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Xiubin Li, Catherine Sivignon, Pedro da Silva, Yvan Rahbé, Yves Queneau, et al.. Design and synthesis of 3, 5- hetero diesters of 4-deoxy quinic acid and their aphicidal activity against *Acyrthosiphon pisum*. *Tetrahedron*, 2021, pp.131982. 10.1016/j.tet.2021.131982 . hal-03126097

**HAL Id: hal-03126097**

**<https://hal.science/hal-03126097>**

Submitted on 1 Jun 2021


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# Design and synthesis of 3, 5- hetero diesters of 4-deoxy quinic acid and their aphicidal activity against *Acyrtosiphon pisum*.

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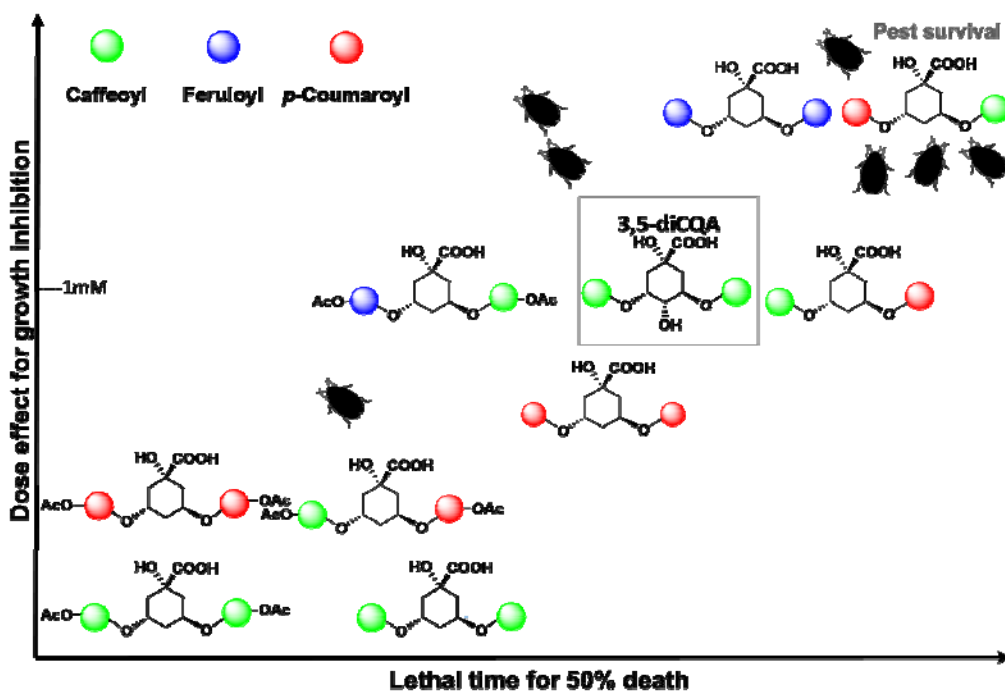
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## Highlights

- Analogs of chlorogenic acids featuring different and various hydroxyl cinnamoyl groups in 3 and 5 positions
- Four compounds were found to exhibit higher aphicidal activities than natural 3,5-di-*O*-caffeoylquinic acid
- Both acetylated 3-*O*-feruloyl-5-*O*-caffeoyl and 3-*O*-caffeoyl-5-*O*-coumaroyl compounds were active
- Observation of an interesting structure-activity difference for two regioisomers

## Graphical abstract



Four analogs of 3,5-dicafeoylquinic acid, including a new heterodiester of 4-deoxyquinic acid, were found toxic against a pea aphid. Several 4-deoxyquinic analogs featuring two different hydroxyl cinnamoyl moieties in position 3 and 5 were prepared for the first time and carefully analysed. Through an assay on a pea aphid larvae, interesting indications on the structure-aphicidal activity relationships and higher levels of toxicity were observed for four compounds related to the reference natural compound.

**Keywords** : chlorogenic acids, deoxy quinic acid, heterodiesters, pest management, growth inhibition

# Design and synthesis of 3, 5- hetero diesters of 4-deoxy quinic acid and their aphicidal activity against *Acyrtosiphon pisum*.

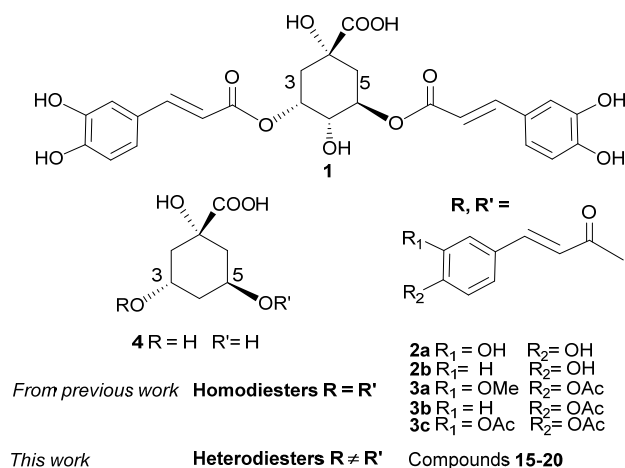
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## Introduction

Aphids, like the pea aphid *Acyrtosiphon pisum*, are severe agricultural pests damaging crops and vectoring plant pathogens. Aphid control strategies tend to be oriented towards more sustainable measures to reply to emerging resistance issues and concerns about environmental, human health and beneficial organism preservation. Natural products are logically regarded as promising alternatives to synthetic pesticides and still source of inspiration to find potentially less noxious chemicals.<sup>1,2</sup>

Hydroxycinnamoyl quinic acids, particularly caffeoylquinic acids, are widespread edible plant secondary metabolites. Most of these compounds, mono-, di- or triesters of hydroxycinnamoyl acids and polyol quinic acid, are grouped into a family named chlorogenic acids. Commonly used *via* traditional herbal medicines, different *in vitro* bioassays have evaluated their potential biological activities, among antioxidant,<sup>3</sup> antifungal,<sup>4</sup> antiviral,<sup>5</sup> renoprotective,<sup>6</sup> neuroprotective,<sup>7,8</sup> inhibitors of  $\alpha$ -glucosidase,<sup>9,10</sup> or as modulators of the intestinal microbiota in high-fat-diet-fed mice.<sup>11</sup>

The underlying biological mechanisms for host plant resistance to aphids are worth of interest.<sup>12</sup> For example, the correlation between chlorogenic acids concentration and priming of plants<sup>13</sup> was shown for the carrot fly larval damage,<sup>14</sup> for fungal infection<sup>4</sup> or for cultured tobacco cells.<sup>15</sup> The resistance of lettuce cultivars to *Pemphigus bursarius*<sup>16</sup> or the negative effect of chlorogenic acid on Western flower thrips *Frankliniella occidentalis* were also reported.<sup>17</sup> The cultivar *Rubira* peach tree, parent of a trait mapped to Rm2 gene<sup>18</sup> had shown a strong induced resistance to *Myzus persicae*, the green peach aphid which represents a threat for many agro-industrial crops.<sup>19</sup> An accumulation of metabolite, later identified as 3,5-dicaffeoyl quinic acid **1** (3,5-diCQA), had been previously detected in aphid-infested leaves,<sup>20</sup> and also later observed in a fungal-pear tree pathosystem.<sup>21</sup> While aphicidal activity was demonstrated by positive preliminary results of *in vitro* artificial diets assays adding **1** in nutritive medium for aphids,<sup>22</sup> the biological mode of action is not yet elucidated. To get preliminary insight into the structure activity relationship and/or to find more active compounds, we had considered the preparation of various synthetic analogs. To prevent isomerization of dihydroxycinnamoyl quinic acids during *in vitro* assays,<sup>22,23</sup> model compounds with a 4-deoxy quinic acid nucleus had been designed. Eight hydroxycinnamoyl homodiesters of a new 4-deoxy quinic acid or its methyl ester had been synthesized from the new triol **4**.<sup>24</sup> Their influence on the feeding behaviour of the pea aphid *Acyrtosiphon pisum* was evaluated. Two homodiesters with a free carboxylic function, compounds **2a** and **2b**, namely “3,5-dicaffeate” and “3,5-dicoumarate” had been identified as more toxic than the natural 3,5-diCQA **1** (Figure 1).



**Figure 1** : Representative compounds discussed in this paper

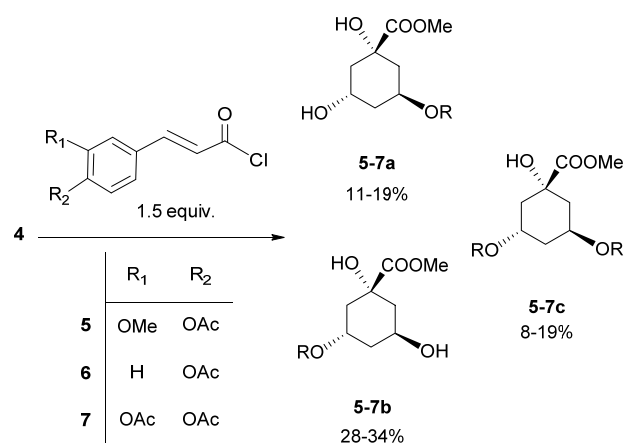
To extend our study with a second growth inhibition assay, different other structural parameters were addressed. As a very low activity was measured for methyl esters derivatives, only carboxylic acids would be included. First, some previously described but not assayed intermediates, **3a**, **3b**, **3c** could be incorporated in this new investigation to determine the influence of the acetylation of the phenol(s). Secondly, we aimed to study the possible correlation between aphicidal activity and consistent structural modifications

1 such as heterosubstitution in C-3 and C-5 positions and so the putative influence of the stereochemical position of each  
 2 hydroxycinnamoyl group. To refine our previous results, some questions were addressed: are two caffeoyl or *p*-coumaroyl groups  
 3 mandatory for such activity and if not, is their position in C-3 or C-5 determinant? We thus designed other diesters among which  
 4 those featuring a single caffeoyl and/or a single *p*-coumaroyl residues. We could anticipate that such preparation would require a clear  
 5 structural elucidation of defined intermediates to identify regioisomers. Natural caffeoyl-feruloyl quinic acids are interesting  
 6 «hybrids» not well studied albeit their probable existence was first noted in 1965.<sup>25</sup> Characterization for such compounds were then  
 7 however proposed by NMR<sup>26, 27, 28,29,30</sup> or by LC-MS<sup>n</sup> analysis of a methanolic coffee bean extract<sup>31</sup> or of sweet potato *Ipomea batatas*  
 8 from China.<sup>32</sup> Synthesis of methyl *muco*-quinates, heterosubstituted in 1 and 3 positions, was reported by Jaiswal *et al.*<sup>33</sup> To the best  
 9 of our knowledge, there were no reported synthesis for other 3,5-hetero diacylquinic acids. Here we describe our results on the  
 10 preparation of novel heterocinnamoyl chlorogenic acid analogs : “hybrid diesters or heterodiester” of 4-deoxy quinic acid **4** (Figure  
 11 1) were synthesized, carefully characterized and a complementary evaluation of the toxicity of eight compounds against the pea aphid  
 12 *Acyrtosiphon pisum* is reported.

## 13 Results and discussion

14 Partial selectivity observed during monoesterifications of other quinate derivatives (Li, X. unpublished results) encouraged us to  
 15 embark into the preparation of newly designed heterodiester by a sequential procedure, starting from the methyl 4-deoxy quinate **4**,  
 16 of two consecutive esterifications with different cinnamoyl chlorides. The first and key step was to identify reproducible conditions of  
 17 preparation, isolation and characterization of defined monosubstituted compounds from **4**<sup>24</sup> bearing a caffeoyl, feruloyl or *p*-  
 18 coumaroyl residue on the 3 or 5 positions (Scheme1). Then a second different cinnamoyl chloride could be introduced towards  
 19 different combinations of 3, 5-heterodiester of **4** and then selective deprotections would give 3, 5-heterodiester of 4-deoxy quinic  
 20 acid with acetylated or free phenols.

