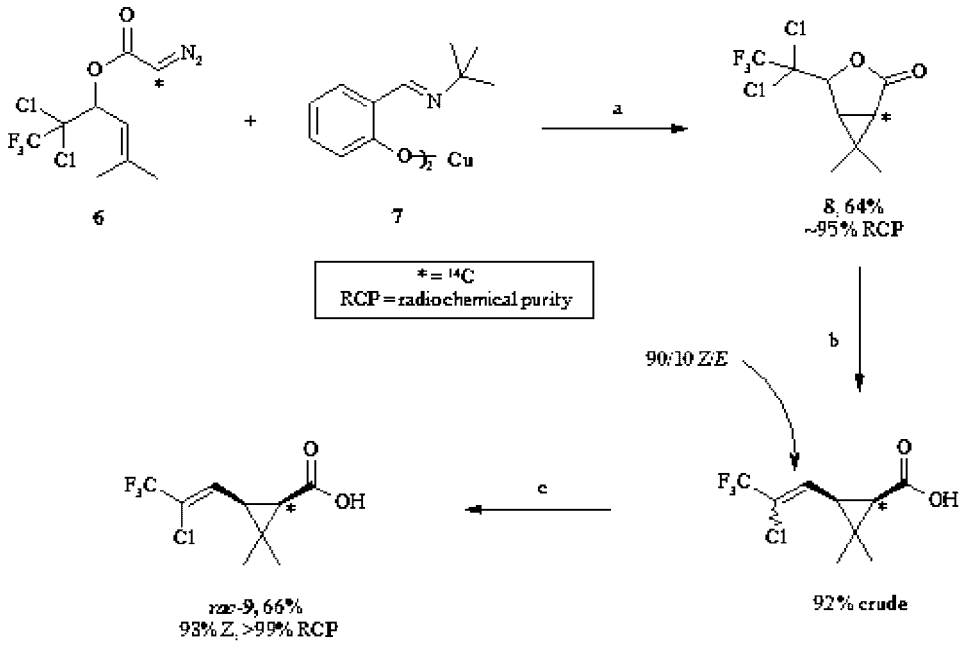
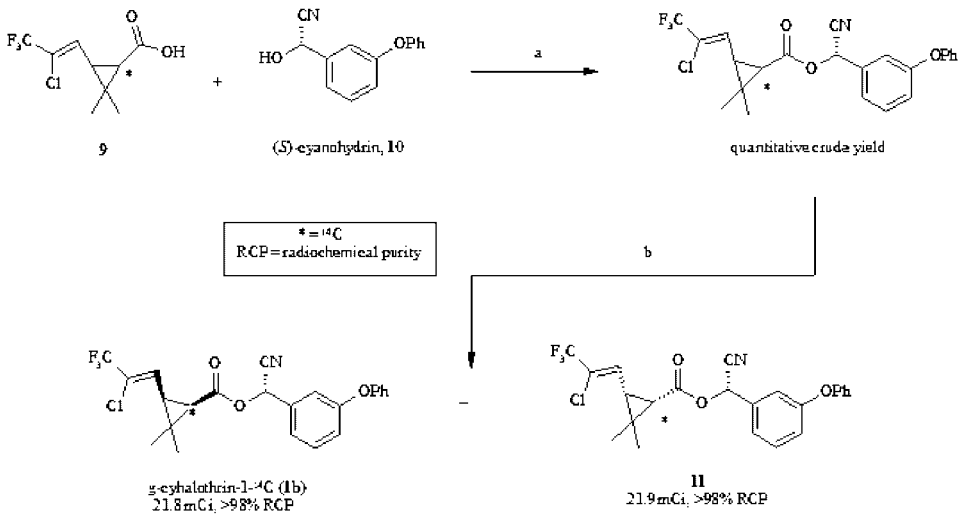


Scheme 3 (a) 10 mol% catalyst 7, 1,2-dichloroethane, reflux; (b) Zn(0), methanol, reflux; (c) recrystallized four times from hexanes.



Scheme 4 (a) *N,N*-diisopropylcarbodiimide, cat. DMAP, toluene; (b) normal phase preparative HPLC.

cyclopropanecarboxylic acid, **9**, which was >98% *Z* olefin isomer and >99% radiochemical pure.

