(αS,Z,1R,3R)-[4′,4″-^{3}H]Cyhalothrin and -[4″,6′-^{3}H]4′-Fluorocyhalothrin: Synthesis of Candidate Pyrethroid Radioligands for the Sodium Channel

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SUMMARY

(αS,Z,1R,3R)-Cyhalothrin (1) and (αS,Z,1R,3R)-4′-fluorocyhalothrin (2), highly potent insecticides, were selected as candidate radioligands for studies on pyrethroid-sodium channel interactions. This report describes the synthesis of dihalo derivatives of 1 and 2 and their reductive dehalogenation to the corresponding deuterium- and tritium-labelled pyrethroids. Thus, reduction of 4″,6′-dibromo-2 with deuterium gas, platinum oxide and potassium carbonate in ethyl acetate went quantitatively to [4″,6′-^{2}H]-2; however, the use of tritium instead of deuterium failed to yield [4″,6′-^{3}H]-2 giving instead decomposed materials. Fortunately the use of the iodo compounds 4″,4′-diiodo-1 and 4″,6′-diiodo-2 with tritium gas and palladium on carbon in absolute ethanol gave [4″,4′-^{3}H]-1 and [4″,6′-^{3}H]-2 in near quantitative yields at 55 Ci/mmol.

Key Words: cyhalothrin, 4′-fluorocyhalothrin, insecticide, pyrethroid, sodium channel, tritium labelling

INTRODUCTION

The insecticidal activity of pyrethroids and DDT is attributed to disruption of the voltage-sensitive sodium channel[1,2]. The molecular basis of this interaction is not known, due in part to the lack of a suitable radioligand for binding studies with neuronal membranes. Sodium channel blockers such as [^{3}H]batrachotoxinin A 20α-benzoate and [^{3}H]saxitoxin bind at sites different

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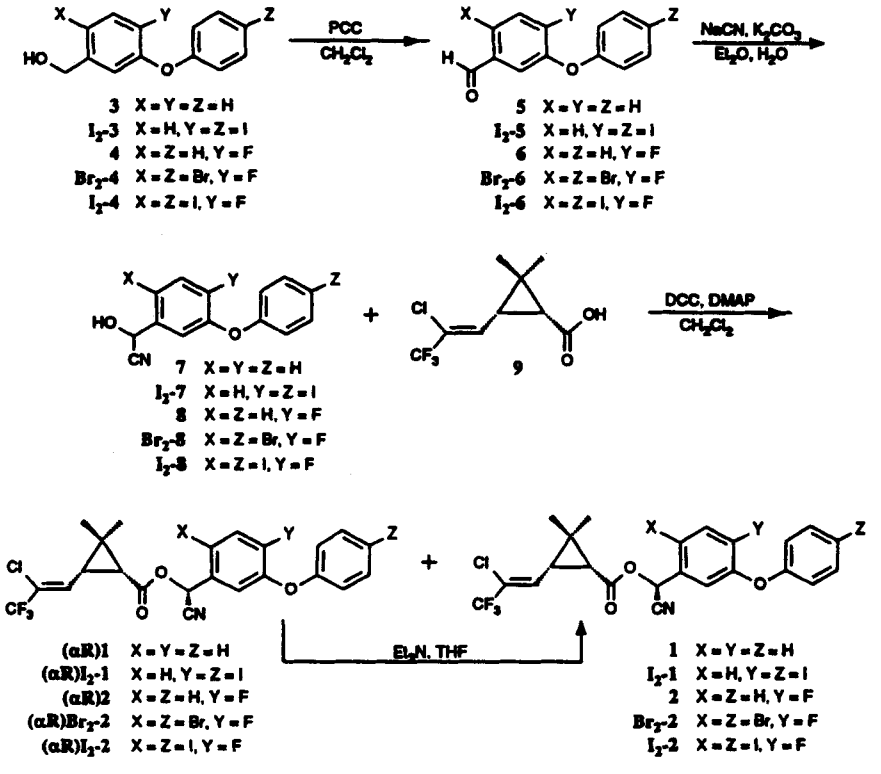
than those involved for the pyrethroids and DDT[3,4,5]. Early attempts to use radiolabelled pyrethroids and DDT as candidate radioligands in directly identifying the mechanism of insecticide-sodium channel interaction were not successful perhaps because of low specific activity and less than optimal neuroactivity[6,7,8]. Several recent studies focused on optimization of [^{3}H]pyrethroids as radioligands. In one report unspecified [^{3}H]pyrethroids of high potency were found to give unacceptably high nonspecific binding relative to the specific binding component of rat brain synaptosomes or insect neuronal membranes[4]. A second investigation prepared [^{3}H]acrinathrin (51 Ci/mmol)[9], and a third reported [^{3}H]-decyano-4-azidofenvalerate (17 Ci/mmol)[10]. The goal of the present study was to select highly potent pyrethroids and label them at nonexchangeable positions at high specific activity. The most potent pyrethroids known so far[11-14], and therefore the target compounds for radiolabelling in the present investigation, are (S)-α-cyano-3-phenoxybenzyl (Z)-(1R,3R)-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate [(αS,Z,1R,3R)-cyhalothrin] (1) and (αS,Z,1R,3R)-4'-fluorocyhalothrin (2).

