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ARTICLE

Synthesis and insecticidal efficacy of pyripyropene derivatives. Part II—Invention of afidopyropen

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Abstract

The synthesis and insecticidal activity of a series of pyripyropene derivatives with cyclopropanecarbonyloxy group(s) at the C-1, C-7 and/or C-11 position(s) were investigated to find novel insecticides. Insecticidal screening of the synthesized PP derivatives revealed that derivative **13**, which had cyclopropanecarbonyloxy groups at the C-1 and C-11 positions and a hydroxyl group at the C-7 position, showed the highest insecticidal activity against aphids in laboratory tests. Finally, we selected **13** as a new insecticide candidate for agricultural sucking pests, which is now commercialized under the common name afidopyropen.

Introduction

In previous studies, pyripyropene (PP) analogs were isolated from the culture broth of *Aspergillus fumigatus* FO-1289 and shown to be inhibitors of acyl-CoA:cholesterol *O*-acyltransferase (ACAT) by Ōmura et al. at the Kitasato Institute [1–5] and from *Penicillium coprobium* PF1169 as anthelmintic compounds by Meiji Seika Pharma [6], separately.

The research group at the Kitasato Institute has investigated the synthesis and evaluation of several series of PP derivatives that function as potent ACAT inhibitors [7–14].

Previously, we found that PP-A exhibited high aphicidal activity through Meiji's insecticidal screening tests of natural products [15]. Further research on chemical derivatization at the C-1, C-7 and C-11 positions of PP derivatives revealed that several PP derivatives, such as PP-I and derivative **1** (see Fig. 1), had higher aphicidal activity than that of PP-A [16].

Sucking pests such as aphids are serious pests that infest a variety of crops, including cereals, vegetables, fruits and ornamentals. They can greatly damage crop production and quality [17] by direct growth inhibition and by mediating the transmission of plant viruses to crops through sucking. Furthermore, a variety of resistance problems to existing insecticides have been reported [18]. As well as aphids, whiteflies also damage crops and have become resistant to many insecticides [19].

Surprisingly, **1** showed quite high aphicidal activity under laboratory conditions, but it did not show stable efficacy under field conditions, especially at the vegetative stage when many new leaves emerges. Thus, since it is not so effective on the untreated leaves newly emerging, then overall field efficacy will be diminished.

In this study, we focused on PP derivatives with a cyclopropanecarbonyl group, the most effective substituent group for aphicidal activity [16]. We investigated the structure–activity relationship (SAR) of these PP derivatives to select those with the highest efficacy against aphids, superior to that of derivative **1**, taking systemic activity into consideration. In the control of sucking pests like aphid, it is essential that the insecticidal ingredient is translocated or moved from treated roots, leaves, or stems to untreated newly emerging young leaves and its insecticidal activity appears (in other words, systemic activity). After screening

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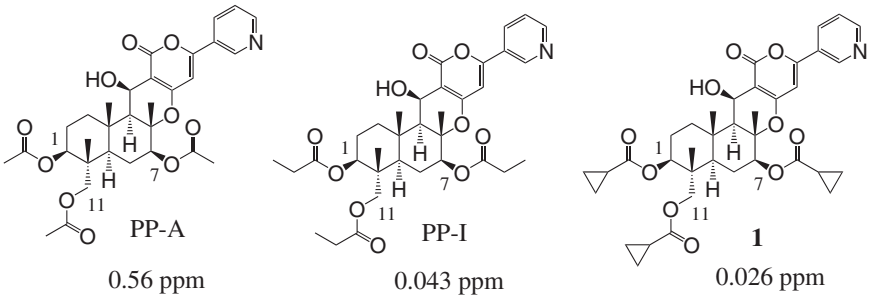


Fig. 1 Structures of PP-A, PP-I and **1** and insecticidal activities (LC_{90}) against *M. persicae*

for insecticidal and systemic activity, we identified a candidate insecticide to control sucking pests such as aphid and whitefly. In this report, we explain the SAR of PP derivatives and the process to select the best PP derivative.

Results and discussion

First, we explored the effects of adding different numbers of cyclopropanecarbonyloxy groups at different substituent positions by synthesizing several PP derivatives with one or two cyclopropanecarbonyloxy group(s) at the C-1, C-7 or C-11 position(s).

As shown in Scheme 1, mono-substituted derivatives (**3**, **7** and **12**) and di-substituted derivatives (**4**, **13** and **16**) were obtained by the following methods: The acylation of **2** obtained by hydrolysis of the triacetate of PP-A gave a mixture of **3** and **4**, which was successively separated by silica gel chromatography to afford pure **3** and **4** as single compounds. Then, **7** was obtained by three steps from **2**: acetonide protection of diol at the C-1 and C-11 positions of **2** [20]; introduction of a cyclopropanecarbonyl group into the hydroxy group at the C-7 position; and then deprotection of the foregoing acetonide-protecting group of **6** using acetic acid. Next, **12** was synthesized by five steps from acetonide **5**: *tert*-butyldimethylsilyl (TBS) protection of the hydroxyl group at the C-7 position of **5** [20]; deprotection of the acetonide-protecting group of **8** [20]; TBS protection of the hydroxyl group at the C-11 position of **9**; introduction of a cyclopropanecarbonyl group into the hydroxy group at the C-1 position; and finally deprotection of the TBS-protecting groups of **11** using the hydrogen fluoride-pyridine complex.

Derivative **13** was synthesized by regioselective hydrolysis at the C-7 position of **1** by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Then, **16** was obtained from **2** in three steps: TBS protection of the hydroxyl group at the C-11 position of **2**; introduction of cyclopropanecarbonyl groups into the hydroxy groups at the C-1 and C-7 positions; and last, deprotection of the TBS-protecting group of **15**.

The insecticidal activities of the synthesized mono-substituted and di-substituted derivatives against aphids, *Myzus persicae* and *Aphis gossypii* were evaluated.

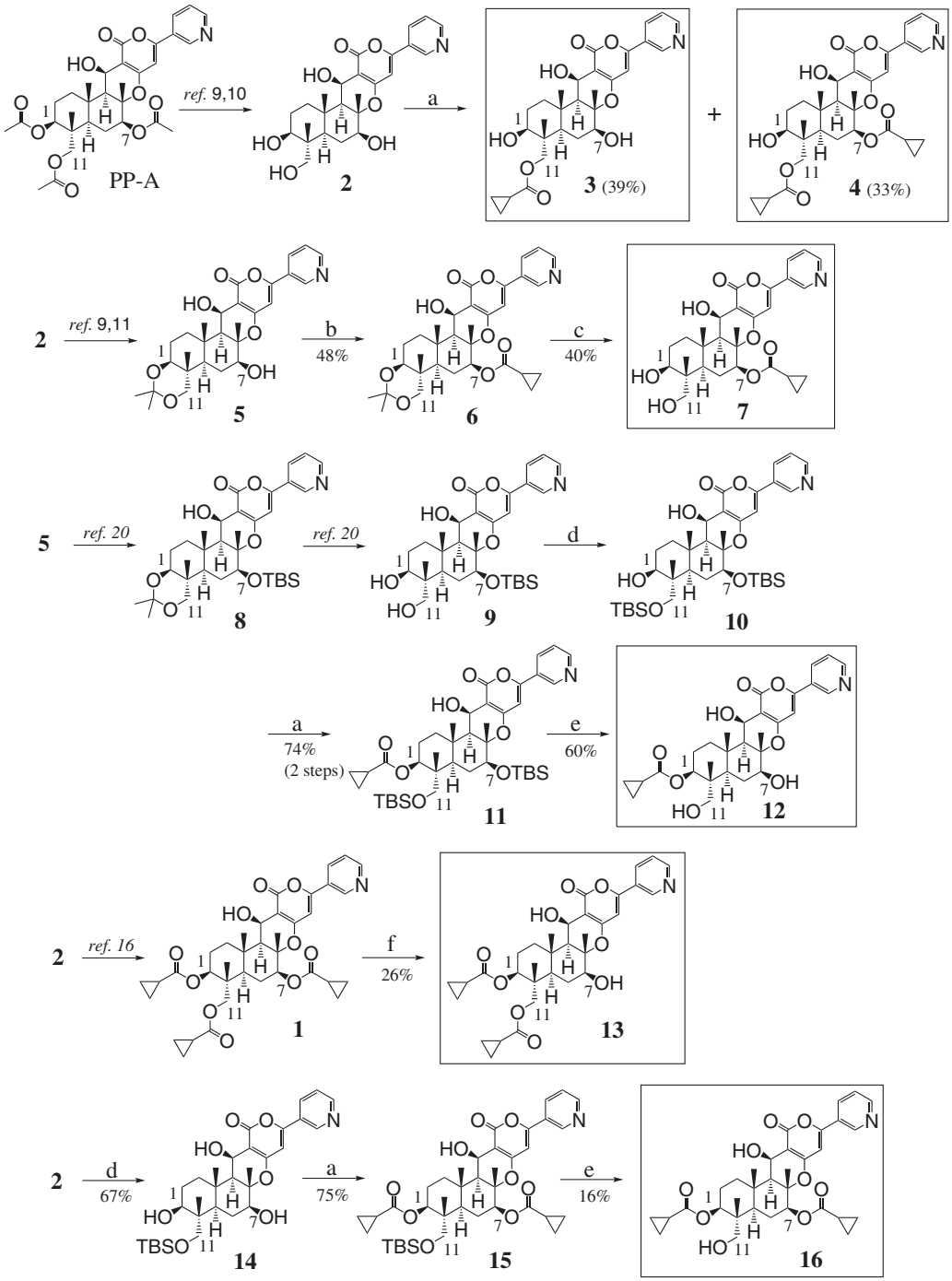
The structures and insecticidal activities are shown in Table 1. Interestingly, **13**, which had two cyclopropanecarbonyloxy groups at the C-1 and C-11 positions and a hydroxyl group at the C-7 position, exhibited much higher insecticidal activity against both aphids than PP-A (four times higher against *M. persicae* and six times higher against *A. gossypii* compared with the lead compound **1**). The mono-substituted derivatives **3** and **12** showed moderate to low activity against both aphids, while **7** showed low activity against both aphids. The insecticidal activity of mono-substituted derivatives was inferior to that of PP-A.

These results suggested that the presence of two cyclopropanecarbonyloxy groups at the C-1 and C-11 positions of the PP structure were important for high insecticidal activity.

Next, chemical modifications at the hydroxyl group at the C-7 position of **13** were made to try and improve its insecticidal activity. As shown in Scheme 2, derivatives **17a-g** were prepared by a previously reported procedure [8, 9], in which the hydroxyl group at the C-7 position of **13** was acylated using a corresponding carboxylic anhydride with triethylamine or carboxylic acid with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), respectively. As shown in Scheme 3, **18** was synthesized from **13** by regioselective oxidation at the C-7 position using Dess–Martin periodinan (DMP). The intermediate compound **19** was synthesized from **13** and **20** was obtained by treating **19** with tributyltin hydride (Bu_3SnH) using a previously reported method [10].

Furthermore, some epimers at the C-7 position (**21**, **22** and **23**) were synthesized by the reaction [21] with triflate and the corresponding organolithium reagent, followed by the regioselective hydrolysis of the acetyl group at the C-7 position of **22** to produce **23**, as shown in Scheme 4.

The insecticidal activities of the synthesized derivatives with two cyclopropanecarbonyloxy groups at the C-1 and C-11 positions against *M. persicae* and *A. gossypii* were evaluated in a screening assay (Table 2).

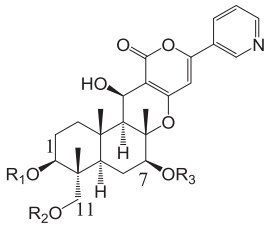


Scheme 1 Synthesis of PP derivatives having one or two cyclopropanecarbonyl group(s): **a** cyclopropanecarboxylic acid, EDCI, DMAP, DMF; **b** cyclopropanecarbonyl chloride, pyridine, AcOEt; **c** AcOH-H_2O, THF; **d** TBSCl, pyridine; **e** HF-pyridine complex, pyridine, THF; **f** DBU, 90% MeOH aq

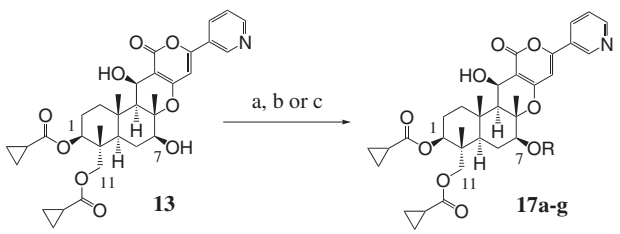
The insecticidal activities of **18** and **20** against *M. persicae* and those of **17a**, **17f**, **17g**, **18**, **20** and **21** against *A. gossypii*, were nearly equal to that of **13**. The derivatives with smaller groups tended to show higher activity. Derivatives with a configuration inversion at the C-7 position such as **21** (Cl) and **23** (OH) also showed high insecticidal activity. However, no derivatives in this series showed higher insecticidal activities than that of **13** against both *M. persicae* and *A. gossypii*.

The results of this study and those reported previously [16] indicated that relatively smaller substituent groups may, in terms of insecticidal activity, be preferable to bulky ones at the C-1, C-7 or C-11 position(s). Therefore, we introduced some small acyl groups such as acetyl groups or

Table 1 Insecticidal activity of PP derivatives having one or two acyl group(s) for *M. percicae* and *A. gossypii*



compound	R_1	R_2	R_3	Insecticidal activity	
				M. persicae (LC_{90}, ppm)	*A. gossypii* (LC_{90}, ppm)
PP-A				0.56	0.30
1				0.026	0.078
12		H	H	0.91	>1.3
3	H		H	1.0	0.36
7	H	H		>1.3	>1.3
13			H	0.0066	0.012
16		H		>1.3	>1.3
4	H			0.60	>1.3



Scheme 2 Synthesis of PP derivatives **17a–g**: **a** R_2O, Et_3N, DMAP, DMF; **b** ROH, EDCI, DMAP, DMF; **c** CH_3SO_2Cl, pyridine

propionyl groups at the C-1 and C-7 positions of a PP derivative with a cyclopropanecarbonyl group at the C-11 position.

As shown in Scheme 5, **24a** and **24b** were, respectively, obtained by acylation of **3** using acetic anhydride or propionic anhydride. Successive regioselective hydrolysis of the acyl group at the C-7 position of **24a** or **24b** gave **25a** or **25b**, respectively.

Table 3 shows the insecticidal activities of **24a–b** and **25a–b**. Although these derivatives showed moderate activities, they were inferior to those of **1** and **13**, especially against *A. gossypii*.

Through a series of optimization studies for substituent groups at the C-1, C-7 and C-11 positions, we concluded that the preferable combination for high insecticidal activity was two cyclopropanecarbonyl groups at the C-1 and C-11 positions and one hydroxyl group at the C-7 position.

