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ARTICLE

Synthesis and insecticidal efficacy of pyripyropene derivatives focusing on the C-1, C-7, and C-11 positions' substituent groups

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Abstract

The C-1, C-7, and C-11 positions of pyripyropene A were chemically modified to improve the insecticidal activity. Some derivatives showed higher insecticidal activities against aphids than pyripyropene A. In particular, the derivative **5c**, which possesses three cyclopropyl carbonyl groups at the C-1, C-7, and C-11 positions, had excellent insecticidal activity levels in field and laboratory trials.

Introduction

Pyripyropene (PP) analogs were first isolated as inhibitors toward acyl-CoA:cholesterol O-acyltransferase (ACAT), which is the target of an antilipotropic drug derived from the culture broth of *Aspergillus fumigatus* FO-1289 by Ōmura et al. at the Kitasato Institute [1–5] and were next isolated from *Penicillium coprobium* PF1169 as anthelmintic compounds by Meiji Seika Pharma [6]. The structure of PP consists of poly-oxygenated mixed polyketide-terpenoid metabolites, which are categorized as meroterpenoids, containing a fused pyridyl α-pyrone moiety and eight contiguous stereocenters [7].

As reported previously, PP derivatives have been investigated as a potent ACAT inhibitor by the Kitasato Institute [8–14]. PP-A (Fig. 1), which is a natural PP analog, has a high level of insecticidal activity against aphids in insecticidal screening tests of Meiji's natural product library [15]. Furthermore, PP-A is highly effective by both foliar application and soil drench, having a narrow but unique insecticidal spectrum. Aphids and whiteflies commonly occur and seriously damage a variety of crops. Unlike for lepidopteran pests, few genetically modified crops for controlling these sucking pests are not available, even though some toxins for aphid control have been discovered [16]. Control of these pests has mainly been implemented by chemicals and biological products, such as natural enemies and insecticidal fungi. Recently, because sucking pests are reported to frequently develop resistance to commercial standards, such as neonicotinoid, organophosphate, and synthetic pyrethroid insecticides, new insecticides to control such problematic sucking pests are strongly desired [17, 18]. In the previous toxicological information report for PP-A, no serious issues were observed related to mammalian toxicity [15]. Thus PP-A has promise as a novel insecticide; therefore, its optimization was initiated.

In this report, we investigated the effects on the insecticidal activities caused by chemical modifications at the C-1, C-7, and C-11 positions to determine the derivatives having stronger activities than PP-A against insects. The insecticidal spectrums of the derivatives with high insecticidal activity were also evaluated. Furthermore, we conducted the field trials of the most promising derivative to confirm the efficacy on practical uses in the field. Since a foliar spray cannot often cover the whole leaves and shoots under field conditions, it is commonly crucial for the agrochemicals to exhibit good systemicity on/into the leaves or to the young developing leaves to control sucking pests like aphids that preferably infest on young leaves' crops.

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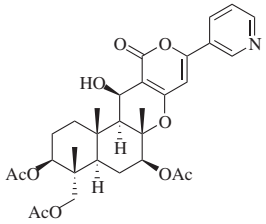


pyripyropene A

Fig. 1 Structure of pyripyropene A (PP-A)

Results and Discussion

First, the evaluation of the insecticidal activities of several PP derivatives (**1a–g**) with chemical modifications at the C-1, C-7, and C-11 positions, which were reported by the Kitasato Institute [9], was conducted, focusing on the insecticidal activity against *Myzus persicae*, an important aphid in agriculture.

The structures and insecticidal activities of PP derivatives are shown in Table 1.

Interestingly, the insecticidal activities of **1f** (pyripyropene I, PP-I) [4] and **1g** having propionyl and *n*-butyryl groups, respectively, at the C-1, C-7 and C-11 positions are stronger than that of PP-A. Among these derivatives, **1f** (PP-I) had the highest insecticidal activity, at 10 times higher, against aphids. Among the derivatives with other substituent groups at the C-7 position, **1e**, having a 3-pyridyl carbonyl group, showed relatively high insecticidal activities, while **1a** (hydrogen atom), **1b** (propionyl group), **1c** (*n*-butyryl group), and **1d** (benzoyl group) showed weak insecticidal activities. Thus the substituent groups at the C-1, C-7, and C-11 positions are important for the high insecticidal activity.

Next, the structural conversion of the propionyl group at the C-7 position of **1f** (PP-I) to other acyl groups was attempted to further improve the insecticidal activity. The synthesis of PP derivatives with chemical modifications at the C-7 position, including the key step for regioselective hydrolysis, was reported by our group [8]. The preparation of novel PP derivatives **4a–n** commenced with the hydrolysis of the triacetate of PP-A, followed by tripropionylation to produce pyripyropene I (**1f**), which was successively subjected to regioselective hydrolysis at the C-7 position using 1.8-diazabicyclo[5.4.0]-undec-7-ene (DBU) to furnish 7-depropionylpyripyropene I (**3**). Finally, acylation at the C-7 position using a corresponding carboxylic anhydride with triethylamine or carboxylic acid with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) in the presence of 4-(dimethylamino) pyridine (DMAP) produced **4a–n** as shown in Scheme 1.

The structures and insecticidal activities of **4a–n** are shown in Table 2.

The **4** series were evaluated for insecticidal activity against aphids using the same screening assay.

As a result of this study, **4g** (3-pyridylcarbonyl group) showed the highest activity level against aphids. The LC_{90} value of this compound was lower than **4h** (2-pyridylcarbonyl group) and **4i** (4-pyridylcarbonyl group) and was similar to that of the lead compound **1f**. Interestingly, introducing some substituents (chloro, trifluoromethyl, or methyl group) on the 3-pyridine ring at the C-7 position of **4g**, such as **4j**, **4k**, **4l**, **4m**, or **4n**, resulted in a decreased activity level. The conversion to a hydrogen atom (**3**), acetyl (**4a**), *i*-butyryl (**4b**), pivaloyl (**4c**), cyclopropylcarbonyl (**4d**), cyclobutylcarbonyl (**4e**), or benzoyl group (**4f**) at the C-7 position of **1f** did not increase the activity compared with that of **1f**. Thus the 3-pyridylcarbonyl group could be valuable at the C-7 position in PP derivatives having propionyl groups at the C-1 and C-11 positions.

In parallel with the chemical conversion at the C-7 position of **1f**, the novel derivatives **5a–j**, which have the same acyl group at the C-1, C-7, and C-11 positions, were generated by the treatment of **2** with a corresponding carboxylic anhydride with triethylamine or carboxylic acid with EDCI in the presence of DMAP using the synthetic route shown in Scheme 2.

The structures and insecticidal activities of **5a–j** are shown in Table 3.

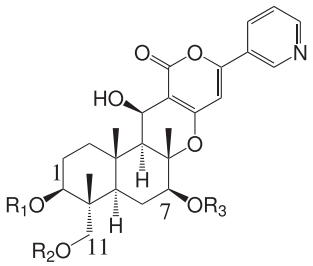
The **5** series were evaluated for insecticidal activity against aphids using the same screening assay.

As the result of this study, **5c** (cyclopropylcarbonyl group) and **5d** (cyclobutylcarbonyl group) showed higher activity levels against aphids than lead compound **1f**. In contrast, the derivatives possessing a hydrogen atom (**2**), *i*-butyryl (**5a**), pivaloyl (**5b**), cyclohexylcarbonyl (**5e**), benzoyl (**5f**), or pyridylcarbonyl group (**5g**, **5h**, **5i**, or **5j**) at the C-1, C-7, and C-11 positions did not increase the activity level compared with lead compound **1f**. Thus the cyclopropylcarbonyl or cyclobutylcarbonyl group could be valuable at the C-1, C-7, and C-11 positions in PP derivatives having the same substituents at the C-1, C-7, and C11 positions.

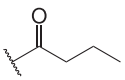
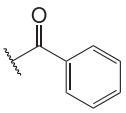
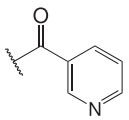
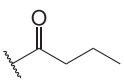
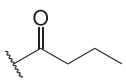
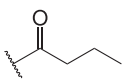
Here **5c** showed the highest insecticidal activity against aphids and **5c** was over 21 times stronger than PP-A based on the LC_{90} values.

