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Synthesis and Stereostructure–Activity Relationship of Three Asymmetric Center Pyrethroids: 2-Methyl-3-phenylcyclopropylmethyl 3-Phenoxybenzyl Ether and Cyanohydrin Ester

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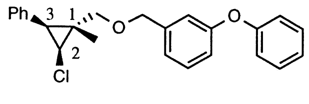
Abstract—2-Methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether **2** and cyanohydrin ester **3**, a couple of pyrethroids with *three asymmetric centers*, were synthesized. Of each of the four diastereomers of **2** and **3**, only the (1*R**,2*R**,3*R**)-**2a** and **3a** showed significant insecticidal activities. Dual sets of enantiomers [(1*R*,2*R*,3*R*)-(−)-**2a** and (1*S*,2*S*,3*S*)-(+)-**2a**] and [(1*R*,2*R*,3*R*)-(−)-**3a** and (1*S*,2*S*,3*S*)-(+)-**3a**] were synthesized through the asymmetric cyclopropanation using the Aratani catalyst. Significant separations of insecticidal activities were observed between both the enantiomers against the tobacco cutworm (*Spodoptera litura*) and the common mosquito (*Culex pipiens pallens*); (1*S*,2*S*,3*S*)-(+)-**2a** and (+)-**3a** showed higher activities than their antipodes (1*R*,2*R*,3*R*)-(−)-**2a** and (−)-**3a**. This result is the second example of such synthetic pyrethroids with *three asymmetric centers*. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Extensive research on the stereostructure–activity relationship of synthetic pyrethroid insecticides has progressed in the past few decades.[1] Considerable attention has been focused on the differences in insecticidal activities between their comparable diastereoisomers and enantioisomers, due to both the academic interest and recent environmental requirements for the pesticides.

Apparent chiral discrimination for insecticidal activities is observed in several cyclopropanecarboxylic acid series and related isosters (parentheses indicate the absolute configuration of the active form): [a] chrysanthemic acid and the dihalovinyl analogues[1] (1*R*, 3*R* or 3*S*); [b] fencyclate[2] (*S*); [c] the ring-opening analogues, fenvalerate,[3] fluvalinate,[4] and flucythrinate[5] (*S*); [d] their CF_3 analogue[6] (*R*); and [e] the 2-chloro-1-methyl-3-phenylcyclopropane-type **1**[7] (1*R*,2*S*,3*S*).



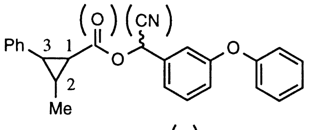
(1*R*,2*S*,3*S*)-**1**

This background and information prompt us to further investigate the pyrethroid derivative of type-[e] **1** with *three asymmetric centers*. In close connection with our continuing interest in the utilization of *gem*-dihalo- and halocyclopropanes,[8] we report here syntheses and stereostructure–activity relationships of a new isoster of cyclopropane pyrethroids with *three asymmetric centers*: 3-methyl-2-phenylcyclopropylmethyl 3-phenoxybenzyl ether **2** and cyano(3-phenoxyphenyl)methyl 3-methyl-2-phenylcyclopropanecarboxylate **3**.

Results and Discussion

Synthesis of all four racemic diastereomers of 2-methyl-3-phenylcyclopropane ether-type pyrethroids (2a–d)

Cu catalyzed cyclopropanation of ethyl diazoethylacetate with *E*-1-phenyl-1-propene (*trans*-β-methylstylene)



2 (**3**)