### 21 Synthesis of monoesters



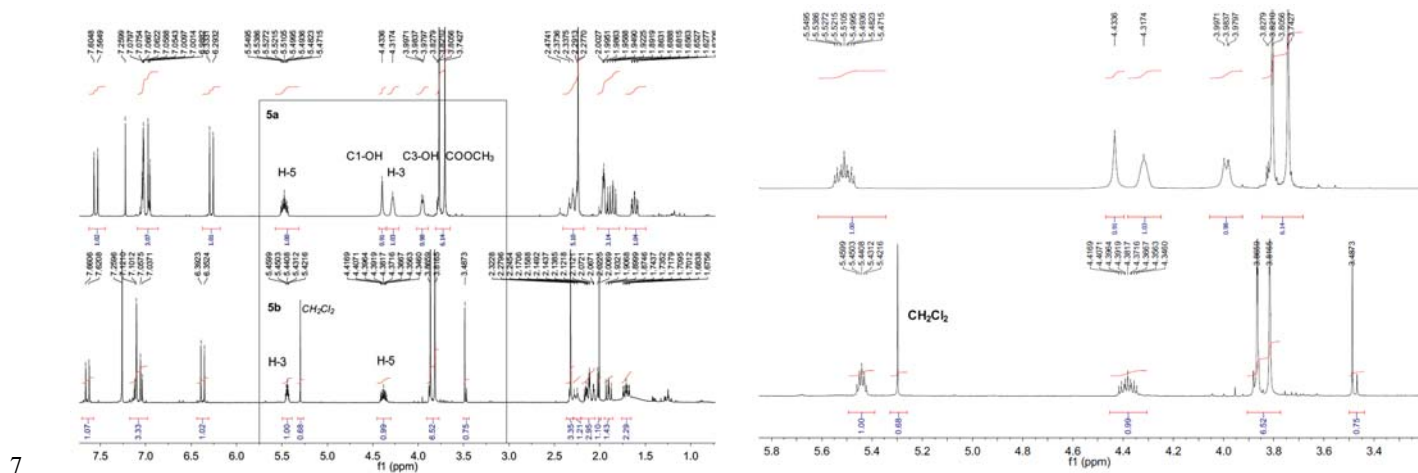
22  
 23 **Scheme 1** : Synthesis of monoesters. Reagents and conditions. For **5** and **6** : Conditions A DMF/Pyridine 3/2, 0.4M at 45°C, 4h-  
 24 6h : **5a** (15%) ; **5b** (33%) **5c** (18%) ; **6a** (19%) ; **6b** (28%) ; **6c** (19%) ; For **7** Conditions B CH<sub>2</sub>Cl<sub>2</sub>/Pyridine 5/1, DMAP 20 mol. %,   
 25 0.1M, -18°C-0°C to r.t, 4h: **7a** (11%) ; **7b** (34%) ; **7c** (8%).

26 To get an optimal conversion of **4** in reaction with acetylated feruloyl, *p*-coumaroyl or caffeoyl chloride into monoesters **5-7a/b**  
 27 and to limit the formation of homodiester **5-7c** resulted in reacting **4** with 1.5 equiv. acyl chloride under previously identified  
 28 conditions.<sup>24</sup> A conversion rate of about 65% and a ratio monoesters/3,5-diester up to 2.7/1 could be reached. Best results were  
 29 obtained under these conditions with feruloyl chloride and *p*-coumaroyl chloride (Scheme1). With caffeoyl chloride, a disappointing  
 30 even distribution forced to switch to more usual conditions, in CH<sub>2</sub>Cl<sub>2</sub>/Pyridine/DMAP, with an addition of caffeoyl chloride at 0°C  
 31 favouring **7b**, isolated with 34% yield on a 600 mg scale of **4** (details in Table S1).

### 32 NMR identification of the 3 and 5-substituted isomers

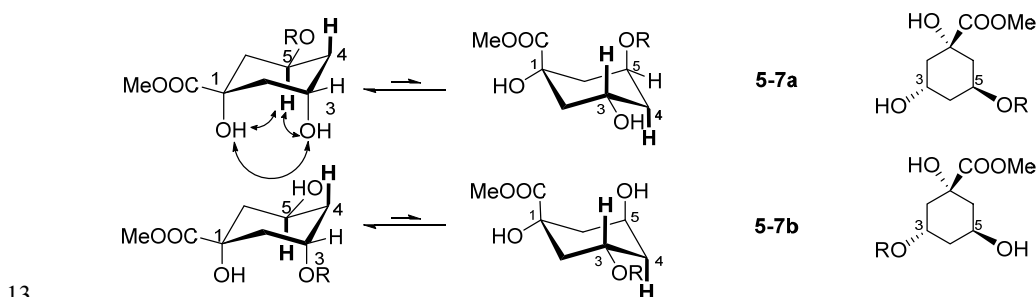
33 Despite moderate yields and selectivity, isolated monoesters **5-7a** and **5-7b** could be all isolated for characterization after the  
 34 successful, albeit tedious, chromatographic separation of main products, diester, monoesters and unreacted triol **4** : the structural  
 35 identification of each members of the pairs of 3-*O* or 5-*O* monoesters **5-7 a** or **b** was indeed required for the formation of defined  
 36 heterodiester.

1 The position of the esterification in monoesters **5a/5b**, **6a/6b** or **7a/7b** was determined using complete 1D-2D NMR analysis.  
 2 Despite <sup>1</sup>H NMR spectra in CDCl<sub>3</sub> for **5a/5b** are very close (Figure 2, left) (similar analysis could be done for **6a/6b** and **7a/7b**, see  
 3 supporting information), a slight discrimination could be however done in the 3.0-6.0 ppm region where could be found the respective  
 4 signals for : H-3, H-5, OH-1, COOCH<sub>3</sub> and the unaffected OH in position 3 or 5 (Figure 2, right). Esterification of the OH-1, the  
 5 tertiary hydroxyl group, was first discarded as in both spectra, the signal of one proton (H-3 or H-5) shifted downfield from 4.2-4.4  
 6 ppm for **4** to 5.3-5.6 ppm for **5a** or **5b**.



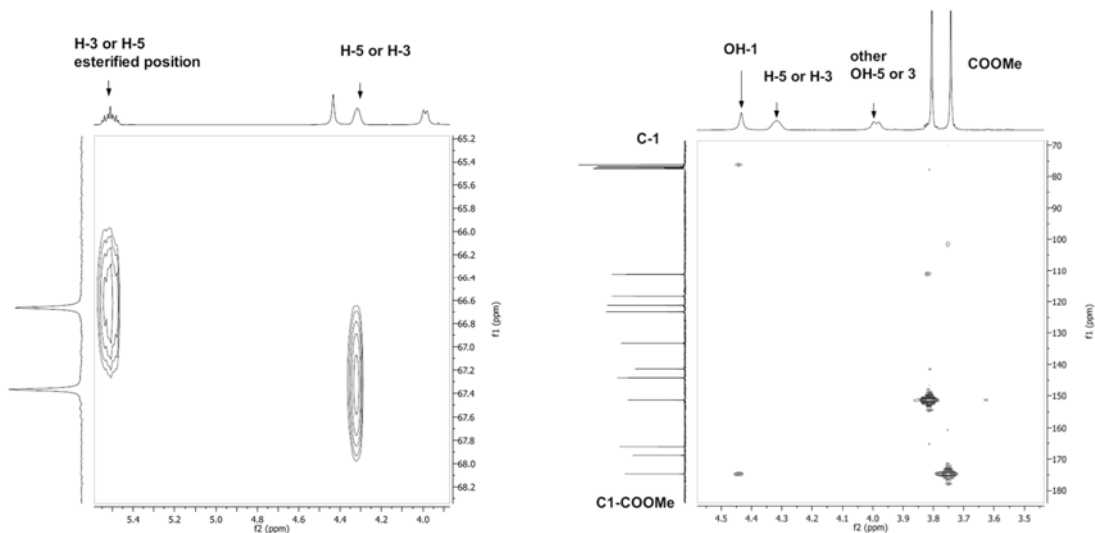
7  
 8 **Figure 2 Left** : <sup>1</sup>H NMR spectra in CDCl<sub>3</sub> for isolated monoesters **5a/5b** ; **Right** : Zoom on the 3.0-6.0 ppm region

9 The large *trans*-diaxial coupling constant measured between the **axial** proton H-4a (1.5-2.5 ppm) and one of the proton H-3 or H-  
 10 5 (about <sup>3</sup>J 10.3-11.5 Hz for monoesters **5a/5b**) supports more favoured chair conformations of 3- and 5-cinnamoyl monoesters as  
 11 depicted in Scheme 2 (H-4a and *trans*-diaxial configuration in bold). Moreover, the carboxyl or the carboxymethyl groups were found  
 12 preferentially in an equatorial conformation in quinic derivatives.<sup>34</sup>



13  
 14 **Scheme 2** : Chair conformations of 5- and 3-cinnamoyl monoesters of methyl deoxy quinate **5-7a** and **5-7b**

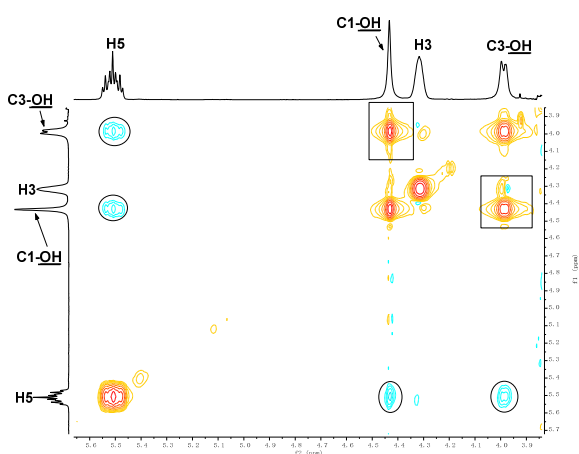
15 First, according to the <sup>1</sup>H-<sup>13</sup>C HSQC 2D NMR spectrum of monoester **5a** (Figure 3, left), the signals at 5.51 ppm (<sup>2</sup>J 11.2 Hz and  
 16 <sup>3</sup>J 4.4 Hz) and at 4.35 – 4.28 ppm were assigned to a secondary carbon CH proton at the esterified position (thus H-3 or H-5) and to  
 17 the other (H-5 or H-3) proton respectively. Then, thanks to <sup>1</sup>H-<sup>13</sup>C HMBC correlations (Figure 3, right), the signal at 4.43 ppm could  
 18 be assigned to the tertiary hydroxyl group C1-OH and the one at 4.00 ppm to C3 or C5-OH.



1

2 **Figure 3** : 2D NMR analysis of **5a** (CDCl<sub>3</sub>): Left: Partial <sup>1</sup>H-<sup>13</sup>C HSQC (CDCl<sub>3</sub>); Right: Partial <sup>1</sup>H-<sup>13</sup>C HMBC (CDCl<sub>3</sub>)

3 In <sup>1</sup>H-<sup>1</sup>H NOESY spectrum (Figure 4), the two such assigned signals for hydroxyl groups C1-OH and C3 or C5-OH exhibit  
 4 interactions with each other (rectangles in Figure 4) indicating their relative *cis* positions, which is only consistent with a mean  
 5 conformation for 5-feruloyl monoester **5a** (Scheme 2). Additionally, the signal for an axial proton at 5.51 ppm is also correlated  
 6 (circles in Figure 4) with these two signals for hydroxyl groups. **5a** corresponds to a monoester with a feruloyl group in position 5  
 7 with a predominant conformation with an equatorial methyl ester group in CDCl<sub>3</sub> and **5b** is the 3-*O*-isomer (Scheme 1). The acylation  
 8 positions of *p*-coumaroyl and caffeoyl in other monoesters **6a/6b** and **7a/7b** were analogously confirmed.