Moreover, in evaluating the insecticidal spectra of the derivatives with higher activity than PP-A of **1f**, **4g**, and **5c** against other important sucking pests, **5c** exhibited higher insecticidal activities against *Aphis gossypii* and *Trialeurodes vaporariorum* than PP-A (Table 4). Interestingly, the efficacies of **1f** and **4g** against *A. gossypii* and *T. vaporariorum* did not show comparable increases. However, the activity was also not increased against *Frankliniella occidentalis*.

Table 1 Insecticidal activity of **1** for *Myzus percicae*

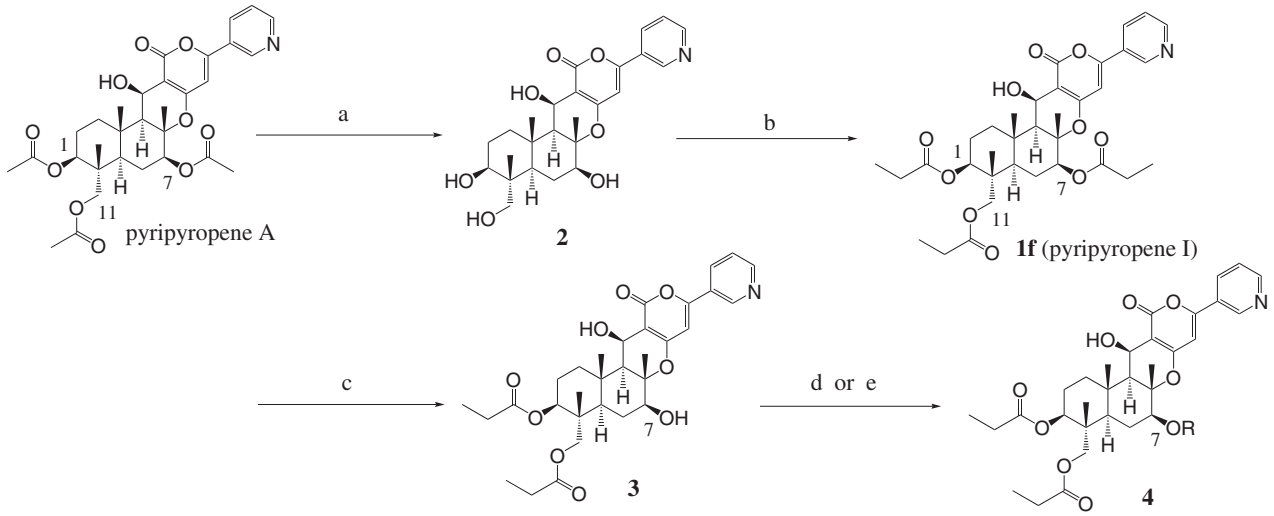


1

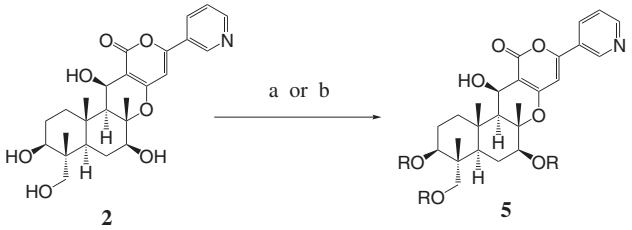
compound	R_1	R_2	R_3	Insecticidal activity against *Myzus persicae* (LC_{90}, ppm)
pyripyropene A				0.56
1a			H	1.2
1b				20
1c				20
1d				3.8
1e				0.45
1f (pyripyropene I)				0.043
1g				0.15

After finding the promising candidate, **5c**, in the screening test, we conducted field trials against aphids to evaluate the effectiveness of this compound.

In the field trial against *B. brassicae* by a foliar application (Fig. 2), the wettable powder (WP) formulation of **5c** had an excellent efficacy similar to the market standard, pymetrozine, which is a controlling agent for sucking pests on vegetables and fruits [19]. In the field trial against *A. gossypii* on potato (Fig. 3), **5c** WP showed a good efficacy even when there was a high infestation level at



Scheme 1 Synthesis of compound **4**: (a) NaOMe, 50% MeOH aq., 93% yield; (b) propionic anhydride, Et_3N, DMAP, DMF, 89% yield; (c) DBU, 80% MeOH aq., 56% yield; (d) R_2O, Et_3N, DMAP, DMF; (e) ROH, EDCI, DMAP, DMF



Scheme 2 Synthesis of compound **5**: (a) R_2O, Et_3N, DMAP, DMF; (b) ROH, EDCI, DMAP, DMF

application time but it was slightly lower than that of pymetrozine.

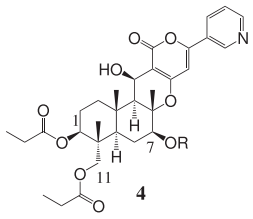
In the preliminary field trial, **5c** exhibited a good insecticidal activity against aphids, especially on developed leaves, but the efficacy was slightly less efficient on upper young leaves compared with the market standard. Under such conditions, with young leaves expanding, the efficacy was not improved, even at high dose of 75 g a.i./ha (data not shown). While the trial against *Brevicoryne brassicae* was conducted under low aphid infestation conditions and a low level of new entries from surrounding untreated plots, the trial against *A. gossypii* was conducted under higher infestation conditions and a lot of new entries were also observed.

To improve the insecticidal activity, we synthesized PP derivatives with chemical modifications at the C-1, C-7, or C-11 positions and evaluated their insecticidal activities against *M. persicae*.

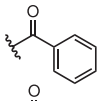
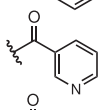
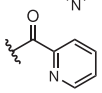
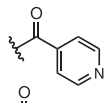
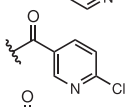
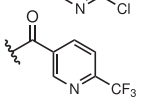
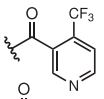
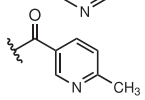
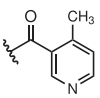
Among these PP derivatives, **1f**, **4g**, **5c**, and **5d** showed higher insecticidal activities against the aphids than PP-A. Interestingly, the aphicidal activity of **1f** is stronger than that of PP-A, while, as previously reported by the Kitasato Institute, **1f** showed a significant lower activity compared with PP-A with respect to ACAT-inhibiting activity (IC_{50} values of the ACAT-inhibiting activities of PP-A and **1f**, which were 0.058 μM [1] and 2.45 μM [4], respectively). Thus there may be no correlation between structure and insecticidal and ACAT-inhibiting activities.

Among these derivatives (**1f**, **4g**, **5c**, and **5d**), **5c** had the highest insecticidal activities against *M. persicae*. Based on the aphicidal spectrum, the derivatives that showed higher activities against *M. persicae* were active against *A. gossypii*, another important pest. Furthermore, the highly aphicidal compounds exhibited preferable activities against whiteflies, which are important target pests worldwide, especially on greenhouse crops. Unfortunately, another important pest on vegetables and fruits, thrips, were not target pests. However, the relationship between the insecticidal activities against *M. persicae* and *A. gossypii* were not in proportion. While PP-A showed equivalent activities against both aphids, derivatives, like **1f**, **4g**, and **5c**, that were highly active against *M. persicae* tended to be lower than expected against *A. gossypii*. This might result from the low systemicity into the leaves of these derivatives because the level is more important for a good activity in the assay against *A. gossypii* where the compounds were sprayed only the leaves. On the other hand, since the compounds were sprayed directly onto aphid bodies and the leaves in the assay against *M. persicae*, the compounds possibly exhibit high activities without good systemicity. Furthermore, **5c** exhibited a good efficacy against aphids in field trials against *B. brassicae*. However, this compound was not superior to a market standard, pymetrozine, in the potato trial. Furthermore, the efficacy did not improve even at high dose,