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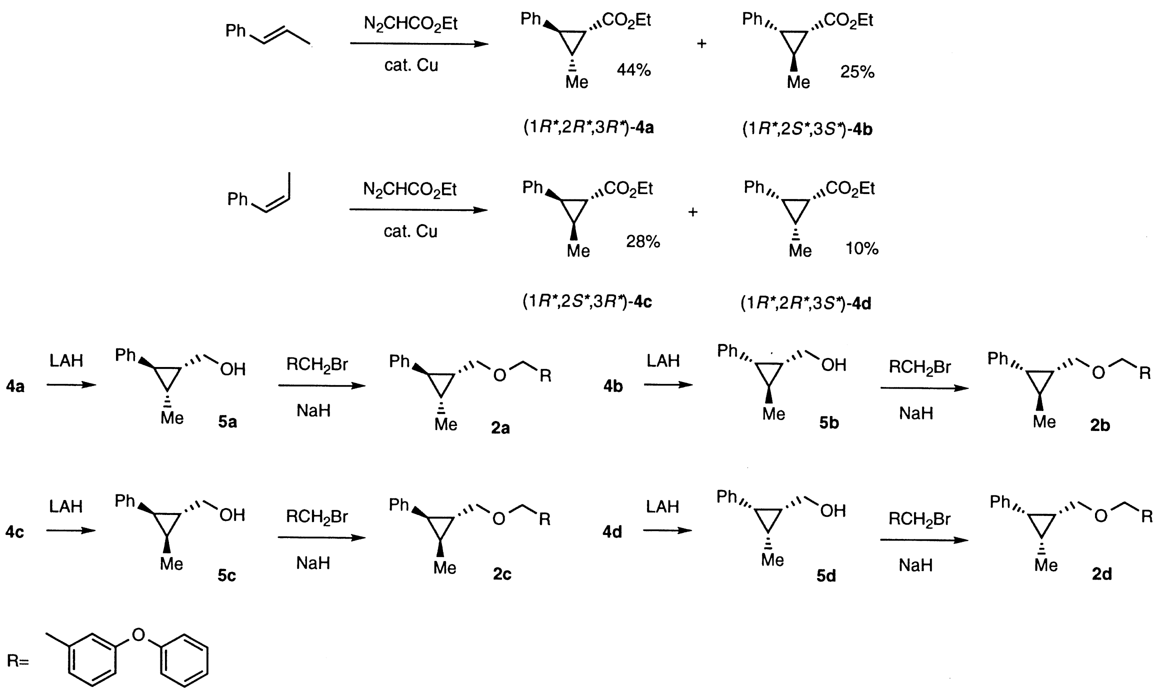
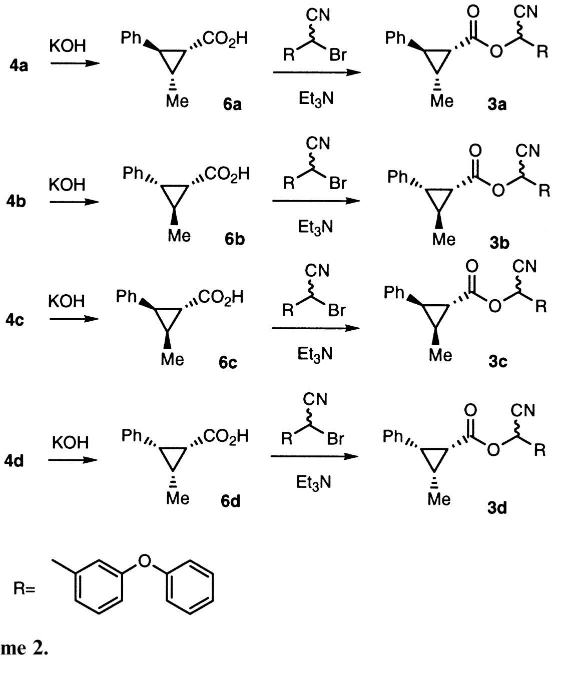


Scheme 1.

gave ethyl (1R*,2R*,3R*)-2-methyl-3-phenylcyclopropane carboxylate **4a** (44%) and the (1R*,2S*,3S*)-diastereomer **4b** (25%). Similarly, the reaction using Z-1-phenyl-1-propene (*cis*-β-methylstylene) gave the diastereomeric compounds (1R*,2S*,3R*)-**4c** (28%) and (1R*,2R*,3S*)-**4d** (10%). The LAH reduction of **4a–d** gave the corresponding 2-methyl-3-phenylcyclopropylmethanols **5a–d**, respectively. The independent couplings of **5a–d** with 3-phenoxybenzyl bromide furnished the desired four ether compounds (1R*,2R*,3R*)-**2a**, (1R*,2S*,3S*)-**2b**, (1R*,2S*,3R*)-**2c**, and (1R*,2R*,3S*)-**2d**. Scheme 1 illustrates these transformations.



Scheme 2.

Results of the bioassay revealed that only (1R*,2R*,3R*)-**2a** racemic diastereomer showed significant insecticidal activities against the tobacco cutworm and the common mosquito (vide infra).

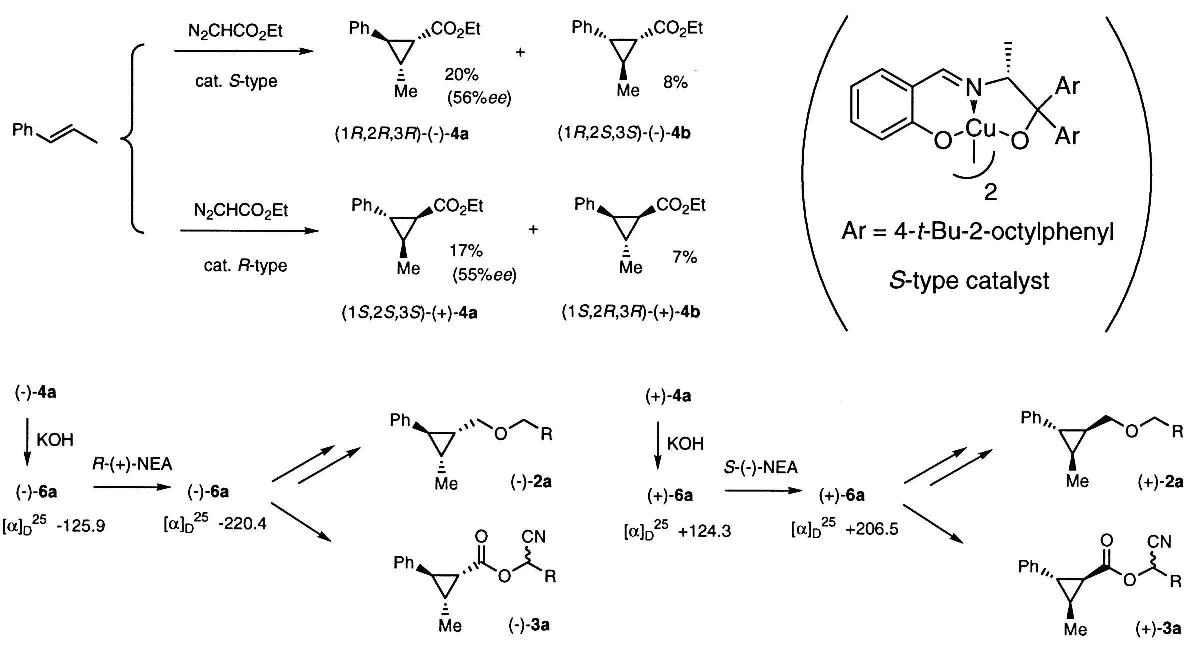
Synthesis of all four racemic diastereomers of 2-methyl-3-phenylcyclopropane cyanohydrin-type pyrethroids (3a–d)