9

10 **Figure 4** : <sup>1</sup>H-<sup>1</sup>H NOESY (in CDCl<sub>3</sub>) of **5a**

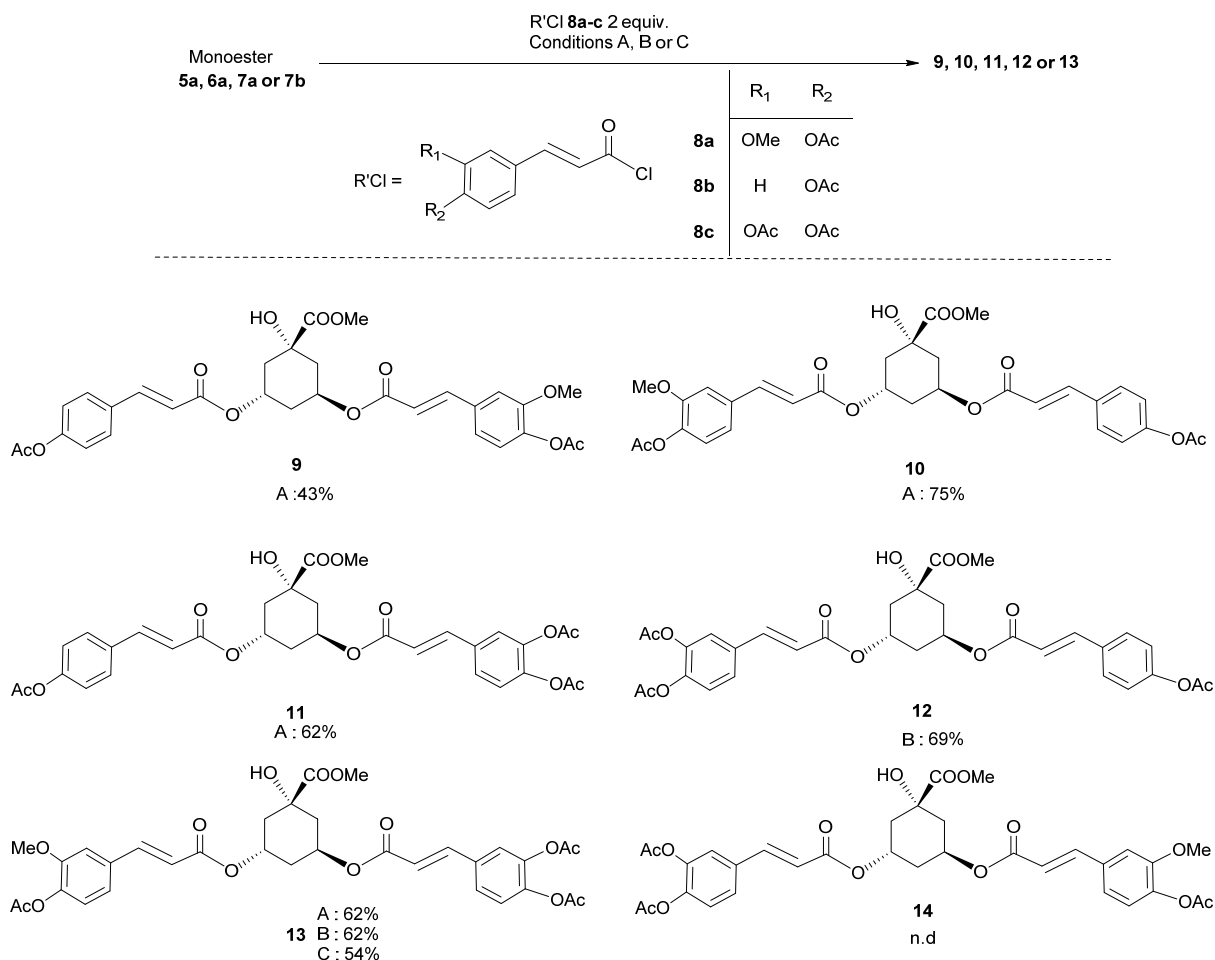
11

## 12 Preparation of various heterodiester

13 Compounds with various combinations of the three chosen hydroxycinnamoyl moieties were targeted: replacing one of active  
 14 coumaroyl residue (from **2b**) by a feruloyl or caffeoyl one (Scheme 3, **9-12**), or a caffeoyl (from **2a**) by a feruloyl or coumaroyl  
 15 residue (**11-14**). **9**, **10**, **11** could be prepared from **5a**, **6a** or **7a** with 43%, 75% or 62% isolated yields using the appropriate acyl  
 16 chloride **8a** or **8b** (Scheme 3). The reaction between **7b** and **8b** at 0°C led to **12** in 69% yield while the reverse combination using **6a**  
 17 and **8c** was unproductive to get **12**. Interestingly coupling **7a** with **8c** provided **13** in reproducible yields 54-62% whatever the  
 18 conditions. Surprisingly, despite our efforts to find the right combination as for **12**, in coupling either **5a** and **8c** or **7b** and **8a**, we  
 19 never managed to get a pure sample of the isomer **14** from a partial conversion outcome and a too complex crude mixture.

20

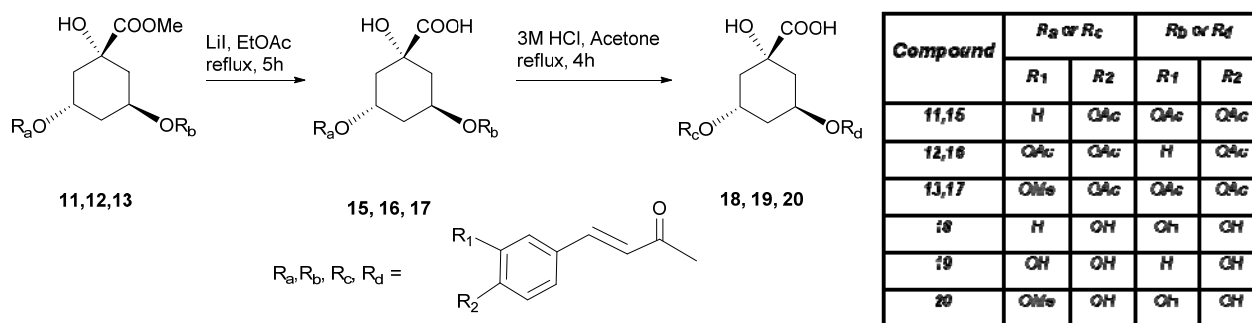
21



**Scheme 3** : Synthesis of heterodiester. Reagents and conditions <sup>a</sup> For **9-11** Conditions A : DMF/Pyridine 3/2 at 45°C; For **12** Conditions B : DMF/Pyridine 3/2 at 0°C to rt; For **13** 62% in conditions A; 62% in conditions B; 54% in conditions C: DCM/Pyridine 5/1, DMAP 20% at 0.1M, from 0°C to room temperature.

### Cleavage of protecting groups

Targeted compounds had to exhibit a carboxylic acid group on C-1 but either with acetylated or free phenols groups on the hydroxycinnamoyl moiety. Due to required optimisation and tedious purifications for each multi-step synthesis, **9** and **10** featuring feruloyl groups, unfortunately had to be discarded for the next steps, insufficient amounts of pure samples being obtained. Indeed to run insecticidal assays within a given time and with a representative amount of selected samples, responding to the questions addressed above, only **11**, **12** and **13** were engaged into the next steps. A first transformation of the methyl esters led to the three corresponding carboxylic acids **15**, **16**, **17** subsequently giving **18**, **19**, **20** in quantitative yields after the cleavage of aromatic acetates (Scheme 4).



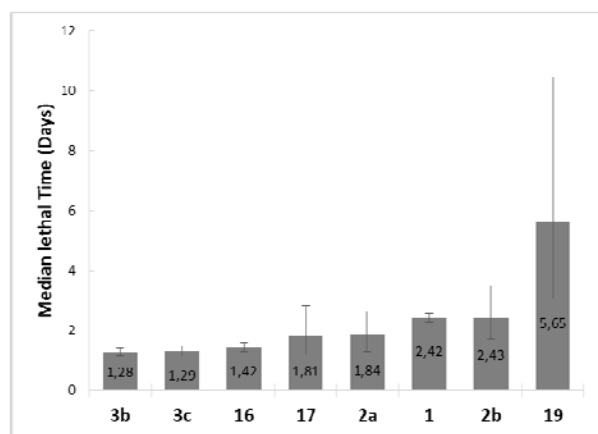
**Scheme 4** : Cleavage of protecting groups

## UPLC-HRMS analysis of compounds **18** and **19**

The structural similarity makes difficult the discrimination of positional and geometric isomers of acyl quinic acids. To fulfil some limits of IR or NMR spectral methods, Kuhnert, Clifford and collaborators have developed a structure-diagnostic LC-MS<sup>n</sup> for monoacyl and diacyl chlorogenic acids<sup>31</sup> or methyl esters<sup>35</sup> without the need to isolate the pure compounds. This identification method is based on the selective MS<sup>n</sup> fragmentation pattern observed in tandem mass spectra of chlorogenic acids. Previous characterization of caffeoyl-feruloyl quinic acids<sup>31</sup> and of 3,5- caffeoyl-*p*-coumaroyl quinic acids<sup>36</sup> showed that discrimination was possible between regioisomers according to MS<sup>n</sup> spectra (n=2 to 3): m/z values for base peaks but also peak intensities for secondary ions already differ in MS<sup>2</sup> from the two regioisomers of heterodiester. Indeed targeted m/z 499 for parent ion of 3, 5-caffeoyl-*p*-coumaroyl quinic acids gave either fragment-targeted MS<sup>2</sup> m/z 337 (first loss of caffeoyl in position 5) or m/z 353 (first loss of *p*-coumaroyl in position 5).<sup>36</sup>

We were keen to compare such analysis on regioisomers deoxy compounds **18** and **19**. The two compounds were indeed separable by chromatography and a same m/z 483 for the parent [M-H] ion was found. MS<sup>2</sup> spectra revealed a difference as base peaks found either at m/z 321 for **18** which corresponds to the loss of a caffeoyl residue instead of m/z 337 resulting of a loss of *p*-coumaroyl moiety for **19**. Secondary peaks at m/z 163 and 179 respectively are characteristic of *p*-coumaroyl and caffeoyl fragments.<sup>31</sup> The identifications of **18** as the 3-*p*-coumaroyl-5-caffeoyl-4-deoxy quinic acid and **19** as the 3-caffeoyl-5-*p*-coumaroyl -4-deoxy quinic acid are also consistent with an acylating residue first removed in position 5 in the deoxy series (see Supporting Information).

## Mortality data and growth inhibition assay over nymphal development (7 days) of the pea aphid *Acyrtosiphon pisum*



**Figure 5** : Survival analysis. Lethal Time LT<sub>50</sub> mean values per active compound (0.5 mM) **3a**, **18**, **20** giving a mean LT<sub>50</sub> superior to 20 days are not represented

Together with the three acetylated homodiester **3a-3c**,<sup>24</sup> five heterodiester **16**, **17**, **18**, **19**, **20** were included in a new assay in comparison with the natural compound **1**. The total available amount of acetylated heterodiester **15**, isomer of **16**, had to be dedicated to the preparation of **18**, isomer of **19**. Influence of the regioisomeric position of the more active caffeoyl and coumaroyl residues was yet possible.

Bioassays were first scored for mortality data, summarized as median lethal time 50% (LT<sub>50</sub>) resulting from a survival analysis (*i.e.* the median time necessary for killing 50% of the insect population). All concentrations were analysed separately in a parametric survival analysis with a log-normal fit, taking the “compound” as a factor (nominal, 9 levels). Dose 0.5 mM gave the most discriminating analysis (likelihood ratio test with a  $\chi^2$  of 262.1,  $p=4.9 \times 10^{-39}$ ), and we will only discuss this dose level. One may summarize the activity (toxicity) of the eight tested compounds as follows, by decreasing activities (mean LT<sub>50</sub>, in days, and confidence interval under log-normal model, see supporting information). Results are summarized in Figure 5 (**3a**, **18**, **20** giving a mean LT<sub>50</sub> superior to 20 days are not represented). Three compounds, **3b**, **3c** and **16** appeared more toxic than **1** at 0.5 mM while results obtained for **17**, like previously tested **2a**, includes median lethal time 50% (LT<sub>50</sub>) for **1**. This confirms the correlation between the structural requirements of at least one caffeoyl or *p*-coumaroyl residue to compete with **1** as diferulate **3a** also led to weak mortality. Moreover, in general, the activity range of acetylated compounds displayed more apparent toxicity than phenolic compounds.<sup>24</sup> For example at a 0.5 mM dose level, 1.29 days [1.12-1.48] was measured for acetylated **3c** in comparison with 1.84 days [1.29-2.62] for the deacetylated derivative **2a**, whereas 1.28 days [1.15-1.42] was found for acetylated **3b** vs 2.43 days [1.71-3.48] for the deacetylated derivative **2b**. **16** and **17** are also more active than **19** and **20** respectively. If only one deacetylated caffeoyl residue is present in C-5 position, combined with a *p*-coumaroyl (**18**) or a feruloyl residue (**20**), median LT<sub>50</sub> at 0.5 mM overpasses 20



1 days. Notably, this drops down to 5.65 days for **19**, regioisomer of **18**. When acetylation is maintained, the structural requirement of a dihydroxycinnamoyl over a hydroxycinnamoyl residue seems minimized (same mortality range for **3b**, **3c** and **16**).