Table 2 Structure and insecticidal activity for *Myzus percicae* of **4**



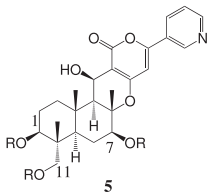
4

compound	R	yield (from compound **3**)	Insecticidal activity against *Myzus persicae* (LC_{90}, ppm)
1f (pyripyropene I)		-	0.043
3	H	-	0.17
4a[a)]		42%	0.15
4b[a)]		33%	0.080
4c[a)]		68%	0.084
4d[b)]		54%	0.14
4e[b)]		43%	43
4f[b)]		95%	0.15
4g[b)]		76%	0.038
4h[b)]		85%	0.075
4i[b)]		43%	1.6
4j[b)]		82%	0.17
4k[b)]		90%	0.21
4l[b)]		49%	0.16
4m[b)]		63%	0.52
4n[b)]		66%	0.27

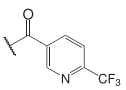
[a] Reaction condition; R_2O, Et_3N, DMAP, DMF

[b] Reaction condition; ROH, EDCI, DMAP, DMF

Table 3 Structure and insecticidal activity for *Myzus percicae* of **5**



5

compound	R	yield (from compound **2**)	Insecticidal activity against *Myzus persicae* (LC_{90}, ppm)
1f (pyripyropene I)		-	0.043
2	H	-	>100
5a		15%[c]	0.66
5b[a]		60%	1.3
5c[b]		78%	0.026
5d[b]		63%	0.030
5e[b]		63%	18
5f[b]		75%	88
5g[b]		68%	16
5h[b]		84%	18
5i[b]		48%	>100
5j[b]		56%	>100

[a] Reaction condition; R_2O, Et_3N, DMAP, DMF

[b] Reaction condition; ROH, EDCI, DMAP, DMF

[c] Refer to ref. [9]

which indicated that systemicity was necessary for a good residual efficacy in potato in which young leaves develop rapidly after application. These improved compounds did not show high acute toxicities against mammalian animals, rat, or mouse at 1000 mg/kg body weight using an oral application (data not shown). In summary, based on the strength of the insecticidal activity, the preferable insecticidal spectrum, the highly aphicidal compound **5c** is very

Table 4 Insecticidal activities of PP-A, **1f**, **4g**, and **5c** against agricultural sucking pests

	Myzus persicae LC_{90} (ppm)	*Aphis gossypii* LC_{90} (ppm)	*Trialeurodes vaporariorum* % mortality at 5 ppm	*Frankliniella occidentalis* % mortality at 200 ppm
PP-A	0.56	0.30	80	0
1f	0.043	0.14	18	53
4g	0.038	0.28	89	60
5c	0.026	0.078	100	60

promising, but suitable systemic properties such as those of PP-A could be important for a better field efficacy.

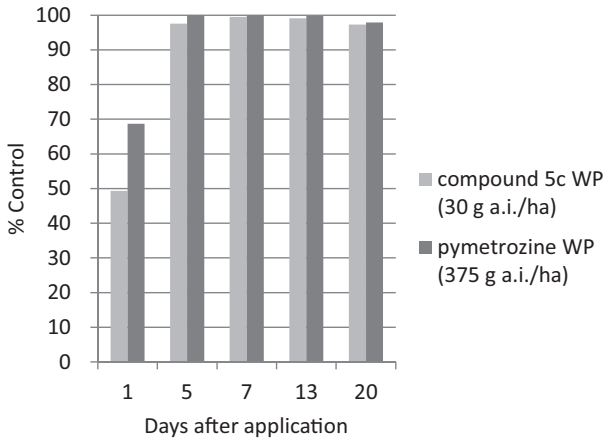


Fig. 2 Efficacy of **5c** wettable powder (WP) formulation against *Brevicoryne brassicae* on cotton using a foliar application

Experimental procedures

General methods

Reagents were obtained from commercial suppliers and were used without purification. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were measured on JEOL Lambda 400 MHz and BRUKER Ascend 400 MHz and 500 MHz spectrometers in $CDCl_3$. Mass spectra were obtained on JEOL JMS-FABmate spectrometer or JEOL JMS-700 mass spectrometer or Agilent Technologies 6530-Q-TOF LC/MS mass spectrometer. All infrared spectra were measured on a Horiba FT-210 spectrometer. Optical rotations were measured by using JASCO P-1010 polarimeter. Melting points were measured on OptiMelt (Stanford Research Systems) apparatus. Column chromatography was carried out on silica gel (Varian: Mega Bond Elut) and preparative thin-layer chromatography (PTLC) (Merck: Silica Gel 60 F_{254} 0.5 mm).

1, 7, 11-Tri-deacetyl-1, 11-di-*O*-propionylpyripyropene A (3)

To a solution of trideacetyl-1,7,11-tri-*O*-propionylpyripyropene A (**1f**, PP-I) (890 mg, 1.42 mmol), synthesized by the method previously reported [9], in an 80% aqueous MeOH solution (40 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (216 mg, 1.42 mmol) and stirred at room temperature for 1.5 h. The reaction mixture was quenched with AcOH, and the mixture was concentrated under reduced pressure and diluted with $CHCl_3$. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by chromatography on silica gel (acetone: hexane = 1: 1) to afford **3** (451 mg, 0.793 mmol) as a solid in 56% yield. ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3H), 1.13 (t, $J = 5.1$ Hz, 3H), 1.14 (t, $J = 5.1$ Hz, 3H), 1.26 (s, 1H), 1.32–1.40 (m, 1H), 1.42 (s, 3H), 1.45 (d, $J = 2.7$ Hz, 1H), 1.49–1.51 (m, 2H), 1.66 (s, 3H), 1.81–1.91 (m, 2H), 2.13–2.18 (m, 1H), 2.24–2.37 (m, 4H), 2.90 (m, 1H), 3.79 (m, 3H), 4.80 (dd, $J = 7.6$, 3.5 Hz, 1H), 4.99–5.00 (m, 1H), 6.52 (s, 1H), 7.42 (dd, $J = 5.4$, 3.5 Hz, 1H), 8.11 (dt, $J = 5.4$, 1.4 Hz, 1H), 8.70 (d, $J = 2.4$ Hz, 1H), 9.00 (s, 1H); mass spectrometry (MS) (fast atom bombardment (FAB)) *m/z* 570 $(M+H)^+$; high-resolution mass spectrometry (HRMS) (electrospray ionization (ESI)) *m/z* calcd. for $C_{31}H_{40}NO_9$ 570.2703, found 570.2701 $(M+H)^+$.

1, 11-Di-deacetyl-1, 11-di-*O*-propionylpyripyropene A (4a)

To a solution of **3** (30 mg, 0.0527 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (1 ml) were added triethylamine (Et_3N) (88 µl, 0.632 mmol), 4-(dimethylamino)pyridine (DMAP) (13 mg, 0.105 mmol) and acetic anhydride (31 µl, 0.316 mmol) and stirred at room temperature for 30 min. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by PTLC (acetone: hexane = 1:1) to afford **4a** (14 mg, 0.0222 mmol) as a solid in 42% yield. ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H), 1.12 (t, $J = 7.8$ Hz, 3H), 1.13 (t, $J = 7.8$ Hz, 3H), 1.19 (s, 1H), 1.25–1.34 (m, 1H), 1.44 (s, 3H), 1.53–1.63 (m, 3H), 1.69 (s, 3H), 1.73–1.90 (m, 2H), 2.10 (m, 1H), 2.16 (s, 3H), 2.33 (dq, $J = 7.6$, 2.4 Hz, 2H), 2.36 (dq, $J = 7.6$, 3.2 Hz, 2H), 2.87 (m, 1H), 3.72 (m, 2H), 4.81 (dd, $J = 11.6$, 4.6 Hz, 1H), 4.97–5.00 (m, 2H), 6.46 (s, 1H), 7.40 (dd, $J = 8.1$, 4.6 Hz, 1H), 8.10 (m, 1H), 8.69 (d, $J = 4.9$ Hz, 1H), 9.00 (s, 1H); MS (ESI) *m/z* 612 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{33}H_{42}NO_{10}$ 612.2809, found 612.2801 $(M+H)^+$.