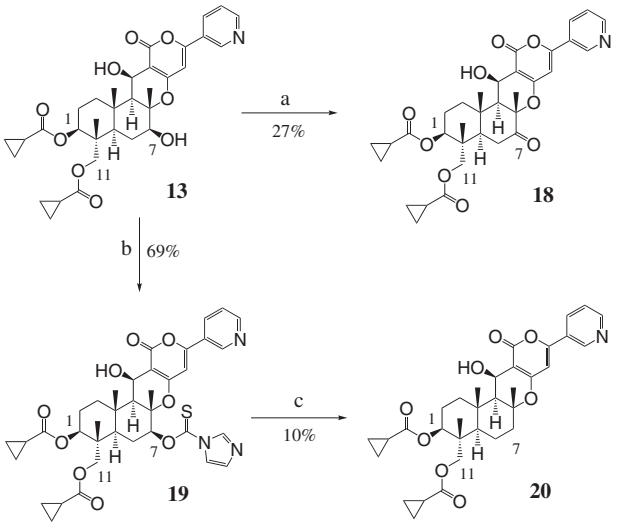
Subsequently, we chemically modified the hydroxyl group at the C-13 position of **13** with two cyclopropanecarbonyloxy groups at the C-1 and C-11 positions and a hydroxyl group at the C-7 position to find a suitable

substituent at the C-13 position of PP derivatives as shown in Scheme 6.

We obtained **26** by regioselective oxidation at the C-13 position of **13**. Elimination of the hydroxyl group at the C-13 position of **13** by treatment with *p*-toluenesulfonic acid monohydrate gave **27**.

Derivative **30** was synthesized from **17a** by three steps; acetylation and methoxylation at the C-13 position and successive regioselective hydrolysis of the acetyl group at the C-7 position. We prepared **32** from **17a** using two steps; introduction of a cyclopropanecarbonyl group into the hydroxy group at the C-13 position and regioselective hydrolysis of the acetyl group at the C-7 position.

Table 4 shows the insecticidal activities of **26**, **27**, **30** and **32**.



Scheme 3 Synthesis of PP derivatives **18** and **20**: **a** Dess–Martin periodinan, CH_2Cl_2; **b** 1, 1′-thiocarbonylimidazole, toluene; **c** Bu_3SnH, toluene

Compared with the LC_{90} value of **13**, those of **30** and **32** against *A. gossypii* were nearly equal. However, these derivatives were inferior to **13** in terms of their insecticidal activity against *M. persicae*. Compared with **13**, derivatives **26** and **27** showed much weaker insecticidal activity against both aphids.

The results of this study showed that the preferable substituent group at the C-13 position should be a hydroxyl group, the same substituent group as that in PP-A, for high insecticidal activity against *M. persicae* and *A. gossypii*.

Finally, derivatives with cyclopropanecarbonyl group(s) derived from the major PP natural analogs such as PP-E, PP-O, 13-deoxy PP-A [22] (**37**) and phenylpyropene A were investigated.

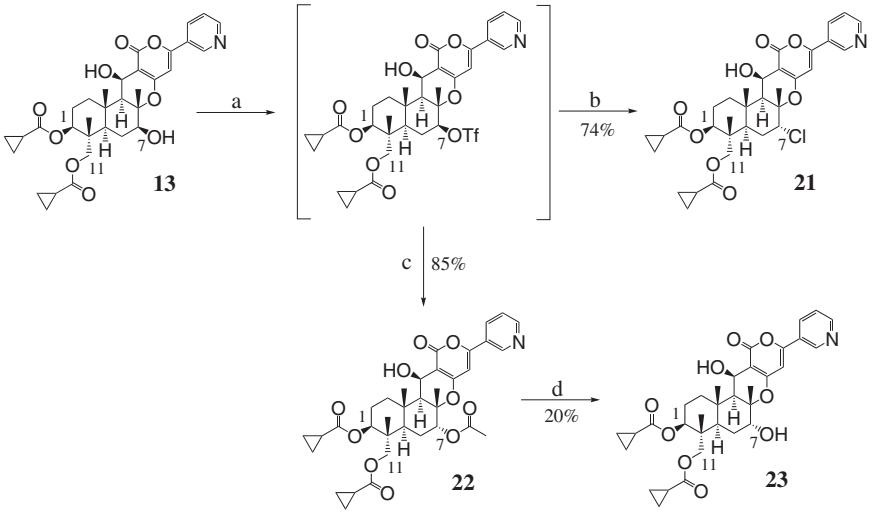
The syntheses of **34**, **36** and **40** are shown in Scheme 7. First, **33** was obtained from PP-O by hydrolysis of the two acetyl groups. Acylation of the hydroxyl groups at the C-1 and C-11 positions by treatment with cyclopropanecarbonyl chloride gave **34**. Then, using similar method to that of **34**, **36** was obtained from PP-E in two steps.

Derivative **40** was synthesized from **37** in three steps: hydrolysis of three acetyl groups [6]; introduction of cyclopropanecarbonyl groups into hydroxyl groups; and successive regioselective hydrolysis at the C-7 position, similar to the synthesis of **13**.

As shown in Scheme 8, **46** with a phenyl ring moiety was synthesized from **41** [23] by a previously reported procedure [12] with minor modifications; that is, the rearrangement of the PP skeleton by introducing a phenyl ring moiety instead of a 3-pyridine ring moiety into the PP structure.

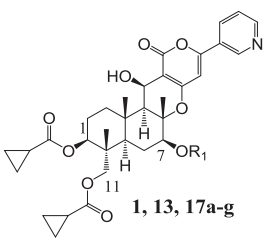
Table 5 shows the insecticidal activities of derivatives **34**, **36**, **40** and **46**, which had similar substitution patterns as PP natural analogs.

Derivative **40** did not have a hydroxyl group at the C-13 position and showed lower but still relatively high

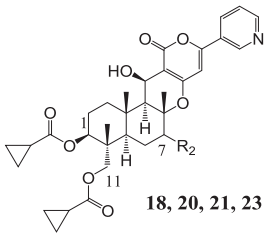


Scheme 4 Synthesis of PP derivatives **21** and **23**: **a** Tf_2O, DMAP, CH_2Cl_2; **b** LiCl DMF; **c** LiOAc, DMF-HMPA; **d** K_2CO_3, 90% MeOH aq

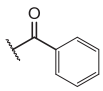
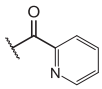
Table 2 Structures and insecticidal activity for *M. percicae* and *A. gossypii* of PP derivatives having various substituent groups at the C-7 position



1, 13, 17a-g



18, 20, 21, 23

compound	R_1	R_2	Insecticidal activity	
			M. persicae (LC_{90}, ppm)	*A. gossypii* (LC_{90}, ppm)
1		—	0.026	0.078
13	H	—	0.0066	0.012
17a[a)]		—	0.052	0.014
17b[a)]		—	0.28	0.14
17c[a)]		—	0.072	0.11
17d[a)]		—	0.31	0.55
17e[b)]		—	0.44	0.13
17f[b)]		—	0.17	0.039
17g[c)]		—	0.051	0.053
18	—		0.015	0.023
20	—		0.016	0.034
21	—		0.056	0.061
23	—		0.73	0.15

a) reaction condition; R_2O, Et_3N, DMAP, DMF.

b) reaction condition; ROH, EDCI, DMAP, DMF.

c) reaction condition; CH_3SO_2Cl, pyridine.

Scheme 5 Synthesis of PP derivatives **24a–b** and **25a–b**: **a** Ac_2O, Et_3N, DMAP, DMF; **b** $(CH_3CH_2CO)_2O$, Et_3N, DMAP, DMF; **c** DBU, 90% MeOH aq

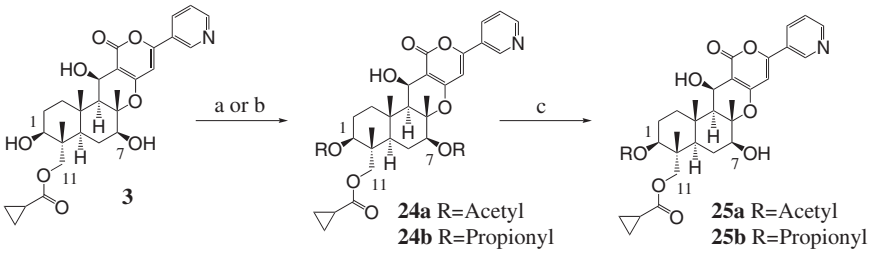
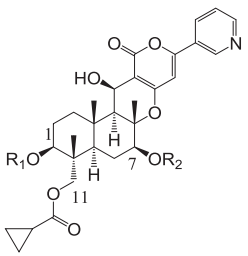


Table 3 Structures and insecticidal activities for *M. persicae* and *A. gossypii* of PP derivatives **24a–b** and **25a–b**



compound	R_1	R_2	Insecticidal activity	
			M. persicae (LC_{90}, ppm)	*A. gossypii* (LC_{90}, ppm)
1			0.026	0.078
13		H	0.0066	0.012
24a			0.20	0.32
25a		H	0.13	0.25
24b			0.078	0.14
25b		H	0.097	0.99

insecticidal activity compared with that of **13**. Derivatives **34** and **36**, with the absence of two or three hydroxyl groups at the C-7, C-11, or C-13 positions, showed much lower activities. Interestingly, **46**, which had a phenyl ring, showed no insecticidal activity, even at the maximum dose rate. These results suggested that the PP-A structure with a 3-pyridine ring and three hydroxyl groups at C-7, C-11 and C-13 positions was preferable in terms of high insecticidal activity.

Table 6 shows the insecticidal activities of the highly potent derivatives **1**, **13** and **18**. Among these derivatives, **13** was the most potent. Its LC_{90} against *M. persicae* and *A. gossypii* was 85 and 25 times higher, respectively, than that of the original lead compound, PP-A. The LC_{90} value of **18** was also much higher than those of PP-A and **1**. The activities of **13** and **18** against *Trialeurodes vaporariorum* were similar to that of PP-A and both derivatives showed low activity against *Frankliniella occidentalis* (Table 7).

Scheme 6 Synthesis of PP derivatives **26**, **27**, **30**, and **32**: **a** Dess–Martin periodinan, CH_2Cl_2; **b** *p*-TsOH, THF; **c** Ac_2O, Et_3N, DMAP, DMF; **d** 5% HCl, MeOH; **e** K_2CO_3, 90% MeOH aq.; **f** cyclopropanecarbonyl chloride, pyridine, AcOEt

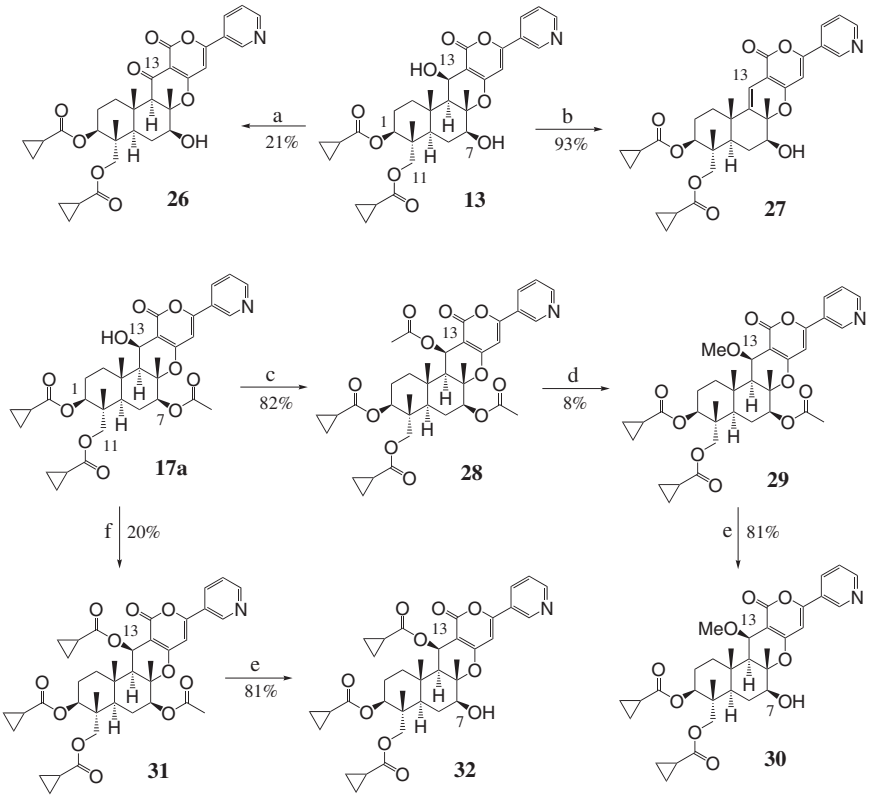
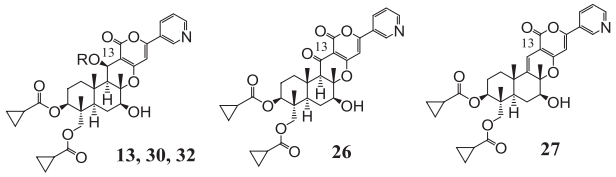


Table 4 Structures and insecticidal activities for *M. persicae* and *A. gossypii* of PP derivatives **26**, **27**, **30**, and **32**

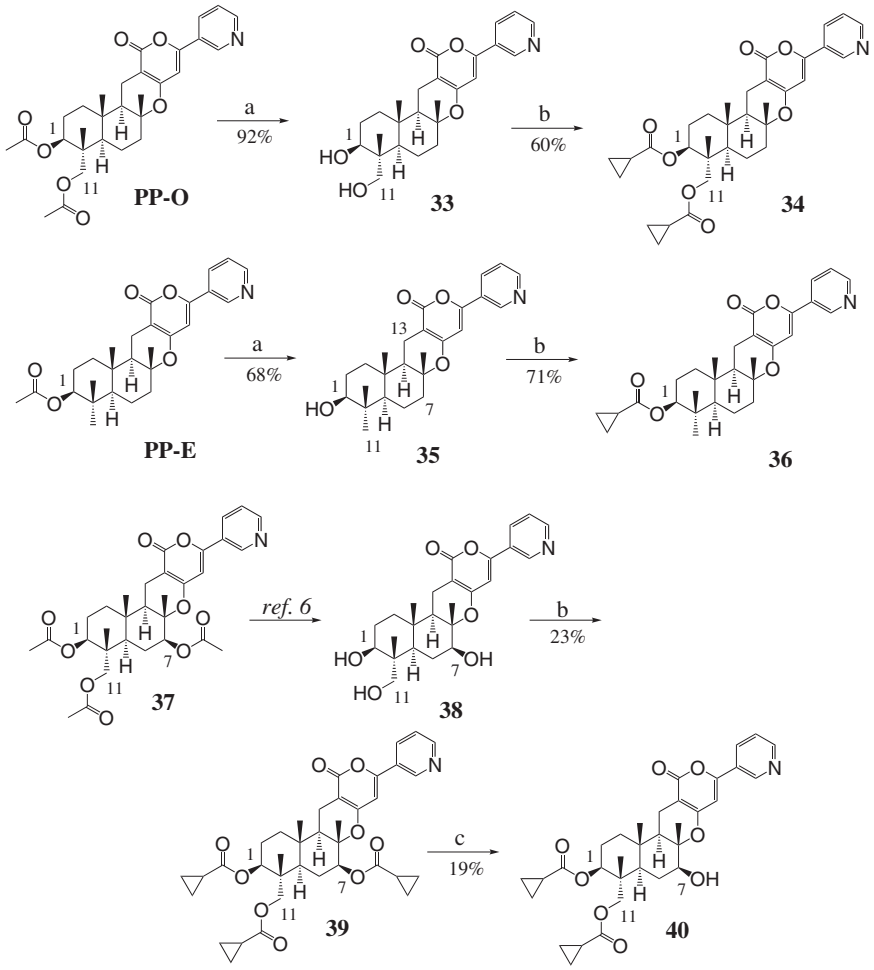


compound	R	Insecticidal activity	
		M. persicae (LC_{90}, ppm)	*A. gossypii* (LC_{90}, ppm)
13	H	0.0066	0.012
26	–	>1.3	0.29
27	–	>1.3	>1.3
30	CH_3	0.91	0.017
32		0.12	0.019