Ethyl esters **4a–d** were hydrolyzed with KOH/MeOH-H_2O to give the corresponding carboxylic acids **6a–d**, respectively. The independent couplings of the acids **6a–d** with bromo(3-phenoxyphenyl)acetonitrile gave the desired cyanohydrin esters (1R*,2R*,3R*)-**3a**, (1R*,2S*,3S*)-**3b**, (1R*,2S*,3R*)-**3c**, and (1R*,2R*,3S*)-**3d**. Scheme 2 illustrates these transformations.

The results of bioassay revealed that only one racemic diastereomer (1R*,2R*,3R*)-**3a** showed significant insecticidal activity against the tobacco cutworm (vide infra).

Synthesis of a couple of optically active enantiomers of the most insecticidally active racemic diastereomers (1R*,2R*,3R*)-2a and -3a

For this purpose, we applied asymmetric cyclopropanation utilizing the Aratani catalyst.[9] As depicted in Scheme 3, the reaction of ethyl diazoacetate with *trans*-β-methylstylene by the action of the S-type catalyst mainly yielded (1R,2R,3R)-(−)-**4a** (20%; $[\alpha]_D^{25}$ −105.3) and (1R,2S,3S)-(−)-**4b** (8%; $[\alpha]_D^{25}$ −10.2). Following the similar manner using the antipodal R-type catalyst produced (1S,2S,3S)-(+)-**4a** (17%; $[\alpha]_D^{25}$ +103.2) and (1S,2R,3R)-(+)-**4b** (7%; $[\alpha]_D^{25}$ +10.3). Ethyl esters (−)-**4a** and (+)-**4a** were hydrolyzed to give carboxylic acids (1R,2R,3R)-(−)-**6b** ($[\alpha]_D^{25}$ −125.9) and (1S,2S,3S)-(+)-**6a** ($[\alpha]_D^{24}$ +124.3). The optical purities of these acids (−)-**6a** and (+)-**6b** were enriched by a further resolution



Scheme 3.

using optically active 1-(1-naphthyl)ethanamine (abbreviated NEA): use of *R*-(+)-NEA gave a purer sample of (−)-**6a** ($[\alpha]_D^{24}$ −220.4) and use of *S*-(−)-NEA gave that of (+)-**6a** ($[\alpha]_D^{24}$ +206.5).

The absolute configuration of these enantiomers was determined by applying Aratani's proposed mechanism according to the result of styrene.[9] The enriched samples of (−)-**4a** and (+)-**4a** were reduced by LAH to give alcohols (1*R*,2*R*,3*R*)-(−)-**5d** (92% ee by HPLC analysis) and (1*S*,2*S*,3*S*)-(+)-**5c** (86% ee by HPLC analysis), which were converted into the desired ethers (1*R*,2*R*,3*R*)-(−)-**2a** and (1*S*,2*S*,3*S*)-(+)-**2a**, respectively. Cyanohydrin esters (1*R*,2*R*,3*R*)-(−)-**3a** and (1*S*,2*S*,3*S*)-(+)-**3a** were also synthesized from (−)-**4a** and (+)-**4a** with bromo(3-phenoxyphenyl)acetonitrile, respectively.

Stereostructure–activity relationship of dual sets of four racemic diastereomers, 2a–d and 3a–d, and dual sets of (+)- and (−)-2a, (+)- and (−)- 3a

The insecticidal activity against the tobacco cutworm (*Spodoptera litura*) and the common mosquito (*Culex pipiens pallens*) was assessed for dual sets of all four racemic diastereomers **2a–d**. As listed in Table 1, the bioassay showed that racemic ether (1*R**,2*R**,3*R**)-**2a** had more significant insecticidal activities than the other three diastereomers **2b–d**. A similar tendency was observed on the stereostructure–activity relationship of cyanohydrin esters **3a–d**. In addition, there appeared a distinctive difference in the activities of both sets of the enantiomers **2a** and **3a**; (1*S*,2*S*,3*S*)-(+)-**2a** and **-3a** were active, while, in contrast (1*R*,2*R*,3*R*)-(−)-**2a** and **-3a** were inactive.

It should be noted that the relative configuration of either **2a** or **3a** was different from that of the active diastereomer of 2-chloro-1-methyl-3-phenylcyclopropane-type (1*R**,2*S**,3*S**)-**1**. Moreover, the absolute configurations of both 1- and 3-positions in (1*S*,2*S*,3*S*)-(+)-**2a** and **-3a** were reverse against the active (1*R*, 2*S*,3*S*)-**1** (cf. the reverse configuration of the C-3 position in **2** and **3** is indicated due to the sequence rule). This is the second example of the separation of activities of cyclopropane-type pyrethroids having *three asymmetric centers* in the cyclopropane ring. The stereochemistry of (1*S*,2*S*,3*S*)-**2a** and **-3a** would be superimposable to that of chrysanthemates and their dihalovinyl analogues[1] (1*R*,3*R* or 3*S*) (cf. also here, the reverse configurations of C-1 and C-3 positions are indicated). Cyanohydrin (+)-**3a** showed somewhat higher activities against both insects than ether (+)-**2a**. These results indicate the subtle nature of the relationship between insecticidal activity and geometry around the asymmetric center of these pyrethroids.

