Supplementary Materials

Figure S1. Generation of 3-phenoxybenzaldehyde (PBA) under basic conditions through aqueous β-elimination of the cyanohydrin to the corresponding aldehyde.

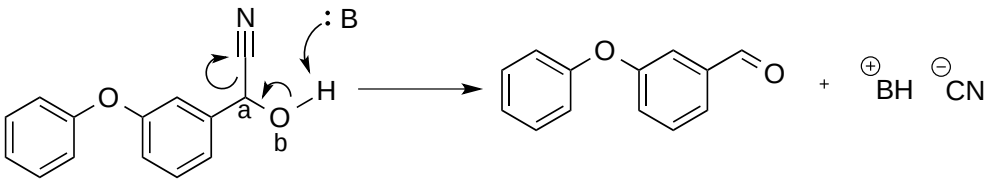

Table S1. Acronyms of pyrethroids and their respective constituents hydrolysis products.

Compound	Acronyms
Transfluthrin	TF
Permethrin	PM
Deltamethrin	DM
Esfenvalerate	FV
Natural pyrethrum	NP
Bifenthrin	BF
Phenothrin	PN
Transfluthrin acid (also acid of permethrin)	TFA
1*R*-*trans*-chrysanthemic acid (acid of natural pyrethrum)	TCA
1*R*,3*S*-*trans*-3-(2,2-difluoroethenyl)-2,2-dimethylcyclopropane-1-carboxylic acid	FTFA
Metofluthrin acid	MFA
Fenverate acid	FVA
Deltamethrin acid	DMA
Bifenthrin acid	BFA
Phenothrin acid	PNA

Transfluthrin alcohol	TF-OH
Metofluthrin alcohol	MF-OH
Permethrin alcohol (also the alcohol of phenothrin)	PM-OH
Tetramethrin alcohol	TM-OH
Kadethrin alcohol	KD-OH
3-phenoxybenzaldehyde	PBA

Text S1: Methods for the preparation of pyrethroid acids

Method A. Pyrethroid (1 equiv) was suspended in $NaOH_{(aq)}$ or $KOH_{(aq)}$ (1M, 5 equiv) and methanol (10 mL/mmol) and refluxed for 16 hours. The mixture was cooled to room temperature, concentrated by roto-evaporation, and extracted with ethyl acetate. The organic layer obtained through extraction from the basic aqueous layer was collected, dried with magnesium sulfate, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to afford the hydrolyzed alcohol. The basic aqueous layer was then collected and acidified with 1M $HCl_{(aq)}$. The acidified aqueous layer was then extracted with ethyl acetate. The organic layer obtained through extraction from the acidic aqueous layer was collected, dried with magnesium sulfate, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to afford the hydrolyzed carboxylic acid.

Method B. KOH (10 equiv) was added to a solution of pyrethroid (1 equiv) in $MeOH/H_2O$ (5 mL/mmol) and stirred for 16 hours at room temperature. The mixture was concentrated by rotoevaporation and extracted with ethyl acetate. The organic layer obtained through extraction from the basic aqueous layer was collected, dried with magnesium sulfate, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to afford the hydrolyzed alcohol. The basic aqueous layer was then collected and acidified with 1M HCl. The acidified aqueous layer

was then extracted with ethyl acetate. The organic layer obtained through extraction from the acidic aqueous layer was collected, dried with magnesium sulfate, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography to afford the hydrolyzed carboxylic acid.

Method C. 1M HCl (10 equiv) was added to pyrethroid (1 equiv) in dioxane (5 mL/mmol), and the solution was refluxed for 5 hours. The mixture was concentrated to half volume under reduced pressure, neutralized with $NaHCO_{3\,(aq)}$, and extracted with ethyl acetate. The organic layers were collected and washed with water. The water was collected, acidified with 1M HCl_{aq} and extracted with ethyl acetate. All the organic layers were combined, dried with magnesium sulfate, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography.

2,2-dimethyl-3-(prop-1-en-1-yl)cyclopropane-1-carboxylic acid (MFA): Prepared from the general procedure above (*Method A*) from metofluthrin (121.9 mg, 0.338 mmol), 1M $NaOH_{(aq)}$ (1.69 mL), and methanol (1 mL). The crude organic extract obtained from extraction of the acidified aqueous layer was purified by automated flash chromatography to afford the product as a clear oil (28 mg, 54% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.62 (dd, *J* = 7.7, 5.8 Hz, 1H), 5.15 (ddd, *J* = 10.4, 8.4, 1.8 Hz, 1H), 2.24 – 2.18 (m, 1H), 1.73 (dd, *J* = 6.9, 1.8 Hz, 3H), 1.48 (d, *J* = 5.4 Hz, 1H), 1.34 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 179.10, 127.42, 126.71, 34.79, 32.49, 29.83, 22.19, 20.39, 13.44.