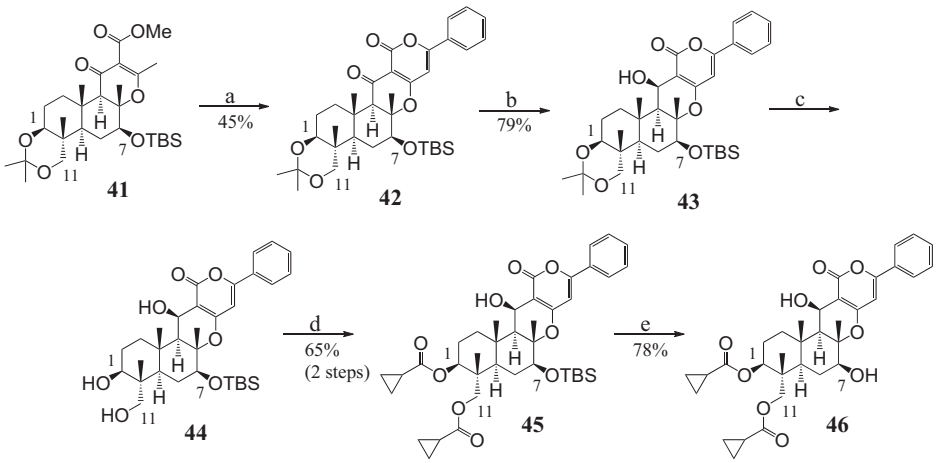
To select the best candidates in the test against another problematic species of aphid, we compared the activities of **13** and **18**. These derivatives were applied to the leaves of wheat to test their efficacy against *Rhopalosiphum padi*. In this screening test, **13** exhibited higher activity than **18** (Fig. 2). Consequently, we selected **13** as the candidate for a new insecticide. In the test by systemic application, where the compound was absorbed by plant roots and transported to upper leaves and stems, **13** showed outstandingly improved activity against *M. persicae*, compared with those of PP-A and **1** (shown in Fig. 3). We prepared prototype wettable powder (WP) formulations of **1** and **13** and applied these WPs to the leaves of 5-week-old cabbage plants. Derivative **13** exhibited much better and quicker activity than that of **1** (Fig. 4). Similar results were obtained in an *A. gossypii* test (data not shown). According to these results, **13** proved to be the most promising candidate among all the tested derivatives as a control agent for sucking pests.

Conclusion

The results of SAR studies on PP derivatives with and without substitutions at the C-1, C-7 and C-11 positions revealed that the cyclopropanecarbonyl group was the key



Scheme 7 Synthesis of PP derivatives **34**, **36**, and **40**: **a** K_2CO_3, 90% MeOH aq., **b** cyclopropanecarbonyl chloride, pyridine, AcOEt, **c** DBU, 90% MeOH aq

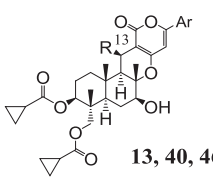


Scheme 8 Synthesis of PP derivative **46**: **a** (i) LHMDS, TMEDA, THF, (ii) 1-benzoylbenzotriazole, THF; **b** $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH; **c** AcOH-H_2O, THF; **d** cyclopropanecarbonyl chloride, pyridine, DMF; **e** HF-pyridine complex, pyridine, THF

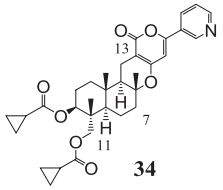
substituent group at these positions for high aphicidal activity. Among all the tested derivatives with chemical modifications at the C-1, C-7 and C-11 positions, **13** with two cyclopropanecarbonyloxy groups at the C-1 and C-11 positions and a hydroxyl group at the C-7 position showed the highest insecticidal activity against *M. persicae* and *A. gossypii*. None of the derivatives with different substituents at the C-13 position or a pyridine ring moiety exhibited higher activity than that of **13**.

Figure 5 summarizes the SAR between PP derivatives and insecticidal activity against *M. persicae*. The LC_{90} values of PP-A, **1,** and **13** were 0.56 ppm, 0.026 ppm and

Table 5 Structures and insecticidal activities for *M. persicae* and *A. gossypii* of PP derivatives **34**, **36**, **40** and **46**



13, 40, 46



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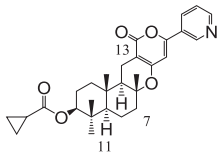

36

compound	Ar	R	Insecticidal activity	
			M. persicae (LC_{90}, ppm)	*A. gossypii* (LC_{90}, ppm)
13	3-pyridyl	OH	0.0066	0.012
34	–	–	0.31	0.26
36	–	–	>1.3	0.31
40	3-pyridyl	H	0.083	0.063
46	phenyl	OH	>1.3	>1.3

Table 6 Historical aphicidal activity of PP derivatives

Compound	*M. persicae*	*A. gossypii*
	LC_{90} (ppm)	LC_{90} (ppm)
PP-A	0.56	0.3
1	0.026	0.078
13	0.0066	0.012
18	0.015	0.023

Table 7 Efficacy of high aphicidal derivatives against other sucking pests

Compound	*T. vaporariorum*		*F. occidentalis*
	% mortality against adult		% mortality against 1st instar larvae
	5 ppm	1.25 ppm	200 ppm
PP-A	80	9	0
1	100	0	60
13	100	16	43
18	100	14	39

0.0066 ppm, respectively. Thus, the insecticidal activity of **13** was more than 80 times higher than that of PP-A, the lead natural analog and more than four times higher than that of **1**, the second lead compound.

In this study, **13** showed stable efficacy across several species of aphids and significantly better systemic activity than those of PP-A and **1**, the other derivatives with three acyl groups at C-1, C-7 and C-11. In the greenhouse tests (except the test summarized in Fig. 4), foliar-applied **13** showed stable and high efficacy repeatedly. We presume that **13** will show good persistence on crops, leading to reproducible excellent efficacy in controlling aphids.

Physico-chemical properties such as log P or water solubility, compared with those of commercial standards, are often referred as indexes of systemicity. The log P value of **13** was lower than that of **1** (Log P; 3.45 for **13**, 4.80 for **1**) and tended to be higher than those of standard compounds used to control sucking pests (log P of imidacloprid, clothianidin and sulfoxaflor with good systemicity are around 0–3) [24]. Considering both the contact insecticidal activity in aphid tests with leaf disks and the systemic activity, optimization to maximize the efficacy was achieved. Other than **13**, **18** also showed high

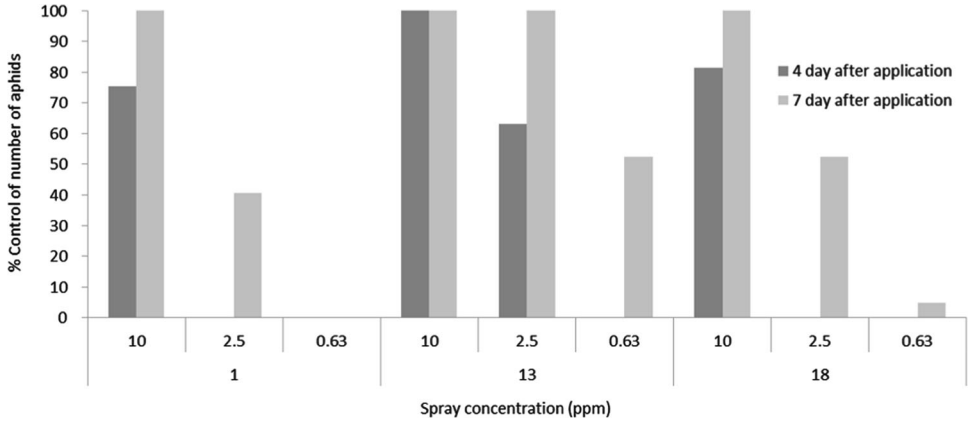

Fig. 2 Efficacy of high aphicidal derivatives, **1**, **13**, and **18**, against *R. padi* on wheat by foliar application; The number of aphids per plant in untreated plot at the timing of 0 day (just after aphids released), 4 day and 7 day after released was 4, 28.5, and 20.5

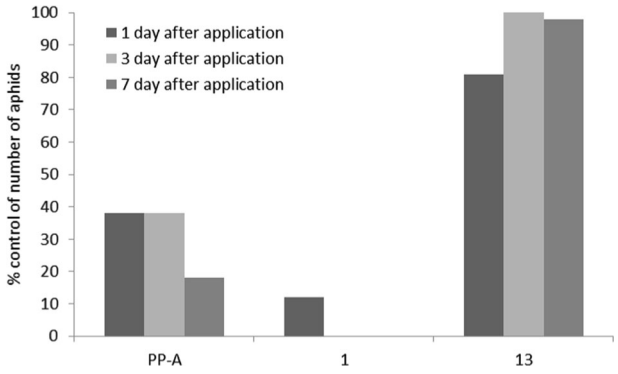

Fig. 3 Efficacy of high aphicidal derivatives, PP-A, **1** and **13**, against *M. persicae* on cabbage by soil drenching; The number of aphids per plant in untreated plot at the timing of 0 day (just after aphids released), 1, 3, and 7 day after released was 5, 13, 44, and 47

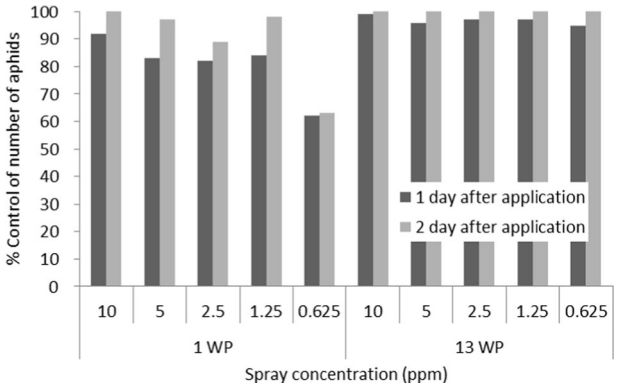

Fig. 4 Efficacy of **13** and the lead compound **1** against *M. persicae* by foliar application to cabbage pot; The number of aphids per plant in untreated plot at the timing of 0 day (before application), 1 day and 2 day after application was 17, 23, and 33.5

aphicidal activity. However, its efficacy was slightly but apparently lower than that of **13** in the *R. padi* test under the conditions where systemic activity contributed to efficacy. Strangely, all the highly active derivatives showed similar efficacy against whitefly adults. The contribution of contact and oral exposure to insecticidal activity may differ between aphids and whiteflies. As well as insecticidal properties, toxicological and eco-toxicological properties are also important. It is desirable for any insecticide to have low impacts against non-target organisms. We have not described these properties in this paper, but this issue and the potential practical uses will be discussed separately.

Although PP derivatives have been studied as ACAT inhibitors, they also might work as insecticides by activating TRPV (vanilloid-type transient receptor potential) channels in insect chordotonal organs. Compound **13** is the most potent insect TRPV channel modulator known [25].

In summary, we selected **13**, which is now known as the common name afidopyropen, as a promising insecticide candidate for agricultural sucking pests because it showed preferable insecticidal activity, better systemic efficacy and improved performance on crops than the lead compound **1**.

Experimental procedure

General methods

The PP natural analogs PP-A, PP-E, PP-O and 13-deoxy PP-A (**37**) were produced and purified according to our established methods [6]. The reagents were obtained from commercial suppliers and were used without purification. The ^{1}H and ^{13}C NMR spectra were measured using JEOL Lambda 400 MHz, BRUKER Ascend 400 MHz and 500 MHz spectrometers in $CDCl_3$. Mass spectra were obtained using a JEOL JMS-FAB mate spectrometer, a JEOL JMS-700 mass spectrometer, or an Agilent Technologies 6530-Q-TOF LC/MS mass spectrometer. Column chromatography was carried out on silica gel (Mega Bond Elut, Varian) and preparative thin-layer chromatography (PTLC) (Silica Gel 60 F_{254} 0.5 mm, Merck).

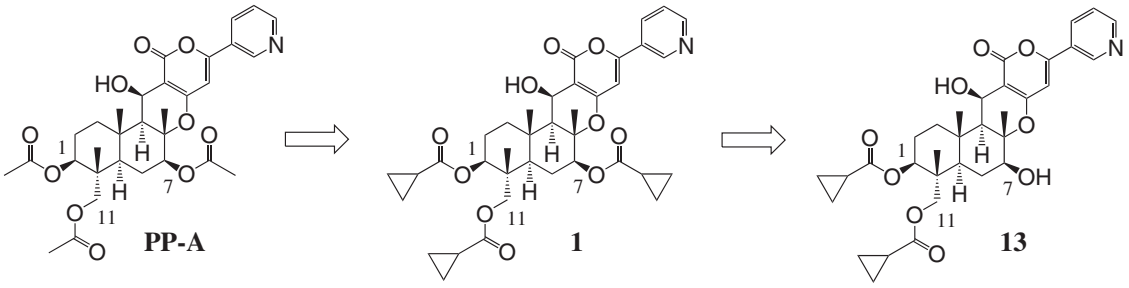

Fig. 5 Summary of SAR between PP derivatives and insecticidal activity (LC_{90}) against *M. percicae*

11-*O*-Cyclopropylcarbonyl-1, 7, 11-tri-deacetylpyripyropene A (3)

7, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetylpyripyropene A (4)

To a solution of **2** (20 mg, 0.0436 mmol), which synthesized by the method previously reported [9, 10] and cyclopropanecarboxylic acid (19 mg, 0.218 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (1 ml) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (84 mg, 0.436 mmol) and 4-(dimethylamino)pyridine (DMAP) (5 mg, 0.0436 mmol) and the mixture was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with AcOEt. 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 ($CHCl_3$: MeOH = 10: 1) to afford **3** (9.0 mg, 0.0171 mmol) as a solid in 39% yield and **4** (8.6 mg, 0.0145 mmol) as a solid in 33% yield.