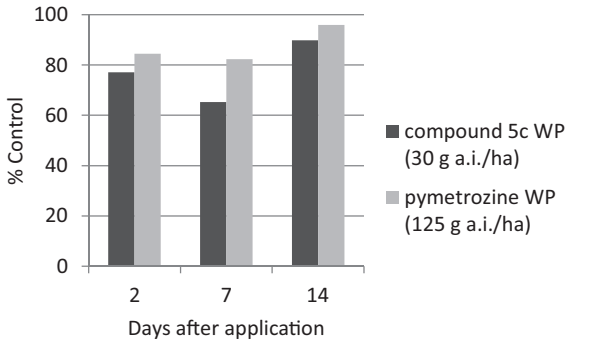


Fig. 3 Efficacy of **5c** wettable powder (WP) formulation against *Aphis gossypii* on potato using a foliar application

1, 7, 11-Tri-deacetyl-7-*O*-isobutyryl-1, 11-di-*O*-propionylpyripyropene A (4b)

Reaction of **3** (30 mg, 0.0527 mmol) with isobutyric anhydride (53 µl, 0.316 mmol) gave **4b** (11 mg, 0.0172 mmol) as a solid in 33% yield by a similar procedure to **4a**. ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H), 1.13 (t, $J = 7.6$ Hz, 6H), 1.19 (s, 1H), 1.24 (d, $J = 4.6$ Hz, 3H), 1.26 (d, $J = 4.6$ Hz, 3H), 1.33–1.38 (m, 1H), 1.45 (s, 3H), 1.54 (d, $J = 3.8$ Hz, 1H), 1.60–1.64 (m, 2H), 1.67 (s, 3H), 1.75–1.90 (m, 2H), 2.15–2.19 (m, 1H), 2.32 (q, $J = 7.6$ Hz, 2H), 2.38 (q, $J = 7.6$ Hz, 2H), 2.65 (quint., $J = 7.6$ Hz, 1H), 2.88 (d, $J = 1.6$ Hz, 1H), 3.68 (d, $J = 12.4$ Hz, 1H), 3.83 (d, $J = 11.9$ Hz, 1H), 4.80 (dd, $J = 11.3$, 4.9 Hz, 1H), 5.00 (m, 2H), 6.38 (s, 1H), 7.40 (dd, $J = 8.1$, 4.6 Hz, 1H), 8.09 (dt, $J = 8.1$, 1.9 Hz, 1H), 8.69 (dd, $J = 4.6$, 1.6 Hz, 1H), 9.00 (d, $J = 1.6$ Hz, 1H); MS (ESI) *m/z* 640 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{35}H_{46}NO_{10}$ 640.3122, found 640.3130 $(M+H)^+$.

1, 7, 11-Tri-deacetyl-7-*O*-pivaloyl-1, 11-di-*O*-propionylpyripyropene A (4c)

Reaction of **3** (30 mg, 0.0527 mmol) with pivalic anhydride (64 µl, 0.316 mmol) gave **4c** (23 mg, 0.0358 mmol) as a solid in 68% yield by a similar procedure to **4a**. ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3H), 1.13 (t, $J = 7.8$ Hz, 3H), 1.16 (t, $J = 7.8$ Hz, 3H), 1.25 (s, 1H), 1.28 (s, 9H), 1.30–1.40 (m, 1H), 1.45 (s, 3H), 1.54 (d, $J = 3.8$ Hz, 1H), 1.60–1.66 (m, 2H), 1.71 (s, 3H), 1.75–1.90 (m, 2H), 2.15–2.19 (m, 1H), 2.32 (q, $J = 7.6$ Hz, 2H), 2.38 (q, $J = 7.6$ Hz, 2H), 2.89 (s, 1H), 3.66 (d, $J = 11.6$ Hz, 1H), 3.83 (d, $J = 11.6$ Hz, 1H), 4.79 (dd, $J = 11.3$, 5.4 Hz, 1H), 4.97–5.00 (m, 2H), 6.34 (s, 1H), 7.40 (dd, $J = 8.4$, 4.9 Hz, 1H), 8.09 (dt, $J = 8.4$, 2.2 Hz, 1H), 8.69 (d, $J = 4.9$ Hz, 1H), 9.00 (d, J = 2.2 Hz, 1H); MS (ESI) *m/z* 654 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{36}H_{48}NO_{10}$ 654.3278, found 654.3278 $(M+H)^+$.

1, 7, 11-Tri-deacetyl-1, 11-di-*O*-propionyl-7-*O*-(3-pyridylcarbonyl)pyripyropene A (4g)

To a solution of **3** (30 mg, 0.0527 mmol) and nicotinic acid (13 mg, 0.105 mmol) in anhydrous DMF (3 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (15 mg, 0.0791 mmol) and DMAP (6.4 mg, 0.0527 mmol) and stirred at room temperature for 4.5 h. The reaction mixture was poured into water and then extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified by PTLC (acetone: hexane = 1: 1) to give **4g** (27 mg, 0.0402 mmol) as a solid in 76% yield. ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3H), 1.14 (t, $J = 7.6$ Hz, 3H), 1.20 (t, $J = 7.6$ Hz, 3H), 1.26 (s, 1H), 1.42–1.50 (m, 1H), 1.59 (s, 3H), 1.61–1.83 (m, 3H), 1.85 (s, 3H), 1.83–2.00 (m, 2H), 2.18–2.23 (m, 1H), 2.33 (q, $J = 7.6$ Hz, 2H), 2.43 (q, $J = 7.6$ Hz, 2H), 2.94 (m, 1H), 3.72 (d, $J = 11.9$ Hz, 1H), 3.82 (d, $J = 12.7$ Hz, 1H), 4.83 (dd, $J = 11.3$, 4.9 Hz, 1H), 5.03–5.06 (m, 1H), 5.27 (dd, $J = 11.3$, 4.9 Hz, 1H), 6.42 (s, 1H), 7.38 (dd, $J = 8.1$, 4.9 Hz, 1H), 7.45 (dd, $J = 8.1$, 4.9 Hz, 1H), 8.07 (dt, $J = 8.1$, 2.2 Hz, 1H), 8.36 (dt, $J = 8.1$, 1.9 Hz, 1H), 8.67 (dd, $J = 5.1$, 1.9 Hz, 1H), 8.83 (dd, $J = 4.9$, 1.9 Hz, 1H), 8.97 (d, $J = 1.9$ Hz, 1H), 9.30 (d, $J = 1.9$ Hz, 1H); MS (FAB) *m/z* 675$(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{37}H_{43}N_2O_{10}$ 675.2918, found 675.2919 $(M+H)^+$.

7-*O*-Cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-1, 11-di-*O*-propionylpyripyropene A (4d)

Reaction of **3** (30 mg, 0.0527 mmol) with cyclopropanecarboxylic acid (25 µl, 0.310 mmol) gave **4d** (18 mg, 0.0286 mmol) as a solid in 54% yield by a similar procedure to **4g**. ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H), 0.93 (d, $J = 2.7$ Hz, 2H), 0.96 (d, $J = 2.7$ Hz, 2H), 1.03–1.19 (m, 6H), 1.26 (s, 1H), 1.32–1.39 (m, 1H), 1.45 (s, 3H), 1.52 (d, $J = 3.8$ Hz, 1H), 1.61–1.69 (m, 3H), 1.71 (s, 3H), 1.73–1.94 (m, 2H), 2.14–2.19 (m, 1H), 2.24–2.40 (m, 4H), 2.95 (m, 1H), 3.68 (d, $J = 11.9$ Hz, 1H), 3.81 (d, $J = 11.9$ Hz, 1H), 4.79 (dd, $J = 11.3$, 5.4 Hz, 1H), 4.96–5.00 (m, 2H), 6.45 (s, 1H), 7.40 (dd, $J = 8.1$, 4.6 Hz, 1H), 8.10 (dt, $J = 8.1$, 1.9 Hz, 1H), 8.68 (m, 1H), 9.01 (m, 1H); MS (FAB) *m/z* 638 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{35}H_{44}NO_{10}$ 638.2965, found 638.2968 $(M+H)^+$.