3 Growth over nymphal development was analysed afterwards by a set of two one-way ANOVA (Table 1), comparing either the  
 4 dose effects per compound (capital lettering) or the compound effect, dose per dose (small lettering). As four independent  
 5 experiments (Experiments 1-4) were needed to score all compounds, a standard normalisation of data by the results of the control  
 6 condition (diet alone) was performed. Using this normalisation for weights resulted in a quite reproducible scoring of growth  
 7 inhibition for the control natural molecule **1** used for every experimental batch: a two way ANOVA for dose/experiment, with  
 8 interactions, resulted in a very significant “dose” effect ( $p < 0.001$ ), and a non-significant interaction ( $p = 0.23$ ). The effect of **1** was  
 9 therefore represented in Table 1 by the global results of the 4 batches used for this molecule. These growth inhibition analyses  
 10 confirmed that **3c** is the most active compound as at 125 $\mu$ M, total inhibition had occurred over 7 days. A concentration of 250 $\mu$ M  
 11 was required to reach the same activity for **3b** and **16** and 1mM for **1**. Albeit acetylated, “diferulate” **3a** showed no inhibitory effect  
 12 below 1mM. Results obtained for deacetylated heterodiesters **18** and **19**, in comparison to respective homodiesters dicaffeate **2a** and  
 13 dicoumarate **2b** (found more active than **1** in our first study at 125 $\mu$ M and 500 $\mu$ M respectively) showed the benefit of  
 14 homosubstitution on toxicity to surpass the activity of **1**. If only one dihydroxycinnamoyl residue is present in C-5 position, growth  
 15 inhibition was limited (positive control at day 7 at 1mM for **18** and **20**). No survivor at day 7 was however observed for 1mM of **19**,  
 16 regioisomer of **18**. The same dose for total inhibition was required for compound **17** featuring an acetylated feruloyl residue. The  
 17 most striking phenotypical effect, observed with **3b**, **16**, **17**, **18**, **19**, **20** compound intoxication, was a statistically significant growth  
 18 impairment of the **surviving pea aphids** at all doses in comparison of those in the control experiment, with an increased growth  
 19 inhibition with increased doses (Table 1). As a result from all the “compound” factor ANOVAs (dose by dose), that read vertically in  
 20 Table 1, one might rank the global toxicity index of compounds as: **3c** > **3b**  $\approx$  **16** > **19** > **17**  $\approx$  **1** > **18**  $\approx$  **20** > **3a**.

21

22 **Table 1: Growth inhibition assay** over nymphal development (7 days) of the pea aphid *Acyrtosiphon pisum*. Results are shown  
 23 as means (% of control growth)  $\pm$  SE, with ANOVA and mean comparisons (Tukey-Kramer HSD test) over lines (dose effect, capital  
 24 lettering,  $\rightarrow$ ) and over columns (molecule effect, small lettering,  $\downarrow$ ).

Compound	control	Dose (mM)				Anova	p	Experiment
	0	0.125	0.25	0.5	1	F-ratio		
<b>1</b> <sup>†</sup>	1.00 $\pm$ 0.04 ?A,a?	0.97 $\pm$ 0.04 A,b	0.68 $\pm$ 0.03 C,bc	0.36 $\pm$ 0.04 C,c	0 $\ddagger$ -	58.3	1.6 e-18	1-4
<b>3a</b>	1.00 $\pm$ 0.04 A,a	0.97 $\pm$ 0.06 A,a	1.07 $\pm$ 0.07 A,a	1.08 $\pm$ 0.08 A,a	1.00 $\pm$ 0.07 A,a	1.4	0.23 (ns)	1
<b>3b</b>	1.00 $\pm$ 0.04 A,a	0.60 $\pm$ 0.04 A,b	0 $\ddagger$ -	0 $\ddagger$ -	0 $\ddagger$ -	51.8	3.3 e-9	2
<b>3c</b>	1.00 $\pm$ 0.03 A	0 $\ddagger$ -	0 $\ddagger$ -	0 $\ddagger$ -	0 $\ddagger$ -	na $\S$	na $\S$	1
<b>16</b>	1.00 $\pm$ 0.04 A,a	0.56 $\pm$ 0.05 A,b	0 $\ddagger$ -	0 $\ddagger$ -	0 $\ddagger$ -	40.4	7.8 e-8	3
<b>17</b>	1.00 $\pm$ 0.04 A,a	0.69 $\pm$ 0.04 A,b	0.68 $\pm$ 0.04 C,b	0.61 $\pm$ 0.04 BC,b	0 $\ddagger$ -	19.0	4.4 e-9	2
<b>18</b>	1.00 $\pm$ 0.04 A,a	0.85 $\pm$ 0.04 AB,ab	0.85 $\pm$ 0.03 BC,ab	0.64 $\pm$ 0.04 B,c	0.28 $\pm$ 0.02 B,d	27.8	1.8 e-15	4
<b>19</b>	1.00 $\pm$ 0.06 A,a	0.75 $\pm$ 0.05 BC,b	0.46 $\pm$ 0.06 D,c	0.38 $\pm$ 0.05 C,c	0 $\ddagger$ -	68.5	2.3 e-23	4
<b>20</b>	1.00 $\pm$ 0.04 A,a	0.90 $\pm$ 0.04 AB,a	0.71 $\pm$ 0.05 C,b	0.70 $\pm$ 0.04 B,b	0.56 $\pm$ 0.05 B,b	16.0	1.6 e-10	3
<b>Anova</b>	na $\S$	12.0	27.6	26.5	22.8			
<b>F-ratio</b>	na $\S$	12.0	27.6	26.5	22.8			
<b>p</b>	na $\S$	1.6 e-12	7.2 e-19	2.9 e-20	1.1 e-10			

25 <sup>†</sup> **1** was the repeated control condition for all experiments; presented data are that of all grouped experiments. See text for inter-  
 26 experiment statistics.

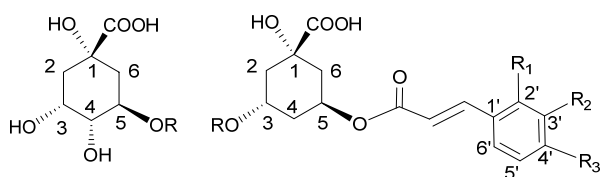
27 <sup>‡</sup> 0 is no survivor at day 7

28 <sup>§</sup> not applicable

## 29 Experimental

### 30 General

1 Reagents and solvents were supplied by Aldrich, Acros, Lancaster, Alfa Aesar, Fluka or TCI and purchased at the highest  
 2 commercial quality to be used without further purification. NMR spectra were recorded on a Bruker 300 (<sup>1</sup>H: 300 MHz; <sup>13</sup>C: 75  
 3 MHz), Bruker 400 (<sup>1</sup>H: 400 MHz; <sup>13</sup>C: 100 MHz), or Bruker 500 (<sup>1</sup>H: 500 MHz; <sup>13</sup>C: 125 MHz) spectrometers, at 295-298K, using  
 4 CDCl<sub>3</sub>, CD<sub>3</sub>OD or D<sub>2</sub>O as solvents. The chemical shifts (δ ppm) are referenced to the solvent residual peak and coupling constants *J*  
 5 in Hz are reported in the standard fashion. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t  
 6 = triplet, q = quartet, quint. = quintuplet, sext. = sextuplet, hept. = heptuplet, m = multiplet, br = broad; Ar is used for Aromatic and  
 7 for the assignment of <sup>13</sup>C carbon signals : C<sub>q</sub> = quaternary carbon. Electrospray ionization (ESI) mass spectrometry (MS) experiments  
 8 were performed on a Thermo Finnigan LCQ Advantage mass. High-resolution mass spectra (HRMS) were recorded on a Finnigan  
 9 Mat 95xL mass spectrometer using electrospray. Analytical thin-layer chromatography was carried out on silica gel Merck 60 D254  
 10 (0.25 mm). Flash chromatography was performed on Merck Si 60 silica gel (40–63 μm). Infra-red (IR) spectra were recorded with a  
 11 IRAffinity-1 Shimadzu spectrometer using Attenuated Total Reflectance (ATR Miracle), and the wavenumbers are expressed in cm<sup>-1</sup>.  
 12 Optical rotations were measured on a Perkin Elmer 241 or Jasco P1010 polarimeter with a 10 cm cell (concentration *c* expressed in  
 13 g/100 mL). Melting points were measured using Büchi apparatus B-540. All data for chlorogenic acids or related derivatives  
 14 presented in this paper use the recommended IUPAC numbering system. The assignment of NMR signals has been made according to  
 15 the numbering shown in the general structures below (Figure 6).<sup>37</sup>



16  
 17 **Figure 6** : Numbering for CQA and deoxy analogs

18 **Synthetic procedures**

19 General procedures for the preparation of monoesters **5-7a** and **b**.

20 **Conditions A** : To a solution of triol **4**<sup>24</sup> in DMF / pyridine (v/v 3/2, *c* = 0.4M) under nitrogen, was added the appropriate  
 21 acetylated hydroxycinnamoyl chloride (1.5 equiv.) and the mixture was heated at 45°C under stirring until a maximum of conversion  
 22 was reached. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc,  
 23 washed with 1M HCl then with a saturated NaHCO<sub>3</sub> solution then with brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated  
 24 and purified by flash chromatography on silica using the appropriate eluent.

25 **Conditions B** : Same procedure as above replacing solvents by dichloromethane / pyridine (v/v 5/1, *c* = 0.1M) and adding DMAP  
 26 (20% mol.). The acetylated hydroxycinnamoyl chloride was added at a temperature between -18°C and 0°C then the mixture was  
 27 stirred cooling up to room temperature until a maximum of conversion was reached. The work-up and isolation procedures are  
 28 identical.

29 **5a** (EtOAc / petroleum ether = 1/1 to 3/1, second fraction, light yellow oil, 15%), [ $\alpha$ ]<sub>D</sub><sup>25</sup> - 5.8 (*c* 0.89 in CH<sub>2</sub>Cl<sub>2</sub>); IR(ATR) 2934,  
 30 1763, 1736, 1707, 1638, 1601, 1508, 1456 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, 298K, CDCl<sub>3</sub>) δ 7.58 (d, 1H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 7.08 –  
 31 7.05 (m, 2H, H<sub>Ar</sub>), 7.00 (d, 1H, *J*<sub>ortho</sub> 8.6 Hz, H<sub>Ar</sub>), 6.31 (d, 1H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 5.51 (tt, 1H, <sup>3</sup>*J* 11.2 Hz, <sup>3</sup>*J* 4.4 Hz, H<sub>5</sub>), 4.43  
 32 (s, 1H, OH<sub>1</sub>), 4.32 (m, 1H, H<sub>3</sub>), 3.98 (m, 1H, OH<sub>3</sub>), 3.82 (s, 3H, COOCH<sub>3</sub>), 3.74 (s, 3H, OCH<sub>3</sub>), 2.47 – 2.29 (m, 2H, H<sub>4</sub> and H<sub>6</sub>), 2.27  
 33 (s, 3H, OCOCH<sub>3</sub>), 2.04 – 1.99 (m, 2H, 2xH<sub>2</sub>), 1.91 (dd, 1H, <sup>2</sup>*J* 12.6 Hz, <sup>3</sup>*J* 11.2 Hz, H<sub>6a</sub>), 1.65 (ddd, 1H, <sup>2</sup>*J* 12.7 Hz, <sup>3</sup>*J* 11.5 Hz, <sup>3</sup>*J* 3.0  
 34 Hz, H<sub>4a</sub>); <sup>13</sup>C NMR (100 MHz, 298K, CDCl<sub>3</sub>) δ = 174.7 (COOCH<sub>3</sub>), 168.8 (OCOCH<sub>3</sub>), 166.0 (CH=CHCO), 151.4 (C<sub>q</sub> Ar), 144.3  
 35 (CH=CHCO), 141.4 (C<sub>q</sub> Ar), 133.3 (C<sub>q</sub> Ar), 123.2 (CH<sub>Ar</sub>), 121.2 (CH<sub>Ar</sub>), 118.3 (CH=CHCO), 111.3 (CH<sub>Ar</sub>), 76.2 (C<sub>1</sub>), 67.4 (C<sub>3</sub>), 66.7  
 36 (C<sub>5</sub>), 55.9 (OCH<sub>3</sub>), 53.0 (COOCH<sub>3</sub>), 39.7 (C<sub>6</sub>), 38.1 (C<sub>4</sub>), 38.0 (C<sub>2</sub>), 20.6 (OCOCH<sub>3</sub>); HRMS (ESI): calcd for C<sub>20</sub>H<sub>24</sub>NaO<sub>9</sub> [M + Na<sup>+</sup>]:  
 37 431.1313, found: 431.1332.