3: ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3H), 0.88–0.95 (m, 2H), 1.00–1.08 (m, 2H), 1.26 (m, 1H), 1.33 (m, 1H), 1.40 (s, 3H), 1.43 (m, 1H), 1.57–1.74 (m, 2H), 1.67 (s, 3H), 1.79–1.88 (m, 2H), 1.93 (m, 1H), 2.15 (m, 1H), 2.97 (s, 1H), 3.41 (dd, J = 11.2, 5.2 Hz, 1H), 3.75 (d, J = 11.6 Hz, 1H), 3.82 (dd, J = 11.6, 5.2 Hz, 1H), 4.28 (d, J = 11.6 Hz, 1H), 5.00 (d, J = 4.0 Hz, 1H), 6.53 (s, 1H), 7.43 (dd, J = 8.0, 4.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.70 (m, 1H), 9.02 (m, 1H); MS (ESI) *m/z* 526 $(M + H)^+$; high resolution mass spectrometry (HRMS) (ESI) *m/z* calcd. for $C_{29}H_{36}NO_8$ 526.2441, found 526.2440 $(M + H)^+$.

4: ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3H), 0.89–0.98 (m, 4H), 1.02-1.13 (m, 4H), 1.28 (dt, J = 12.0, 4.4 Hz, 1H), 1.39–1.42 (m, 1H), 1.42 (s, 3H), 1.51 (d, J = 4.0 Hz, 1H), 1.61–1.73 (m, 3H), 1.72 (s, 3H), 1.81–1.84 (m, 2H), 1.90 (m, 1H), 2.16 (m, 1H), 3.37 (dd, J = 11.2, 5.2 Hz, 1H), 3.62 (d, J = 12.0 Hz, 1H), 4.35 (d, J = 12.0 Hz, 1H), 5.00 (d, J = 4.4 Hz, 1H), 5.02–5.06 (m, 1H), 6.46 (s, 1H), 7.42 (m, 1H), 8.11 (d, J = 8.0 Hz, 1H), 8.70 (m, 1H), 9.02 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.0, 174.1, 164.3, 162.5, 157.5, 151.7, 147.0, 133.3, 127.3, 124.0, 103.1, 99.7, 83.7, 77.9, 71.6, 65.9, 60.3, 54.9, 51.3, 45.6, 42.4, 38.1, 36.7, 25.5, 17.7, 16.4, 13.3, 12.9, 12.6, 12.0, 9.0, 8.9, 8.7; MS (ESI) *m/z* 594 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{33}H_{40}NO_9$ 594.2703, found 594.2706 $(M+H)^+$.

7-*O*-Cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-1, 11-*O*-isopropylidenepyripyropene A (6)

To a solution of **5** (100 mg, 0.201 mmol), which synthesized by the method previously reported [9, 11], in AcOEt (2 ml) were added pyridine (126 mg, 1.61 mmol) and cyclopropanecarbonyl chloride (63 mg, 1.21 mmol) and the mixture was stirred at room temperature for 24 h. The reaction mixture was poured into water and extracted with AcOEt. 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 **6** (54.1 mg, 0.0958 mmol) as a solid in 48% yield. ^{1}H NMR ($CDCl_3$) δ 0.95–0.98 (m, 2H), 1.10 (s, 3H), 1.04–1.15 (m, 3H), 1.37 (dt, J = 13.2, 3.2 Hz, 1H), 1.43 (s, 3H), 1.44 (s, 6H), 1.50 (d, J = 4.0 Hz, 1H), 1.58-1.66 (m, 3H), 1.71 (s, 3H), 1.68-1.74 (m, 1H), 1.76–1.83 (m, 1H), 2.22 (m, 1H), 3.04 (brs, 1H), 3.48 (s, 2H), 3.54 (dd, J = 12.0, 3.6 Hz, 1H), 4.97–5.01 (m, 2H), 6.47 (s, 1H), 7.42 (dd, J = 8.0, 4.8 Hz, 1H), 8.11 (ddd, J = 8.0, 2.0, 2.0 Hz, 1H), 8.69 (dd, J = 4.8, 2.0 Hz, 1H), 9.02 (d, J = 2.0 Hz, 1H); MS (ESI) *m/z* 566 $(M + H)^+$.

7-*O*-Cyclopropylcarbonyl-1, 7, 11-tri-deacetylpyripyropene A (7)

To a cold (0 °C) solution of **6** (42 mg, 0.0743 mmol) in THF (2 ml) were added AcOH (1 ml) and water (0.6 ml) and the mixture was stirred at room temperature for 21 h. $CHCl_3$ and saturated aqueous $NaHCO_3$ were added to the mixture. The precipitate was washed with cooled $CHCl_3$ and dried *in vacuo* to give **7** (15.7 mg, 0.0299 mmol) as a solid in 40% yield. ^{1}H NMR (DMSO) δ 0.57 (s, 3H), 0.89–0.99 (m, 4H), 1.14–1.25 (m, 1H), 1.30 (s, 3H), 1.40–1.70 (m, 6H), 1.67 (s, 3H), 1.78 (m, 1H), 1.94 (m, 1H), 2.99 (m, 1H), 3.34 (m, 1H), 3.46 (m, 1H), 4.27 (d, J = 4.8 Hz, 1H), 4.51 (t, J = 4.8 Hz, 1H), 4.78 (m, 1H), 4.88 (dd, J = 11.2, 5.2 Hz, 1H), 5.43 (d, J = 5.6 Hz, 1H), 6.88 (s, 1H), 7.52 (dd, J = 8.0, 4.8 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 8.66 (d, J = 4.8 Hz, 1H), 9.08

(s, 1H); MS (ESI) *m/z* 526 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{29}H_{36}NO_8$ 526.2441, found 526.2439.

7, 11-Di-*O*-*tert*-butyldimethylsilyl-1, 7, 11-tri-deacetylpyripyropene A (10)

To a solution of **9** (700 mg, 1.23 mmol), which synthesized by the method previously reported [20], in pyridine (7 ml) was added *tert*-butyldimethylsilyl chloride (550 mg, 3.68 mmol) and the mixture was stirred at room temperature for 14 h. The reaction mixture was concentrated and the residue was dissolved in AcOEt. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. This residue was used in the following step with no further purification. MS (ESI) *m/z* 686 $(M + H)^+$.

7, 11-Di-*O*-tert-butyldimethylsilyl-1-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetylpyripyropene A (11)

Reaction of crude **10** with cyclopropanecarbonyl chloride (1.0 g, 9.84 mmol) gave **11** (684 mg, 0.908 mmol) as a solid in 74% yield (2 steps from **9**) by a similar procedure to **6**. ^{1}H NMR ($CDCl_3$) δ -0.01 (s, 3H), 0.01 (s, 3H), 0.12 (s, 3H), 0.16 (s, 3H), 0.78 (s, 3H), 0.82–0.84 (m, 2H), 0.88 (s, 9H), 0.96 (s, 9H), 0.94–0.98 (m, 2H), 1.24–1.28 (m, 1H), 1.38 (s, 3H), 1.38–1.40 (m, 1H), 1.55–1.63 (m, 3H), 1.59 (s, 3H), 1.67–1.71 (m, 1H), 1.75–1.82 (m, 1H), 1.88–1.94 (m, 1H), 2.08–2.11 (m, 1H), 2.79 (d, $J = 1.7$ Hz, 1H), 3.18 (d, $J = 10.4$ Hz, 1H), 3.24 (d, $J = 10.0$ Hz, 1H), 3.72 (dd, $J = 10.4$, 5.0 Hz, 1H), 4.82 (dd, $J = 11.9$, 4.6 Hz, 1H), 4.97–4.98 (m, 1H), 6.35 (s, 1H), 7.41 (dd, $J = 8.1$, 4.8 Hz, 1H), 8.10 (dt, $J = 8.4$, 1.8 Hz, 1H), 8.69 (dd, $J = 4.8$, 1.7 Hz, 1H), 9.00 (d, $J = 1.6$ Hz, 1H); MS (ESI) *m/z* 754 $(M + H)^+$.

1-*O*-Cyclopropylcarbonyl-1, 7, 11-tri-deacetylpyripyropene A (12)

To a cold (0 °C) solution of **11** (350 mg, 0.465 mmol) in THF (2 ml) were added pyridine (0.5 ml) and HF-pyridine complex (0.6 ml) and the mixture was stirred at room temperature for 22 h. The reaction mixture was cooled to 0 °C and saturated aqueous $NaHCO_3$ was added and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography ($CHCl_3$: MeOH) to afford **12** (146 mg, 0.279 mmol) as a solid in 60% yield. ^{1}H NMR ($CDCl_3$) δ 0.75 (s, 3H), 0.87–0.95 (m, 2H), 1.01–1.05 (m, 2H), 1.24–1.35 (m, 2H), 1.41 (s, 3H), 1.49 (m, 1H), 1.59-1.74 (m, 3H), 1.65 (s, 3H), 1.95-2.06 (m, 2H), 2.18 (m, 1H), 2.45 (brs, 1H), 2.90 (s, 1H), 2.93 (d, $J = 12.7$ Hz, 1H), 3.34 (m, 1H), 3.91 (dd, $J = 11.6$, 5.2 Hz, 1H), 4.89 (dd, $J = 12.2$, 4.6 Hz, 1H), 4.97 (d, $J = 4.0$ Hz, 1H), 6.54 (s, 1H), 7.41 (dd, $J = 8.0$, 4.4 Hz, 1H), 8.11 (ddd, $J = 8.4$, 1.6, 1.4 Hz, 1H), 8.69 (dd, $J = 4.6$, 1.6 Hz, 1H), 9.01 (d, $J = 1.7$ Hz,); MS (ESI) *m/z* 526 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{29}H_{36}NO_8$ 526.2441, found 526.2432 $(M+H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetylpyripyropene A (13)

To a solution of **1** (2.95 g, 4.46 mmol), synthesized by the method previously reported [16], in an 90% aqueous MeOH solution (200 ml) was added 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (0.75 g, 4.91 mmol) and the mixture was stirred at room temperature for 14 h. The reaction was quenched with AcOH and the mixture was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by chromatography on silica gel (acetone: hexane) to afford **13** (0.69 g, 1.17 mmol) as a solid in 26% yield. ^{1}H NMR ($CDCl_3$) δ 0.85–0.88 (m, 4H), 0.92 (s, 3H), 0.96–1.01 (m, 4H), 1.35 (dt, $J = 12.6$, 4.0 Hz, 1H), 1.42 (s, 3H), 1.45–1.50 (m, 2H), 1.56–1.63 (m, 3H), 1.66 (s, 3H), 1.79–1.93 (m, 3H), 2.14 (m, 1H), 2.17 (d, $J = 3.6$ Hz, 1H), 2.85 (d, $J = 2.0$ Hz, 1H), 3.74 (d, $J = 12.$ 0 Hz, 1H), 3.78-3.82 (m, 1H), 3.86 (d, $J = 11.6$ Hz, 1H), 4.82 (dd, $J = 11.6$, 5.2 Hz, 1H), 4.99 (m, 1 H), 6.52 (s, 1H), 7.42 (dd, $J = 8.0$, 4.8 Hz, 1H), 8.11 (dt, $J = 8.1$, 1.9 Hz, 1H), 8.70 (dd, $J = 4.8$, 1.6 Hz, 1H), 9.00 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 174.5, 174.1, 164.0, 162.4, 157.3, 151.6, 146.8, 133.0, 127.3, 123.7, 103.2, 99.3, 85.5, 77.6, 73.4, 65.1, 60.3, 54.4, 45.7, 40.7, 38.1, 36.2, 27.6, 22.7, 17.6, 15.4, 13.2, 12.9, 8.7, 8.6, 8.5; MS (FAB) *m/z* 594 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{33}H_{39}NNaO_9$ 616.2523, found 616.2518 $(M+Na)^+$.

11-*O*-*tert*-Butyldimethylsilyl-1, 7, 11-tri-deacetylpyripyropene A (14)

Reaction of **2** (20 mg, 0.0437 mmol), which synthesized by the method previously reported [9, 10], with *tert*-butyldimethylsilyl chloride (39 mg, 0.262 mmol) gave **14** (17 mg, 0.0292 mmol) as a solid in 67% yield by a similar procedure to **10**. ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.88 (s, 3H), 0.91 (s, 9H), 1.22–1.28 (m, 2H), 1.37 (m, 1H), 1.39 (s, 3H), 1.61–1.67 (m, 1H), 1.65 (s, 3H), 1.74–1.81 (m, 3H), 2.11–2.15 (m, 2H), 2.82 (d, $J = 2.1$ Hz, 1H), 3.03 (s, 1H), 3.33 (d, $J = 9.4$ Hz, 1H), 3.62–3.67 (m, 1H), 3.65 (d, $J = 9.4$ Hz, 1H), 3.77–3.80 (m, 1H), 4.90 (m, 1H), 6.50 (s, 1H), 7.41 (dd, $J = 7.4$, 4.8 Hz, 1H), 8.10 (dt, $J = 8.3$, 1.8 Hz, 1H), 8.69 (dd, $J = 4.8$, 1.5 Hz, 1H), 9.00 (d, $J = 1.6$ Hz, 1H); MS (ESI) *m/z* 572 $(M + H)^+$.

11-*O*-*tert*-Butyldimethylsilyl-1, 7-di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetylpyripyropene A (15)

Reaction of **14** (12 mg, 0.0210 mmol) with cyclopropanecarboxylic acid (22 mg, 0.252 mmol) gave **15** (11 mg, 0.0158 mmol) as a solid in 75% yield by a similar procedure to **3**. ^{1}H NMR ($CDCl_3$) δ -0.05 (s, 3H), 0.03 (s, 3H), 0.79 (s, 3H), 0.81–0.84 (m, 2 H), 0.88 (s, 9H), 0.91–0.97 (m, 4H), 1.01–1.06 (m, 1H), 1.10–1.14 (m, 1H), 1.29–1.37 (m, 1H), 1.42 (s, 3H), 1.48 (d, $J = 4.0$ Hz, 1H), 1.56–1.68 (m, 4H), 1.70 (s, 3H), 1.77–1.94 (m, 3H), 2.11 (dt, $J = 13.0$,

3.1 Hz, 1H), 2.88 (d, $J = 1.8$ Hz, 1H), 3.19 (s, 2H), 4.87 (dd, $J = 11.8$, 4.7 Hz, 1H), 4.97-5.01 (m, 2H), 6.46 (s, 1H), 7.40 (dd, $J = 8.1$, 4.8 Hz, 1H), 8.08–8.11 (m, 1H), 8.68 (dd, $J = 4.9$, 1.6 Hz, 1H), 9.01 (d, $J = 2.3$ Hz, 1H); MS (ESI) *m/z* 708 $(M + H)^+$.