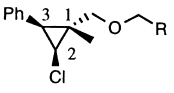
Taking these results into consideration, we interpret that **2a** and **3a** would resemble the chrysanthemate series whose cyanohydrins showed potent activities, rather than ether-type **1**. This study would shed some light on the question of which prochiral methyl group of chrysanthemate analogues orients itself to the receptor site in three dimensions.[10]

In conclusion, of the eight stereoisomers including the enantiomers of the synthetic pyrethroids, 2-methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether **2** and the cyanohydrin ester **3**, which have been synthesized, their (1*S*,2*S*,3*S*)-forms showed significant insecticidal activity against the tobacco cutworm and the common mosquito. These results suggest that total geometry around the three asymmetric centers of the (1*R*,2*S*,3*S*)-enantiomers is significant for the compound to be an active insecticide.**Scheme 2.**

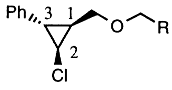
Table 1. Insecticidal activity of ethers **2** and cyanohydrin esters **3**[a]

Compound		Mortality (%)					
		Tobacco cutworm			Common mosquito[b]		
		500	200	50 (ppm)	500	200	50 (ppm)
1*R**,2*R**,3*R**	**2a**	100	—	—	A-B	—	—
1*R**2*S**3*S**	**2b**	0	—	—	C	—	—
1*R**,2*S**,3*R**	**2c**	0	—	—	C	—	—
1*R**,2*R**,3*S**	**2d**	0	—	—	B-C	—	—
1*R*,2*R*,3*R*	(−)-**2a**	95	15	0	B	C	C
1*S*,2*S*,3*S*	(+)-**2a**	100	90	45	A	B	C
1*R**,2*R**,3*R**	**3a**	100	—	—	A	—	—
1*R**,2*S**,3*S**	**3b**	0	—	—	C	—	—
1*R**,2*S**,3*R**	**3c**	0	—	—	B	—	—
1*R*,2*R**,3*S**	**3d**	0	—	—	C	—	—
1*R*,2*R*,3*R*	(−)-**3a**	100	55	5	B	B-C	C
1*S*,2*S*,3*S*	(+)-**3a**	100	100	100	A	A	A
Untreated	—	0	0	0	C	C	C

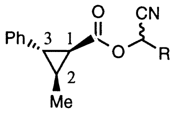
[a] Method of bioassay is described in Experimental section.
[b] Criteria of the mortality are as follows: A, >90%; B, 10–90%; C, <10%.



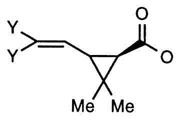
(1*R*,2*S*,3*S*)-(-)-**1**



(1*S*,2*S*,3*S*)-(+)-**2a**



(1*S*,2*S*,3*S*)-(+)-**3a**



Y = Me, halogen, CF_3

(1*R*,3*R* or 3*S*)

chrysanthemate analogs

Experimental

Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and are uncorrected. ^1H NMR spectra were recorded on a JEOL α (400 MHz) or EX-90 (90 MHz) spectrometer using a TMS internal standard in $CDCl_3$. IR spectra were recorded on a JASCO FT/IR-8000 spectrophotometer. All reagents and solvents were purified prior to use. Silica gel column chromatography was performed on a Merck Art. 7734 and 9385. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter and given in units of 10^{-1} deg cm^2 g^{-1}. HPLC analyses were performed using a Shimadu LC-10A system with UV (254 nm) detector.

Ethyl (1*R,2*R**,3*R**)- and (1*R**,2*S**,3*S**)-2-methyl-3-phenylcyclopropanecarboxylates (4a and 4b).**[11] Ethyl diazoacetate (1 M CH_2Cl_2 solution; 11.0 mL, 11 mmol) was added to a stirred suspension of *E*-1-phenyl-1-propene (5.39 g, 46 mmol) and Cu-powder (50 mg) at 60–65 °C, and the mixture was stirred for 2 h at that temp. The mixture was filtered through paper and was subjected to SiO_2 column chromatography (hexane:ether = 20:1) to give (1*R**,2*R**,3*R**)-**4a** (987 mg, 44%) and (1*R**,2*S**,3*S**)-**4b** (561 mg, 25%). **4a**: Colourless oil; ^1H NMR (400 MHz) δ 1.28 (3H, t, J = 7.2 Hz), 1.35 (3H, d, J = 6.1 Hz), 1.63–1.73 (1H, m), 2.02 (1H, dd, J_{trans} = 4.9 Hz, J_{cis} = 9.3 Hz), 2.41 (1H, dd, J_{trans} = 5.0 Hz, J_{trans} = 6.5 Hz), 4.17 (2H, q, J = 7.2 Hz), 7.06–7.11 (2H, m), 7.14–7.22 (1H, m), 7.24–7.35 (2H, m). **4b**: ^1H NMR (400 MHz) δ 0.98 (3H, t, J = 7.2 Hz), 1.35 (3H, d, J = 6.1 Hz), 1.82 (1H, dd, J_{trans} = 5.1 Hz, J_{cis} = 9.3 Hz), 2.03–2.12 (1H, m), 2.35 (1H, dd, J_{trans} = 6.8 Hz, J_{cis} = 9.3 Hz), 3.87 (2H, q, J = 7.2 Hz), 7.15–7.35 (5H, m).