7-*O*-Cyclobutylcarbonyl-1, 7, 11-tri-deacetyl-1, 11-di-*O*-propionylpyripyropene A (4e)

Reaction of **3** (30 mg, 0.0527 mmol) with cyclobutanecarboxylic acid (29 µl, 0.310 mmol) gave **4e** (15 mg, 0.0229 mmol) as a solid in 43% yield by a similar procedure to **4g**. ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H), 1.13 (t, $J = 7.6$ Hz, 3H), 1.17 (t, $J = 7.6$ Hz, 3H), 1.26 (s, 1H), 1.34–1.40 (m,

1H), 1.44 (s, 3H), 1.54 (d, $J = 4.3$ Hz, 1H), 1.61–1.67 (m, 2H), 1.69 (s, 3H), 1.72–2.42 (m, 12H), 2.91 (m, 1H), 3.23 (quint., $J = 8.1$ Hz, 1 H), 3.69 (d, $J = 11.9$ Hz, 1H), 3.81 (d, $J = 11.9$ Hz, 1H), 4.80 (dd, $J = 11.3$, 4.9 Hz, 1H), 4.99–5.04 (m, 2H), 6.40 (s, 1H), 7.39 (dd, $J = 8.1$, 4.9 Hz, 1H), 8.09 (dt, $J = 8.1$, 1.6 Hz, 1H), 8.69 (dd, $J = 4.6$, 1.6 Hz, 1H), 9.01 (d, $J = 1.6$ Hz, 1H); MS (ESI) *m/z* 652 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{36}H_{45}NO_{10}$ 652.3077, found 652.3125 $(M+H)^+$.

7-*O*-Benzoyl-1, 7, 11-tri-deacetyl-1, 11-di-*O*-propionylpyripyropene A (4f)

Reaction of **3** (30 mg, 0.0527 mmol) with benzoic acid (85 mg, 0.696 mmol) gave **4f** (34 mg, 0.0505 mmol) as a solid in 95% yield by a similar procedure to **4g**. ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3H), 1.14 (t, $J = 7.6$ Hz, 3H), 1.20 (t, $J = 7.6$ Hz, 3H), 1.26 (s, 1H), 1.37–1.46 (m, 1H), 1.51 (s, 3H), 1.62 (d, $J = 3.8$ Hz, 1H), 1.68–1.82 (m, 2H), 1.87 (s, 3H), 1.91–2.00 (m, 2H), 2.18–2.23 (m, 1H), 2.33 (q, $J = 7.6$ Hz, 2H), 2.43 (dq, $J = 7.6$, 1.4 Hz, 2H), 2.97 (s, 1H), 3.70 (d, $J = 11.9$ Hz, 1H), 3.84 (d, $J = 11.9$ Hz, 1H), 4.83 (dd, $J = 11.1$, 5.1 Hz, 1H), 5.05 (d, $J = 4.3$ Hz, 1H), 5.27 (dd, $J = 11.1$, 4.6 Hz, 1H), 6.45 (s, 1H), 7.39–7.66 (m, 4H), 8.05–8.13 (m, 3H), 8.70 (d, $J = 4.6$ Hz, 1H), 9.00 (s, 1H); MS (FAB) *m/z* 674 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{38}H_{44}NO_{10}$ 674.2965, found 674.2958 $(M+H)^+$.

1, 7, 11-Tri-deacetyl-1, 11-di-*O*-propionyl-7-*O*-(2-pyridylcarbonyl)pyripyropene A (4h)

Reaction of **3** (30 mg, 0.0527 mmol) with picolinic acid (13 mg, 0.105 mmol) gave **4h** (40 mg, 0.0446 mmol) as a solid in 85% yield by a similar procedure to **4g**. ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3H), 1.13 (t, $J = 7.6$ Hz, 3H), 1.20 (t, $J = 7.6$ Hz, 3H), 1.26 (s, 1H), 1.37–1.46 (m, 1H), 1.50 (s, 3H), 1.63–1.75 (m, 2H), 1.87 (s, 3H), 1.83–1.96 (m, 2H), 2.13–2.23 (m, 1H), 2.32 (q, $J = 7.6$ Hz, 2H), 2.41 (dq, $J = 7.6$, 1.4 Hz, 2H), 2.99 (m, 1H), 3.67 (d, $J = 11.9$ Hz, 1H), 3.83 (d, $J = 11.9$ Hz, 1H), 4.83 (dd, $J = 11.3$, 5.4 Hz, 1H), 4.98–5.06 (m, 1H), 5.38 (dd, $J = 10.8$, 5.4 Hz, 1H), 6.43 (s, 1H), 7.35–7.44 (m, 1H), 7.50–7.55 (m, 1H), 7.89 (dt, $J = 7.6$, 1.6 Hz, 1H), 8.07 (dt, $J = 8.1$, 1.6 Hz, 1H), 8.18 (d, $J = 7.6$ Hz, 1H), 8.67 (dd, $J = 4.9$, 1.6 Hz, 1H), 8.82–8.84 (m, 1H), 8.97 (d, $J = 2.4$ Hz, 1H); MS (FAB) *m/z* 675 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{37}H_{43}N_2O_{10}$ 675.2918, found 675.2911 $(M+H)^+$.

1, 7, 11-Tri-deacetyl-1, 11-di-*O*-propionyl-7-*O*-(4-pyridylcarbonyl)pyripyropene A (4i)

Reaction of **3** (30 mg, 0.0527 mmol) with isonicotinic acid (13 mg, 0.105 mmol) gave **4i** (15 mg, 0.0225 mmol) as a solid in 43% yield by a similar procedure to **4g**. ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3H), 1.14 (t, $J = 7.6$ Hz, 3H), 1.20 (t, $J = 7.6$ Hz, 3H), 1.26 (s, 1H), 1.38–1.42 (m, 1H), 1.50 (s, 3H), 1.64–1.78 (m, 3H), 1.85 (s, 3H), 1.88–2.05 (m, 2H), 2.17–2.23 (m, 1H), 2.33 (q, $J = 7.6$ Hz, 2H), 2.42 (dq, $J = 7.6$, 1.1 Hz, 2H), 2.99 (m, 1H), 3.72 (d, $J = 12.4$ Hz, 1H), 3.81 (d, $J = 11.5$ Hz, 1H), 4.83 (dd, $J = 11.5$, 4.9 Hz, 1H), 5.03–5.05 (m, 1H), 5.25 (dd, $J = 11.5$, 5.4 Hz, 1H), 6.41 (s, 1H), 7.37 (dd, $J = 8.1$, 5.2 Hz, 1H), 7.91 (dd, $J = 4.6$, 1.6 Hz, 2H), 8.07 (dt, $J = 8.1$, 1.6 Hz, 1H), 8.67 (dd, $J = 4.9$, 1.9 Hz, 1H), 8.83 (dd, $J = 4.3$, 1.6 Hz, 2H), 8.97 (d, $J = 1.6$ Hz, 1H); MS (FAB) *m/z* 675 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{37}H_{42}N_2O_{10}$ 674.2839, found 674.2841 $(M)^+$.

7-*O*-(6-Chloro-3-pyridylcarbonyl)-1, 7, 11-tri-deacetyl-1,11-di-*O*-propionylpyripyropene A (4j)

Reaction of **3** (30 mg, 0.0527 mmol) with 6-chloronicotinic acid (16 mg, 0.105 mmol) gave **4j** (31 mg, 0.0431 mmol) as a solid in 82% yield by a similar procedure to **4g**. ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3H), 1.14 (t, $J = 7.6$ Hz, 3H), 1.20 (t, $J = 7.6$ Hz, 3H), 1.26 (s, 1H), 1.38–1.46 (m, 1H), 1.50 (s, 3H), 1.61 (m, 1H), 1.66–1.78 (m, 2H), 1.84 (s, 3H), 1.87–1.99 (m, 2H), 2.12–2.23 (m, 1H), 2.31 (q, $J = 7.6$ Hz, 2H), 2.41 (q, $J = 7.6$ Hz, 2H), 2.95 (m, 1H), 3.73 (d, $J = 11.9$ Hz, 1H), 3.81 (d, $J = 11.9$ Hz, 1H), 4.83 (dd, $J = 11.3$, 4.9 Hz, 1H), 5.04 (m, 1H), 5.25 (dd, $J = 11.3$, 4.9 Hz, 1H), 6.40 (s, 1H), 7.38 (dd, $J = 7.8$, 4.6 Hz, 1H), 7.47 (d, $J = 8.1$ Hz, 1H), 8.06 (dt, $J = 7.8$, 1.6 Hz, 1H), 8.30 (dd, $J = 8.1$, 2.4 Hz, 1H), 8.67 (dd, $J = 4.6$, 1.4 Hz, 1H), 8.97 (d, $J = 2.4$ Hz, 1H), 9.06 (d, $J = 2.7$ Hz, 1H); MS (FAB) *m/z* 709$(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{37}H_{42}ClN_2O_{10}$ 709.2528, found 709.2524 $(M+H)^+$.