1, 7-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetylpyripyropene A (16)

To a solution of **15** (11 mg, 0.0156 mmol) in THF (0.5 ml) was added tetrabutylammonium fluoride in 1.0 M THF solution (47 µl, 0.0467 mmol) and the mixture was stirred at room temperature for 17 h. The reaction mixture was then poured into water, extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was purified by PTLC (acetone: hexane = 1: 1) to afford **16** (1.5 mg, 0.00253 mmol) as a solid in 16% yield. ^{1}H NMR ($CDCl_3$) δ 0.74 (s, 3H), 0.87–1.01 (m, 6H), 1.08–1.16 (m, 2H), 1.34–1.41 (m, 1H), 1.43 (s, 3H), 1.50–1.65 (m, 4H), 1.67–1.69 (m, 1H), 1.71 (s, 3H), 1.75–1.81 (m, 3H), 1.95–2.01 (m, 1H), 2.16–2.19 (m, 1H), 2.87 (s, 1H), 3.65 (s, 2H), 4.92 (dd, $J = 12.1$, 4.5 Hz, 1H), 4.98 (m, 1H), 5.11 (dd, $J = 11.6$, 4.8 Hz, 1H), 6.46 (s, 1H), 7.40 (dd, $J = 8.0$, 4.9 Hz, 1H), 8.09–8.11 (m, 1H), 8.69 (d, $J =$ 3.7 Hz, 1H), 9.02 (d, $J = 2.2$ Hz, 1H); MS (ESI) *m/z* 594 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 11-di-deacetylpyripyropene A (17a)

To a solution of **13** (30 mg, 0.0506 mmol) in anhydrous DMF (1 ml) were added triethylamine (Et_3N) (46 mg, 0.455 mmol), 4-(dimethylamino)pyridine (DMAP) (12 mg, 0.101 mmol) and acetic anhydride (31 mg, 0.303 mmol) and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water and extracted with AcOEt. 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 **17a** (30 mg, 0.0479 mmol) as a solid in 95% yield. ^{1}H NMR ($CDCl_3$) δ 0.84–0.89 (m, 4H), 0.89 (s, 3H), 0.90–1.06 (m, 4H), 1.37 (dt, $J = 13.2$, 3.8 Hz, 1H), 1.45 (s, 3H), 1.53 (d, $J = 4.0$ Hz, 1H), 1.55–1.67 (m, 4H), 1.70 (s, 3H), 1.79–1.87 (m, 2H), 1.89–1.94 (m, 2H), 2.14–2.18 (m, 1H), 2.16 (s, 3H), 2.97 (d, $J = 2.0$ Hz, 1H), 3.77 (s, 2H), 4.81 (dd, $J = 11.7$, 4.8 Hz, 1H), 5.00 (m, 1H), 5.02 (dd, $J = 11.4$, 5.0 Hz, 1H), 6.46 (s, 1H), 7.40 (dd, $J = 8.0$, 4.9 Hz, 1H), 8.09 (dt, $J = 8.1$, 1.9 Hz, 1H), 8.68 (dd, $J = 4.8$, 1.6 Hz, 1H), 9.00 (d, $J = 2.0$ Hz, 1H); MS (ESI) *m/z* 636 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{35}H_{42}NO_{10}$ 636.2809, found 636.2809 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-7-*O*-propionylpyripyropene A (17b)

Reaction of **13** (20 mg, 0.0337 mmol) with propionic anhydride (26 mg, 0.200 mmol) gave **17b** (14 mg, 0.0216 mmol) as a solid in 64% yield by a similar procedure to **17a**. ^{1}H NMR ($CDCl_3$) δ 0.84–0.89 (m, 4H), 0.90 (s, 3H), 0.96–1.16 (m, 4H), 1.23 (t, $J = 7.6$ Hz, 3H), 1.34–1.41 (m, 1H), 1.44 (s, 3H), 1.53–1.65 (m, 4H), 1.69 (s, 3H), 1.78–1.94 (m, 4H), 2.15–2.18 (m, 1H), 2.41–2.48 (m, 2H), 2.94 (s, 1H), 3.74 (d, $J = 12.0$ Hz, 1H), 3.81 (d, $J = 12.0$ Hz, 1H), 4.81 (dd, $J = 11.6$, 4.8 Hz, 1H), 5.00–5.05 (m, 2H), 6.44 (s, 1H), 7.41 (dd, $J = 7.9$, 4.8 Hz, 1H), 8.10 (m, 1H), 8.69 (d, $J = 4.6$ Hz, 1H), 9.01 (s, 1H); MS (ESI) *m/z* 650 $(M+H)^+$; HRMS (ESI) *m/z* calcd. for $C_{36}H_{44}NO_{10}$ 650.2965, found 650.2965 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-7-*O*-isobutyrylpyripyropene A (17c)

Reaction of **13** (20 mg, 0.0337 mmol) with isobutyric anhydride (32 mg, 0.202 mmol) gave **17c** (18 mg, 0.0277 mmol) as a solid in 82% yield by a similar procedure to **17a**. ^{1}H NMR ($CDCl_3$) δ 0.83–0.89 (m, 4H), 0.91 (s, 3H), 0.96–1.09 (m, 4H), 1.26 (d, $J = 6.8$ Hz, 6H), 1.35–1.42 (m, 1H), 1.45 (s, 3H), 1.53–1.67 (m, 4H), 1.71 (s, 3H), 1.78–1.94 (m, 4H), 2.15–2.18 (m, 1H), 2.58–2.74 (m, 1H), 2.98 (d, $J = 1.9$ Hz, 1H), 3.73 (d, $J = 12.0$ Hz, 1H), 3.83 (d, $J = 12.0$ Hz, 1H), 4.81 (dd, $J = 11.7$, 4.9 Hz, 1H), 4.94–5.13 (m, 2H), 6.39 (s, 1H), 7.41 (dd, $J = 8.0$, 4.9 Hz, 1H), 8.09 (dt, $J = 8.2$, 2.0 Hz, 1H), 8.69 (d, $J = 3.9$ Hz, 1H), 9.01 (s, 1H); MS (ESI) *m/z* 664 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{37}H_{46}NO_{10}$ 664.3122, found 664.3119 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-7-*O*-pivaloylpyripyropene A (17d)

Reaction of **13** (20 mg, 0.0337 mmol) with pivalic anhydride (38 mg, 0.202 mmol) gave **17d** (3.2 mg, 0.00472 mmol) as a solid in 14% yield by a similar procedure to **17a**. ^{1}H NMR ($CDCl_3$) δ 0.84–0.89 (m, 4H), 0.91 (s, 3H), 0.96–1.07 (m, 4H), 1.29 (s, 9H), 1.38–1.42 (m, 1H), 1.45 (s, 3H), 1.53–1.66 (m, 4H), 1.71 (s, 3H), 1.78–1.92 (m, 4H), 2.15–2.18 (m, 1H), 2.89 (d, $J = 1.9$ Hz, 1H), 3.71 (d, $J =$ 11.6 Hz, 1H), 3.85 (d, $J = 11.6$ Hz, 1H), 4.80 (dd, $J = 11.4$, 5.1 Hz, 1H), 4.98-5.01 (m, 2H), 6.35 (s, 1H), 7.41 (dd, $J =$ 8.2, 5.0 Hz, 1H), 8.09 (dt, $J = 8.1$, 2.0 Hz, 1H), 8.69 (d, $J =$ 4.1 Hz, 1H), 9.00 (s, 1H); MS (ESI) *m/z* 678 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{38}H_{48}NO_{10}$ 678.3278, found 678.3286 $(M + H)^+$.

7-*O*-Benzoyl-1, 11-di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetylpyripyropene A (17e)

Reaction of **13** (20 mg, 0.0337 mmol) with benzoic acid (25 mg, 0.202 mmol) gave **17e** (21 mg, 0.0300 mmol) as a solid in 89% yield by a similar procedure to **3**. ^{1}H NMR ($CDCl_3$) δ 0.86-0.91 (m, 4H), 0.92 (s, 3H), 0.96-0.99 (m, 2H), 1.03–1.11 (m, 2H), 1.39–1.45 (m, 1H), 1.50 (s, 3H), 1.55–1.69 (m, 4H), 1.76–2.05 (m, 4H), 1.86 (s, 3H), 2.18–2.22 (m, 1H), 2.99 (s, 1H), 3.75 (d, $J = 11.6$ Hz, 1H), 3.85 (d, $J = 11.6$ Hz, 1H), 4.84 (dd, $J = 11.4$, 4.4 Hz, 1H), 5.04 (m, 1H), 5.30 (dd, $J = 11.6$, 4.7 Hz, 1H), 6.43 (s, 1H), 7.38–7.39 (m, 1H), 7.48-7.52 (m, 2H), 7.60–7.64 (m, 1H),

8.06 (dd, $J = 8.0$, 1.7 Hz, 1H), 8.13 (d, $J = 8.0$ Hz, 2H), 8.67 (d, $J = 4.6$ Hz, 1H), 8.97 (s, 1H); MS (ESI) *m/z* 698 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for C40H44NO10 698.2965, found 698.2957 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-7-*O*-(2-pyridylcarbonyl)pyripyropene A (17 f)

Reaction of **13** (20 mg, 0.0337 mmol) with picolinic acid (25 mg, 0.202 mmol) gave **17 f** (23 mg, 0.0327 mmol) as a solid in 97% yield by a similar procedure to **3**. ^{1}H NMR ($CDCl_3$) δ 0.85-0.90 (m, 4H), 0.92 (s, 3H), 0.97–1.16 (m, 4H), 1.38–1.46 (m, 1H), 1.50 (s, 3H), 1.56–1.60 (m, 1H), 1.63–1.73 (m, 3H), 1.81–2.05 (m, 4H), 1.87 (s, 3H), 2.18-2.22 (m, 1H), 2.99 (d, $J = 2.0$ Hz, 1H), 3.75 (d, $J = 12.0$ Hz, 1H), 3.83 (d, $J = 12.0$ Hz, 1H), 4.84 (dd, $J = 11.4$, 4.9 Hz, 1H), 5.05 (m, 1H), 5.41 (dd, $J = 11.6$, 5.5 Hz, 1H), 6.43 (s, 1H), 7.38 (dd, $J = 8.0$, 4.9 Hz, 1H), 7.53 (dd, $J = 7.6$, 4.6 Hz, 1H), 7.90 (t, $J = 7.2$ Hz, 1H), 8.06 (d, $J = 8.0$ Hz, 1H), 8.19 (d, $J = 7.8$ Hz, 1H), 8.67 (d, $J = 4.4$ Hz, 1H), 8.84 (d, $J = 4.4$ Hz, 1H), 8.97 (d, $J = 1.9$ Hz, 1H); MS (ESI) *m/z* 699 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{39}H_{43}N_2O_{10}$ 699.2918, found 699.2906 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-7-*O*-methanesulfonylpyripyropene A (17 g)

To a cold (0 °C) solution of **13** (40 mg, 0.0674 mmol) in pyridine (1 ml) was added methanesulfonyl chloride (23 mg, 0.202 mmol) and the mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated in vacuo. The resulting residue was purified by PTLC ($CHCl_3$: MeOH = 10: 1) to afford **17 g** (7.4 mg, 0.0110 mmol) as a solid in 16% yield. ^{1}H NMR ($CDCl_3$) δ 0.87–0.90 (m, 4H), 0.93 (s, 3H), 0.98–1.00 (m, 2H), 1.04–1.16 (m, 2H), 1.32–1.39 (m, 1H), 1.45 (s, 3H), 1.48–1.51 (m, 1H), 1.56–1.65 (m, 3H), 1.71 (s, 3H), 1.78–1.95 (m, 3H), 2.06–2.10 (m, 1H), 2.15–2.18 (m, 1H), 2.93 (d, $J = 2.0$ Hz, 1H), 3.18 (s, 3H), 3.72 (d, $J = 12.0$ Hz, 1H), 3.98 (d, $J = 11.7$ Hz, 1H), 4.67 (dd, $J = 12.2$, 5.1 Hz, 1H), 4.82 (dd, $J = 11.8$, 4.8 Hz, 1H), 5.01 (m, 1H), 6.45 (s, 1H), 7.42 (dd, $J = 7.9$, 4.8 Hz, 1H), 8.10 (d, $J = 8.1$ Hz, 1H), 8.70 (s, 1H), 9.02 (s, 1H); MS (ESI) *m/z* 672 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{34}H_{42}NO_{11}S$ 672.2479, found 672.2476 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-7-dehydropyripyropene A (18)

To a cold (0 °C) solution of **13** (20 mg, 0.0337 mmol) in CH_2Cl_2 (1 ml) was added Dess–Martin periodinan (21 mg, 0.0506 mmol) and the mixture was stirred at 0 °C for 3 h. The reaction was quenched with 10% aqueous Na_2SO_3 and $CHCl_3$ was added to the mixture. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by PTLC (acetone: hexane = 1: 1) to afford **18** (5.4 mg, 0.00913 mmol) as a solid in 27% yield. ^{1}H NMR ($CDCl_3$) δ 0.83–1.00 (m, 8H), 0.96 (s, 3H), 1.44 (m, 1H), 1.53–1.61 (m, 2H), 1.63 (s, 3H), 1.76 (d, $J = 3.7$ Hz, 1H), 1.81 (s, 3H), 1.87 (m, 2H), 1.94–1.97 (m, 1H), 2.21 (m, 1H), 2.53 (dd, $J = 14.9$, 2.6 Hz, 1H), 2.78 (t, $J = 14.9$ Hz, 1H), 2.91 (d, $J = 1.5$ Hz, 1H), 3.66 (d, $J = 12.0$ Hz, 1H), 3.84 (d, $J = 12.0$ Hz, 1H), 4.82 (dd, $J = 11.7$, 4.8 Hz, 1H), 5.06 (m, 1H), 6.71 (s, 1H), 7.41 (dd, $J = 8.0$, 4.8 Hz, 1H), 8.09 (dt, $J = 8.0$, 1.7 Hz, 1H), 8.70 (dd, $J = 4.8$, 1.7 Hz, 1H), 9.02 (d, $J = 1.7$ Hz, 1H); MS (ESI) *m/z* 592 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{33}H_{38}NO_9$ 592.2547, found 592.2545 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-7-*O*-thiocarbonylimidazoyl pyripyropene A (19)

To a solution of **13** (50 mg, 0.0843 mmol) in toluene (3 ml) was added 1, 1'-thiocarbonyldiimidazole (90 mg, 0.506 mmol) and the mixture was refluxed for 3 h. The reaction mixture was cooled to room temperature and AcOEt and water were added to the mixture. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by PTLC (acetone: hexane = 1: 1) to afford **19** (41 mg, 0.0584 mmol) as a solid in 69% yield. ^{1}H NMR ($CDCl_3$) δ 0.86–0.91 (m, 4H), 0.93 (s, 3H), 0.98–1.01 (m, 2H), 1.04–1.08 (m, 2H), 1.39–1.45 (m, 1H), 1.51 (s, 3H), 1.64–1.72 (m, 4H), 1.75–1.84 (m, 2H), 1.87 (s, 3H), 1.95–1.98 (m, 1H), 2.18–2.25 (m, 2H), 2.95 (d, $J = 1.7$ Hz, 1H), 3.73 (d, $J = 12.0$ Hz, 1H), 3.81 (d, $J = 12.0$ Hz, 1H), 4.86 (dd, $J = 11.7$, 4.6 Hz, 1H), 5.05 (m, 1H), 5.69 (dd, $J = 11.0$, 4.9 Hz, 1H), 6.48 (s, 1H), 7.10 (s, 1H), 7.40 (dd, $J = 8.2$, 5.0 Hz, 1H), 7.69 (s, 1H), 8.09 (dt, $J = 8.2$, 1.9 Hz, 1H), 8.40 (s, 1H), 8.69 (d, $J = 3.4$ Hz, 1H), 9.00 (d, $J = 1.7$ Hz, 1H); MS (ESI) *m/z* 704 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-7-deacetoxy -1, 11-di-deacetylpyripyropene A (20)