38 **5b** (EtOAc / petroleum ether = 1/1 to 3/1, light yellow oil, 33%), [ $\alpha$ ]<sub>D</sub><sup>25</sup> + 3.3 (*c* 0.81 in CH<sub>3</sub>OH); IR(ATR) 3443, 2951, 2926,  
 39 1763, 1732, 1705, 1634, 1599, 1510, 1454 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, 298K, CDCl<sub>3</sub>) δ 7.64 (d, 1H, <sup>3</sup>*J* 15.9 Hz, CH=CHCO), 7.12 –  
 40 7.04 (m, 3H, H<sub>Ar</sub>), 6.37 (d, 1H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 5.44 (m, 1H, <sup>3</sup>*J* 3.9 Hz, H<sub>3</sub>), 4.38 (tt, 1H, <sup>3</sup>*J* 10.2 Hz, <sup>3</sup>*J* 4.1 Hz, H<sub>5</sub>), 3.87 (s,  
 41 3H, OCH<sub>3</sub>), 3.82 (s, 3H, COOCH<sub>3</sub>), 2.32 (s, 3H, OCOCH<sub>3</sub>), 2.26 (m, 1H, H<sub>4</sub>), 2.15 – 2.07 (m, 2H, H<sub>2</sub> and H<sub>6</sub>), 2.02 (m, 1H, H<sub>2</sub>), 1.90  
 42 (dd, 1H, <sup>2</sup>*J* 12.9 Hz, <sup>3</sup>*J* 10.1 Hz, H<sub>6a</sub>), 1.71 (ddd, 1H, <sup>2</sup>*J* 13.6 Hz, <sup>3</sup>*J* 10.3 Hz, <sup>3</sup>*J* 3.4 Hz, H<sub>4a</sub>); <sup>13</sup>C NMR (100 MHz, 298K, CDCl<sub>3</sub>) δ =  
 43 175.8 (COOCH<sub>3</sub>), 168.9 (OCOCH<sub>3</sub>), 166.1 (CH=CHCO), 151.5 (C<sub>q</sub> Ar), 144.7 (CH=CHCO), 141.6 (C<sub>q</sub> Ar), 133.4 (C<sub>q</sub> Ar), 123.4 (CH<sub>Ar</sub>),  
 44 121.6 (CH<sub>Ar</sub>), 118.4 (CH=CHCO), 111.3 (CH<sub>Ar</sub>), 75.2 (C<sub>1</sub>), 69.5 (C<sub>3</sub>), 63.5 (C<sub>5</sub>), 56.1 (OCH<sub>3</sub>), 53.4 (COOCH<sub>3</sub>), 43.1 (C<sub>6</sub>), 38.5 (C<sub>4</sub>),  
 45 37.1 (C<sub>2</sub>), 20.7 (OCOCH<sub>3</sub>); HRMS (ESI): calcd for C<sub>20</sub>H<sub>24</sub>NaO<sub>9</sub> [M + Na<sup>+</sup>]: 431.1313, found: 431.1298.

1 **6a** (EtOAc / petroleum ether = 1/1 to 3/1, light yellow oil, 19%),  $[\alpha]_D^{25} + 3.6$  (*c* 1.03 in CH<sub>2</sub>Cl<sub>2</sub>); IR(ATR) 1765, 1736, 1709, 1638,  
2 1506, 1435 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, 298K, CDCl<sub>3</sub>) δ 7.63 (d, 1H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 7.51 and 7.01 (2d, 2x2H, <sup>3</sup>*J* 8.0 Hz,  
3 H<sub>Ar</sub>), 6.33 (d, 1H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 5.53 (tt, 1H, <sup>2</sup>*J* 11.3 Hz, <sup>3</sup>*J* 4.4 Hz, H<sub>5</sub>), 4.33 (m, 1H, <sup>3</sup>*J* 3.3 Hz, H<sub>3</sub>), 3.84 (s, 1H, OH), 3.78  
4 (s, 3H, COOCH<sub>3</sub>), 2.36 (m, 2H, H<sub>4</sub> and H<sub>6</sub>), 2.29, (s, 3H, OCOCH<sub>3</sub>), 2.00 (m, 2H, H<sub>2</sub>), 1.90 (dd, 1H, <sup>2</sup>*J* ≈ <sup>3</sup>*J* 11.5 Hz, H<sub>6a</sub>), 1.67 (ddd,  
5 1H, <sup>2</sup>*J* 13.6 Hz, <sup>3</sup>*J* 10.3 Hz, <sup>3</sup>*J* 3.4 Hz, H<sub>4a</sub>); <sup>13</sup>C NMR (100 MHz, 298K, CDCl<sub>3</sub>) with traces of **6b** or **6c** δ 175.0 (COOCH<sub>3</sub>), 169.3  
6 (OCOCH<sub>3</sub>), 166.1 (CH=CHCO), 152.2 (C<sub>q</sub> Ar), 144.0 (CH=CHCO), 132.1 (C<sub>q</sub> Ar), 129.3 (CH<sub>Ar</sub>), 122.2 (CH<sub>Ar</sub>), 118.3 (CH=CHCO),  
7 76.3 (C<sub>1</sub>), 67.5 (C<sub>3</sub>), 66.6 (C<sub>5</sub>), 53.2 (COOCH<sub>3</sub>), 39.8 (C<sub>6</sub>), 38.2 (C<sub>4</sub>), 38.0 (C<sub>2</sub>), 21.2 (OCOCH<sub>3</sub>); HRMS (ESI): calcd for C<sub>19</sub>H<sub>22</sub>NaO<sub>8</sub>  
8 [M + Na<sup>+</sup>]: 401.1207, found: 401.1196.

9 **6b** (EtOAc / petroleum ether = 1/1 to 3/1, light yellow oil, 28%),  $[\alpha]_D^{25} + 27.8$  (*c* 0.97, CH<sub>2</sub>Cl<sub>2</sub>); IR(ATR) 3406, 2947, 1759, 1724,  
10 1680, 1634, 1601, 1508, 1446 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, 295K, CDCl<sub>3</sub>) δ = 7.65 (d, 1H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 7.52 and 7.11 (2d,  
11 2x2H, <sup>3</sup>*J* 8.0 Hz, H<sub>Ar</sub>), 6.37 (d, 1H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 5.42 (m, 1H, <sup>3</sup>*J* 3.9 Hz, H<sub>3</sub>), 4.36 (tt, 1H, <sup>3</sup>*J* 10.1 Hz, <sup>3</sup>*J* 4.0 Hz, H<sub>5</sub>), 3.80  
12 (s, 3H, COOCH<sub>3</sub>), 2.30 (s, 3H, OCOCH<sub>3</sub>), 2.22 (m, 1H, H<sub>4</sub>), 2.16 – 2.00 (m, 3H, 2xH<sub>2</sub> and H<sub>6</sub>), 1.90 (dd, 1H, <sup>2</sup>*J* 13.0 Hz, <sup>3</sup>*J* 9.9 Hz,  
13 H<sub>6a</sub>), 1.71 (ddd, 1H, <sup>2</sup>*J* 13.6 Hz, <sup>3</sup>*J* 10.2 Hz, <sup>3</sup>*J* 3.4 Hz, H<sub>4</sub>); <sup>13</sup>C NMR (100 MHz, 295K, CDCl<sub>3</sub>) δ = 175.8 (COOCH<sub>3</sub>), 169.3  
14 (OCOCH<sub>3</sub>), 166.2 (CH=CHCO), 152.2 (C<sub>q</sub> Ar), 144.2 (CH=CHCO), 132.1 (C<sub>q</sub> Ar), 129.4 (CH<sub>Ar</sub>), 122.2 (CH<sub>Ar</sub>), 118.4 (CH=CHCO),  
15 75.2 (C<sub>1</sub>), 69.5 (C<sub>3</sub>), 63.4 (C<sub>5</sub>), 53.3 (COOCH<sub>3</sub>), 43.0 (C<sub>6</sub>), 38.4 (C<sub>4</sub>), 37.1 (C<sub>2</sub>), 21.3 (OCOCH<sub>3</sub>); HRMS (ESI): calcd for C<sub>19</sub>H<sub>22</sub>NaO<sub>8</sub>  
16 [M + Na<sup>+</sup>]: 401.1207, found: 401.1197.

17 **7a** (diethyl ether/ dichloromethane = 1/10 to 1/4, light yellow oil, 11%),  $[\alpha]_D^{25} + 6.5$  (*c* 1.22 in CH<sub>2</sub>Cl<sub>2</sub>); IR(ATR) 1770, 1736, 1711,  
18 1639, 1504 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, 296K, CDCl<sub>3</sub>) δ 7.58 (d, 1H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 7.39 – 7.33 (m, 2H, H<sub>Ar</sub>), 7.19 (d, 1H,  
19 *J*<sub>ortho</sub> 8.3 Hz, H<sub>Ar</sub>), 6.32 (d, 1H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 5.51 (tt, <sup>3</sup>*J* 11.4 Hz, <sup>3</sup>*J* 4.4 Hz, 1H, H<sub>5</sub>), 4.32 (s, 1H, H<sub>3</sub>), 4.32 and 3.88 (2m,  
20 2H, OH<sub>1</sub> and OH<sub>3</sub>), 3.77 (s, 3H, COOCH<sub>3</sub>), 2.39-2.27 (m, 8H, H<sub>4</sub>, H<sub>6</sub> and 2xOCOCH<sub>3</sub>), 2.00 (m, 2H, 2xH<sub>2</sub>), 1.88 (dd, 1H, <sup>2</sup>*J* ≈ <sup>3</sup>*J* 11.5  
21 Hz, H<sub>6a</sub>), 1.65 (ddd, 1H, <sup>2</sup>*J* 13.6 Hz, <sup>3</sup>*J* 10.2 Hz, <sup>3</sup>*J* 3.4 Hz, H<sub>4</sub>); <sup>13</sup>C NMR (100 MHz, 297K, CDCl<sub>3</sub>) δ 174.9 (COOCH<sub>3</sub>), 168.2 and  
22 168.1 (2xOCOCH<sub>3</sub>), 165.9 (CH=CHCO), 143.6 (C<sub>q</sub> Ar), 143.1 (CH=CHCO), 142.5 and 133.3 (C<sub>q</sub> Ar), 126.5, 124.0 and 122.8 (CH<sub>Ar</sub>),  
23 119.3 (CH=CHCO), 76.3 (C<sub>1</sub>), 67.5 (C<sub>3</sub>), 66.8 (C<sub>5</sub>), 53.2 (COOCH<sub>3</sub>), 39.7 (C<sub>6</sub>), 38.1 (C<sub>4</sub>), 38.0 (C<sub>2</sub>), 20.71 (2xOCOCH<sub>3</sub>); HRMS  
24 (ESI): calcd for C<sub>21</sub>H<sub>24</sub>NaO<sub>10</sub> [M + Na<sup>+</sup>]: 459.1262, found: 459.1251.

25 **7b** (diethyl ether/ dichloromethane = 1/10 to 1/4, light yellow oil, 34%)  $[\alpha]_D^{25} + 24.7$  (*c* 0.93 in CH<sub>2</sub>Cl<sub>2</sub>); IR(ATR) 1773, 1732, 1707,  
26 1639, 1504 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, 296K, CDCl<sub>3</sub>) probably contaminated with **7a** and **7c** δ 7.60 (d, 1H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO),  
27 7.41 – 7.34 (m, 2H, H<sub>Ar</sub>), 7.20 (d, 1H, *J*<sub>ortho</sub> 8.3 Hz, H<sub>Ar</sub>), 6.36 (d, 1H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 5.40 (m, 1H, <sup>3</sup>*J* 3.9 Hz, H<sub>3</sub>), 4.34 (m,  
28 1H, H<sub>5</sub>), 3.78 (s, 3H, COOCH<sub>3</sub>), 3.23 (m, 1H, OH-1 or OH-5), 2.29 and 2.28 (2s, 6H, 2xOCOCH<sub>3</sub>), 2.22 – 1.98 (m, 4H, H<sub>2</sub>, H<sub>4</sub> and/or  
29 H<sub>6</sub>), 1.89 (dd, 1H, <sup>2</sup>*J* 12.9 Hz, <sup>3</sup>*J* 10.0 Hz, H<sub>6a</sub>), 1.69 (ddd, 1H, <sup>2</sup>*J* 13.6 Hz, <sup>3</sup>*J* 10.2 Hz, <sup>3</sup>*J* 3.3 Hz, H<sub>4a</sub>); <sup>13</sup>C NMR (100 MHz, 297K,  
30 CDCl<sub>3</sub>) δ 175.7 (COOCH<sub>3</sub>), 168.2 and 168.1 (2xOCOCH<sub>3</sub>), 165.9 (CH=CHCO), 143.5 (C<sub>q</sub> Ar), 143.3 (CH=CHCO), 142.4 (C<sub>q</sub> Ar),  
31 133.2 (C<sub>q</sub> Ar), 126.5 (CH<sub>Ar</sub>), 124.0 (CH<sub>Ar</sub>), 122.9 (CH<sub>Ar</sub>), 119.4 (CH=CHCO), 75.1 (C<sub>1</sub>), 69.5 (C<sub>3</sub>), 63.2 (C<sub>5</sub>), 53.1 (COOCH<sub>3</sub>), 42.8  
32 (C<sub>6</sub>), 38.2 (C<sub>4</sub>), 36.9 (C<sub>2</sub>), 20.7 (2xOCOCH<sub>3</sub>); HRMS (ESI): calcd for C<sub>21</sub>H<sub>24</sub>NaO<sub>10</sub> [M + Na<sup>+</sup>]: 459.1262, found: 459.1253.