Ethyl (1*R,2*S**,3*R**)- and (1*R**,2*R**,3*S**)-2-methyl-3-phenylcyclopropanecarboxylates (4c and 4d).**[11] Following similar procedure using *Z*-1-phenyl-1-propene in the place of *E*-1-phenyl-1-propene, (1*R**,2*S**,3*R**)-**4c** (28%) and (1*R**,2*R**,3*S**)-**4d** (10%) were obtained. **4c**: ^1H NMR (400 MHz) δ 0.92 (3H, d, J = 6.1 Hz), 1.30 (3H, t, J = 7.3 Hz), 1.68–1.95 (2H, m), 2.76 (1H, dd, J_{cis} = 9.5 Hz, J_{trans} = 5.1 Hz), 4.18 (2H, q, J = 7.3 Hz), 7.15–7.34 (5H, m). **4d**: ^1H NMR (400 MHz) δ 1.18 (3H, t, J = 7.1 Hz), 1.30 (1H, d, J = 6.6 Hz), 1.69–1.93 (1H, m), 2.06 (1H, dd, J_{cis} = 9.0 Hz, J_{cis} = 8.8 Hz), 2.62 (1H, dd, J_{cis} = 9.3 Hz, J_{cis} = 9.6 Hz), 4.05 (2H, q, J = 7.3 Hz), 7.15–7.34 (5H, m).

(1*R,2*R**,3*R**)-2-Methyl-3-phenylcyclopropylmethanol (5a).**[12] Ester (1*R**,2*R**,3*R**)-**4a** (262 mg, 1.49 mmol) in THF (1.0 mL) was added to a stirred suspension of $LiAlH_4$ (57 mg, 1.49 mmol) in THF (1.0 mL) at 0–5 °C, and the mixture was stirred for 1 h at that temp. Aqueous satd. Na_2SO_4 was added to the mixture, which was filtered with Celite using ether. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The crude oil was subjected to SiO_2 column chromatography (hexane:AcOEt = 3:1) to give (1*R**,2*R**,3*R**)-**5a** (241 mg, 70%). Colourless liquid; ^1H NMR (400 MHz) δ 1.27 (3H, d, J = 5.9 Hz), 1.26–1.38 (1H, m), 1.47–1.57 (2H, m), 1.50–1.77 (1H, br, OH), 3.54–3.72 (1H, m), 3.87–3.93 (1H, m), 7.00–7.36 (5H, m).

Following a similar procedure as described above, alcohols (1*R**,2*S**,3*S**)-**5b** (81%), (1*R**,2*S**,3*R**)-**5c** (79%) and (1*R**,2*R**,3*S**)-**5d** (74%) were prepared from esters **4b**, **4c** and **4d**, respectively. **5b**: Colourless liquid; ^1H NMR (400 MHz) δ 1.20–1.33 (2H, m), 1.24 (3H, d, J = 5.4 Hz), 1.65 (H, brs, OH), 1.99 (1H, dd, J_{cis} = 8.5 Hz,

J_{trans} = 5.4 Hz), 3.30 (1H, dd, J = 8.2 Hz, J = 11.6 Hz), 3.44–3.60 (1H, dd, J = 6.1 Hz, J = 11.6 Hz), 7.14–7.31 (5H, m). **5c**: colourless liquid; ^{1}H NMR (400 MHz) δ 0.86 (3H, d, J = 6.1 Hz), 1.06–1.16 (1H, m), 1.34–1.42 (1H, m), 2.00 (1H, dd, J_{cis} = 9.3 Hz, J_{trans} = 5.1 Hz), 3.66 (2H, d, J = 7.1 Hz), 7.16–7.32 (5H, m). **5d**: colourless liquid; ^{1}H NMR (90 MHz) δ 0.70–1.70 (3H, m), 1.02 (3H, d, J = 6.3 Hz), 2.25 (1H, m), 3.30–3.62 (1H, m), 3.60–3.96 (1H, m), 7.08–7.62 (5H, m).

(1R*,2R*,3R*)-2-Methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether (2a). A mixture of alcohol (1R*,2R*,3R*)-**5a** (162 mg, 1.0 mmol) and 3-phenoxybenzyl bromide (316 mg, 1.2 mmol) in DMF (1.0 mL) was added to a stirred suspension of NaH (60%, 29 mg, 1.2 mmol) in DMF (1.0 mL) at 0–5 °C and the mixture was stirred at room temp for 2 h. Water was added to the mixture, which was extracted with ether. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The crude oil was subjected to SiO_2 column chromatography (hexane:AcOEt = 20:1) to give the desired ether (1R*,2R*,3R*)-**2a** (241 mg, 70%). Colourless liquid; ^{1}H NMR (400 MHz) δ 1.19 (3H, d, J = 6.1 Hz), 1.24–1.36 (1H, m), 1.45 (1H, dd, J_{trans} = 5.1 Hz, J_{trans} = 5.1 Hz), 1.46–1.55 (1H, m), 3.46 (1H, d, J = 8.5 Hz, J_{gem} = 10.2 Hz), 3.75 (1H, dd, J = 5.9 Hz, J_{gem} = 10.2 Hz), 4.49 (1H, d, J_{gem} = 12.2 Hz), 4.55 (1H, d, J_{gem} = 12.2 Hz), 6.90–7.38 (14H, m); IR (neat) 2866, 1586, 1487 cm^{-1}. Anal. calcd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.3; H, 6.7.