1, 7, 11-Tri-deacetyl-1, 11-di-*O*-propionyl-7-*O*-(6-trifluoromethyl-3-pyridylcarbonyl)pyripyropene A (4k)

Reaction of **3** (30 mg, 0.0527 mmol) with 6-(trifluoromethyl)nicotinic acid (30 mg, 0.158 mmol) gave **4k** (35 mg, 0.0477 mmol) as a solid in 90% yield by a similar procedure to **4g**. ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3H), 1.14 (t, $J = 7.6$ Hz, 3H), 1.21 (t, $J = 7.6$ Hz, 3H), 1.26 (s, 1H), 1.44 (m, 1H), 1.50 (s, 3H), 1.57–1.62 (m, 1H), 1.67–1.80 (m, 2H), 1.85 (s, 3H), 1.91–1.95 (m, 2H), 2.17–2.24 (m, 1H), 2.33 (q, $J = 7.6$ Hz, 2H), 2.42 (q, $J = 7.6$ Hz, 2H), 2.92 (m, 1H), 3.74 (d, $J = 11.9$ Hz, 1H), 3.81 (d, $J = 11.9$ Hz, 1H), 4.84 (dd, $J = 11.1$, 4.9 Hz, 1H), 5.04 (m, 1H), 5.27 (dd, $J = 11.1$, 4.9 Hz, 1H), 6.40 (s, 1H), 7.38 (dd, $J = 8.1$, 4.9 Hz, 1H), 7.84 (d, $J = 8.4$ Hz, 1H), 8.05–8.08 (m, 1H), 8.54 (d, $J = 8.1$ Hz, 1H), 8.67 (d, $J = 4.6$ Hz, 1H), 8.96 (d, $J = 2.2$ Hz, 1H), 9.38 (s, 1H); MS

(FAB) *m/z* 743 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{38}H_{42}F_3N_2O_{10}$ 743.2792, found 743.2794 $(M+H)^+$.

1, 7, 11-Tri-deacetyl-1, 11-di-*O*-propionyl-7-*O*-(4-trifluoromethyl-3-pyridylcarbonyl)pyripyropene A (4l)

Reaction of **3** (30 mg, 0.0527 mmol) with 4-(trifluoromethyl)nicotinic acid (30 mg, 0.158 mmol) gave **4l** (19 mg, 0.0257 mmol) as a solid in 49% yield by a similar procedure to **4g**. ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 3H), 1.14 (t, J = 7.6 Hz, 3H), 1.19 (t, J = 7.6 Hz, 3H), 1.26 (s, 1H), 1.38–1.47 (m, 1H), 1.48 (s, 3H), 1.57–1.71 (m, 3H), 1.75 (s, 3H), 1.83–1.97 (m, 2H), 2.10–2.22 (m, 1H), 2.33 (q, J = 7.6 Hz, 2H), 2.41 (dq, J = 7.6, 1.6 Hz, 2H), 2.96 (m, 1H), 3.74–3.80 (m, 2H), 4.83 (dd, J = 11.6, 5.7 Hz, 1H), 5.02–5.03 (m, 1H), 5.28 (dd, J = 11.6, 5.4 Hz, 1H), 6.41 (s, 1H), 7.40 (dd, J = 7.6, 5.4 Hz, 1H), 7.69 (d, J = 5.4 Hz, 1H), 8.08 (dt, J = 8.1, 2.2 Hz, 1H), 8.69 (dd, J = 4.9, 1.6 Hz, 1H), 8.97 (d, J = 4.6 Hz, 1H), 9.00 (d, J = 2.4 Hz, 1H), 9.16 (s, 1H); MS (FAB) *m/z* 743 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{38}H_{42}F_3N_2O_{10}$ 743.2792, found 743.2789 $(M+H)^+$.

1, 7, 11-Tri-deacetyl-7-*O*-(6-methyl-3-pyridylcarbonyl)-1, 11-di-*O*-propionylpyripyropene A (4m)

Reaction of **3** (20 mg, 0.0351 mmol) with 6-methylnicotinic acid (29 mg, 0.210 mmol) gave **4m** (15 mg, 0.0219 mmol) as a solid in 63% yield by a similar procedure to **4g**. ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3H), 1.12 (t, J = 7.8 Hz, 3H), 1.15 (t, J = 7.7 Hz, 3H), 1.26 (s, 1H), 1.39–1.47 (m, 1H), 1.50 (s, 3H), 1.61 (d, J = 2.4 Hz, 1H), 1.69–1.81 (m, 2H), 1.85 (s, 3H), 1.90–1.99 (m, 2H), 2.18–2.21 (m, 1H), 2.33 (dq, J = 7.7, 1.2 Hz, 2H), 2.41 (dq, J = 7.6 Hz, 2.7 Hz, 2H), 2.66 (s, 3H), 2.96 (m, 1H), 3.72 (d, J = 11.7 Hz, 1H), 3.83 (d, J = 12.0 Hz, 1H), 4.83 (dd, J = 11.4, 4.9 Hz, 1H), 5.04 (m, 1H), 5.25 (dd, J = 11.7, 5.3 Hz, 1H), 6.41 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.38 (dd, J = 8.1, 4.9 Hz, 1H), 8.07 (dt, J = 8.1, 2.2 Hz, 1H), 8.24 (dd, J = 8.0, 2.2 Hz, 1H), 8.67 (dd, J = 4.9, 1.5 Hz, 1H), 8.97 (d, J = 2.2 Hz, 1H), 9.18 (d, J = 2.2 Hz, 1H); MS (FAB) *m/z* 689 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{38}H_{44}N_2O_{10}$ 688.2996, found 688.2994 $(M)^+$.

1, 7, 11-Tri-deacetyl-7-*O*-(4-methyl-3-pyridylcarbonyl)-1, 11-di-*O*-propionylpyripyropene A (4n)

Reaction of **3** (20 mg, 0.0351 mmol) with 4-methylnicotinic acid hydrochloride (36 mg, 0.210 mmol) gave **4n** (16 mg, 0.0232 mmol) as a solid in 66% yield by a similar procedure to **4g**. ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 3H), 1.14 (t, J = 7.6 Hz, 3H), 1.20 (t, J = 7.6 Hz, 3H), 1.26 (s, 1H), 1.33–1.44 (m, 1H), 1.50 (s, 3H), 1.61 (m, 1H), 1.68–1.77 (m, 2H), 1.84 (s, 3H), 1.91–1.99 (m, 2H), 2.17–2.23 (m, 1H), 2.32 (q, J = 7.6 Hz, 2H), 2.43 (dq, J = 7.6, 3.0 Hz, 2H), 2.69 (s, 3H), 2.96 (m, 1H), 3.75 (d, J = 12.2 Hz, 1H), 3.80 (d, J = 12.2 Hz, 1H), 4.48 (dd, J = 11.1, 5.1 Hz, 1H), 5.04 (d, J = 4.1 Hz, 1H), 5.23 (dd, J = 10.8, 5.4 Hz, 1H), 6.42 (s, 1H), 7.24 (d, J = 5.9 Hz, 1H), 7.39 (dd, J = 8.1, 4.9 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.61 (d, J = 5.1 Hz, 1H), 8.67 (d, J = 3.5 Hz, 1H), 8.98 (s, 1H), 9.17 (s, 1H); MS (FAB) *m/z* 689 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{38}H_{44}N_2O_{10}$ 688.2996, found 688.2992 $(M)^+$.