To a solution of tributyltin hydride (20 mg, 0.700 mmol) in toluene (2 ml) was added **19** (41 mg, 0.0583 mmol) in toluene (1 ml) and the mixture was refluxed for 3 h. After cooled to room temperature, AcOEt and water were added to the mixture. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was purified by PTLC (acetone: hexane = 1: 1) to afford **20** (3.5 mg, 0.00606 mmol) as a solid in 10% yield. ^{1}H NMR ($CDCl_3$) δ 0.84-1.00 (m, 8H), 0.90 (s, 3H), 1.12-1.16 (m, 1H), 1.25 (s, 1H), 1.35–1.46 (m, 1H), 1.41 (s, 3H), 1.56–1.70 (m, 5H), 1.66 (s, 3H), 1.78–1.89 (m, 2H), 2.12–2.17 (m, 2H), 2.82 (d, $J = 1.4$ Hz, 1H), 3.69 (d, $J = 11.9$ Hz, 1H), 3.91 (d, $J = 11.9$ Hz, 1H), 4.83 (dd, $J = 11.5$, 5.1 Hz, 1H), 4.99 (m, 1H), 6.46 (s, 1H), 7.42 (m, 1H), 8.11 (dt, $J = 8.0$, 1.7 Hz, 1H), 8.69 (m, 1H), 9.01 (m, 1H); MS (ESI) *m/z* 578 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{33}H_{40}NO_8$ 578.2754, found 578.2748 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-7-deacetoxy-1, 11-di-deacetyl-7- epichloropyripyropene A (21)

To a cold (0 °C) solution of **13** (50 mg, 0.0843 mmol) in CH_2Cl_2 (3 ml) were added DMAP (30 mg, 0.253 mmol) and

trifluoromethanesulfonic anhydride (35 mg, 0.126 mmol) and the mixture was stirred at room temperature for 3 h. $CHCl_3$ and water were added to the reaction mixture. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford a crude compound (82 mg). To a cold (0 °C) solution of this crude compound in DMF (1 ml) and was added lithium chloride (130 mg, 3.07 mmol) and stirred at room temperature for 20 h. The reaction mixture was diluted with AcOEt and washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was purified by PTLC (acetone: hexane = 1: 1) to afford **21** (38 mg, 0.0622 mmol) as a solid in 74% yield. ^{1}H NMR ($CDCl_3$) δ 0.81–0.87 (m, 4H), 0.90 (s, 3H), 0.98–1.03 (m, 4H), 1.45 (s, 3H), 1.45–1.54 (m, 1H), 1.56–1.64 (m, 2H), 1.78 (s, 3H), 1.80–1.88 (m, 1H), 1.92–1.96 (m, 1H), 1.99–2.00 (m, 2H), 2.10–2.22 (m, 3H), 2.88 (d, J = 3.5 Hz, 1H), 3.61 (d, J = 11.9 Hz, 1H), 3.95 (d, J = 11.9 Hz, 1H), 4.43 (t, J = 2.7 Hz, 1H), 4.93 (dd, J = 11.7, 4.8 Hz, 1H), 5.05 (dd, J = 3.4, 3.2 Hz, 1H), 6.53 (s, 1H), 7.41 (dd, J = 8.0, 4.8 Hz, 1H), 8.10 (ddd, J = 8.0, 1.8, 1.2 Hz, 1H), 8.69 (dd, J = 4.8, 1.2 Hz, 1H), 9.02 (d, J = 1.8 Hz, 1H); MS (ESI) *m/z* 612 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{33}H_{39}ClNO_8$ 612.2364, found 612.2368 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-7-deacetoxy-1, 11-di-deacetyl-7- epiacetoxypyripyropene A (22)

To a cold (0 °C) solution of **13** (300 mg, 0.506 mmol) in CH_2Cl_2 (3 ml) were added DMAP (246 mg, 2.01 mmol) and trifluoromethanesulfonic anhydride (285 mg, 1.01 mmol) and the mixture was stirred at room temperature for 2 h. Water was added to the mixture and the mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. To a cold (0 °C) solution of the residue in DMF (2 ml) and hexamethylphosphoric triamide (HMPA) (2 ml) was added lithium acetate (334 mg, 5.06 mmol) and stirred at 60 °C for 14 h. The reaction mixture was diluted with AcOEt and washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was purified by chromatography on silica gel (acetone: hexane) to afford **22** (274 mg, 0.431 mmol) as a solid in 85% yield. ^{1}H NMR ($CDCl_3$) δ 0.81–0.88 (m, 4H), 0.91 (s, 3H), 0.96–1.04 (m, 4H), 1.44 (s, 3H), 1.45–1.49 (m, 1H), 1.54–1.59 (m, 2H), 1.72 (s, 3H), 1.79–1.84 (m, 2H), 1.85–1.92 (m, 3H), 1.95–1.98 (m, 1H), 2.07 (s, 3H), 2.16–2.20 (m, 1H), 2.90 (s, 1H), 3.74 (s, 2H), 4.87 (dd, J = 11.5, 5.1 Hz, 1H), 5.03 (dd, J = 3.8, 2.7 Hz, 1H), 5.29 (dd, J = 3.0, 2.4Hz, 1H), 6.44 (s, 1H), 7.40 (dd, J = 8.0, 4.8 Hz, 1H), 8.09 (ddd, J = 8.1, 2.2, 1.8 Hz, 1H), 8.69 (dd, J = 4.8, 1.6 Hz, 1H), 9.02 (d, J = 1.7 Hz, 1H); MS (ESI) *m/z* 636 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{35}H_{42}NO_{10}$ 636.2809, found 636.2813 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-7-deacetoxy-1, 11-di-deacetyl-7- epihydroxypyripyropene A (23)

To a cold (0 °C) solution of **22** (270 mg, 0.425 mmol) in an 90% aqueous MeOH solution (5 ml) was added potassium carbonate (58 mg, 3.56 mmol) and the mixture was stirred at 0 °C for 4 h. The reaction was quenched with AcOH and the mixture was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by PTLC (acetone: hexane = 1: 1) to afford **23** (51 mg, 0.0860 mmol) as a solid in 20% yield. ^{1}H NMR ($CDCl_3$) δ 0.80–0.86 (m, 4H), 0.89 (s, 3H), 0.96–1.10 (m, 4H), 1.40 (s, 3H), 1.42–1.44 (m, 1H), 1.56–1.62 (m, 2H), 1.64 (s, 3H), 1.77–1.81 (m, 2H), 1.83–1.91 (m, 2H), 1.96 (d, J = 4.0 Hz, 1H), 2.03 (dd, J = 12.5, 2.0 Hz, 1H), 2.13 (dt, J = 13.1, 3.4 Hz, 1H), 2.41 (s, 1H), 2.87 (d, J = 1.8 Hz, 1H), 3.61 (d, J = 11.6 Hz, 1H), 3.96 (d, J = 11.6 Hz, 1H), 3.97 (m, 1H), 4.86 (dd, J = 11.6, 4.8 Hz, 1H), 5.01 (m, 1H), 6.51 (s, 1H), 7.41 (dd, J = 7.8, 4.7 Hz, 1H), 8.11 (dt, J = 8.2, 2.1 Hz, 1H), 8.69 (dd, J = 4.8, 1.6 Hz, 1H), 9.01 (d, J = 2.0 Hz, 1H); MS (ESI) *m/z* 594 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{33}H_{40}NO_9$ 594.2703, found 594.2703 $(M + H)^+$.

11-*O*-Cyclopropylcarbonyl-11- deacetylpyripyropene A (24a)

Reaction of **3** (30 mg, 0.0571 mmol) with acetic anhydride (70 mg, 0.685 mmol) gave **24a** (27 mg, 0.0445 mmol) as a solid in 78% yield by a similar procedure to **17a**. ^{1}H NMR ($CDCl_3$) δ 0.86–0.90 (m, 2H), 0.89 (s, 3H), 1.02–1.06 (m, 1H), 1.12–1.16 (m, 1H), 1.35–1.41 (m, 1H), 1.45 (s, 3H), 1.53–1.65 (m, 3H), 1.70 (s, 3H), 1.75–1.95 (m, 4H), 2.05 (s, 3H), 2.09 (m, 1H), 2.17 (s, 3H), 2.97 (d, J = 2.2 Hz, 1H), 3.73 (d, J = 12.0 Hz, 1H), 3.82 (d, J = 12.0 Hz, 1H), 4.79 (dd, J = 11.7, 4.6 Hz, 1H), 5.01–5.05 (m, 2H), 6.46 (s, 1H), 7.41 (dd, J = 8.0, 4.9 Hz, 1H), 8.10 (dt, J = 8.0, 1.9 Hz, 1H), 8.69 (dd, J = 4.7, 1.3 Hz, 1H), 9.01 (d, J = 1.7 Hz, 1H); MS (ESI) *m/z* 610 $(M + H)^+$.

11-*O*-Cyclopropylcarbonyl-7, 11-di-deacetylpyripyropene A (25a)

Reaction of **24a** (27 mg, 0.0445 mmol) with DBU (7 mg, 0.0491 mmol) gave **25a** (6.6 mg, 0.0116 mmol) as a solid in 26% yield by a similar procedure to **13**. ^{1}H NMR ($CDCl_3$) δ 0.87–0.92 (m, 2H), 0.90 (s, 3H), 0.99–1.02 (m, 1H), 1.11–1.16 (m, 1H), 1.33–1.36 (m, 1H), 1.43 (s, 3H), 1.46–1.51 (m, 2H), 1.58–1.63 (m, 2H), 1.66 (s, 3H), 1.79–1.89 (m, 3H), 2.05 (s, 3H), 2.10–2.18 (m, 1H), 2.28 (m, 1H), 2.90 (s, 1H), 3.77–3.85 (m, 3H), 4.78–4.81 (m, 1H), 5.00 (s, 1H), 6.53 (s, 1H), 7.41–7.44 (m, 1H), 8.11 (d, J = 6.8 Hz, 1H), 8.70 (s, 1H), 9.01 (s, 1H); MS (ESI) *m/z* 568 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{31}H_{38}NO_9$ 568.2547, found 568.2536 $(M + H)^+$.

11-*O*-Cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-1, 7-di-*O*-propionylpyripyropene A (24b)

Reaction of **3** (30 mg, 0.0571 mmol) with propionic anhydride (89 mg, 0.685 mmol) gave **24b** (18 mg, 0.0284 mmol) as a solid in 50% yield by a similar procedure to **17a**. ^{1}H NMR ($CDCl_3$) δ 0.88–0.90 (m, 2H), 0.90 (s, 3H), 1.02–1.06 (m, 1H), 1.12–1.18 (m, 1H), 1.13 (t, $J = 7.2$ Hz, 3H), 1.23 (t, $J = 7.6$ Hz, 3H), 1.37–1.40 (m, 1H), 1.45 (s, 3H), 1.54–1.64 (m, 3H), 1.70 (s, 3H), 1.78–1.92 (m, 4H), 2.15–2.18 (m, 1H), 2.29–2.35 (m, 2H), 2.44–2.47 (m, 2H), 2.95 (s, 1H), 3.72 (d, $J = 12.0$ Hz, 1H), 3.83 (d, $J = 12.0$ Hz, 1H), 4.77–4.81 (m, 1H), 5.01–5.07 (m, 2H), 6.44 (s, 1H), 7.40–7.43 (m, 1H), 8.10 (d, $J = 7.6$ Hz, 1H), 8.69 (s, 1H), 9.02 (s, 1H); MS (ESI) *m/z* 638 $(M + H)^+$.

11-*O*-Cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-1-*O*-propionylpyripyropene A (25b)

Reaction of **24b** (18 mg, 0.0284 mmol) with DBU (5 mg, 0.0312 mmol) gave **25b** (5.8 mg, 0.00998 mmol) as a solid in 35% yield by a similar procedure to **13**. ^{1}H NMR ($CDCl_3$) δ 0.85–0.92 (m, 2H), 0.91 (s, 3H), 0.97–1.01 (m, 2 H), 1.14 (t, $J = 7.6$ Hz, 3H), 1.34–1.37 (m, 1H), 1.42 (s, 3H), 1.46–1.51 (m, 2H), 1.57–1.64 (m, 2H), 1.66 (s, 3H), 1.78–1.94 (m, 3H), 2.14–2.18 (m, 1H), 2.30–2.36 (m, 3H), 2.91 (d, $J = 1.5$ Hz, 1H), 3.75–3.83 (m, 1H), 3.77 (d, $J = 12.0$ Hz, 1H), 3.84 (d, $J = 12.0$ Hz, 1H), 4.80 (dd, $J = 11.7$, 4.9 Hz, 1H), 5.00 (m, 1H), 6.53 (s, 1H), 7.43 (dd, $J = 8.0$, 4.9 Hz, 1H), 8.11 (dt, $J = 8.0$, 1.8 Hz, 1H), 8.70 (d, $J = 3.7$ Hz, 1H), 9.01 (s, 1H); MS (ESI) *m/z* 582 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{32}H_{40}NO_9$ 582,2703, found 582.2702 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-13-dehydropyripyropene A (26)

Reaction of **13** (20 mg, 0.0337 mmol) with Dess–Martin periodinan (21 mg, 0.0506 mmol) gave **26** (4 mg, 0.00693 mmol) as a solid in 21% yield by a similar procedure to **18**. ^{1}H NMR ($CDCl_3$) δ 0.83–0.92 (m, 4H), 0.90 (s, 3H), 0.94–1.03 (m, 4H), 1.14–1.20 (m, 1H), 1.22 (s, 3H), 1.42–1.49 (m, 1H), 1.53 (s, 3H), 1.55–1.66 (m, 4H), 1.74–1.84 (m, 1H), 1.87–1.91 (m, 1H), 2.54 (s, 1H), 2.79 (dt, $J = 13.6$, 3.4 Hz, 1H), 3.65 (s, 1H), 3.74 (d, $J = 12.0$ Hz, 1H), 3.89 (d, $J = 11.7$ Hz, 1H), 4.03 (dd, $J = 11.0$, 4.6 Hz, 1H), 4.81 (dd, $J = 11.4$, 5.2 Hz, 1H), 6.57 (s, 1H), 7.46 (dd, $J = 8.1$, 4.9 Hz, 1H), 8.19 (dt, $J = 8.1$, 1.8 Hz, 1H), 8.76 (d, $J = 3.7$ Hz, 1H), 9.05 (s, 1H); MS (ESI) *m/z* 592 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{33}H_{38}NO_9$ 592.2547, found 592.2543 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-5-dehydro-13-deoxypyripyropene A (27)

To a solution of **13** (100 mg, 0.169 mmol) in anhydrous THF (1 ml) was added *p*-toluenesulfonic acid monohydrate (160 mg, 0.841 mmol) and the mixture was stirred at room temperature for 25 h. The reaction mixture was diluted with AcOEt and washed with aqueous $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by PTLC (acetone: hexane = 1: 1) to afford **27** (90 mg, 0.157 mmol) as a solid in 93% yield. ^{1}H NMR ($CDCl_3$) δ 0.84–0.88 (m, 4H), 0.91 (s, 3H), 0.96–1.00 (m, 4H), 1.24 (s, 3H), 1.56 (s, 3H), 1.57–1.65 (m, 5H), 1.74–1.80 (m, 1H), 1.87–1.91 (m, 1H), 1.95–1.99 (m, 1H), 2.04–2.07 (m, 1H), 2.58 (d, $J = 3.2$ Hz, 1H), 3.75 (d, $J = 12.0$ Hz, 1H), 3.92 (d, $J = 12.0$ Hz, 1H), 4.05 (dd, $J = 7.3$, 3.8Hz, 1H), 4.81 (dd, $J = 11.8$, 4.6Hz, 1H), 6.33 (s, 1H), 6.57 (s, 1H), 7.41 (dd, $J = 8.0$, 4.9Hz, 1H), 8.12 (dt, $J = 8.1$, 1.9Hz, 1H), 8.67 (dd, $J = 4.7$, 1.6Hz, 1H), 9.01 (d, $J = 2.2$Hz, 1H); MS (ESI) *m/z* 576 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{33}H_{38}NO_8$ 576.2597, found 576.2590 $(M + H)^+$.