Following a similar procedure as described above, ethers (1R*,2S*,3S*)-**2b** (67%), (1R*,2S*,3R*)-**2c** (65%), and (1R*,2R*,3S*)-**2d** (60%) were prepared from alcohols **5b**, **5c** and **5d**, respectively. **2b**: Colourless liquid; ^{1}H NMR (400 MHz) δ 1.17–1.28 (2H, m), 1.22 (3H, d, J = 6.3 Hz), 1.96 (1H, dd, J_{trans} = 4.5 Hz, J_{cis} = 8.7 Hz), 3.15 (1H, dd, J = 6.2 Hz, J_{gem} = 10.4 Hz), 3.28 (1H, d, J = 7.4 Hz, J_{gem} = 10.4 Hz), 4.24 (1H, d, J_{gem} = 12.0 Hz), 4.27 (1H, d, J_{gem} = 12.0 Hz), 6.84–7.40 (14H, m); IR (neat) 2866, 1586, 1489 cm^{-1}. **2c**: Colourless liquid; ^{1}H NMR (400 MHz) δ 0.84 (3H, d, J = 6.3 Hz), 1. 08-1.12 (1H, m), 1.29–1.37 (1H, m), 1.96 (1H, dd, J_{trans} = 5.1 Hz, J_{cis} = 9.3 Hz), 3.43–3.50 (1H, m), 3.54–3.60 (1H, m), 4.55 (2H, s), 6.90–7.38 (14H, m); IR (neat) 2865, 1586, 1487 cm^{-1}. **2d**: Colourless liquid; ^{1}H NMR (400 MHz) δ 0.97 (3H, d, J = 6.6 Hz), 1.29–1.40 (1H, m), 1.43–1.53 (1H, m), 2.23 (1H, dd, J_{cis} = 9.0 Hz, J_{cis} = 9.0 Hz), 3.28–3.36 (1H, m), 3.52–3.58 (1H, m), 4.44 (2H, s), 6.90–7.36 (14H, m); IR (neat) 2857, 1586, 1487 cm^{-1}.

(1R*,2R*,3R*)-2-Methyl-3-phenylcyclopropanecarboxylic acid (6a).[13] A mixture of ester (1R*,2R*,3R*)-**4a** (0.50 g, 2.43 mmol) and KOH (1.37 g, 24.4 mmol) in H_2O:MeOH (1:2, 9 mL) was stirred at room temp. for 3 h. After evaporation of MeOH, aqueous 4 M HCl was added to the mixture for adjusting this to pH 2. The mixture was extracted with ether and the organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give (1R*,2R*,3R*)-**6a** (400 mg, 93%). Colourless crystals; mp 66–68 °C; ^{1}H NMR (400 MHz) δ 1.40 (3H, d, J = 6.3 Hz), 1.78–1.83 (1H, m), 2.03 (1H, dd, J_{trans} = 5.0 Hz, J_{cis} = 9.1 Hz), 2.47 (1H, dd, J_{trans} = 5.0 Hz, J_{trans} = 6.8 Hz), 7.06–7.11 (2H, m), 7.16–7.23 (1H, m), 7.24–7.32 (2H, m).

Following a similar as procedure described above, acids (1R*,2S*,3S*)-**6b** (94%), (1R*,2S*,3R*)-**6c** (92%) and (1R*,2R*,3S*)-**6d** (92%) were prepared from esters **4b**, **4c** and **4d**, respectively. **6b**: Colourless crystals; mp 87–91 °C; ^{1}H NMR (400 MHz) δ 1.26 (3H, d, J = 5.9 Hz), 1.78 (1H, dd, J_{cis} = 9.1 Hz, J_{trans} = 5.0 Hz), 1.95–2.08 (1H, m), 2.41 (1H, dd, J_{trans} = 7.3 Hz, J_{cis} = 9.1 Hz), 7.15–7.35 (5H, m). **6c**: Colourless crystals; mp 63–67 °C; ^{1}H NMR (400 MHz) δ 0.94 (3H, d, J = 5.9 Hz), 1.78–1.83 (1H, m), 1.82–1.92 (2H, m), 2.84 (1H, dd, J_{trans} = 5.0 Hz, J_{cis} = 9.5 Hz), 7.20–7.40 (5H, m). **6d**: Colourless crystals; ^{1}H NMR (400 MHz) δ 1.28 (3H, d, J = 6.6 Hz), 1.76–1.87 (1H, m), 2.05 (1H, dd, J_{cis} = 8.6 Hz, J_{cis} = 8.8 Hz), 2.70 (1H, dd, J_{cis} = 8.7 Hz, J_{cis} = 9.0 Hz), 7.20–7.40 (5H, m).