The final stage of the synthesis of carbon-14 labeled γ-cyhalothrin (**1b**) was to couple the racemic cyclopropanecarboxylic acid **9** with the optically active cyanohydrin **10** and then separate the diastereomers. To this end, the carbon-14 labeled cyclopropanecarboxylic acid **9** was coupled with (2S)-hydroxy(3-phenoxyphenyl)ethanenitrile (**10**) with the aid of diisopropylcarbodiimide in toluene (Scheme 4). This gave a quantitative yield of the ester as a 1:1 mixture of diastereomers in high radiochemical purity. The diastereomers were separated by normal phase preparative HPLC. This yielded 21.8 mCi of

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γ-cyhalothrin-1-^{14}C (**1b**) in extremely high chemical and radiochemical purity. Also isolated was 21.9 mCi of the (1*S*,3*S*) diastereomer, **11**, in high chemical and radiochemical purity.

Experimental

General

2,2-Dichloro-3,3,3-trifluoroethane was purchased from Avacado Research Chemicals. 3-Methyl-2-butenal was purchased from Aldrich. (2*S*)-hydroxy(3-phenoxyphenyl) ethanenitrile was obtained from Cheminova. *N*-*t*-Boc-glycine-2-^{14}C was purchased from Amersham Pharmacia. Mass spectra were obtained using a Hewlett-Packard HP-5985 GC/MS. Nuclear magnetic resonance spectra were recorded on a Varian Gemini 300 spectrometer (300 MHz) using tetramethylsilane as an internal standard. Coupling constants (*J*) are given in hertz (Hz). Infrared spectra were recorded using a Digilabs FTS-40 spectrometer. Analytical HPLC was conducted on a Beckman System Gold HPLC with a 126 solvent module and a 168 UV detector equipped with a PDA and a β-RAM radioactivity detector from INUS. HPLC analysis, unless otherwise stated, were run on a 4.6 × 150 mm, 5 μm, 120 Å YMC ODS-AM column, using a linear gradient from 95% H_2O/5% acetonitrile to 95% acetonitrile/5% H_2O (each containing 0.5% acetic acid, v/v) and a flow rate of 1 ml/min.

2,2-dichloro-1,1,1-trifluoro-5-methyl-4-hexen-3-ol (3)

A solution of sodium *t*-butoxide (15.86 g, 165 mmol, 1.1 equivalents) in 50 ml of THF was added dropwise to a solution of 3-methyl-2-butenal (14.5 ml, 150 mmol) and 2,2-dichloro-3,3,3-trifluoroethane (24.16 g, 158 mmol, 1.05 equivalents) in 150 ml of THF, under N_2, while cooling in a dry ice/acetone bath (−78°C). The addition was done at such a rate to maintain the internal temperature below −75°C. After 60 min at −78°C, GC analysis showed 3–4% of the aldehyde starting material still present. The reaction was allowed to stir at −78°C for an additional 60 min (2 h total) and then quenched by the dropwise addition of saturated NH_4Cl (50 ml), keeping the temperature below −50°C. The resultant mixture was allowed to warm to −30°C, poured into 250 ml of saturated NH_4Cl and extracted with Et_2O (3 × 250 ml). The combined Et_2O extracts were washed with H_2O (3 × 200 ml), saturated NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give 36.00 g of a yellow oil. Distillation using a vacuum jacketed Vigreux column gave 29.94 g (84% yield) of the desired product as a colorless liquid: bp 66–72°C (1 mmHg) [lit.,[8] bp 65°–67°C (0.6 mmHg)]; ^{1}H NMR ($CDCl_3$): δ 5.40 (broad d, 1 H, *J*=8.1), 4.84 (dd, 1 H, *J*=7.5, 8.6), 2.14 (d, 1 H, *J*=6.9), 1.83 (d, 3 H, *J*=1.2), 1.78 (dd, 3 H, *J* = 1.2); MS(EI): 236(M^+), 221, 151, 127, 117, 101, 85 (base); IR(neat): 3384 (broad), 1673, 1446, 1381, 1256, 1198, 871 cm^{-1}.