13-*O*-Acetyl-1, 11-di-*O*-cyclopropylcarbonyl-1, 11-di-deacetylpyripyropene A (28)

Reaction of **17a** (1.0 g, 1.57 mmol) with acetic anhydride (1.6 g, 15.7 mmol) gave **28** (0.88 g, 1.29 mmol) as a solid in 82% yield by a similar procedure to **17a**. ^{1}H NMR ($CDCl_3$) δ 0.83–0.90 (m, 4H), 0.87 (s, 3H), 0.96–0.98 (m, 2H), 1.02–1.08 (m, 2H), 1.13 (s, 3H), 1.26–1.32 (m, 1H), 1.53–1.69 (m, 4H), 1.71 (s, 3H), 1.75 (m, 2H), 1.79–1.90 (m, 2H), 2.11 (s, 3H), 2.18 (s, 3H), 2.34–2.47 (m, 1H), 3.74 (d, $J = 12.0$Hz, 1H), 3.78 (d, $J = 12.0$Hz, 1H), 4.82 (dd, $J = 11.7$, 4.6Hz, 1H), 5.02-5.06 (m, 1H), 6.38 (d, $J = 3.4$Hz, 1H), 6.42 (s, 1H), 7.41 (dd, $J = 7.6$, 4.9Hz, 1H), 8.11 (dt, $J = 8.1$, 2.0Hz, 1H), 8.69 (dd, $J = 4.8$, 1.6Hz, 1H), 9.00 (d, $J = 1.7$Hz, 1H); MS (ESI) *m/z* 678 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 11-di-deacetyl-13-*O*-methylpyripyropene A (29)

To a solution of **28** (2.3 g, 3.40 mmol) in MeOH (50 ml) was added 5% hydrochloric acid (2 ml) and the mixture was stirred at room temperature for 4 days. The reaction was quenched with Et_3N and the mixture was concentrated in vacuo. The resulting residue was purified by chromatography on silica gel (acetone: hexane) to afford **29** (172 mg, 0.265 mmol) as a solid in 8% yield. ^{1}H NMR ($CDCl_3$) δ 0.84–0.88 (m, 4H), 0.90 (s, 3H), 0.97–1.06 (m, 4H), 1.33–1.36 (m, 1H), 1.38 (s, 3H), 1.46 (d, $J = 3.0$Hz, 1H), 1.52–1.66 (m, 4H), 1.71 (s, 3H), 1.78–1.86 (m, 2H), 1.92–1.96 (m, 1H), 2.02–2.05 (m, 1H), 2.16 (s, 3H), 3.61 (s, 3H), 3.76 (s, 2H), 4.68 (d, $J = 3.0$Hz, 1H), 4.81 (dd, $J = 11.8$, 4.7Hz, 1H), 4.96 (dd, $J = 11.5$, 5.0Hz, 1H), 6.38 (s, 1H), 7.39 (ddd, $J = 8.0$, 4.9, 0.7Hz, 1H), 8.08–8.11 (m, 1H), 8.68 (dd, $J = 4.8$, 1.6Hz, 1H), 9.00 (d, $J = 1.7$Hz, 1H); MS (ESI) *m/z* 650 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-13-*O*-methylpyripyropene A (30)

Reaction of **29** (170 mg, 0.262 mmol) with potassium carbonate (36 mg, 0.262 mmol) gave **30** (129 mg, 0.212 mmol) as a solid in 81% yield by a similar procedure to **23**. ^{1}H NMR ($CDCl_3$) δ 0.84-0.87 (m, 4H), 0.91 (s, 3H), 0.94-

1.04 (m, 4H), 1.31–1.43 (m, 1H), 1.36 (s, 3H), 1.39 (d, $J =$ 3.0Hz, 1H), 1.45 (d, $J = 12.0$Hz, 1H), 1.56–1.63 (m, 3H), 1.68 (s, 3H), 1.79–1.93 (m, 3H), 2.01–2.05 (m, 1H), 3.61 (s, 3H), 3.70–3.75 (m, 2H), 3.85 (d, $J = 11.8$Hz, 1H), 4.67 (d, $J = 2.8$Hz, 1H), 4.81 (dd, $J = 11.6$, 4.9Hz, 1H), 6.46 (s, 1H), 7.41 (dd, $J = 8.0$, 4.9Hz, 1H), 8.11 (m, 1H), 8.68 (dd, $J = 4.8$, 1.2Hz, 1H), 8.99 (d, $J = 1.9$Hz, 1H); MS (ESI) *m/z* 608 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{34}H_{42}NO_9$ 608.2860, found 608.2859 $(M + H)^+$.

1, 11, 13-Tri-*O*-cyclopropylcarbonyl-1, 11-di-deacetylpyripyropene A (31)

To a cold (0 °C) solution of **17a** (1.0 g, 1.57 mmol) in AcOEt (10 ml) were added pyridine (3.73 g, 47.1 mmol) and cyclopropanecarbonyl chloride (4.90 g, 47.1 mmol) and the mixture was stirred at 40 °C for 8 h. The reaction was quenched with MeOH and the mixture was concentrated under reduced pressure and the residue was dissolved in AcOEt. 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 chromatography on silica gel (acetone: hexane) to afford **31** (0.223 g, 0.317 mmol) as a solid in 20% yield. ^{1}H NMR ($CDCl_3$) δ 0.83–0.92 (m, 6H), 0.87 (s, 3H), 0.96–1.16 (m, 6H), 1.14 (s, 3H), 1.24–1.30 (m, 1H), 1.53–1.66 (m, 4H), 1.67–1.74 (m, 1H), 1.73 (s, 3H), 1.75–1.90 (m, 3H), 2.18 (s, 3H), 2.42–2.45 (m, 1H), 3.73–3.79 (m, 2H), 4.82 (dd, $J = 12.0$, 4.7Hz, 1H), 5.01–5.05 (m, 1H), 6.39 (d, $J = 3.0$Hz, 1H), 6.41 (s, 1H), 7.40 (dd, $J = 8.0$, 4.1Hz, 1H), 8.10 (dt, $J =$ 8.2, 1.9Hz, 1H), 8.68 (dd, $J = 4.8$, 1.6Hz, 1H), 9.00 (d, $J =$ 2.2Hz, 1H); MS (ESI) *m/z* 704 $(M + H)^+$.

1, 11, 13-Tri-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetylpyripyropene A (32)

Reaction of **31** (430 mg, 0.612 mmol) with potassium carbonate (24 mg, 0.184 mmol) gave **32** (328 mg, 0.496 mmol) as a solid in 81% yield by a similar procedure to **23**. ^{1}H NMR ($CDCl_3$) δ 0.84–0.92 (m, 6H), 0.88 (s, 3H), 0.95–1.03 (m, 6H), 1.23 (s, 3H), 1.24–1.26 (m, 1H), 1.45–1.48 (m, 1H), 1.54–1.62 (m, 4H), 1.65 (d, $J = 3.5$Hz, 1H), 1.70 (s, 3H), 1.72–1.75 (m, 1H), 1.84–1.88 (m, 2H), 2.31 (br s, 1H), 2.42 (dt, $J = 13.2$, 3.0Hz, 1H), 3.72 (d, $J =$ 12.0Hz, 1H), 3.79–3.82 (m, 1H), 3.86 (d, $J = 11.8$Hz, 1H), 4.82 (dd, $J = 12.0$, 4.7Hz, 1H), 6.38 (d, $J = 3.4$Hz, 1H), 6.48 (s, 1H), 7.41 (dd, $J = 8.5$, 5.0Hz, 1H), 8.11 (dt, $J = 8.1$, 1.9Hz, 1H), 8.69 (dd, $J = 4.8$, 1.6Hz, 1H), 9.00 (d, $J =$ 1.7Hz, 1H); MS (ESI) *m/z* 662 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{37}H_{44}NO_{10}$ 662.2965, found 662.2955 $(M + H)^+$.

1, 11-Di-deacetylpyripyropene O (33)

Reaction of PP-O (30 mg, 0.0589 mmol) with potassium carbonate (20 mg, 0.145 mmol) gave **33** (23 mg, 0.0541 mmol) as a solid in 92% yield by a similar procedure to **23**. ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 3H), 0.97 (s, 3H), 1.14 (dt, $J =$ 12.8, 4.2Hz, 1H), 1.20–1.25 (m, 1H), 1.28 (s, 3H), 1.45–1.59 (m, 3H), 1.64–1.75 (m, 3H), 1.82 (dt, $J = 9.6$, 3.5Hz, 1H), 2.11–2.14 (m, 1H), 2.25 (dd, $J = 17.1$, 12.8Hz, 1H), 2.54 (dd, $J = 17.1$, 4.6Hz, 1H), 3.45 (d, $J = 10.3$Hz, 1H), 3.68 (dd, $J = 11.2$, 5.0Hz, 1H), 3.75 (d, $J = 10.3$Hz, 1H), 6.42 (s, 1H), 7.39 (dd, $J = 8.0$, 4.8Hz, 1H), 8.10 (dt, $J = 8.0$, 2.0Hz, 1H), 8.65 (dd, $J = 4.8$, 1.6Hz, 1H), 8.99 (d, $J = 2.0$Hz, 1H); MS (ESI) *m/z* 426 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 11-di-deacetylpyripyropene O (34)

Reaction of **33** (22 mg, 0.0517 mmol) with cyclopropanecarbonyl chloride (22 mg, 0.207 mmol) gave **34** (17 mg, 0.0310 mmol) as a solid in 60% yield by a similar procedure to **6**. ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 3H), 0.99 (s, 3H), 0.84–1.08 (m, 8H), 1.21 (dt, $J = 13.4$, 3.6Hz, 1H), 1.28 (s, 3H), 1.43–1.48 (m, 2H), 1.56–1.73 (m, 6H), 1.81–1.85 (m, 2H), 2.13–2.16 (m, 1H), 2.26 (dd, $J = 17.1$, 12.8Hz, 1H), 2.55 (dd, $J = 17.1$, 4.6Hz, 1H), 3.71 (d, $J = 11.7$Hz, 1H), 3.93 (d, J = 11.7Hz, 1H), 4.82 (dd, $J = 12.0$, 4.7Hz, 1H), 6.44 (s, 1H), 7.41 (dd, $J = 8.0$, 4.8Hz, 1H), 8.12 (ddd, $J = 8.0$Hz, 1H, 2.0, 1.4), 8.66 (dd, $J = 4.8$, 1.4Hz, 1H), 9.00 (d, J = 2.0Hz, 1H); MS (ESI) *m/z* 562 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{33}H_{40}NO_7$ 562.2805, found 562.2809 $(M + H)^+$.

1-Deacetylpyripyropene E (35)

Reaction of PP-E (29 mg, 0.0643 mmol) with potassium carbonate (53 mg, 0.384 mmol) gave **35** (18 mg, 0.0440 mmol) as a solid in 68% yield by a similar procedure to **23**. ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3H), 0.92 (s, 3H), 0.99–1.02 (m, 1H), 1.03 (s, 3H), 1.12 (dt, $J = 12.8$, 4.0Hz, 1H), 1.27 (s, 3H), 1.40-1.46 (m, 1H), 1.50 (dd, $J = 12.8$, 4.4Hz, 1H), 1.62–1.74 (m, 3H), 1.79–1.83 (m, 2H), 2.14 (dt, $J = 12.4$, 3.2Hz, 1H), 2.24 (dd, $J = 16.8$, 12.4Hz, 1H), 2.53 (dd, $J =$ 16.8, 4.8Hz, 1H), 3.25 (dd, $J = 11.2$, 4.0Hz, 1H), 6.42 (s, 1H), 7.38 (dd, $J = 8.0$, 4.8Hz, 1H), 8.10 (dt, $J = 8.0$, 2.0Hz, 1H), 8.65 (dd, $J = 4.8$, 1.6Hz, 1H), 8.99 (d, $J = 2.0$Hz, 1H); MS (ESI) *m/z* 410 $(M + H)^+$.

1-*O*-Cyclopropylcarbonyl-1 -deacetylpyripyropene E (36)

Reaction of **35** (10 mg, 0.0244 mmol) with cyclopropanecarbonyl chloride (10 mg, 0.0976 mmol) gave **36** (8.3 mg, 0.0174 mmol) as a solid in 71% yield by a similar procedure to **6**. ^{1}H NMR ($CDCl_3$) δ 0.84–0.88 (m, 2H), 0.91 (s, 3H), 0.92 (s, 3H), 0.95 (s, 3H), 0.98–1.01 (m, 2H), 1.07–1.11 (m, 1H), 1.18 (dt, $J = 13.1$, 3.6Hz, 1H), 1.27 (s, 3H), 1.40–1.48 (m, 1H), 1.52 (dd, $J = 12.8$, 4.8Hz, 1H), 1.59–1.74 (m, 4H), 1.79–1.83 (m, 2H), 2.14 (dt, $J = 12.6$, 3.1Hz, 1H), 2.24 (dd, $J = 17.2$, 13.0Hz, 1H), 2.52 (dd, $J = 17.2$, 4.7Hz, 1H), 4.51 (dd, $J = 11.6$, 4.8Hz, 1H), 6.43 (s, 1H), 7.39 (dd, $J = 8.0$, 4.8Hz, 1H), 8.11 (ddd, $J = 8.0$, 1.6, 1.6Hz, 1H), 8.66 (dd, $J = 4.8$, 1.6Hz, 1H), 9.00 (d, $J = 1.6$Hz, 1H); MS (FAB) *m/z* 478 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{29}H_{36}NO_5$ 478.2593, found 478.2589 $(M + H)^+$.