Cyano(3-phenoxyphenyl)methyl (1R*,2R*,3R*)-2-methyl-3-phenylcyclopropanecarboxylate (3a). Et_3N (58 mg, 0.57 mmol) was added to a stirred mixture of carboxylic acid **6a** (92 mg, 0.52 mmol) and bromo(3-phenoxyphenyl) acetonitrile (150 mg, 0.52 mmol) in acetone (1.0 mL) at 0–5 °C, and the mixture was stirred at room temp. for 2 h. Aqueous 1 M HCl was added to the mixture, which was extracted with ether. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The crude oil was subjected to SiO_2 column chromatography (hexane:AcOEt = 12:1) to give cyanohydrin ester (1R*,2R*,3R*)-**3a** (139 mg, 70%). Yellow oil; ^{1}H NMR (400 MHz) δ 1.31 (3H × 1/2, d, J = 6.1 Hz), 1.39 (3H × 1/2, d, J = 6.4 Hz), 1.75–1.90 (1H, m), 2.08 (1H × 1/2, dd, J_{trans} = 4.4 Hz, J_{cis} = 9.3 Hz), 2.08 (1H × 1/2, dd, J_{trans} = 4.6 Hz, J_{cis} = 9.0 Hz), 2.47 (1H × 1/2, dd, J_{trans} = 4.9 Hz, J_{trans} = 6.8 Hz), 2.51 (1H × 1/2, dd, J_{trans} = 4.9 Hz, J_{trans} = 6.8 Hz), 6.40 (1H × 1/2, s), 6.43 (1H × 1/2, s), 7.00–7.43 (14H, m); IR (neat) 2359, 1740, 1588 cm^{-1}. Anal. calcd for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52. Found: C, 78.1; H, 5.1.

Following the similar procedure described above, cyanohydrin esters (1R*,2S*,3S*)-**3b** (47%), (1R*,2S*,3R*)-**3c** (60%), and (1R*,2R*,3S*)-**3d** (66%) were prepared from esters **6b**, **6c** and **6d**, respectively. **3b**: ^{1}H NMR (400 MHz) δ 1.29 (3H × 1/2, d, J = 6.1 Hz), 1.31 (3H × 1/2, d, J = 6.1 Hz), 1.91 (3H × 1/2, dd, J_{trans} = 4.9 Hz, J_{cis} = 8.8 Hz), 1.93 (3H × 1/2, dd, J_{trans} = 5.1 Hz, J_{cis} = 9.0 Hz), 2.07–2.20 (1H, m), 2.46–2.56 (1H, m), 6.11 (1H × 1/2, s), 6.12 (1H × 1/2, s), 6.90–7.43 (14H, m); IR (neat) 2365, 1741, 1588 cm^{-1}. **3c**: ^{1}H NMR (400 MHz) δ 0.93 (3H × 1/2, d, J = 6.1 Hz), 0.96 (3H × 1/2, d, J = 6.1 Hz), 1.84–1.95 (2H, m), 2.82–2.90 (1H, m), 6.41 (1H × 1/2, s), 6.42 (1H × 1/2, s), 7.00–7.43 (14H, m); IR (neat) 2361, 1740, 1588 cm^{-1}. **3d**; ^{1}H NMR (400 MHz) δ 1.27 (3H × 1/2, d, J = 6.6 Hz), 1.31 (3H × 1/2, d, J = 6.8 Hz), 1.76–1.96 (1H, m), 2.16 (1H × 1/2, dd, J_{cis} = 9.0 Hz, J_{cis} = 8.5 Hz), 2.17 (1H × 1/2, dd, J_{cis} = 9.0 Hz, J_{cis} = 8.5 Hz), 2.77 (1H × 1/2, dd, J_{cis} = 9.0 Hz, J_{cis} = 9.3 Hz), 2.82 (1H × 1/2, dd, J_{cis} = 9.0 Hz, J_{cis} = 9.3 Hz), 6.32 (1H × 1/2, s), 6.33 (1H × 1/2, s), 6.99–7.44 (14H, m); IR (neat) 2361, 1750, 1588 cm^{-1}.

Ethyl (1*S*,2*S*,3*S*)-(+)- and (1*S*,2*R*,3*R*)-(+)-2-methyl-3-phenylcyclopropanecarboxylates [(+)-4a and (+)-4b].[14] Ethyl diazoacetate (1 M CH_2Cl_2 solution; 10.0 mL, 10 mmol) was added to a stirred suspension of *E*-1-phenyl-1-propene (1.53 g, 13 mmol) and the *R*-type Aratani catalyst[9] (160 mg, 0.10 mmol) at 60–65 °C, and the mixture was stirred for 2 h at 80 °C. After being cooled down, the mixture was subjected to SiO_2 column chromatography (hexane:ether = 20:1) to give (1*R*,2*R*,3*R*)-(+)-**4a** (400 mg, 17%) and (1*R*,2*S*,3*S*)-(+)-**4b** (158 mg, 7%). (+)-**4a**: Colourless oil; $[\alpha]_D^{25}$ +103.2 (*c* 0.47, $CHCl_3$); 55% *ee* estimated by that of (+)-**5a** determined by HPLC analysis. (+)-**4b**: Colourless oil; $[\alpha]_D^{25}$ +10.3 (*c* 0.77, $CHCl_3$).

Ethyl (1*R*,2*R*,3*R*)-(−)- and (1*R*,2*S*,3*S*)-(−)-2-methyl-3-phenylcyclopropanecarboxylates [(−)-4a and (−)-4b]. Following a similar procedure as described above, using the *S*-type catalyst[9] in the place of *R*-type catalyst, (1*R*,2*R*,3*R*)-(−)-**4a** (20%) and (1*R*,2*S*,3*S*)-(−)-**4b** (8%) were prepared. (−)-**4a**: Colourless oil; $[\alpha]_D^{25}$ −105.3 (*c* 0.75, $CHCl_3$), 56% *ee*. (−)-**4b**: Colourless oil; $[\alpha]_D^{25}$ −10.2 (*c* 0.11, $CHCl_3$).