1, 7, 11-Tri-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetylpyripyropene A (5c)

To a solution of **2** (30 mg, 0.0656 mmol), which was synthesized by the method previously reported [9], and cyclopropanecarboxylic acid (103 µl, 1.31 mmol) in anhydrous DMF (2 mL) were added 1-ethyl-3-(3-dimethylformamide)-carbodiimide hydrochloride (76 mg, 0.394 mmol) and DMAP (32 mg, 0.262 mmol) and stirred at room temperature for 68 h. The reaction mixture was then poured into water and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by PTLC (acetone: hexane = 1:1) to afford **5c** (34 mg, 0.0510 mmol) as a solid in 78% yield. ^{1}H NMR ($CDCl_3$) δ 0.83–1.12 (m, 12H), 0.91 (s, 3H), 1.26 (s, 1H), 1.33–1.41 (m, 1H), 1.45 (s, 3H), 1.52–1.69 (m, 6H), 1.71 (s, 3H), 1.81–1.93 (m, 2H), 2.14–2.18 (m, 1H), 2.92 (m, 1H), 3.72 (d, J = 11.9Hz, 1H), 3.82 (d, J = 11.9 Hz, 1H), 4.80 (dd, J = 11.4, 4.9 Hz, 1H), 4.99–5.04 (m, 2H), 6.46 (s, 1H), 7.41 (dd, J = 8.3, 4.9 Hz, 1H), 8.10 (dt, J = 8.3, 1.7 Hz, 1H), 8.69 (dd, J = 4.9, 1.5 Hz, 1H), 9.01 (d, J = 1.4 Hz, 1H); MS (FAB) *m/z* 662 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{37}H_{43}NNaO_{10}$ 684.2785, found 684.2778 $(M+Na)^+$.

1, 7, 11-Tri-deacetyl-1, 7, 11-tri-*O*-pivaloylpyripyropene A (5b)

To a solution of **2** (30 mg, 0.0656 mmol) in anhydrous DMF (2 ml) were added Et_3N (60 mg, 0.590 mmol), DMAP (8 mg, 0.00656 mmol), and pivalic anhydride (239 µl, 1.18 mmol) and stirred at room temperature for 16 h. The reaction mixture was added to water and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by PTLC (acetone: hexane = 1:1) to give **5b** (28 mg, 0.0390 mmol) as a solid in 60% yield. ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 3H), 1.19 (s, 9H), 1.24 (s, 9H), 1.26 (s, 1H), 1.28 (s, 9H), 1.37–1.40 (m, 1H),

1.46 (s, 3H), 1.50–1.66 (m, 3H), 1.72 (s, 3H), 1.81–1.89 (m, 2H), 2.16–2.21 (m, 1H), 3.68 (d, $J = 12.0$ Hz, 1H), 3.74 (d, $J = 12.0$ Hz, 1H), 4.77 (dd, $J = 11.2$, 5.2 Hz, 1H), 4.92–4.97 (m, 1H), 5.01 (d, $J = 4.0$ Hz, 1H), 6.35 (s, 1H), 7.40 (dd, $J = 8.0$, 4.0 Hz, 1H), 8.09 (dt, $J = 8.0$, 1.6 Hz, 1H), 8.69 (dd, $J = 4.8$, 1.6 Hz, 1H), 9.00 (d, $J = 2.0$ Hz, 1H); MS (FAB) *m/z* 710 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{40}H_{56}NO_{10}$ 710.3904, found 710.3906 $(M+H)^+$.

1, 7, 11-Tri-*O*-cyclobutylcarbonyl-1, 7, 11-tri-deacetylpyripyropene A (5d)

Reaction of **2** (30 mg, 0.0656 mmol) with cyclobutanecarboxylic acid (124 µl, 1.31 mmol) gave **5d** (29 mg, 0.0411 mmol) as a solid in 63% yield by a similar procedure to **5c**. ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H), 1.26 (s, 1H), 1.32–1.41 (m, 1H), 1.44 (s, 3H), 1.51–1.63 (m, 3H), 1.69 (s, 3H), 1.79–2.04 (m, 8H), 2.17–2.40 (m, 13H), 2.89 (m, 1H), 3.08–3.26 (m, 3H), 3.67 (d, $J = 11.9$ Hz, 1H), 3.78 (d, $J = 11.9$ Hz, 1H), 4.79 (dd, $J = 11.1$, 5.4 Hz, 1H), 4.97–5.00 (m, 2H), 6.41 (s, 1H), 7.41 (dd, $J = 8.1$, 4.9 Hz, 1H), 8.09 (dt, $J = 8.4$, 1.9 Hz, 1H), 8.68 (m, 1H), 9.00 (m, 1H); MS (FAB) *m/z* 704 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{40}H_{50}NO_{10}$ 704.3435, found 704.3429 $(M+H)^+$.

1, 7, 11-Tri-*O*-cyclohexylcarbonyl-1, 7, 11-tri-deacetylpyripyropene A (5e)

Reaction of **2** (20 mg, 0.0436 mmol) with cyclohexanecarboxylic acid (109 µl, 0.871 mmol) gave **5e** (22 mg, 0.0273 mmol) as a solid in 63% yield by a similar procedure to **5c**. ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3H), 1.45 (s, 3H), 1.70 (s, 3H), 1.10–2.05 (m, 37H), 2.14–2.49 (m, 3H), 3.04 (s, 1H), 3.65 (d, $J = 11.3$ Hz, 1H), 3.77 (d, $J = 11.9$ Hz, 1H), 4.78 (dd, $J = 10.8$, 5.4 Hz, 1H), 4.97–5.01 (m, 2H), 6.41 (s, 1H), 7.42 (dd, $J = 8.1$, 4.9 Hz, 1H), 8.11 (dd, $J = 8.1$, 1.9 Hz, 1H), 8.69 (d, $J = 4.3$ Hz, 1H), 9.01 (s, 1H); MS (FAB) *m/z* 788 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{46}H_{62}NO_{10}$ 788.4374, found 788.4362 $(M+H)^+$.

1, 7, 11-Tri-*O*-benzoyl-1, 7, 11-tri-deacetylpyripyropene A (5f)

Reaction of **2** (30 mg, 0.0656 mmol) with benzoic acid (160 mg, 1.31 mmol) gave **5f** (38 mg, 0.0494 mmol) as a solid in 75% yield by a similar procedure to **5c**. ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 3H), 1.26 (s, 1H), 1.57 (s, 3H), 1.65 (m, 1H), 1.77–1.82 (m, 2H), 1.88 (s, 3H), 1.94–2.05 (m, 3H), 2.13–2.31 (m, 1H), 2.95 (m, 1H), 4.16 (s, 2H), 5.06 (dd, $J = 6.5$, 2.4 Hz, 1H), 5.17–5.32 (m, 2H), 6.42 (s, 1H), 7.34–7.64 (m, 10H), 8.01–8.12 (m, 7H), 8.66 (dd, $J = 5.1$, 1.6 Hz, 1H), 8.97 (d, $J = 1.9$ Hz, 1H); MS (FAB) *m/z* 770 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{46}H_{44}NO_{10}$ 770.2965, found 770.2952 $(M+H)^+$.

1, 7, 11-Tri-deacetyl-1, 7, 11-tri-*O*-(3-pyridylcarbonyl)pyripyropene A (5g)

Reaction of **2** (30 mg, 0.0656 mmol) with nicotinic acid (161 mg, 1.31 mmol) gave **5g** (34 mg, 0.0443 mmol) as a solid in 68% yield by a similar procedure to **5c**. ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 3H), 1.25 (s, 1H), 1.47–1.55 (m, 1H), 1.60 (s, 3H), 1.66 (d, $J = 4.0$ Hz, 1H), 1.81 (d, $J = 11.5$ Hz, 1H), 1.90 (s, 3H), 1.90–1.98 (m, 1H), 2.02–2.15 (m, 1H), 2.20–2.24 (m, 1H), 2.29–2.32 (m, 1H), 3.02 (s, 1H), 4.12 (d, $J = 12.0$ Hz, 1H), 4.25 (d, $J = 12.0$ Hz, 1H), 5.07 (d, $J = 3.7$ Hz, 1H), 5.18–5.29 (m, 2H), 6.42 (s, 1H), 7.36–7.47 (m, 4H), 8.07 (dt, $J = 8.0$, 2.0 Hz, 1H), 8.28 (dd, $J = 8.0$, 2.0 Hz, 1H), 8.32–8.36 (m, 2H), 8.67 (dd, $J = 4.8$, 1.6 Hz, 1H), 8.79 (dt, $J = 4.8$, 1.6 Hz, 2H), 8.83 (dd, $J = 4.8$, 1.6 Hz, 1H), 8.98 (dd, $J = 2.0$, 0.8 Hz, 1H), 9.22 (dd, $J = 2.0$, 0.8 Hz, 1H), 9.30 (ddd, $J = 5.2$, 2.0, 0.8 Hz, 2H); MS (ESI) *m/z* 773 $(M+H)^+$; HRMS(ESI) *m/z* calcd. for $C_{43}H_{41}N_4O_{10}$ 773.2823, found 773.2825 $(M+H)^+$.