1, 7, 11-Tri-deacetyl-13-deoxypyripyropene A (38)

The crude **38** (5.0 g), including **2** as a major component, which was obtained by the method previously reported [6],

was purified by chromatography on silica gel ($CHCl_3$: MeOH) and HPLC (CH_3CN: H_2O) to afford **38** (0.44 g) as a solid. ^{1}H NMR (DMSO) δ 0.55 (s, 3H), 0.85 (s, 3H), 0.97–1.03 (m, 1H), 1.14 (s, 3H), 1.26–1.34 (m, 1H), 1.37–1.44 (m, 2H), 1.53–1.57 (m, 3H), 1.72 (m, 1H), 2.19 (dd, $J = 17.0$, 12.6Hz, 1H), 2.31 (dd, $J = 17.0$, 4.8Hz, 1H), 3.06 (dd, $J = 10.5$, 4.8Hz, 1H), 3.35–3.38 (m, 1H), 3.43–3.47 (m, 1H), 3.60 (m, 1H), 4.24 (d, $J = 5.1$Hz, 1H), 4.51 (t, $J = 5.0$Hz, 1H), 4.99 (d, $J = 5.2$Hz, 1H), 6.91 (s, 1H), 7.51 (dd, $J = 7.9$, 4.8Hz, 1H), 8.21 (dt, $J = 7.9$, 2.0Hz, 1H), 8.65 (dd, $J = 4.8$, 1.8Hz, 1H), 9.03 (d, $J = 2.0$Hz, 1H); MS (ESI) *m/z* 442 $(M + H)^+$.

1, 7, 11-Tri-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-13-deoxypyripyropene A (39)

Reaction of **38** (1.0 g, 2.27 mmol) with cyclopropanecarbonyl chloride (2.4 g, 22.7 mmol) gave **39** (0.34 g, 0.527 mmol) as a solid in 23% yield by a similar procedure to **6**. ^{1}H NMR ($CDCl_3$) δ 0.84–0.89 (m, 4H), 0.89 (s, 3H), 0.91–0.99 (m, 4H), 1.02 (s, 3H), 1.03–1.11 (m, 4H), 1.16–1.24 (m, 1H), 1.34 (s, 3H), 1.50–1.77 (m, 7H), 1.81–1.91 (m, 3H), 2.34 (dd, $J = 17.2$, 12.8Hz, 1H), 2.58 (dd, $J = 17.2$, 4.8Hz, 1H), 3.73 (d, $J = 11.6$Hz, 1H), 3.84 (d, $J = 11.6$Hz, 1H), 4.79 (dd, $J = 11.6$, 4.8Hz, 1H), 5.04 (dd, $J = 11.6$, 4.8Hz, 1H), 6.43 (s, 1H), 7.38 (dd, $J = 8.0$, 4.8Hz, 1H), 8.10 (ddd, $J = 8.0$, 2.0, 2.0Hz, 1H), 8.65 (dd, $J = 4.8$, 2.0Hz, 1H), 9.00 (d, $J = 2.0$Hz, 1H); MS (ESI) *m/z* 646 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{37}H_{44}NO_9$ 646.3016, found 646.3014 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetyl-13-deoxypyripyropene A (40)

Reaction of **39** (0.34 g, 0.527 mmol) with DBU (40 mg, 0.264 mmol) gave **40** (57 mg, 0.0988 mmol) as a solid in 19% yield by a similar procedure to **13**. ^{1}H NMR ($CDCl_3$) δ 0.83–0.90 (m, 4H), 0.89 (s, 3H), 0.96–1.04 (m, 4H), 1.00 (s, 3H), 1.15–1.22 (m, 1H), 1.29 (s, 3H), 1.50–1.62 (m, 5H), 1.65–1.76 (m, 1H), 1.80–1.89 (m, 3H), 2.34 (dd, $J = 16.8$, 13.2Hz, 1H), 2.56 (dd, $J = 16.8$, 4.8Hz, 1H), 3.77 (d, $J = 11.6$Hz, 1H), 3.81–3.84 (m, 1H), 3.87 (d, $J = 11.6$Hz, 1H), 4.81 (dd, $J = 11.6$, 4.8Hz, 1H), 6.49 (s, 1H), 7.40 (dd, $J = 8.0$, 4.8Hz, 1H), 8.11 (ddd, $J = 8.0$, 1.6, 1.6Hz, 1H), 8.67 (dd, $J = 4.8$, 1.6Hz, 1H), 8.99 (d, $J = 1.6$Hz, 1H); MS (ESI) *m/z* 578 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{33}H_{40}NO_8$ 578.2754, found 578.2746 $(M + H)^+$.

7-*O*-*tert*-Butyldimethylsilyl-1, 7, 11-tri-deacetyl-1, 11-*O*-isopropylidene-13-dehydrophenylpyropene A (42)

To a cold (0 °C) solution of lithium bis(trimethylsilyl) amide (LHMDS, 1.6M solution in THF, 8.7 ml, 14.0 mmol) was added *N, N, N', N'*-tetramethylethylenediamine (TMEDA, 0.39 ml, 3.36 mmol) and after stirring for 10 min, **41** (1.5 g, 2.80 mmol), which was synthesized by the method previously reported [23], in THF (10 ml) was added. The reaction mixture was stirred at 0 °C for 1 h, then cooled to −20 °C. To the resulting mixture was slowly added 1-benzoylbenzotriazole (1.25 g, 5.60 mmol) in THF (10 ml) at −20 °C. The reaction mixture was stirred at same temperature for 2 h, then quenched with AcOH. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. To a solution of the residue in benzene (15 ml) was added DBU (853 mg, 5.60 mmol) at room temperature. The mixture was stirred at 40 °C for 15 min, then cooled to room temperature and quenched with AcOH. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was purified by chromatography on silica gel (acetone: hexane) to afford **42** (773 mg, 1.27 mmol) as a solid in 45% yield. ^{1}H NMR ($CDCl_3$) δ 0.15 (s, 3H), 0.20 (s, 3H), 0.96 (s, 9H), 1.05–1.07 (m, 1H), 1.09 (s, 3H), 1.09–1.16 (m, 1H), 1.21 (s, 3H), 1.44 (s, 3H), 1.46 (s, 3H), 1.47 (s, 3H), 1.48–1.57 (m, 3H), 1.67–1.75 (m, 1H), 2.54 (s, 1H), 2.78–2.87 (m, 1H), 3.35–3.60 (m, 3H), 3.98 (dd, $J = 11.3$, 4.9Hz, 1H), 6.37 (s, 1H), 7.51–7.63 (m, 3H), 7.74–7.86 (m, 2H); MS (ESI) *m/z* 609 $(M + H)^+$.

7-*O*-*tert*-Butyldimethylsilyl-1, 7, 11-tri-deacetyl-1, 11-*O*-isopropylidenephenylpyropene A (43)

To a solution of **42** (770 mg, 1.27 mmol) in EtOH (50 ml) was added cerium (III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$, 2.4 g, 6.35 mmol) and mixture was stirred at room temperature for 10 min, then cooled to 0 °C. To a cold mixture was added sodium borohydride ($NaBH_4$, 480 mg, 12.7 mmol) and the reaction mixture was stirred for 15 h. The reaction mixture was diluted with $CHCl_3$ and washed with 0.1N aqueous NaOH. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was purified by chromatography on silica gel (acetone: hexane) to afford **43** (610 mg, 1.00 mmol) as a solid in 79% yield. ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 3H), 0.17 (s, 3H), 0.96 (s, 9H), 1.02–1.05 (m, 1H), 1.11 (s, 3H), 1.25–1.45 (m, 2H), 1.40 (s, 3H), 1.447 (s, 3H), 1.454 (s, 3H), 1.55–1.68 (m, 3H), 1.59 (s, 3H), 1.78–1.84 (m, 1H), 2.19–2.20 (m, 1H), 3.44 (d, $J = 10.5$Hz, 1H), 3.50–3.56 (m, 2H), 3.72 (dd, $J = 11.7$, 5.1Hz, 1H), 5.02 (d, $J = 4.1$Hz, 1H), 6.31 (s, 1H), 7.35–7.50 (m, 3H), 7.76–7.78 (m, 2H); MS (ESI) *m/z* 611 $(M + H)^+$.

7-*O*-*tert*-Butyldimethylsilyl-1, 7, 11-tri-deacetylphenyl pyropene A (44)

To a solution of **43** (0.92 g, 1.51 mmol) in THF (20 ml) was added 80% aqueous AcOH solution (30 ml) and mixture was stirred at room temperature for 10 days. The reaction mixture was cooled to 0 °C and then saturated aqueous $NaHCO_3$ was added to the mixture. The mixture was extracted with AcOEt and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered

and concentrated in vacuo. This residue (0.86 g) was used in the following step with no further purification. MS (ESI) *m/z* 571 $(M + H)^+$.

7-*O*-*tert*-Butyldimethylsilyl-1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetylphenylpyropene A (45)

To a solution of crude **44** (0.86 g) in DMF (5 ml) were added pyridine (1.1 g, 13.6 mmol) and cyclopropanecarbonyl chloride (0.95 g, 9.1 mmol) and the mixture was stirred at room temperature for 8 h. The reaction mixture was then poured into water, extracted with AcOEt. 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 chromatography on silica gel (acetone: hexane) to afford **45** (0.70 g, 0.986 mmol) as a solid in 65% yield (two steps from **43**). ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 3H), 0.16 (s, 3H), 0.83–0.89 (m, 4H), 0.90 (s, 3H), 0.96 (s, 9H), 0.96–1.00 (m, 4H), 1.30–1.36 (m, 1H), 1.41 (s, 3H), 1.42 (m, 1H), 1.44–1.47 (m, 1H), 1.59 (s, 3H), 1.55–1.64 (m, 4H), 1.78–1.91 (m, 2H), 2.13–2.18 (m, 1H), 2.85 (d, $J = 1.6$Hz, 1H), 3.65 (d, $J = 11.7$Hz, 1H), 3.67–3.72 (m, 1H), 3.91 (d, $J = 12.0$Hz, 1H), 4.81 (dd, $J =$ 11.7, 4.7Hz, 1H), 4.98 (dd, $J = 3.9$, 2.0Hz, 1H), 6.30 (s, 1H), 7.39–7.54 (m, 3H), 7.73–7.84 (m, 2H); MS (ESI) *m/z* 707 $(M + H)^+$.

1, 11-Di-*O*-cyclopropylcarbonyl-1, 7, 11-tri-deacetylphenylpyropene A (46)

To a cold (0 °C) solution of **45** (200 mg, 0.283 mmol) in THF (1 ml) were added pyridine (0.3 ml) and HF-pyridine complex (0.36 ml) and mixture was stirred at room temperature for 2 days. The reaction mixture was cooled to 0 °C and then saturated aqueous $NaHCO_3$ was added to the mixture. The mixture was extracted with AcOEt and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was purified by chromatography on silica gel (acetone: hexane) to afford **46** (130 mg, 0.220 mmol) as a solid in 78% yield. ^{1}H NMR ($CDCl_3$) δ 0.83–0.89 (m, 4H), 0.91 (s, 3H), 0.95–1.04 (m, 4H), 1.35 (dt, $J = 13.2$, 3.9Hz, 1H), 1.42 (s, 3H), 1.45 (d, $J = 4.1$Hz, 1H), 1.48–1.50 (m, 1H), 1.55–1.64 (m, 3H), 1.66 (s, 3H), 1.79–1.91 (m, 3H), 2.14–2.15 (m, 1H), 2.24 (d, $J = 3.8$Hz, 1H), 2.91 (d, $J =$ 1.9Hz, 1H), 3.75 (d, $J = 11.7$Hz, 1H), 3.77–3.81 (m, 1H), 3.86 (d, $J = 11.7$Hz, 1H), 4.82 (dd, $J = 11.5$, 4.9Hz, 1H), 4.99 (dd, $J = 3.8$, 2.5Hz, 1H), 6.45 (s, 1H), 7.34–7.49 (m, 3H), 7.78–7.80 (m, 2H); MS (ESI) *m/z* 593 $(M + H)^+$; HRMS (ESI) *m/z* calcd. for $C_{34}H_{41}O_9$ 593.2751, found 593.2743 $(M + H)^+$.

(1) **Insecticidal test against agricultural pests:**

The PP derivatives were evaluated by an insecticidal test against green peach aphid (*M. persicae*), using the method described in our previous report [15]. Tests against cotton aphid (*A. gossypii*), greenhouse whitefly (*T. vaporariorum*) and western flower thrips (*F. occidentalis*) was conducted using the methods reported previously [26, 27].

(2) **Efficacy against wheat aphid (*R. padi*) on wheat by foliar application:**

The trial was conducted using 2-week-old seedlings grown in pots in a greenhouse. The leaves of each seedling were sprayed with 1.5 ml of the test compound dissolved in 10% aqueous acetone solution containing 0.05% Tween 20. After the leaves dried, four adult aphids were released onto each plant. At 4 and 7 days after application, the number of aphids was counted in each plot. This test was conducted in duplicate. The density index was calculated as follows:

$$\text{Density index} = (\text{number of aphids in treated plot at 4 or 7 days after application})/(\text{number of aphids in untreated plot at 4 or 7 days after application}) \times 100. \quad (1)$$

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

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

(3) **Efficacy against green peach aphid (*M. persicae*) on cabbage by soil drenching:**

The trial was conducted using 5-week-old cabbage seedlings grown in pots in a greenhouse. The test compound (5 ml of the test compound dissolved in 10% aqueous acetone solution) was added to the soil in each pot. At 3 days after application, five adult aphids were released onto each plant. At 4 and 7 days after application, the number of aphids on each plant was counted. This test was conducted in duplicate. The density index and % control were calculated using the formulae shown above.

(4) **Efficacy of compound 1 and 13 against green peach aphid (*M. persicae*) on cabbage by foliar application:**

The trial was conducted on 5-week-old cabbage seedlings grown in pots in a greenhouse. Each test compound was formulated into a wettable powder (WP). This formulation, including 5% (w/w) each derivative, was prepared as described previously [27]. Four adult aphids were placed on each plant. After 6 days, 2 ml diluted solution of **1** and **13** WP in water was sprayed onto each plant. The number of aphids on each plant was counted before application and at 1 and 2 days after application. This test was

conducted in duplicate. The corrected density index was calculated as follows:

$$\text{Corrected density index} = \left[\begin{array}{c}(\text{number of aphids on treated plant at 1 or 2 days after application})/\\(\text{number of aphids on treated plant before application})\end{array}\right]\times \left[\begin{array}{c}(\text{number of aphids on untreated plant before application})/\\(\text{number of aphids on untreated plant at 1 or 2 days after application})\end{array}\right]\times 100. \quad (3)$$

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

$$\%\,\text{control} = 100-(\text{corrected density index}). \quad (4)$$

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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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