(1*S*,2*S*,3*S*)-(+)- and (1*R*,2*R*,3*R*)-(−)-2-Methyl-3-phenylcyclopropanecarboxylic acids [(+)-6a and (−)-6a]. Following similar procedure for the hydrolysis of **4a**, carboxylic acid a (1*S*,2*S*,3*S*)-(+)-**6a** {$[\alpha]_D^{25}$ +124.3 (*c* 0.32, $CHCl_3$)} and (1*S*,2*R*,3*R*)-(−)-**6a** {$[\alpha]_D^{25}$ −125.9 (*c* 1.00, $CHCl_3$)} were prepared from esters (+)-**4a** and (−)-**4a**, respectively. This (+)-**6a** (400 mg, 2.3 mmol) and *S*-(−)-NEA (393 mg, 2.3 mmol) in EtOH (8 mL) was seeded with material from a small-scale recrystallization, and allowed to stand at room temp. for 24 h. The first salt (271 mg, 34%) obtained was decomposed with 1 M HCl and extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated to give more optically active (+)-**6a** (137 mg, 59%) as colourless crystals: mp 80–84 °C; $[\alpha]_D^{25}$ +206.5 (*c* 0.40, $CHCl_3$). Similarly, more optically active (−)-**6a** was obtained using *R*-(+)-NEA as colourless crystals: mp 83–87 °C, $[\alpha]_D^{25}$ −220.4 (*c* 1.00, $CHCl_3$).

(1*S*,2*S*,3*S*)-(+)- and (1*R*,2*R*,3*R*)-(−)-2-Methyl-3-phenylcyclopropylmethanol [(+)-5a and (−)-5a]. Following a similar procedure for the reduction of **6a**, alcohols (1*S*,2*S*,3*S*)-(+)-**5a** and (1*R*,2*R*,3*R*)-(-)-**5a** were prepared from (+)-**6a** (91%) and (−)-**6a** (92%), respectively. (+)-**5a**: Colourless oil; $[\alpha]_D^{24}$ +9.5 (*c* 0.20, $CHCl_3$); 86% *ee* (HPLC analysis). (−)-**5a**: $[\alpha]_D^{25}$ −10.0 (*c* 0.15, $CHCl_3$), 92% *ee* (HPLC analysis). Procedure of the determination of *ee*: (+)-**5a** was analyzed with HPLC (Chiralcel OB; Daicel, 4.6f×250 mm, C_6H_{14}:MeOH 98:2, 1.0 ml/min as eluent, column temperature of 24.0 °C, UV detection at 255 nm). R_t of (−)-**5a** was 24.0 min, and R_t of (+)-**5a** was 27.0 min.

(1*S*,2*S*,3*S*)-(+)- and (1*R*,2*R*,3*R*)-(−)-2-Methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ethers [(+)-2a and (−)-2a]. Following a similar procedure for the coupling using alcohol **4a**, ethers (1*S*,2*S*,3*S*)-(+)-**2a** (71%) and (1*R*,2*R*,3*R*)-(−)-**2a** (70%) were prepared from alcohols (+)-**4a** and (−)-**4a**, respectively. (+)-**2a**: Colourless oil; $[\alpha]_D^{25}$ +27.4 (*c* 0.93, $CHCl_3$). (−)-**2a**: Colourless oil, $[\alpha]_D^{25}$ −27.7 (*c* 0.98, $CHCl_3$).

Cyano(3-phenoxyphenyl)methyl (1*S*,2*S*,3*S*)-(+)- and (1*S*,2*R*,3*R*)-(−)-2-methyl-3-phenylcyclopropanecarboxylate [(+)-3a and (−)-3a]. Following the similar procedure for the coupling using acid **6a**, cyanohydrin esters (1*S*,2*S*,3*S*)-(+)-**3a** (60%) and (1*R*,2*R*,3*R*)-(−)-**3a** (68%) were prepared from acids (+)-**6a** and (−)-**6a**, respectively. (+)-**3a**: Colourless oil; $[\alpha]_D^{25}$ +98.3 (*c* 0.53, $CHCl_3$). (−)-**3a**: Colourless oil, $[\alpha]_D^{25}$ −99.7 (*c* 0.48, $CHCl_3$).

Assay of the insecticidal activity against tobacco cutworm (*Spodoptera litura*) and common mosquito (*Culex pipiens pallens*)

1. For the tobacco cutworm (*Spodoptera litura*), an artificial diet method was used. To an artificial diet (13 g, of Insecta·LF; Nippon Nousan Kogyo Co., Ltd.) in a plastic cup were added 2 mL portions of pre-determined concentrations of test samples (500, 200, and 50 ppm). Ten fourth-instar larvae were released on the diet. Six days after the treatment at 25 °C, the mortality was observed (two replicants).
2. For the common mosquito (*Culex pipiens pallens*), an immersion method was used. To de-ionized water (100 mL) was applied 0.7 mL portions of pre-determined concentrations of test samples (500, 200, and 50 ppm). Twenty last-instar larvae were released therein. Mortality was assessed after 24 h (two replicants).

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