1-(1,1-dichloro-2,2,2-trifluoroethyl)-3-methyl-2-butenyl N-(t-butoxycarbonyl)glycinate-2-^{14}C (4)

N-*t*-Boc-glycine-2-^{14}C (**2**) was received from Amersham Pharmacia (150.01 mCi, specific activity=24 mCi/mmol, 6.25 mmol) in a 5 ml conical vial with a rubber septum. Warm toluene was added to the vial (3 × 3 ml) and what dissolved was transferred, via cannula, to a 25 ml round bottom flask containing the allylic alcohol **3** (1.48 g, 6.25 mmol) and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (2–3 mg). The remaining glycine derivative was dissolved in CH_2Cl_2 (2 × 2 ml) and transferred to the reaction mixture. Diisopropylcarbodiimide (0.98 ml, 6.25 mmol) was added dropwise to the reaction mixture (slight exotherm and reaction turned cloudy), under N_2, at room temperature. After 60 min at room temperature, GC analysis indicated that all of the carboxylic acid starting material had been consumed. The reaction mixture was filtered through a plug of Celite in a 10 ml disposable pipet, washing with toluene. The filtrate was concentrated *in vacuo* (40–50°C) to give 2.438 g (99% yield) of the desired product as a colorless oil. Reverse phase HPLC analysis showed ∼95% radiochemical purity. MS(EI): 305/303 (M-57 + M-35), 281/283, 219, 183, 127, 57(base).

1-(1,1-dichloro-2,2,2-trifluoroethyl)-3-methyl-2-butenyl Glycinate-2-^{14}C · hydrochloride (5)

The *N*-*t*-Boc protected glycine ester **4** (2.437 g, 6.18 mmol) was treated with 10 ml of 4 M HCl in 1,4-dioxane, under N_2, at room temperature. After 90 min an aliquot was partitioned between aqueous $NaHCO_3$/Et_2O and analyzed by TLC (80% hexanes/20% ethyl acetate), GC and reverse phase HPLC. All three analyses indicated that the starting material had been consumed. The reaction mixture was concentrated in vacuo. The residual oil was taken up in Et_2O and concentrated (2 × 10 ml). The resultant solid was stirred with hexanes (10 ml) and a small amount of Et_2O (1 ml) for 15 min at which time the supernatant was removed via pipet (two times). The residual solid was dried under vacuum (rotary evaporator, 50°C) to give 1.944 g (95% yield) of the desired product as a white solid. Reverse phase HPLC analysis showed ∼96%

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radiochemical purity. MS(EI): 257/259(M-HCl), 219/221, 184(base), 157, 149, 143, 127, 109, 85, 79.

1-(1,1-dichloro-2,2,2-trifluoroethyl)-3-methyl-2-butenyl Diazoacetate-2-^{14}C (6)

Powdered sodium dihydrogencitrate (1.89 g, 8.82 mmol, 1.5 equivalents) was added in one portion to a solution of the amine·HCl **5** (1.944 g, 5.88 mmol, ~141.12 mCi), in 30 ml of H_2O, under N_2, at room temperature. The mixture was stirred at room temperature for 10 min, during which time it gradually turned into a white slurry. Dibromomethane (25 ml) was added to the rapidly stirred slurry, which was then cooled to ⩽5°C (ice bath) and treated dropwise with 6 M sodium nitrite (1.2 ml, 7.06 mmol, 1.2 equivalents). The mixture was stirred at ⩽5°C (stirring became easier after ~20 min) for 60 min and then allowed to warm to 15°C at which point the lower, dibromomethane, layer was removed via syringe. The aqueous layer was stirred with an additional 20 ml of dibromomethane for 5 min and the dibromomethane layer was removed via syringe. The dibromomethane extracts were dried by passing through a plug of Na_2SO_4 in a disposable pipet, combined and concentrated *in vacuo* (30–40°C) to give 1.50 g of a yellow oil (**Lot-1**).

The aqueous phase was treated with dibromomethane (20 ml) and the mixture cooled in an ice bath (<5°C) and treated dropwise with 6 M sodium nitrite (1.0 ml, 6.0 mmol, 1.0 equivalent). The mixture was stirred at <5°C for 30 min, allowed to warm to 15°C at which time the dibromomethane layer was removed via syringe. The aqueous layer was stirred with an additional 20 ml of dibromomethane for 5 min and the dibromomethane layer was removed via syringe. The dibromomethane extracts were passed through a plug of Na_2SO_4 in a disposable pipet, combined with **Lot-1** and concentrated *in vacuo* (rotory evaporator, 30–40°C) to give 1.68 g of a yellow oil (91% crude yield).

The crude material (1.68 g) was chromatographed on silica gel (flash, Kontes 2.5 × 10 cm Flex Column), eluting with 85% hexanes/15% ethyl acetate. Fractions containing the desired product were combined and concentrated in vacuo to give 1.416 g (79% yield) of the desired product as a light yellow oil. Reverse phase HPLC analysis showed >99% radiochemical purity. TLC (80% hexanes/20% ethyl acetate), HPLC, UV and mass spectra matched standard, unlabeled material. MS(EI): 306/304(M^+), 271/269, 221/219, 200, 183, 147, 127(base), 85, 69.