RESULTS AND DISCUSSION

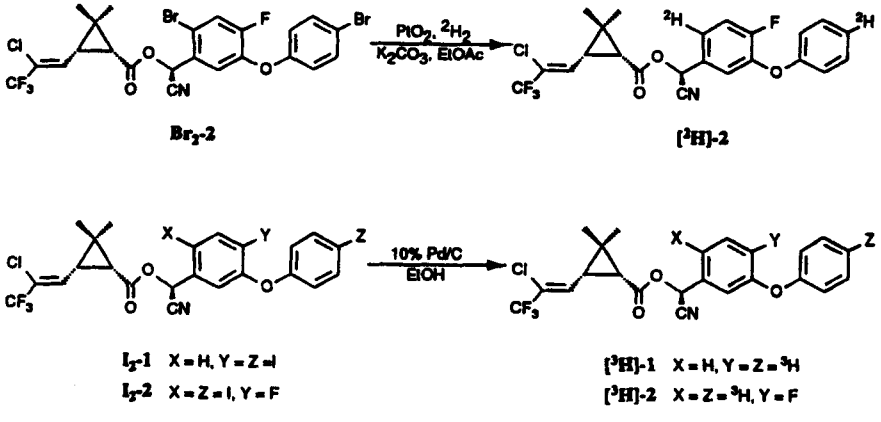
Tritium, the isotope of choice for a pyrethroid radioligand, is normally introduced by reduction with tritium gas in the presence of an appropriate catalyst[15]. All of the highest potency pyrethroids have phenoxybenzyl substituents appropriate for labelling with tritium via a suitable bromo or iodo compound. To use this method, it is necessary to first introduce bromine or iodine into 1 and 2. Model studies using cypermethrin (the dichlorovinyl analog of 1) showed that direct bromination of 1 or 2 was not feasible. An alternative route was therefore developed to the desired brominated and iodinated pyrethroids I_2-1, Br_2-2 and I_2-2 (Scheme 1).

Alcohols 3 and 4 and (Z,1R,3R)-acid 9 were chosen as starting materials. While iodination of 3 with iodomonochloride[16] in chloroform at 50 °C for 4 h gave I_2-3 in 93% yield, treatment of 4 with this reagent at reflux for 12 h gave a mixture of diiodo-alcohol I_2-4 and 4-fluoro-4'-iodo-3-phenoxybenzyl alcohol as an inseparable 23:77 mixture (based on ^{1}H NMR of aldehydes I_2-6 and I-6 described

Scheme 1



Scheme 2



below). Different iodinating reagents[17,18] did not improve the yield. Alcohol 4 was easily brominated with dibromoisocyanuric acid (DBI)[19] to give Br_2-4 in 70% yield. Treatment of I_2-3, Br_2-4 and the I_2-4:I-4 mixture with pyridinium

chlorochromate (PCC) gave the corresponding aldehydes $\underline{I_2}$-5, $\underline{Br_2}$-6 and the $\underline{I_2}$-6:I-6 mixture which were then converted to cyanohydrins $\underline{I_2}$-7, $\underline{Br_2}$-8 and $\underline{I_2}$-8:I-8 using potassium metabisulfite and sodium cyanide in wet diethyl ether[20]. Coupling these cyanohydrins to (Z,1R,3R)-acid 9 proceeded smoothly using standard 1,3-dicyclohexylcarbodiimide (DCC) reaction conditions[21] to give (αRS)$\underline{I_2}$-1 and (αRS)$\underline{Br_2}$-2 as 1:1 diastereomeric mixtures in 98 and 83% yields, respectively. The diastereoisomers were assigned by ^{1}H NMR and were readily separated by chromatography on silica gel with αS being more polar than αR[22]. However, reaction of the 23:77 mixture of $\underline{I_2}$-8:I-8 with acid 9 gave (αS)$\underline{I_2}$-2 in 86% yield and a mixture of (αR)$\underline{I_2}$-2 and (αR)I-2. Stereoselectivity in this esterification may result from the effect of the bulky 6-iodo substituent on the coupling. Racemization of the (αR)$\underline{I_2}$-2 and (αR)I-2 mixture using triethylamine in tetrahydrofuran (THF) gave their anticipated mixture with (αS)$\underline{I_2}$-2 and (αS)I-2. Authentic samples of 1 and 2 were also synthesized by analogous procedures (Scheme 1).