(1R,3R)-3-((Z)-2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethylcyclopropane-1-carboxylic acid (BFA): Prepared from the general procedure above (*Method A*) from bifenthrin (320.4 mg, 0.757 mmol), 1M $NaOH_{(aq)}$ (3.8 mL), and methanol (1 mL). The crude organic extract obtained from extraction of the acidified aqueous layer was purified by automated flash chromatography to afford the product as a viscous clear oil (31.15 mg, 18% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.88 (d, *J* = 9.3 Hz, 1H), 2.25 (t, *J* = 8.8 Hz, 1H), 2.01 (d, *J* = 8.3 Hz, 1H),

1.35 – 1.33 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.63, 129.59, 122.15 (q, *J* = 38.8, 38.3, 38.2 Hz), 120.37 (q, *J* = 270.4 Hz), 31.56, 29.71, 29.48, 28.44, 14.88.

2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylic acid (PNA): Prepared from the general procedure above (*Method A*) from phenothrin (92.1 mg, 0.263 mmol), 1M $NaOH_{(aq)}$ (1.3 mL), and methanol (2 mL). The crude organic extract obtained from extraction of the acidified aqueous layer was purified by automated flash chromatography to afford the product as a viscous clear oil (19.8 mg, 45% yield). 86/14 diastereomeric ratio observed: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.37 (dt, *J* = 8.5, 1.5 Hz, 0.14H), 4.92 (dt, *J* = 7.8, 1.4 Hz, 0.86H), 2.11 (dd, *J* = 7.7, 5.4 Hz, 0.86H), 1.98 (t, *J* = 8.6 Hz, 0.14H), 1.74 – 1.71 (m, 6H), 1.32 (s, 2.58H), 1.27 (s, 0.42H), 1.23 (s, 0.42H), 1.17 (s, 2.58H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 179.17, 177.93, 135.86, 135.07, 120.76, 117.87, 34.65, 33.62, 33.31, 31.16, 29.82, 29.70, 28.91, 27.51, 25.90, 25.54, 22.38 – 22.20 (m), 20.43, 18.56 – 18.44 (m), 18.32.

3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (DMA): Prepared from the general procedure above (*Method A*) from deltamethrin (857.7 mg, 1.7 mmol), 1M $NaOH_{(aq)}$ (8.5 mL), and methanol (8.5 mL). The crude organic extract obtained from extraction of the acidified aqueous layer was purified by automated flash chromatography to afford the product as a white solid (171.8 mg, 34% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.75 (d, *J* = 8.6 Hz, 1H), 2.05 (t, *J* = 8.5 Hz, 1H), 1.88 (d, *J* = 8.4 Hz, 1H), 1.31 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.45, 133.07, 89.81, 36.41, 31.55, 29.72, 28.91 – 27.96 (m), 15.06.

(S)-2-(4-chlorophenyl)-3-methylbutanoic acid (FVA): Prepared from the general procedure above (*Method A*) from esfenvalerate (96.7 mg, 0.23 mmol), 1M $KOH_{(aq)}$ (1.5 mL), and methanol (2.3 mL). The crude organic extract obtained from extraction of the acidified aqueous layer was purified by automated flash chromatography to afford the product as a clear oil (33.91 mg, 69%

yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.85 (s, 1H), 7.30 (s, 4H), 3.16 (d, *J* = 10.5 Hz, 1H), 2.32 (dhept, *J* = 10.5, 6.6 Hz, 1H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 179.94, 136.23, 133.40, 129.96, 128.73, 59.39, 31.66, 21.36, 20.02.

3-phenoxybenzaldehyde (PBA): Prepared from the general procedure above (*Method A*) from esfenvalerate (96.7 mg, 0.23 mmol), 1M $KOH_{(aq)}$ (1.5 mL), and methanol (2.3 mL). The crude organic extract obtained from extraction of the basic aqueous layer was purified by automated flash chromatography to afford the product as a white solid (14.33 mg, 31% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.99 (s, 1H), 7.63 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.49 (s, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.32 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 191.64, 158.43, 156.22, 138.09, 130.45, 130.07, 124.71, 124.60, 124.21, 119.52, 118.15. IR ($OC(CH_3)_2$): 3003*w* (arom. C-H), 2900 (aldehyde C-H), 1700*s* (aldehyde C=O), 1420*m* (arom. C-C).