A stock solution of the diazoester was prepared by dissolving 1.416 g of **6** in 15 ml of 1,2-dichloroethane and storing in a freezer at −20°C.

4-(1,1-dichloro-2,2,2-trifluoroethyl)-6,6-dimethyl-3-oxabicyclo(3.1.0)hexan-2-one-1-^{14}C (8)

Three separate runs were performed to transform the diazoester **6** to the bicyclic lactone **8**. The details for a typical run are given below.

Run #1: A stock solution of the diazoester **6** (5 ml, ~0.472 g, 1.55 mmol) was added dropwise via syringe pump at a rate of 1.0 ml/h to a solution of *bis*-(*N*-*t*-butylsalicyladimininato)copper (II) **7** (65 mg, 0.155 mmol, 10 mol%) in 40 ml of 1,2-dichloroethane, under N_2, while heating at reflux. Once the addition was complete (~5 h) the reaction was stirred for an addition 30 min and then analyzed by TLC (80% hexanes/20% ethyl acetate) and GC. TLC analysis showed that all of the starting material had been consumed and GC showed predominately desired product. The reaction mixture was allowed to cool, transferred to a 100 ml round bottom flask and concentrated *in vacuo*. The residual brown oil was chromatographed on silica gel (flash, Kontes 2.5 × 20 cm Flex Column), eluting with 85% hexanes/15% ethyl acetate. Fractions were analyzed by TLC (Instant Imager radiography and UV) and GC. Fractions containing the desired product in >95% purity for the three separate runs were combined and concentrated in vacuo to give 0.816 g (63% yield, ~70.7 mCi) of the desired product as a yellow solid. Reverse phase HPLC analysis showed ~95% radiochemical purity. MS(EI): 278/276 (M^+), 241/243, 199/197, 143/141, 127/125(base), 99/97, 83/81, 69/67, 55/53.

(cis) 3-((1Z)-2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylic acid-1-^{14}C (rac-9)

The bicyclic lactone **8** (0.816 g, 2.95 mmol) was dissolved in methanol (10 ml), treated with zinc dust (0.231 g, 3.54 mmol, 1.2 equivalents) and the resultant mixture was heated to reflux. After refluxing for 2.5 h, GC analysis indicated that all of the starting material had been consumed. The reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*. The residue was taken up in 0.5 M HCl (8 ml) and extracted with CH_2Cl_2 (4 × 8 ml). The CH_2Cl_2 extracts were dried by passing through a plug of Na_2SO_4 in a disposable pipet, combined and concentrated *in vacuo* to give 0.661 g (92% crude) of the product as a light yellow solid. Reverse phase HPLC [YMC ODS-AM, S-5, 120 Å, 4.6 × 150 mm column, isocratic mobile phase: 50% H_2O/50% CH_3CN (each containing 0.1% H_3PO_4)] analysis showed this to be a 90/10 mixture of olefin isomers in favor of the *Z* isomer (by comparison with an authentic sample of the unlabeled *Z* isomer). The crude

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material was dissolved in hot hexanes, allowed to cool to room temperature (crystal began to form) and then placed in a freezer at −20°C. After ~2 h, the mother-liquor was removed (while still cold) and the remaining crystals washed with cold pentane (2 × 1 ml). The solid was dried with a stream of N_2 and then under vacuum at ambient temperature. This recrystallization process was repeated four times to yield 0.470 g (66% yield) of the desired product as a white solid. Reverse phase HPLC analysis shows <2% of the *E* isomer present and the 6-RAM detector shows >99% radiochemical purity. MS(EI): 244/242(M^+), 209/207(base), 199/197, 163/161, 143/141, 129/127, 93/91, 69, 59.

(S)-Cyano(3-phenoxyphenyl)methyl 3-((1Z)-2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate-1-^{14}C (1b+11)