The reduction conditions for $\underline{Br_2}$-2, $\underline{I_2}$-1 and $\underline{I_2}$-2 had to be suitable to incorporate two tritium atoms without modification of the double bond or the ester, cyano or cyclopropyl group. Reduction of $\underline{Br_2}$-2 with deuterium gas at less than atmospheric pressure using 125 w/w% platinum oxide and 3.0 equivalents of potassium carbonate in ethyl acetate gave [^{2}H]-2 in 52% yield after 6.5 h (Scheme 2). The same procedure with tritium gas failed to yield [^{3}H]-2 indicating possible decomposition in the presence of the large amount of radioactivity present on the catalyst. Tin tritides appeared to be a possible alternative to catalytic tritiolysis with suitable functional group selectivity[23]. Using conditions modified from Neumann and Hillgärtner[24], $\underline{Br_2}$-2 was converted to 2 in 68% yield with 3.3 equivalents of triphenyltin hydride or tributyltin hydride in THF under argon followed by irradiation with 300-400 nm light for 2 h. However, the required tin tritides are not currently available.

$\underline{I_2}$-1 and $\underline{I_2}$-2 were reduced quantitatively in 2 h at a slight positive pressure of hydrogen using 10% palladium on carbon as a catalyst in absolute ethanol. Under the same conditions except with tritium gas at a slight negative pressure there was only partial displacement of the iodine in the 4"-position at 2 h but complete reduction at 5 h.

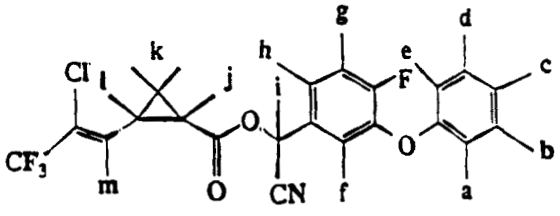
Proton NMR of [^{3}H]-1 (not illustrated) and [^{3}H]-2 showed >95% tritium incorporation without any reduction of the cyano group or the double bond but a trace amount of racemization at the benzylic position (Figure 1). Tritium NMR with proton decoupling showed singlets at 7.4 and 7.2 ppm for [^{3}H]-1 and a doublet at 7.4 ppm ($J_{T\text{-}F}$=4.3 Hz) and a singlet at 7.2 ppm for [^{3}H]-2. Proton coupled tritium NMR of [^{3}H]-1 (not illustrated) and [^{3}H]-2 (Figure 1) were appropriate for the designated structures, e.g. with [^{3}H]-2. Proton coupled tritium NMR of [^{3}H]-2 (Figure 1) showed that tritium at position c is split by protons b/d to give a triplet, and tritium at position h is coupled to protons g and f and the fluorine to give a set of eight peaks (ddd) with coupling constants 8.7, 2.4 and 4.3 Hz, respectively.

MATERIALS AND METHODS

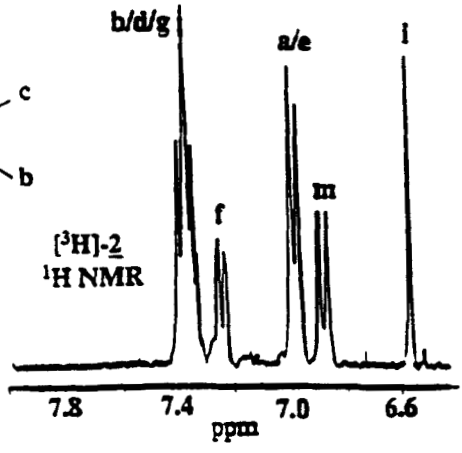
Chemicals and chromatography. 4-Fluoro-3-phenoxybenzyl alcohol 4 was supplied by ICI Americas Inc. (Richmond, CA) or prepared from 3-bromo-4-fluorobenzaldehyde (Aldrich) by protecting the aldehyde as the ketal, coupling to sodium phenolate, deprotection of the aldehyde, and reduction to the alcohol[25]. 3-Phenoxybenzaldehyde 5 was from Aldrich. The required acid 9 was provided by ICI Agrochemicals (Jealott's Hill Research Station, Bracknell, Berkshire, England) and the Chemical Research and Development Center, FMC Corporation (Princeton, NJ). Flash column chromatography and preparative TLC utilized 230-400 mesh silica gel and Analtech silica gel GF plates (1 mm), respectively. Radial chromatography was performed on a Harrison Research Chromatotron model 8924 with Analtech 1 mm silica gel GF rotor plates.

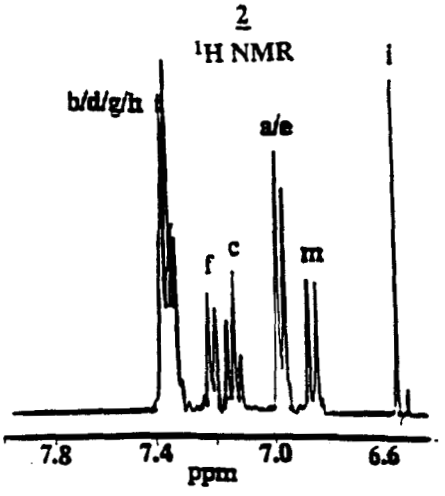
Spectroscopy and analysis. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were measured at 300, 75 and 282 MHz, respectively, on a Bruker AM-300 spectrometer. NMR chemical shifts for the acid moieties of the esters are: ^{1}H NMR (CD_3OD) δ: 6.8 (d, J= 9.0 Hz, m), 2.3 (t, J= 8.6 Hz, l), 2.1 (d, J= 8.2 Hz, j), 1.3 (s, 3H, k), 1.2 (s, 3H, k) (Figure 1): ^{13}C NMR (CD_3OD) δ: 167.9, 129.5, 122.4(m), 118.5, 32.6, 31.6, 29.5, 28.4, 15.0. ^{1}H and ^{3}H NMR spectra of ^{3}H-labelled compounds were recorded on an IBM AF-300 at 300 and 320 MHz, respectively. MS data were determined with the Hewlett Packard 5985B system using EI at 70 eV and the data are tabulated as m/z and percent relative intensity.