33 **General procedures for the preparation of diesters 9-13. Conditions A** : Same procedure as Conditions A for the synthesis of  
34 monoesters using 2 equiv. of the appropriate acetylated hydroxycinnamoyl chloride **8a**, **b** or **c**. **Conditions B** : Same procedure as  
35 Conditions C for the synthesis of monoesters with an addition at 0°C and a reaction at room temperature. **Conditions C** : Same  
36 procedure as Conditions B for the synthesis of monoesters using 2 equiv. of the appropriate acetylated hydroxycinnamoyl chloride **8a**,  
37 **b** or **c**.

38 **9** (EtOAc/ Pentane = 1/1 to 2/1, white solid, 43%), mp: 86 - 87 °C,  $[\alpha]_D^{25} - 74.7$  (*c* 0.95 in CH<sub>2</sub>Cl<sub>2</sub>); IR(ATR) 1765, 1732, 1709,  
39 1638, 1601, 1506 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, 295K, CDCl<sub>3</sub>) δ 7.69 and 7.62 (2d, 2H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 7.55 (d, 2H, *J*<sub>ortho</sub> 8.3  
40 Hz, H<sub>Ar</sub>), 7.14 – 7.04 (m, 5H, H<sub>Ar</sub>), 6.42 and 6.34 (2d, 2H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 5.58 – 5.50 (m, 2H, H<sub>3</sub> and H<sub>5</sub>), 3.86 (s, 3H,  
41 OCH<sub>3</sub>), 3.77 (s, 3H, COOCH<sub>3</sub>), 2.32 and 2.30 (2s, 6H, 2xOCOCH<sub>3</sub>), 2.37 – 2.04 (m, 5H, H<sub>2</sub>, H<sub>6</sub> and H<sub>4</sub>), 1.89 (ddd, 1H, <sup>2</sup>*J* 13.6 Hz,  
42 <sup>3</sup>*J* 10.3 Hz, <sup>3</sup>*J* 3.4 Hz, H<sub>4</sub>); <sup>13</sup>C NMR (100 MHz, 295K, CDCl<sub>3</sub>) δ 175.1 (COOCH<sub>3</sub>), 169.3 and 168.9 (2xOCOCH<sub>3</sub>), 166.2 and 165.9  
43 (2xCH=CHCO), 152.2 and 151.5 (C<sub>q</sub> Ar), 144.5 and 144.3 (CH=CHCO), 141.6, 133.3 and 132.2 (C<sub>q</sub> Ar), 129.7, 129.5, 123.4, 122.4,  
44 122.2 and 121.4 (CH<sub>Ar</sub>), 118.4 and 118.3 (CH=CHCO), 111.3 (CH<sub>Ar</sub>), 74.8 (COOCH<sub>3</sub>), 68.9 and 66.9 (C<sub>3</sub>, C<sub>5</sub>), 56.0 (OCH<sub>3</sub>), 53.2  
45 (COOCH<sub>3</sub>), 39.9 and 36.8 (C<sub>2</sub>, C<sub>6</sub>), 35.1 (C<sub>4</sub>), 21.3 and 20.8 (2xOCOCH<sub>3</sub>); HRMS (ESI): calcd for C<sub>31</sub>H<sub>32</sub>NaO<sub>12</sub> [M + Na<sup>+</sup>]:  
46 619.1786, found: 619.1777.

47 **10** (EtOAc/ Pentane = 1/2 to 1/1, white solid, 75%), mp 87 - 89 °C,  $[\alpha]_D^{25} - 79.7$  (*c* 1.04, CH<sub>2</sub>Cl<sub>2</sub>); IR(ATR) 1762, 1736, 1705,  
48 1636, 1601, 1506 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, 295K, CDCl<sub>3</sub>) δ 7.64 and 7.62 (2d, 2H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 7.52 (d, 2H, *J*<sub>ortho</sub> 8.3  
49 Hz, H<sub>Ar</sub>), 7.10 (m, 4H, H<sub>Ar</sub>), 7.03 (d, 1H, *J*<sub>ortho</sub> 8.3 Hz, H<sub>Ar</sub>), 6.41 and 6.33 (2d, 2H, <sup>3</sup>*J* 16.0 Hz, CH=CHCO), 5.58 – 5.47 (m, 2H, H<sub>3</sub>  
50 and H<sub>5</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 3.76 (s, 3H, COOCH<sub>3</sub>), 2.30 and 2.29 (2s, 6H, 2xOCOCH<sub>3</sub>), 2.37 – 2.03 (m, 5H, H<sub>2</sub>, H<sub>6</sub> and H<sub>4</sub>), 1.87  
51 (ddd, 1H, <sup>2</sup>*J* 13.6 Hz, <sup>3</sup>*J* 10.3 Hz, <sup>3</sup>*J* 3.4 Hz, H<sub>4</sub>); <sup>13</sup>C NMR (100 MHz, 295K, CDCl<sub>3</sub>) δ 175.0 (COOCH<sub>3</sub>), 169.2 and 168.8

1 (2xO<sub>C</sub>COCH<sub>3</sub>), 166.1 and 165.9 (2xCH=CHCO), 152.2 and 151.4 (C<sub>q</sub> Ar), 144.6 and 144.0 (2xCH=CHCO), 141.5, 133.3 and 132.0 (C<sub>q</sub>  
2 Ar), 129.3(2), 123.2, 122.2(2) and 121.6 (CH<sub>Ar</sub>), 118.3 and 118.1 (CH=CHCO), 111.1 (CH<sub>Ar</sub>), 74.8 (C<sub>1</sub>), 68.9 and 66.8 (C<sub>3</sub>, C<sub>5</sub>), 56.0  
3 (OCH<sub>3</sub>), 53.1 (COOCH<sub>3</sub>), 39.8 and 36.8 (C<sub>2</sub>, C<sub>6</sub>), 35.1 (C<sub>4</sub>), 21.2 and 20.7 (2xOCOCH<sub>3</sub>); HRMS (ESI): calcd for C<sub>31</sub>H<sub>33</sub>O<sub>12</sub> [M + H<sup>+</sup>]:  
4 597.1967, found: 597.1944.

5 **11** (EtOAc/ Pentane = 1/1 to 2/1, white solid, 62%), mp 87 - 89 °C, [ $\alpha$ ]<sub>D</sub><sup>25</sup> - 67.5 (c 1.05, CH<sub>2</sub>Cl<sub>2</sub>); IR(ATR) 1767, 1734, 1709,  
6 1638, 1504 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, 295K, CDCl<sub>3</sub>) with CH<sub>2</sub>Cl<sub>2</sub>  $\delta$  7.70 and 7.61 (2d, 2H, <sup>3</sup>J 16.0 Hz, CH=CHCO), 7.57, 7.40, 7.26  
7 (3m, 6H, H<sub>Ar</sub>), 7.14 (d, 1H, *J*<sub>ortho</sub> 8.4 Hz, H<sub>Ar</sub>), 6.44 and 6.35 (d, 1H, <sup>3</sup>J 16.0 Hz, CH=CHCO), 5.59 - 5.51 (m, 2H, H<sub>3</sub> and H<sub>5</sub>), 3.77 (s,  
8 3H, COOCH<sub>3</sub>), 2.34 - 2.05 (m, 14H, 3xOCOCH<sub>3</sub>, H<sub>4</sub>, H<sub>6</sub> and H<sub>2</sub>), 1.90 (ddd, 1H, <sup>2</sup>J 13.6 Hz, <sup>3</sup>J 10.3 Hz, <sup>3</sup>J 3.4 Hz, H<sub>4</sub>); <sup>13</sup>C NMR  
9 (100 MHz, 295K, CDCl<sub>3</sub>) with CH<sub>2</sub>Cl<sub>2</sub>  $\delta$  175.1 (COOCH<sub>3</sub>), 169.2, 168.3 and 168.0 (3xOCOCH<sub>3</sub>), 166.1 and 165.6 (2xCH=CHCO),  
10 152.2 (C<sub>q</sub> Ar), 144.3 (CH=CHCO), 143.7 (C<sub>q</sub> Ar), 143.2 (CH=CHCO), 142.6, 133.3 and 132.2 (C<sub>q</sub> Ar), 129.4(2), 126.5, 124.1, 122.9 and  
11 122.2 (CH<sub>Ar</sub>), 119.3 and 118.4 (2xCH=CHCO), 74.8 (C<sub>1</sub>), 68.9 and 67.0 (C<sub>3</sub>, C<sub>5</sub>), 53.2 (COOCH<sub>3</sub>), 39.9 and 36.8 (C<sub>2</sub>, C<sub>6</sub>), 35.1 (C<sub>4</sub>),  
12 21.24, 20.75 and 20.7 (3xOCOCH<sub>3</sub>); HRMS (ESI): calcd for C<sub>32</sub>H<sub>32</sub>NaO<sub>13</sub> [M + Na<sup>+</sup>]: 647.1735, found: 647.1707.

13 **12** (EtOAc/ Pentane = 1/2 to 1/1, white solid, 69%), mp 87 - 89 °C, [ $\alpha$ ]<sub>D</sub><sup>25</sup> -75.0 (c 1.04, CH<sub>2</sub>Cl<sub>2</sub>); IR(ATR) 1767, 1738, 1707, 1638,  
14 1504 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, 295K, CDCl<sub>3</sub>)  $\delta$  7.63 and 7.62 (2d, 2H, <sup>3</sup>J 16.0 Hz, CH=CHCO), 7.52 (d, 2H, *J*<sub>ortho</sub> 8.4 Hz, H<sub>Ar</sub>), 7.41-  
15 7.36 (m, 2H, H<sub>Ar</sub>), 7.20 and 7.10 (2d, 1H+2H, *J*<sub>ortho</sub> = 8.4 Hz, H<sub>Ar</sub>), 6.40 and 6.33 (2d, 2H, <sup>3</sup>J 16.0 Hz, CH=CHCO), 5.56 - 5.45 (m,  
16 2H, H<sub>3</sub> and H<sub>5</sub>), 3.75 (s, 3H, COOCH<sub>3</sub>), 3.24 (m, 1H, OH-1), 2.29, 2.29, and 2.27 (3s, 9H, 3xOCOCH<sub>3</sub>), 2.27 - 2.05 (m, 5H, H<sub>4</sub>, H<sub>6</sub>  
17 and H<sub>2</sub>), 1.88 (ddd, 1H, <sup>2</sup>J 13.6 Hz, <sup>3</sup>J 10.3 Hz, <sup>3</sup>J 3.4 Hz, H<sub>4a</sub>); <sup>13</sup>C NMR (100 MHz, 295K, CDCl<sub>3</sub>)  $\delta$  175.0 (COOCH<sub>3</sub>), 169.2, 168.1  
18 and 168.0 (3xOCOCH<sub>3</sub>), 165.9 (2xCH=CHCO), 152.2 (C<sub>q</sub> Ar), 144.0 (CH=CHCO), 143.6 (C<sub>q</sub> Ar), 143.4 (CH=CHCO), 142.4, 133.3  
19 and 132.0 (C<sub>q</sub> Ar), 129.3(2), 126.5, 124.0, 123.0, and 122.2(2) (CH<sub>Ar</sub>), 119.4 and 118.2 (2xCH=CHCO), 74.7 (C<sub>1</sub>), 68.9 and 66.8 (C<sub>3</sub>,  
20 C<sub>5</sub>), 53.1 (COOCH<sub>3</sub>), 39.8 and 36.8 (C<sub>2</sub>, C<sub>6</sub>), 35.0 (C<sub>4</sub>), 21.2, 20.7 and 20.6 (3xOCOCH<sub>3</sub>); HRMS (ESI): calcd for C<sub>32</sub>H<sub>32</sub>NaO<sub>13</sub> [M +  
21 Na<sup>+</sup>]: 647.1735, found: 647.1704.