1,3-Diisopropylcarbodiimide (0.30 ml, 1.94 mmol) was added dropwise to a solution of the carbon-14 labeled cyclopropanecarboxylic acid **9** (0.470 g, 1.94 mmol), (2*S*)-hydroxy(3-phenoxyphenyl)ethanenitrile **10** (0.459 g, 2.04 mmol, 1.05 equivalents) and a catalytic amount to 4-*N*,*N*-dimethylaminopyridine (2 mg) in 10 ml of toluene, under N_2, while cooling in an ice bath. After stirring at 0°C for 60 min, the reaction mixture was allowed to warm to room temperature. After 4 h, GC and HPLC analysis indicated that all of the carboxylic acid starting material had been consumed. The reaction mixture was filtered through a plug of Celite, washing with toluene (4 × 2 ml). The filtrate was concentrated *in vacuo* to give 0.899 g (103% yield) of the product as a light tan oil and a 1:1 mixture of diastereomers. The crude material was dissolved in hexanes and filtered through a plug of Celite, washing with hexanes, into a pear-shaped flask. The filtrate was concentrated *in vacuo* to give 0.883 g of a light tan oil. This was dissolved in 4 ml of hexanes and purified by normal phase preparative chromatography, injecting 1 ml of solution per run (4 runs total, ~220 mg per run).

Preparative HPLC Conditions: Beckman System Gold; 127P Solvent Module; 166P Detector; YMC-Guradpack Sil, S-10P μm, 120 Å, 7.5 × 30 mm pre-column; YMC-PACK Sil, S-10P μm, 120 Å, 250 × 30 mm i.d. prep-column; flow rate=20 ml/min (300 psi @ pumps); monitored at 280 nm. An isocratic mobile phase consisting of 96% hexanes/4% EtOAc was used for the separation.

Fractions collected were analyzed by TLC (80% hexanes/20% ethyl acetate) and normal phase HPLC. The following were isolated:

(S)-cyano(3-phenoxyphenyl)methyl (1R,3R)-3-((1Z)-2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate-1-^{14}C (γ-cyhalothrin-1-^{14}C, 1b)

Fractions containing-cyhalothrin-1-^{14}C (**1b**) in >98% radiochemical purity were combined and concentrated *in vacuo* to give 0.411 g of a colorless oil. The oil was dissolved in hexanes/ethyl acetate and filtered through a plug of Celite into a 25 ml round bottom flask. The filtrate was concentrated *in vacuo* to give 0.411 g of a colorless oil. The oil was dissolved in hexanes (3 ml) and placed in a freezer at −20°C. Crystals began to form within 30 min. After 90 min, the mother-liquor was removed via pipet, while still cold. The solid was washed with cold hexanes (1 × 1 ml) and the solvent removed via pipet. The solid was dried under a stream of N_2 and then dried under vacuum (ambient temperature) to constant weight to give 0.391 g (90% yield) of the desired product as white needles. Analysis indicated 21.8 mCi of total activity at a specific activity of 25.1 mCi/mmol and a radiochemical purity of >98% (YMC-Pack Sil, S-5, 120 Å, 4.6 × 250 mm column; isocratic mobile phase consisting of 96% hexanes/4% EtOAc). The carbon-14 labeled standard of γ-cyhalothrin matched an unlabeled standard of γ-cyhalothrin by HPLC retentions times, TLC R_f values, mass spectral analysis and UV spectral analysis (peak shape). MS(EI): 449/451 (M^+/M+2), 349, 225, 208, 197, 181 (base), 161, 152, 141, 115, 77.

(S)-cyano(3-phenoxyphenyl)methyl (1S,3S)-3-((1Z)-2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate-1-^{14}C (11)

Fractions containing undesired diastereomer 11 in >98% radiochemical purity were combined and concentrated in vacuo to give 0.406 g of a colorless oil. The oil was dissolved in ethyl acetate and filtered through a plug of Celite into a 25 ml round bottom flask. The filtrate was concentrated *in vacuo*, to constant weight, to give 0.397 g (90% yield) of **11** as a colorless oil. Analysis indicated 21.9 mCi of total activity at a specific activity of 24.8 mCi/mmol and a radiochemical purity of >98% (YMC-Pack Sil, S-5, 120 Å, 4.6 × 250 mm column; isocratic mobile phase consisting of 96% hexanes/4% EtOAc). MS(EI): 449/451 (M^+/M+2), 349, 225, 208, 197, 181 (base), 161, 152, 141, 115, 77.

Conclusion

A route for the synthesis of γ-cyhalothrin, that would be amenable to the synthesis of a carbon-14 labeled analog, was proposed, verified and optimized on unlabeled material. This route was then successfully

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applied to the synthesis of γ-cyhalothrin-1-^{14}C (**1b**) from commercially available *N*-*t*-Boc-glycine-2-^{14}C (**2**) in a total of seven chemical steps and one chromatographic separation of diastereomers. This resulted in 21.8 mCi of γ-cyhalothrin-1-^{14}C (**1b**) in >98% radiochemical purity and an overall radiochemical yield of 29%.

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