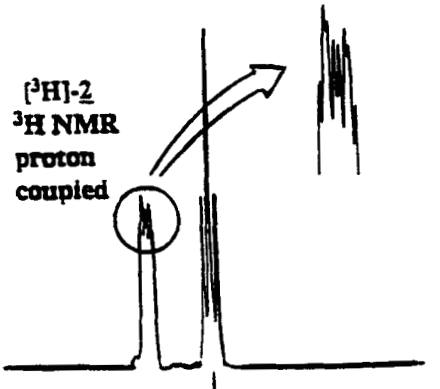
Figure 1. ^1H NMR (CD_3OD) of 2, I_2-2 and [^3H]-2 and ^3H NMR of [^3H]-2 (proton coupled and decoupled)

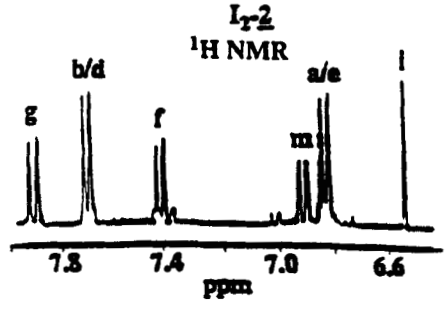


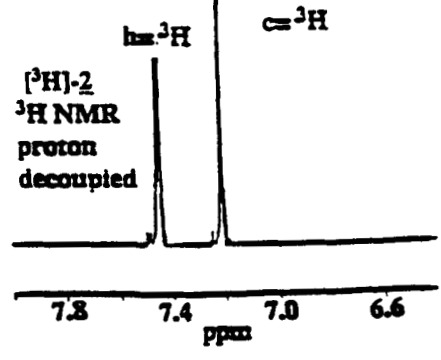
2 c=h=H, I_2-2 c=h=I
[^3H]-2 c=h=^3H











Synthesis

4,4'-Diiodo-3-phenoxybenzyl alcohol (I_2-3): To a solution of 3 (200 mg, 1.0 mmol) in chloroform (5 mL) was added iodomonochloride (325 mg, 2.0 mmol) in chloroform (5 mL). The reaction was stirred for 4 h at 50 °C then diluted with ethyl acetate (30 mL), washed with solutions of 10% $NaHSO_3$ and brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by radial chromatography (10% ethyl acetate/hexane as eluent) gave 420 mg (93%) of a white solid. ^1H NMR ($CDCl_3$)δ : 7.7 (d, J= 8.5 Hz, 1H), 7.6 (d, J= 8.6 Hz, 2H), 7.1 (d, J= 2.5 Hz, 1H), 6.8 (d, J= 8.6 Hz, 2H), 6.7 (dd, J= 2.5, 8.5, 1H), 4.6 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 157.3, 156.5, 144.4, 140.0, 138.7, 129.8, 121.0, 120.3, 119.6, 118.7, 89.0, 86.6, 68.7. MS: M^+ (100).

4',6-Dibromo-4-fluoro-3-phenoxybenzyl alcohol (Br_2-4): A solution of 4 (299 mg, 1.37 mmol) and DBI (393 mg, 1.37 mmol) in glacial acetic acid (7 mL) was stirred under argon for 30 min at 25 °C. The mixture was poured onto ice and extracted with ethyl acetate. The organic layer was washed with water, aqueous $NaHSO_3$, brine and dried (Na_2SO_4). The solvent was removed in vacuo and the residue purified by flash chromatography (15% ethyl acetate/hexane) to yield 360 mg (70%) of a cream-colored solid. ^1H NMR ($CDCl_3$) δ : 7.4 (d, J= 8.7 Hz, 2H), 7.3 (d, J= 9.1 Hz, 1H), 7.2 (d, J= 8.4 Hz, 1H), 6.8 (d, J= 8.7 Hz, 2H), 4.7 (s, 2H). ^{13}C NMR ($CDCl_3$) δ : 156.0, 154.6, 151.3, 143.5, 142.0, 136.7, 132.7, 121.4, 121.1, 119.0, 116.0, 115.9, 64.1. MS: M^++2 (48), M^+ (100), M^+-2 (50).