22 **13** (diethyl ether / dichloromethane = 1/15 to 1/6, white solid, 54-62%), mp 80 - 82 °C, [ $\alpha$ ]<sub>D</sub><sup>25</sup> - 83.5 (c 1.04, CH<sub>2</sub>Cl<sub>2</sub>); IR(ATR)  
23 1767, 1709, 1639, 1506 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, 296K, CDCl<sub>3</sub>)  $\delta$  7.64 and 7.58 (2d, 2H, <sup>3</sup>J 16.0 Hz, CH=CHCO), 7.39 - 7.34 (m,  
24 2H, H<sub>Ar</sub>), 7.19 (d, 1H, *J*<sub>ortho</sub> = 8.4 Hz, H<sub>Ar</sub>), 7.11 - 7.01 (m, 3H, H<sub>Ar</sub>), 6.40 and 6.32 (d, 1H, <sup>3</sup>J 16.0 Hz, CH=CHCO), 5.56 - 5.47 (m,  
25 2H, H<sub>3</sub> and H<sub>5</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 3.75 (s, 3H, COOCH<sub>3</sub>), 3.30 (s, 1H, OH), 2.30, 2.28 and 2.27 (3s, 9H, 3xOCOCH<sub>3</sub>), 2.27-1.92  
26 (m, 5H, H<sub>4</sub>, H<sub>2</sub> and H<sub>6</sub>), 1.86 (ddd, 1H, <sup>2</sup>J 13.6 Hz, <sup>3</sup>J 10.4, <sup>3</sup>J 3.5 Hz, H<sub>4</sub>); <sup>13</sup>C NMR (100 MHz, 297K, CDCl<sub>3</sub>)  $\delta$  175.0 (COOCH<sub>3</sub>),  
27 168.8, 168.1 and 168.0 (3xOCOCH<sub>3</sub>), 166.1 and 165.6 (2xCH=CHCO), 151.4 (C<sub>q</sub> Ar), 144.6 (CH=CHCO), 143.6 (C<sub>q</sub> Ar), 143.2  
28 (CH=CHCO), 142.5, 141.5, 133.3 and 133.1 (C<sub>q</sub> Ar), 126.4, 124.0, 123.2, 122.8 and 121.5 (CH<sub>Ar</sub>), 119.1 and 118.4 (2xCH=CHCO),  
29 111.2 (CH<sub>Ar</sub>), 74.7 (C<sub>1</sub>), 68.8 and 66.9 (C<sub>3</sub>, C<sub>5</sub>), 56.0 (CH<sub>3</sub>), 53.1 (COOCH<sub>3</sub>), 39.7 and 36.7 (C<sub>2</sub>, C<sub>6</sub>), 35.0 (C<sub>4</sub>), 20.7 (3xOCOCH<sub>3</sub>);  
30 HRMS (ESI): calcd for C<sub>33</sub>H<sub>34</sub>NaO<sub>14</sub> [M + Na<sup>+</sup>]: 677.1841, found: 677.1830.

31 **General procedure for the cleavage of methyl ester.** LiI (10 equiv.) was added to a solution of the methyl ester (1 equiv.) in  
32 EtOAc (0.14M) then the mixture was heated under reflux for 5h. After cooling down to room temperature, the mixture was diluted  
33 with EtOAc, and 1M HCl added. After extraction, the organic layer was dried over MgSO<sub>4</sub>, concentrated to give the crude residue,  
34 usually characterized such as and used directly in the next step.

35 **15** (60 mg, quantitative crude yield, light yellow oil); <sup>1</sup>H NMR (400 MHz, 295K, CD<sub>3</sub>OD)  $\delta$  7.70 (d, 2H, <sup>3</sup>J 16.0 Hz, CH=CHCO),  
36 7.63-7.60 and 7.51-7.49 (2m, 5H, ArH + CH=CHCO), 7.24 and 7.13 (2d, 1+2H, J 8 HZ, H<sub>Ar</sub>), 6.52 and 6.45 (2d, 2H, <sup>3</sup>J 16.0 Hz,  
37 CH=CHCO), 5.47 (m, 2H, H<sub>3</sub> and H<sub>5</sub>), 2.42 (dd, 1H, <sup>2</sup>J 13.7 Hz, <sup>3</sup>J 3.8 Hz, H<sub>2</sub>, H<sub>4</sub> or H<sub>6</sub>), 2.36 - 2.20 (m, 1H, H<sub>2</sub>, H<sub>4</sub> or H<sub>6</sub>), 2.28, 2.27  
38 (2s, 9H, 3xOCOCH<sub>3</sub>), 2.11 - 2.00 (m, 3H, H<sub>2</sub>, H<sub>4</sub> and/or H<sub>6</sub>), 1.94 (dd, 1H, <sup>2</sup>J 13.7 Hz, <sup>3</sup>J 6.4 Hz, H<sub>2</sub>, H<sub>4</sub> or H<sub>6</sub>); <sup>13</sup>C NMR (100 MHz,  
39 295K, CD<sub>3</sub>OD)  $\delta$  177.3 (COOH), 170.8, 169.8, and 169.6 (3xOCOCH<sub>3</sub>), 167.7 and 167.2 (2xCH=CHCO), 153.7 (C<sub>q</sub> Ar), 145.2  
40 (CH=CHCO), 145.1 (C<sub>q</sub> Ar), 144.5 (CH=CHCO), 144.0, 134.5 and 133.4 (C<sub>q</sub> Ar), 130.4 (2), 127.7, 125.1, 124.1 and 123.4 (CH<sub>Ar</sub>),  
41 120.1 (2xCH=CHCO), 119.4 (2xCH=CHCO), 75.0 (C<sub>1</sub>), 70.1 and 69.2 (C<sub>3</sub>, C<sub>5</sub>), 39.9, 38.7, 35.9 (C<sub>2</sub>, C<sub>4</sub>, C<sub>6</sub>), 20.9, 20.5(2)  
42 (3xOCOCH<sub>3</sub>); HRMS (ESI): calcd for C<sub>31</sub>H<sub>30</sub>NaO<sub>13</sub> [M + Na<sup>+</sup>]: 663.1579, found: 663.1581.

43 **16** (63 mg, quantitative crude yield, light yellow oil), [ $\alpha$ ]<sub>D</sub><sup>32</sup> - 80.3 (c 1.15 in MeOH) IR(ATR) 2930, 1765, 1705, 1635, 1504 cm<sup>-1</sup>;  
44 <sup>1</sup>H NMR (400 MHz, 295K, CD<sub>3</sub>OD)  $\delta$  7.68-7.62 (m, 4H, H<sub>Ar</sub> + 2xCH=CHCO), 7.49, 7.24 and 7.13 (3m, 2+1+2H, ArH), 6.52 and  
45 6.45 (2d, 2x1H, <sup>3</sup>J 16.0 Hz, 2xCH=CHCO), 5.47 (m, 2H, H<sub>3</sub> and H<sub>5</sub>), 2.42 (dd, 1H, <sup>2</sup>J 13.7 Hz, <sup>3</sup>J 3.8 Hz, H<sub>2</sub>, H<sub>4</sub> or H<sub>6</sub>), 2.34 - 2.30  
46 (m, 1H, H<sub>2</sub>, H<sub>4</sub> or H<sub>6</sub>), 2.28, 2.27 (2s, 9H, 3xOCOCH<sub>3</sub>), 2.12 - 2.00 (m, 3H, H<sub>2</sub>, H<sub>4</sub> and/or H<sub>6</sub>), 1.94 (dd, 1H, <sup>2</sup>J 13.7 Hz, <sup>3</sup>J 6.4 Hz,  
47 H<sub>2</sub>, H<sub>4</sub> or H<sub>6</sub>); <sup>13</sup>C NMR (100 MHz, 295K, CD<sub>3</sub>OD)  $\delta$  177.4 (COOH), 170.8, 169.8, and 169.7 (3xOCOCH<sub>3</sub>), 167.5 (2xCH=CHCO),  
48 153.8 (C<sub>q</sub> Ar), 145.3 (CH=CHCO), 145.1 (C<sub>q</sub> Ar), 144.4 (CH=CHCO), 144.0 (C<sub>q</sub> Ar), 134.6 and 133.4 (C<sub>q</sub> Ar), 130.5 (2), 127.6, 125.1,  
49 124.1 and 123.3(2) (CH<sub>Ar</sub>), 120.5 and 119.1 (2xCH=CHCO), 75.1 (C<sub>1</sub>), 70.3 and 69.0 (C<sub>3</sub>, C<sub>5</sub>), 40.0, 38.6, 35.9 (C<sub>2</sub>, C<sub>4</sub>, C<sub>6</sub>), 20.9,  
50 20.5 (2) (3xOCOCH<sub>3</sub>); HRMS (ESI): calcd for C<sub>31</sub>H<sub>30</sub>NaO<sub>13</sub> [M + Na<sup>+</sup>]: 663.1579, found: 663.1554.

1 **17** (180 mg, 91% crude yield, light yellow oil),  $[\alpha]_D^{26}$  - 106.8 (*c* 0.99 in MeOH); IR(ATR) 3356, 3337, 2941, 2833, 1765, 1707,  
2 1636, 1601, 1508  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, 298K,  $\text{CD}_3\text{OD}$ )  $\delta$  7.66 and 7.59 (2d, 2H,  $^3J$  16.0 Hz, 2xCH=CHCO), 7.49 – 7.43, 7.29 –  
3 7.12 and 7.03 (3m, 2H+3H+1H,  $\text{H}_{\text{Ar}}$ ), 6.52 and 6.43 (2d, 2H,  $^3J$  16.0 Hz, 2xCH=CHCO), 5.47 (m, 2H,  $\text{H}_3$  and  $\text{H}_5$ ), 3.80 (s, 3H,  
4  $\text{OCH}_3$ ), 2.41 (dd, 1H,  $^2J$  13.7 Hz,  $^3J$  3.8 Hz,  $\text{H}_2$ ,  $\text{H}_4$  or  $\text{H}_6$ ), 2.36 – 2.20 (m, 1H,  $\text{H}_2$ ,  $\text{H}_4$  or  $\text{H}_6$ ), 2.27, 2.26, and 2.25 (3s, 9H,  
5 3xOCOCH<sub>3</sub>), 2.05 (m, 3H,  $\text{H}_2$ ,  $\text{H}_4$  and/or  $\text{H}_6$ ), 1.94 (dd, 1H,  $^2J$  13.7 Hz,  $^3J$  6.4 Hz,  $\text{H}_2$ ,  $\text{H}_4$  or  $\text{H}_6$ );  $^{13}\text{C}$  NMR (100 MHz, 295K,  $\text{CD}_3\text{OD}$ )  
6  $\delta$  177.3 ( $\text{COOCH}_3$ ), 170.4, 169.8, and 169.7 ( $\text{OCOCH}_3$ ), 167.7 ( $\text{CH=CHCO}$ ), 167.2 ( $\text{CH=CHCO}$ ), 152.8 ( $\text{C}_{\text{q Ar}}$ ), 145.6 ( $\text{CH=CHCO}$ ),  
7 145.1 ( $\text{C}_{\text{q Ar}}$ ), 144.4 ( $\text{CH=CHCO}$ ), 143.9 ( $\text{C}_{\text{q Ar}}$ ), 142.8 ( $\text{C}_{\text{q Ar}}$ ), 134.7 ( $\text{C}_{\text{q Ar}}$ ), 134.5 ( $\text{C}_{\text{q Ar}}$ ), 127.7 ( $\text{CH}_{\text{Ar}}$ ), 125.1 ( $\text{CH}_{\text{Ar}}$ ), 124.2 ( $\text{CH}_{\text{Ar}}$ ),  
8 124.1 ( $\text{CH}_{\text{Ar}}$ ), 122.4 ( $\text{CH}_{\text{Ar}}$ ), 120.1 ( $\text{CH=CHCO}$ ), 119.5 ( $\text{CH=CHCO}$ ), 112.6 ( $\text{CH}_{\text{Ar}}$ ), 75.0 ( $\text{C}_1$ ), 70.1 ( $\text{C}_3$  or  $\text{C}_5$ ), 69.1 ( $\text{C}_3$  or  $\text{C}_5$ ), 56.5  
9 ( $\text{PhOCH}_3$ ), 39.9 ( $\text{C}_2$  or  $\text{C}_4$  or  $\text{C}_6$ ), 38.7 ( $\text{C}_2$  or  $\text{C}_4$  or  $\text{C}_6$ ), 35.89 ( $\text{C}_2$  or  $\text{C}_4$  or  $\text{C}_6$ ), 20.8, 20.7, and 20.50 ( $\text{OCOCH}_3$ ); HRMS (ESI): calcd  
10 for  $\text{C}_{32}\text{H}_{32}\text{NaO}_{14}$  [ $\text{M} + \text{Na}^+$ ]: 663.1684, found: 663.1678.