(5-benzylfuran-3-yl)methanol (KD-OH): Prepared from the general procedure above (*Method A*) from kadethrin (100 mg, 0.25 mmol), 1M $NaOH_{(aq)}$ (0.5 mL), and methanol (1 mL). The crude organic extract obtained from extraction of the basic aqueous layer was purified by automated flash chromatography to afford the product as a white solid (26.6 mg, 47.4% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.32 (m, 3H), 7.29 – 7.25 (m, 3H), 6.08 (d, *J* = 1.0 Hz, 1H), 4.51 (s, 2H), 3.97 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.72, 138.80, 137.87, 128.76, 128.57, 126.61, 125.92, 106.54, 56.85, 34.63.

Table S2. The repellency EC_{50} in µg/cm^2 (95% confidence intervals) and slope (±SEM) of the concentration- response curves of 2-uncanone alone and 2-undecanone + TFA mixture and on three different species of anopheline mosquitoes.

Parameter	*Anopheles gambiae*	*Anopheles albimanus*	*Anopheles quadrimaculatus*
2-undecanone EC_{50}	39.4 (28–54)	47 (36–62)	49 (42–55)
Slope	–1.7±0.3	–1.1±0.2	–2.1±0.3
EC_{50} (+TFA)	6.7 (5–10)	7 (6–10)	13 (8–43)
Slope (+TFA)	–0.9±0.2	–1.0±0.2	–0.8±0.2
SR	5.9	6.7	3.8

Figure S2. Examples of typical EAG traces of control, TFA, PM, and TFA+PM in mixture (M) and side by side (S) treatment.

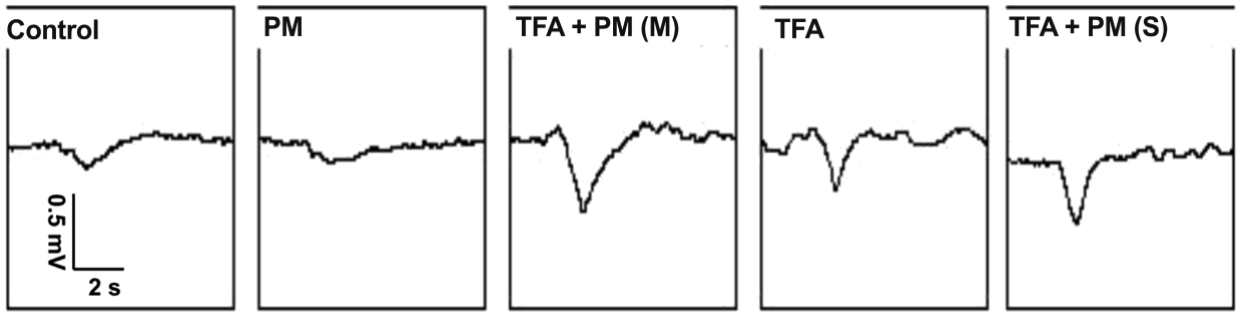

Figure S3. Percentage of baseline nerve firing rate in *Drosophila melanogaster* larval CNS after treatment with TFA, TCA, and transfluthrin (TF). Symbols are means with SEM, and error bars

for DMSO controls, TFA, and TCA are omitted for clarity. Asterisks indicate a significant difference between tested concentration and 0.1% DMSO control at each time point, where statistical significance at *P < 0.05, **P < 0.01, and ***P < 0.001 is by unpaired t-test.

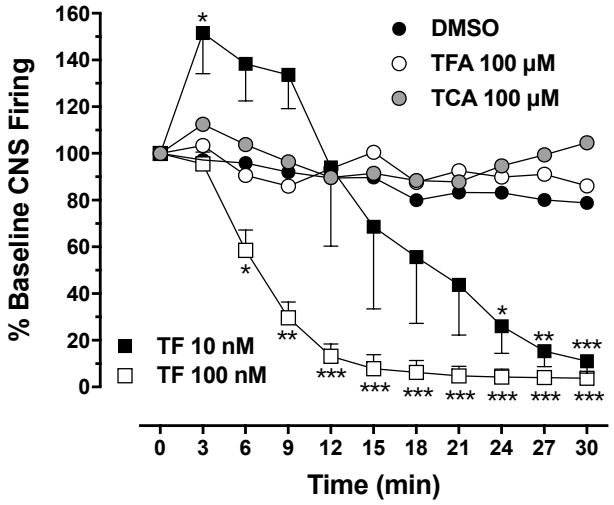

Table S3: The toxicity of selected compounds in a mouse oral toxicity test. Each capital letter represents a treated mouse, where "X" means it failed to survive or was in severe distress and was euthanized, and "O" means survival 24 hr after treatment.

Dose (mg/kg)	TCA	TFA	PBA[a]
2000			XX
1000			OOO
600	XXX	XXX	OO
400		XOO	
200	OOO	OOO	

[a]Co-application of 200 mg/kg TCA with PBA at either 200 mg/kg or 600 mg/kg showed no toxicity to mice.