4',6-Diiodo-4-fluoro-3-phenoxybenzyl alcohol (I_2-4): A solution of 4 (218 mg, 1.0 mmol) and iodomonochloride (324 mg, 2.0 mmol) in chloroform (5 mL) was refluxed overnight with work up as above. The product was isolated by preparative TLC from two byproducts to give 100 mg of a mixture of 23% I_2-4 and 77% of its monoiodo analog. ^1H NMR ($CDCl_3$) δ : 7.6 (m, 3H), 7.2 (m, 2.2H), 6.8 (m, 3.6H), 4.5 (s, 2.6H). ^{13}C NMR ($CDCl_3$) δ : 157.0, 155.5, 138.6, 134.0, 129.7, 129.0, 125.4, 125.2, 122.0, 121.8, 120.2, 119.4, 118.6, 117.5, 92.1, 86.2, 67.1. MS: M^+ (100).

4,4'-Diiodo-3-phenoxybenzaldehyde (I_2-5): To a suspension of PCC (215 mg, 1.0 mmol) in dry methylene chloride (10 mL) was added I_2-4 (200 mg, 0.44 mmol) in methylene chloride (5 mL) under nitrogen. The resulting dark mixture was stirred for 2 h at 25 °C then diluted with methylene chloride (30 mL) and

filtered through a short column of Florisil. The filtrate was concentrated in vacuo to give 190 mg (95%) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ : 9.9 (s, 1H), 7.8 (d, J= 8.5 Hz, 1H), 7.6 (d, J= 8.8, 2H), 7.5 (d, J= 3.0 Hz, 1H), 6.9 (dd, J= 3.0, 8.5 Hz, 1H), 6.8 (d, J= 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ : 194.7, 157.8, 155.6, 141.6, 139.0, 136.2, 130.1, 125.8, 121.5, 119.5, 119.1, 92.5, 87.7. MS: M^+ (100).

4-Fluoro-3-phenoxybenzaldehyde (6): This aldehyde was prepared using the PCC procedure described above from 4 in 92% yield. ^{1}H NMR ($CDCl_3$) δ : 9.8 (s, 1H), 7.6 (ddd, J= 6.5, 4.4, 2.0 Hz, 1H), 7.5 (dd, J= 7.8, 2.0 Hz, 1H), 7.4 (m, 3H), 7.2 (t, J= 6.8 Hz, 1H), 7.0 (d, J= 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ : 190.0, 158.2, 156.1, 143.1, 141.1, 133.4, 130.0, 126.7, 124.2, 120.8, 118.3, 117.8, 117.5.

4',6-Dibromo-4-fluoro-3-phenoxybenzaldehyde (Br_2-6): This compound was obtained as described before using the PCC procedure from Br_2-4 in 96% yield. ^{1}H NMR ($CDCl_3$) δ : 10.2 (s, 1H), 7.6 (d, J= 8.6 Hz, 1H), 7.4 (d, J= 9.6 Hz, 1H), 7.3 (d, J= 8.9 Hz, 2H), 6.8 (d, J= 8.9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ : 189.5, 158.7, 155.3, 154.8, 143.6, 142.1, 133.0, 132.6, 130.4, 121.1, 119.8, 118.0, 117.1.

4',6-Diiodo-4-fluoro-3-phenoxybenzaldehyde (I_2-6): Treatment of 50 mg of the mixture I_2-4:I-4 with PCC as described above gave 40 mg of I_2-6 and I-6. ^{1}H NMR ($CDCl_3$) δ : 10.3 (s, 0.3H), 9.9 (s, 1 H), 7.8 (d, J= 8.5 Hz, 1H), 7.7 (m, 2.6H), 7.5 (m, 1.6H), 7.3 (m, 1H), 6.8 (m, 2.6H). ^{13}C NMR ($CDCl_3$) δ : 193.5, 187.6, 158.7, 155.7, 155.1, 139.0, 138.6, 132.1, 130.1, 128.9, 128.6, 121.5, 120.8, 120.7, 120.3, 119.6, 119.3, 92.9, 87.7.

α-Cyano-3-phenoxybenzyl alcohol (7): Aldehyde 5 (200 mg, 1.0 mmol) was added to potassium metabisulfite (200 mg, 0.9 mmol) and sodium cyanide (137 mg, 1.0 mmol) in wet diethyl ether at 0 °C followed by warming to 25 °C over a period of 2 h to give 30 mg of starting material and 190 mg (93%) of pure 7. ^{1}H NMR ($CDCl_3$) δ : 7.0-7.4 (m, 9H), 5.5 (s, 1H), 3.0 (s, 1H, exchangeable OH).

α-Cyano-4,4'-diiodo-3-phenoxybenzyl alcohol (I_2-7): This cyanohydrin was prepared from I_2-5 in 98% yield using the procedure described for 7. ^{1}H NMR ($CDCl_3$) δ : 7.8 (d, J= 8.7 Hz, 1H), 7.6 (d, J= 8.7 Hz, 2H), 7.4 (d, J= 2.8 Hz, 1H), 6.8 (d, J= 8.7 Hz, 2H), 6.7 (dd, J= 8.7, 2.8 Hz, 1H), 5.7 (s, 1H), 3.9 (s, 1H, exchangeable OH). ^{13}C NMR ($CDCl_3$) δ : 157.9, 155.9, 141.0, 140.8, 139.1,

130.0, 124.4, 121.3, 119.5, 118.6, 118.4, 88.6, 87.4, 67.1. MS: M^+ (2), 450 (100).