1, 7, 11-Tri-deacetyl-1, 7, 11-tri-*O*-(2-pyridylcarbonyl)pyripyropene A (5h)

Reaction of **2** (20 mg, 0.0437 mmol) with picolinic acid (32 mg, 0.262 mmol) gave **5h** (28 mg, 0.0366 mmol) as a solid in 84% yield by a similar procedure to **5c**. ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3H), 1.26 (s, 1H), 1.54–1.55 (m, 1H), 1.59 (s, 3H), 1.70 (d, $J = 4.3$ Hz, 1H), 1.89 (s, 3H), 1.92–1.94 (m, 2H), 1.98–2.13 (m, 1H), 2.16–2.20 (m, 1H), 2.29–2.33 (m, 1H), 2.93 (s, 1H), 4.14 (d, $J = 12.0$ Hz, 1H), 4.26 (d, $J = 12.0$ Hz, 1H), 5.08 (d, $J = 3.9$ Hz, 1H), 5.33 (dd, $J = 7.6$, 5.2 Hz, 1H), 5.45 (dd, $J = 7.6$, 5.2 Hz, 1H), 6.42 (s, 1H), 7.38 (ddd, $J = 8.0$, 4.8, 0.8 Hz, 1H), 7.45–7.46 (m, 2H), 7.51 (ddd, $J = 8.0$, 4.8, 1.2 Hz, 1H), 7.80–7.85 (m, 2H), 7.88 (dt, $J = 8.0$, 2.0 Hz, 1H), 8.04–8.08 (m, 2H), 8.09–8.11 (m, 1H), 8.15–8.18 (m, 1H), 8.67 (dd, $J = 4.8$, 1.6 Hz, 1H), 8.73–8.77 (m, 2H), 8.80–8.82 (m, 1H), 8.97 (d, $J = 1.7$ Hz, 1H); MS (ESI) *m/z* 773 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{43}H_{41}N_4O_{10}$ 773.2823, found 773.2823 $(M+H)^+$.

1, 7, 11-Tri-deacetyl-1, 7, 11-tri-*O*-(6-trifluoromethyl-3-pyridylcarbonyl)pyripyropene A (5i)

Reaction of **2** (30 mg, 0.0656 mmol) with 6-(trifluoromethyl)nicotinic acid (250 mg, 1.31 mmol) gave **5i** (31 mg, 0.0318 mmol) as a solid in 48% yield by a similar procedure to **5c**. ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3H), 1.26 (s,

1H), 1.51–1.54 (m, 1H), 1.60 (s, 3H), 1.64 (d, $J = 4.0$ Hz, 1H), 1.76–1.79 (m, 1H), 1.90 (s, 3H), 1.90–2.00 (m, 1H), 2.10–2.12 (m, 1H), 2.23–2.26 (m, 1H), 2.32–2.35 (m, 1H), 2.96 (d, $J = 1.6$ Hz, 1H), 4.16 (d, $J = 12.0$ Hz, 1H), 4.29 (d, $J = 12.0$ Hz, 1H), 5.06 (dd, $J = 3.9$, 2.4 Hz, 1H), 5.17–5.26 (m, 2H), 6.41 (s, 1H), 7.38 (ddd, $J = 8.1$, 4.8, 0.8 Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 2H), 8.07 (dt, $J = 8.0$, 1.6 Hz, 1H), 8.47 (dd, $J = 8.1$, 1.5 Hz, 1H), 8.54 (dd, $J = 8.2$, 1.9 Hz, 2H), 8.68 (dd, $J = 4.9$, 1.6 Hz, 1H), 8.97 (d, $J = 1.6$ Hz, 1H), 9.30 (d, $J = 1.8$ Hz, 1H), 9.37–9.39 (m, 2H); MS (ESI) *m/z* 977 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{46}H_{38}F_9N_4O_{10}$ 977.2444, found 977.2443 $(M+H)^+$.

1, 7, 11-Tri-deacetyl-1, 7, 11-tri-*O*-(4-trifluoromethyl-3-pyridylcarbonyl)pyripyropene A (5j)

Reaction of **2** (30 mg, 0.0656 mmol) with 4-(trifluoromethyl)nicotinic acid (250 mg, 1.31 mmol) gave **5j** (36 mg, 0.0370 mmol) as a solid in 56% yield by a similar procedure to **5c**. ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 3H), 1.26 (s, 1H), 1.45 (dt, $J = 13.0$, 4.2 Hz, 1H), 1.54 (s, 3H), 1.58 (d, $J = 4.0$ Hz, 1H), 1.77 (s, 3H), 1.77–1.79 (m, 1H), 1.85–1.97 (m, 1H), 2.04–2.09 (m, 2H), 2.26–2.29 (m, 1H), 2.98 (brs, 1H), 4.10 (d, $J = 12.1$ Hz, 1H), 4.29 (d, $J = 12.1$ Hz, 1H), 5.02 (d, $J = 2.9$ Hz, 1H), 5.19 (dd, $J = 11.7$, 5.0 Hz, 1H), 5.29 (dd, $J = 11.7$, 5.0 Hz, 1H), 6.42 (s, 1H), 7.40 (ddd, $J = 8.1$, 4.8, 0.8 Hz, 1H), 7.66 (d, $J = 5.2$ Hz, 2H), 7.69 (d, $J = 5.2$ Hz, 1H), 8.07–8.10 (m, 1H), 8.69 (dd, $J = 4.8$, 1.6 Hz, 1H), 8.95 (d, $J = 5.2$ Hz, 2H), 8.97 (d, $J = 5.2$ Hz, 1H), 9.00 (d, $J = 1.6$ Hz, 1H), 9.11 (s, 1H), 9.17 (s, 1H), 9.25 (s, 1H); MS (ESI) *m/z* 977 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{46}H_{38}F_9N_4O_{10}$ 977.2444, found 977.2433 $(M+H)^+$.

Insecticidal screening against agricultural pests

Pyripyropene derivatives were evaluated by an insecticidal screening against green peach aphid (*M. persicae*) following the method described in our former report [15]. The screening against cotton aphid (*A. gossypii*), greenhouse whitefly (*T. vaporariorum*), and western flower thrips (*F. occidentalis*) were conducted by the method previously reported [20].

Field efficacy of compound 5c in a foliar application against cabbage aphid (*B. brassicae*) on cabbage

The field trial was conducted in a cabbage field of Odawara City, Kanagawa Prefecture in Japan using one of general formulation types, WP. This formulation, including 5% (w/w) active ingredient, was prepared following a preparation method reported previously [20]. The determined amount of diluted solution of **5c** WP in water was applied to cabbage infested with cabbage aphids. Before application and at 1, 5, 7, 13 and 20 days after application, the numbers of aphids were counted in each plot. The corrected density index was calculated as follows:

$$\begin{aligned}&\text{Corrected density index}\\&= \left[\frac{(\text{the number of aphids in treated plot at } X \text{ days after application})}{(\text{the number of aphids in treated plot before application})}\right]\\&\times \left[\frac{(\text{the number of aphids in untreated plot before application})}{(\text{the number of aphids in untreated plot at } X \text{ days after application})}\right]\\&\times 100\end{aligned} \quad (1)$$

Then, compared with untreated plot, the control percentage was calculated as follows:

$$\%\,\text{control} = 100 - (\text{the corrected density index}). \quad (2)$$

Field efficacy of 5c in a foliar application against cotton aphid (*A. gossypii*) on potato

The field trial was conducted in a potato field of Misawa City, Aomori Prefecture in Japan as a non-disclosed trial conducted by the Institute of Japan Plant Protection Association. The WP formulation, including 5% (w/w) active ingredient, was prepared and used in the same way as the field trial against *B. brassicae*. The determined amount of diluted solution of **5c** WP in water was applied to potatoes infested with cotton aphids. Before application and at 2, 7 and 14 days after application, the numbers of aphids were counted in each plot. The corrected density index and percentage of control were calculated by the same formulae as the field trial against cabbage aphid.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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