11 **General procedure for the deprotection of aromatic acetates.** To a solution of the acetylated compound **14**, **15** or **16** in acetone  
12 (1.5 mL for 100 mg) was added a 3M HCl aqueous solution (0.5 mL) and the mixture was refluxed for 4h till completion. After  
13 cooling down to room temperature, the mixture was diluted with EtOAc and washed with a saturated NaCl aqueous solution. The  
14 organic layer was dried then concentrated to give the deprotected heterodiester of 4-deoxy quinic acid **18**, **19** or **20**. A rapid  
15 purification by semi-preparative HPLC was run before insecticidal assays.

16 **18** (light yellow oil, quantitative crude yield),  $[\alpha]_D^{32}$  - 70.2 (*c* 1.16 in MeOH), IR(ATR) 3308, 2945, 2833, 1690, 1632, 1605, 1514  
17  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, 295K,  $\text{CD}_3\text{OD}$ )  $\delta$  7.66 and 7.54 (2d, 2x1H,  $^3J$  16.0 Hz, 2xCH=CHCO), 7.47-6.78 (m, 7H,  $\text{H}_{\text{Ar}}$ ), 6.35 and  
18 6.23 (2d, 2x1H,  $^3J$  16.0 Hz, 2xCH=CHCO), 5.45 (m, 2H,  $\text{H}_3$  and  $\text{H}_5$ ), 2.43-2.29 and 2.11-1.90 (2m, 2H+4H,  $\text{H}_2, \text{H}_4$  and  $\text{H}_6$ );  $^{13}\text{C}$  NMR  
19 (100 MHz, 295K,  $\text{CD}_3\text{OD}$ )  $\delta$  177.5 ( $\text{COOH}$ ), 168.6 ( $\text{CH=CHCO}$ ), 168.3 ( $\text{CH=CHCO}$ ), 161.2(2) and 149.5 ( $\text{C}_{\text{q Ar}}$ ), 147.1 and 146.7  
20 ( $\text{CH=CHCO}$ ), 131.2 (2x $\text{CH}_{\text{Ar}}$ ), 127.8 and 127.2 ( $\text{C}_{\text{q Ar}}$ ), 123.1 116.8(2) and 116.5 ( $\text{CH}_{\text{Ar}}$ ), 115.5 ( $\text{CH=CHCO}$ ), 115.2 ( $\text{CH=CHCO}$ ),  
21 75.1 ( $\text{C}_1$ ), 70.0 and 68.7 ( $\text{C}_3, \text{C}_5$ ), 40.0, 38.7 and 36.0 ( $\text{C}_2, \text{C}_4, \text{C}_6$ ); HRMS (ESI): calcd for  $\text{C}_{25}\text{H}_{24}\text{NaO}_{10}$  [ $\text{M} + \text{Na}^+$ ]: 507.1262, found:  
22 507.1250.

23 **19** (light yellow oil, quantitative crude yield),  $[\alpha]_D^{32}$  - 61.4 (*c* 0.96 in  $\text{CH}_3\text{OH}$ ), IR(ATR) 3320, 2359, 1688, 1603, 1514  $\text{cm}^{-1}$ ;  $^1\text{H}$   
24 NMR (400 MHz, 298K,  $\text{CD}_3\text{OD}$ )  $\delta$  7.60 and 7.58 (2d, 2H,  $^3J$  15.9 Hz, 2xCH=CHCO), 7.46 (m, 2H,  $\text{H}_{\text{Ar}}$ ), 7.07-6.78 (m, 5H,  $\text{H}_{\text{Ar}}$ ),  
25 6.29 and 6.28 (2d, 2H,  $^3J$  15.9 Hz, 2xCH=CHCO), 5.45 (m, 2H,  $\text{H}_3$  and  $\text{H}_5$ ), 2.40-2.30 and 2.06-1.89 (2m, 2H+ 4H,  $\text{H}_2, \text{H}_4, \text{H}_6$ );  $^{13}\text{C}$   
26 NMR (100 MHz, 298K,  $\text{CD}_3\text{OD}$ )  $\delta$  177.6 ( $\text{COOH}$ ), 168.6 and 168.3 ( $\text{CH=CHCO}$ ), 161.3(2) and 149.5 ( $\text{C}_{\text{q Ar}}$ ), 147.0 and 146.7  
27 (2x $\text{CH=CHCO}$ ), 131.2 and 131.0 (2x $\text{CH}_{\text{Ar}}$ ), 127.8 and 127.2 ( $\text{C}_{\text{q Ar}}$ ), 123.0, 116.8(2), 116.5 and 115.5 ( $\text{CH}_{\text{Ar}}$ ), 115.2 and 115.1  
28 (2x $\text{CH=CHCO}$ ), 75.1 ( $\text{C}_1$ ), 70.0 and 68.8 ( $\text{C}_3, \text{C}_5$ ), 40.1, 38.8 and 36.0 ( $\text{C}_2, \text{C}_4, \text{C}_6$ ); HRMS (ESI): calcd for  $\text{C}_{25}\text{H}_{24}\text{NaO}_{10}$  [ $\text{M} + \text{Na}^+$ ]:  
29 507.1262, found: 507.1252.

30 **20** (light yellow oil, quantitative crude yield),  $[\alpha]_D^{32}$  - 77.6 (*c* 0.98 in MeOH), IR(ATR) 3393, 2950, 2360, 1680, 1654, 1629, 1603  
31  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, 298K,  $\text{CD}_3\text{OD}$ )  $\delta$  7.64 and 7.53 (2d, 2H,  $^3J$  15.9 Hz, 2xCH=CHCO), 7.19-6.78 (m, 7H,  $\text{H}_{\text{Ar}}$ ), 6.38 and 6.22  
32 (2d, 2H,  $^3J$  15.9 Hz, 2xCH=CHCO), 5.45 (m, 2H,  $\text{H}_3$  and  $\text{H}_5$ ), 3.89 (s, 3H,  $\text{OCH}_3$ ), 2.42-2.27 and 2.11-1.91 (2m, 2H+ 4H,  $\text{H}_2, \text{H}_4, \text{H}_6$ );  
33  $^{13}\text{C}$  NMR (100 MHz, 298K,  $\text{CD}_3\text{OD}$ )  $\delta$  177.4 ( $\text{COOH}$ ), 168.5 and 168.3 (2x $\text{CH=CHCO}$ ), 150.4, 149.5, 149.3 ( $\text{C}_{\text{q Ar}}$ ), 147.1 and 146.9  
34 (2x $\text{CH=CHCO}$ ), 146.7, 127.8, 127.7 ( $\text{C}_{\text{q Ar}}$ ), 124.1, 123.1, 116.5 and 116.4 ( $\text{CH}_{\text{Ar}}$ ), 115.9 and 115.20 ( $\text{CH=CHCO}$ ), 115.18 and 111.6  
35 ( $\text{CH}_{\text{Ar}}$ ), 75.1 ( $\text{C}_1$ ), 70.0 and 68.7 ( $\text{C}_3, \text{C}_5$ ), 56.4 ( $\text{OCH}_3$ ), 40.0, 38.7 and 36.0 ( $\text{C}_2, \text{C}_4, \text{C}_6$ ); HRMS (ESI): calcd for  $\text{C}_{26}\text{H}_{26}\text{NaO}_{11}$  [ $\text{M} +$   
36  $\text{Na}^+$ ]: 537.1367, found: 537.1366.

### 37 UPLC-MS QTOF Investigation / Mass spectrometry analysis

38 A UPLC apparatus (U3000, Thermo Fisher Scientific) was used, coupled with a high-resolution hybrid QTOF (Impact II, Bruker)  
39 mass spectrometer. For the chromatographic resolution, a biphenyl column (Restek®, 5 cm \* 3 mm ; 2.7  $\mu\text{m}$ ) with a mobile phase of  
40 (A) ultra-pure water (Milli-Q grade) + 0.1% formic acid and (B) Acetonitrile/Methanol (40/60) (optima MS grade, Thermo Fisher  
41 Scientific) + 0.1% formic acid as a mobile phase, at a flow of 800  $\mu\text{L}/\text{min}$  for a 200 nL volume of injection. Mass Spectrometry  
42 detection was performed using negative mode electrospray ionisation (source temperature : 200°C ; Capillary voltage 3000 V,  
43 nebulisation gas pressure : 45 Psi ; Mass range 50 – 1000 Da); UV detection at 250 and 380 nm.

### 44 Mortality data and growth inhibition assay

45 The natural compound **1** (3,5-dicaffeoyl quinic acid), was extracted with ethanol/water (70/30) from lyophilized non-tuberized  
46 roots of sweet potato *Ipomea batatas* and purified by semi-preparative HPLC on a Hibar® 250 mm x 25 mm column filled with  
47 Lichrospher® 100 RP18e 5 $\mu\text{M}$  stationary phase. The compound was eluted with an acidified water/methanol gradient.<sup>22</sup> Compounds  
48 were administrated pure by weighing after HPLC purification, solubilized at 1 mM in a standard AP3 artificial diet for the pea aphid  
49 *Acyrtosiphon pisum*,<sup>38</sup> and diluted 3 times to obtain the experimental dose range (125  $\mu\text{M}$ -1mM). Toxicity was evaluated by scoring

1 survival daily over the whole nymphal life of the pea aphid (7 days), starting from neonate aphids born on faba bean leaves. Growth  
2 was also measured by weighing adult aphids on an analytical microbalance (Mettler AE163) at the closest 10 µg, as fully described  
3 previously for testing peptide toxicity.<sup>39</sup> Aphid weights were analysed by ANOVA followed by Tukey-Kramer HSD test for comparing  
4 multiple means (treating separately either the dose factor for every compound, or the compound factor, at each dose; see Table 1). All  
5 analyses were made with JMP software, v11 (SAS Institute Cary USA, MacOS version).

6 Four separate experiments were needed to test all eight compounds, **3a-3c** and **16, 17, 18, 19, 20** and the original **1** compound was  
7 used/repeated in each test.

## 8 **Conclusions**

9 New heterodiester of 4-deoxy quinic acid were prepared through various combinations of two sequential monoesterifications  
10 with acetylated feruloyl, *p*-coumaroyl or caffeoyl chloride. Five di-(hydroxycinnamoyl)-4-deoxy quinic acids, featuring either  
11 acetylated or free phenol groups could thus be added to three previously described acetylated homodiester for a novel insecticidal  
12 assay to investigate the influence of these structural modifications on aphicidal activity. Much effort was put into the structural  
13 elucidation of different isolated intermediates to ascertain the biological response of structural isomers. An interesting difference was  
14 observed for two regioisomeric deacetylated 3,5-caffeoylcoumaroyl-4-deoxy quinic acids albeit a lower toxicity than natural 3, 5-  
15 dicaffeoylquinic acid. Both mortality data and growth inhibition were analysed and four compounds were found to exhibit higher  
16 aphicidal activities than the reference compound. The acetylation of phenol groups proved to be advantageous to the activity of  
17 homodiester while the presence of at least one caffeoyl moiety on quinic nucleus seems required for significant toxicity.

## 18 **Conflicts of interest**

19 There are no conflict to declare.

## 20 **Acknowledgements**

21 We gratefully acknowledge INSA-Lyon for financial support (BQR 2011) and the China Scholarship Council for a PhD grant to  
22 X.L. We would also like to thank Marie-Noëlle Corre for her help in preparing 3,5-dicaffeoylquinic acid and Alexandra Berlioz-  
23 Barbier (CCSM) for UPLC-HRMS analysis.

24 **Electronic Supplementary Information (ESI) available:** [Table S1 Preparation of monoesters **5a/5b, 6a/6b, 7a/7b**; **Table S2**  
25 Second esterification towards heterodiester; <sup>1</sup>H NMR spectra for couples of monoesters **5a/5b, 6a/6b, 7a/7b**; <sup>1</sup>H and <sup>13</sup>C NMR  
26 spectra for compounds **5a, 5b, 6a, 6b, 7a, 7b, 9-14, 15-20**; UPLC-MS QTOF Investigation / Mass spectrometry analysis; **Table S3**  
27 Survival analysis (LT50 = Lethal time for 50% death of population)].

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