α-Cyano-4-fluoro-3-phenoxybenzyl alcohol (8): This compound was obtained as above from 6 using the procedure described for 7 in 96% yield as a colorless oil. ^1H NMR ($CDCl_3$) δ : 7.3 (m, 2H), 7.2 (m, 4H), 6.9 (m, 2H), 5.5 (s, 1H), 3.2 (s, 1H, exchangeable OH).

α-Cyano-4',6-dibromo-4-fluoro-3-phenoxybenzyl alcohol (Br_2-8): The above conditions converted Br_2-6 to Br_2-8 in 99% yield. ^1H NMR ($CDCl_3$) δ : 7.5 (d, J= 9.6 Hz, 1H), 7.46 (d, J= 8.9 Hz, 2H), 7.43 (d, J=8.6 Hz, 1H), 6.8 (d, J= 8.9 Hz, 2H), 5.7 (d, J= 5.5 Hz, 1H), 3.6 (s, 1H, exchangeable OH).

α-Cyano-4',6-diiodo-4-fluoro-3-phenoxybenzyl alcohol (I_2-8): The same procedure described above for 7 was used to convert 40 mg of the mixture I_2-6:I-6 to 39 mg of the mixture I_2-8 : I-8. ^1H NMR ($CDCl_3$) δ : 7.7 (d, J= 9.3 Hz, 1H), 7.6 (m, 2.6H), 7.4 (m, 2H), 7.3 (m, 0.6H), 6.8 (m, 2.6H), 5.7 (s, 0.3H), 5.6 (s, 1H), 3.3 (s, 1H, exchangeable OH).

(αR and αS,Z,1R,3R)-Cyhalothrin [1 and (αR)-1]: To a solution of 7 (160 mg, 0.71 mmol), DCC (161.5 mg, 0.78 mmol) and 4-dimethylaminopyridine (DMAP) (9.0 mg, 0.07 mmol) in dry methylene chloride (5 mL) was added 9 (172.5 mg, 0.71 mmol) at 25 °C under nitrogen. The resulting cloudy solution was stirred for 2 h then filtered through a short column of silica gel and concentrated *in vacuo*. Purification by radial chromatography using 5% ethyl acetate:hexane as eluent gave 140 mg of (αR)1 and 160 mg of (αS)1, R_f=0.53 and 0.50, respectively, in 20% ethyl acetate/hexane. (αR)1: ^1H NMR ($CDCl_3$) δ : 7.4 (m, 1H), 7.3 (m, 3H), 7.2 (m, 2H), 6.9 (m, 3H), 6.3 (s, 1H). (αS)1: ^1H NMR (CD_3OD) δ : 7.5 (m, 1H, g), 7.4 (m, 2H, b/d), 7.3 (d, J= 7.7 Hz, 1H, 4'), 7.2 (m, 2H, c/f), 7.1 (dd, J= 7.9, 2.3 Hz, 1H, h), 7.0 (d, J= 8.2 Hz, 2H, a/e), 6.6 (s, 1H, i). MS: M^+ (6), 197 (74), 181 (100).

(αR and αS,Z,1R,3R)-4',4"-Diiodocyhalothrin [I_2-1 and (αR)I_2-1]: Cyanohydrin I_2-7 (87 mg, 0.18 mmol) was coupled with 9 (50 mg, 0.2 mmol) as above. Purification by radial chromatography (5% ethyl acetate:hexane) gave 60 mg of (αR)I_2-1 (47%), R_f= 0.53 and 65 mg of (αS)I_2-1 (51%), R_f= 0.50 in 20% ethyl acetate/hexane, both as colorless oils. (αR)I_2-1: ^1H NMR ($CDCl_3$) δ : 7.8 (d, J =8.6 Hz, 1H), 7.7 (d, J= 8.3 Hz, 2H), 7.4 (d, J= 2.5 Hz, 1H), 6.8 (m, 4H), 6.5

(s, 1H). MS: M^+ (3), 197 (100). (αS)$\underline{I_2}$-$\underline{1}$: ^{1}H NMR (CD_3OD) δ : 7.9 (d, $\underline{J}$= 8.7 Hz, 1H, $\underline{g}$), 7.7 (d, $\underline{J}$= 8.6 Hz, 2H, $\underline{b}$/$\underline{d}$), 7.3 (d, $\underline{J}$= 2.8 Hz, 1H, $\underline{f}$) 6.9 (dd, $\underline{J}$= 8.7, 2.8 Hz, 1H, $\underline{h}$), 6.8 (d, $\underline{J}$= 8.6 Hz, 2H, $\underline{a}$/$\underline{e}$), 6.5 (s, 1H, $\underline{i}$). ^{13}C NMR ($CDCl_3$) δ: 158.0, 155.8, 141.3, 139.0, 135.9, 130.1, 124.5, 121.7, 121.4, 119.5, 115.0, 89.3, 87.6, 66.7. ^{19}F NMR ($CDCl_3$, C_6F_6 as a reference) δ : 44.1 (s, CF_3). MS: M^+ (3), 197 (100).

(αR and αS,Z,1R,3R)-4-Fluorocyhalothrin [$\underline{2}$ and (αR)$\underline{2}$]: Cyanohydrin $\underline{8}$ (81 mg, 0.35 mmol) was coupled with $\underline{9}$ as above to yield, after radial chromatography, 54 mg (33%) of (αR)$\underline{2}$ and 49 mg (30%) of $\underline{2}$, both as colorless oils. (αR)$\underline{2}$: ^{1}H NMR ($CDCl_3$) δ : 7.4 (m, 2H), 7.3 (m, 2H), 7.2 (m, 2H), 7.0 (m, 2H), 6.3 (s, 1H). $\underline{2}$: ^{1}H NMR (CD_3OD) δ : 7.4 (m, 2H, $\underline{g}$/$\underline{h}$), 7.3 (d, $\underline{J}$= 8.1 Hz, 2H, $\underline{b}$/$\underline{d}$), 7.2 (d, $\underline{J}$= 6.7 Hz, 1H, $\underline{f}$), 7.1 (t, $\underline{J}$= 7.4 Hz, 1H, $\underline{c}$), 6.9 (d, $\underline{J}$= 8.1 Hz, 2H, $\underline{a}$/$\underline{e}$), 6.6 (s, 1H, $\underline{i}$). ^{13}C NMR ($CDCl_3$) δ : 156.8, 156.3, 153.4, 143.2, 141.0, 130.0, 128.6, 124.0, 123.9, 120.8, 118.0, 117.8, 115.5, 62.0. MS: M^+ (1), 227 (100).

(αR and αS,Z,1R,3R)-4″,6′-Dibromo-4′-fluorocyhalothrin [$\underline{Br_2}$-$\underline{2}$ and (αR)$\underline{Br_2}$-$\underline{2}$]: In a similar manner cyanohydrin $\underline{Br_2}$-$\underline{8}$ (121 mg, 0.30 mml) reacted with $\underline{9}$ followed by radial chromatography purification (1% ethyl acetate/hexane) gave 79 mg (42%) of (αR)$\underline{Br_2}$-$\underline{2}$ and 77 mg (41%) of (αS)$\underline{Br_2}$-$\underline{2}$, both as colorless oils. (αR)$\underline{Br_2}$-$\underline{2}$: ^{1}H NMR ($CDCl_3$) δ : 7.5 (d, $\underline{J}$= 9.6 Hz, 1H), 7.45 (d, $\underline{J}$= 8.9 Hz, 2H), 7.42 (d, $\underline{J}$= 8.1 Hz, 1H), 6.8 (d, $\underline{J}$= 8.9 Hz, 2H), 6.5 (s, 1H). (αS)$\underline{Br_2}$-$\underline{2}$: ^{1}H NMR ($CDCl_3$) δ : 7.5 (d, $\underline{J}$= 9.7 Hz, 1H), 7.47 (d, $\underline{J}$= 8.9 Hz, 2H), 7.41 (d, $\underline{J}$= 7.9 Hz, 1H), 6.9 (d, $\underline{J}$= 8.9 Hz, 2H), 6.6 (s, 1H). ^{13}C NMR ($CDCl_3$) δ : 156.4, 155.4, 153.0, 143.7, 143.0, 133.0, 129.6, 119.1, 118.4, 117.1, 117.0, 116.8, 114.7, 61.9. MS: M^+ (2), 197 (100).

Racemization of (αR)$\underline{Br_2}$-$\underline{2}$: A solution of (αR)$\underline{Br_2}$-$\underline{2}$ (89 mg) in THF (1.0 mL) and triethylamine (0.1 mL) was stirred for 4 h at 25 °C and the solvent was removed in vacuo. Radial chromatography yielded 46 mg (52%) of (αR)$\underline{Br_2}$-$\underline{2}$ and 41 mg of (αS)$\underline{Br_2}$-$\underline{2}$.

(αR and αS,Z,1R,3R)-4″,6′-Diiodo-4′-fluorocyhalothrin ($\underline{I_2}$-$\underline{2}$ and (αR)$\underline{I_2}$-$\underline{2}$): The mixture of cyanohydrins $\underline{I_2}$-$\underline{8}$ (8 mg) and $\underline{I}$-$\underline{8}$ (27 mg) was coupled to $\underline{9}$ as above. Radial chromatography separated a mixture of (αR)$\underline{I}$-$\underline{2}$ and (αR)$\underline{I_2}$-$\underline{2}$ (28 mg) from pure (αS)$\underline{I_2}$-$\underline{2}$ (10 mg). (αR)$\underline{I_2}$-$\underline{2}$: MS: M^+ (2), 197 (100). (αS)$\underline{I_2}$-$\underline{2}$: ^{1}H NMR ($CDCl_3$) δ : 7.9 (d, $\underline{J}$= 9.8 Hz, 1H, $\underline{g}$), 7.7 (d, $\underline{J}$= 8.6 Hz, 2H, $\underline{b}$/$\underline{d}$), 7.4 (d, J_{F-F}=

7.9 Hz, 1H, f), 6.8 (d, J= 8.6 Hz, 2H, a/e), 6.5 (s, 1 H, i). ^{13}C NMR ($CDCl_3$) δ : 156.2, 152.7, 138.9, 131.5, 130.0, 128.8, 121.5, 120.3, 119.6, 118.9, 114.9, 89.9, 87.2, 66.2. ^{19}F NMR ($CDCl_3$) δ: 44.1 (s, CF_3), -11.5 (s, Ar-F). MS: M^+ (2), 197 (100).

(αS,Z,1R,3R)-4',4"-Ditritiocyhalothrin [^{3}H]-1: A solution of I_2-1 (20 mg, 0.03 mmol) in ethanol (3.0 mL) was degassed with three freeze, pump, thaw cycles and then a mixture of 10% palladium on carbon (5.0 mg) was added during the last thaw. The mixture was stirred under slight negative pressure of tritium gas for 5 h at 25 °C. After freeze degassing three times to remove the tritium gas absorbed on the catalyst, the mixture was filtered and lyophilized to give 825 mCi of residue. Purification by radial chromatography gave 300 mCi of monoiodo monotritio product and 380 mCi of pure [^{3}H]-1 in 23% radiochemical yield at 55 Ci/mmol (based on 95% ^{3}H incorporation detected by ^{1}H NMR of [^{3}H]-1). ^{1}H NMR (CD_3OD) δ : 7.5 (m, 3H), 7.1 (d, J= 2.6 Hz, 1H), 7.0 (m, 3H), 6.6 (s, 1H). ^{3}H NMR proton-decoupled (CD_3OD) δ : 7.4 (s, 1 ^{3}H), 7.2 (s, 1 ^{3}H). ^{3}H NMR proton-coupled (CD_3OD) δ : 7.4 (d, J= 8.1 Hz, 1 ^{3}H), 7.2 (t, J= 7.6 Hz, 1 ^{3}H).

(αS,Z,1R,3R)-4",6'-Dideuterio-4'-fluorocyhalothrin [^{2}H]-2: A mixture of Br_2-2 (15 mg, 0.024 mmol), anhydrous potassium carbonate (10 mg, 0.072 mmol) and ethyl acetate (1.0 mL) was degassed with three freeze, pump, thaw cycles and platinum(II) oxide (19 mg, 125 w/w%) was added during the last thaw. The flask was flushed with deuterium gas and the mixture was stirred for 6.5 h at 25 °C under deuterium gas with the pressure maintained below 760 mm Hg. The mixture was filtered through Celite and the solvent removed *in vacuo*. The residue was purified by preparative TLC (10% ethyl acetate/hexane) to yield 5.7 mg of [^{2}H]-2 (52%) as a colorless oil. ^{1}H NMR (CD_3OD) δ : 7.3 (m, 3H, b/d/g), 7.2 (d, J= 7.5 Hz, 1H, f), 6.9 (d, J= 8.5 Hz, 2H, a/e), 6.5 (s, 1H, i). ^{13}C NMR ($CDCl_3$) δ : 156.8, 156.3, 153.4, 144.7, 143.2, 129.8, 128.9, 128.6, 124.0, 120.7, 117.9, 117.7, 115.5, 61.9. MS: M^+ (3), 228 (100).

(αS,Z,1R,3R)-4",6'-Ditritio-4-fluorocyhalothrin [^{3}H]-2: The same procedure described above for I_2-1 was used with I_2-2 (10 mg, 0.014 mmol) with a reaction time of 5 h at 25 °C to give [^{3}H]-2 (278 mCi, after purification by radial chromatography as above in 36% radiochemical yield; 55 Ci/mmol). ^{1}H NMR (CD_3OD) δ : 7.4 (m, 3H, b/d/g), 7.3 (d, J= 6.4 Hz, 1H, f), 7.0 (d, J= 8.1 Hz, 2H, a/e),

6.6 (s,1H, i). ^3H NMR proton-decoupled (CD_3OD) δ : 7.4 (d, $J_{T\text{-}F}$ = 4.3 Hz, 1 ^3H), 7.2 (s, 1 ^3H). ^3H NMR proton-coupled (CD_3OD) δ : 7.4 (ddd, $J_{T\text{-}f}$ = 2.4 Hz, $J_{T\text{-}F}$ = 4.3 Hz, $J_{T\text{-}h}$ = 8.7 Hz, 1 ^3H), 7.2 (t, J= 7.8 Hz, 1 ^3H).

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