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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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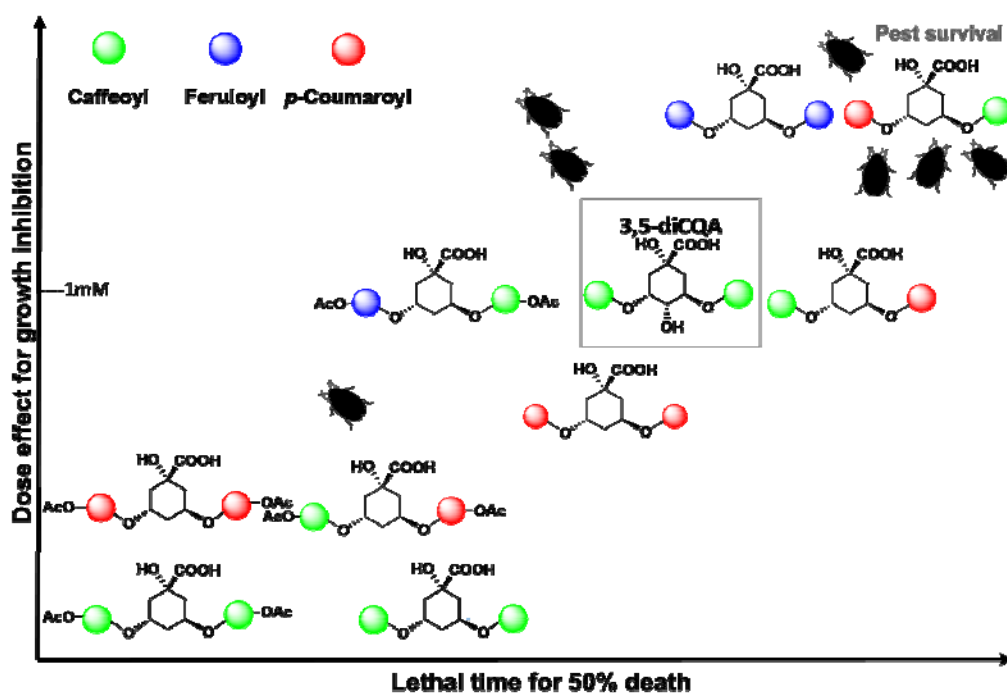
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Highlights

- 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-dicaffeoylquinic 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, deoxyquinic acid, heterodiesters, pest management, growth inhibition

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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.^{1,2}

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,³ antifungal,⁴ antiviral,⁵ renoprotective,⁶ neuroprotective,^{7,8} inhibitors of α -glucosidase,^{9,10} or as modulators of the intestinal microbiota in high-fat-diet-fed mice.¹¹

The underlying biological mechanisms for host plant resistance to aphids are worth of interest.¹² For example, the correlation between chlorogenic acids concentration and priming of plants¹³ was shown for the carrot fly larval damage,¹⁴ for fungal infection⁴ or for cultured tobacco cells.¹⁵ The resistance of lettuce cultivars to *Pemphigus bursarius*¹⁶ or the negative effect of chlorogenic acid on Western flower thrips *Frankliniella occidentalis* were also reported.¹⁷ The cultivar *Rubira* peach tree, parent of a trait mapped to Rm2 gene¹⁸ had shown a strong induced resistance to *Myzus persicae*, the green peach aphid which represents a threat for many agro-industrial crops.¹⁹ An accumulation of metabolite, later identified as 3,5-dicaffeoyl quinic acid **1** (3,5-diCQA), had been previously detected in aphid-infested leaves,²⁰ and also later observed in a fungal-pear tree pathosystem.²¹ While aphicidal activity was demonstrated by positive preliminary results of *in vitro* artificial diets assays adding **1** in nutritive medium for aphids,²² 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,^{22,23} model compounds with a 4-deoxy quinic acid nucleus had been designed. Eight hydroxycinnamoyl homodiester of a new 4-deoxy quinic acid or its methyl ester had been synthesized from the new triol **4**.²⁴ Their influence on the feeding behaviour of the pea aphid *Acyrtosiphon pisum* was evaluated. Two homodiester 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).

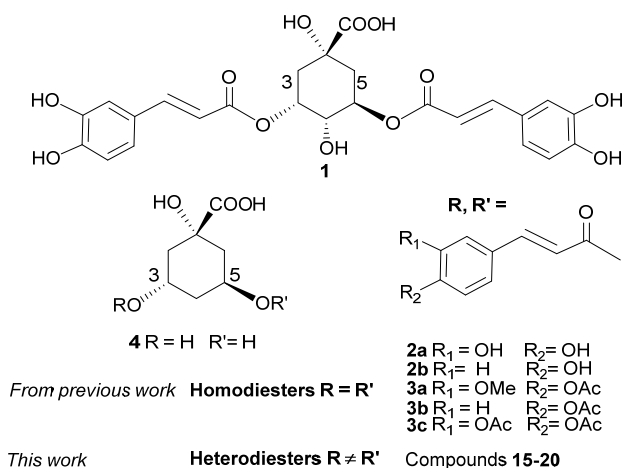


Figure 1 : Representative compounds discussed in this paper

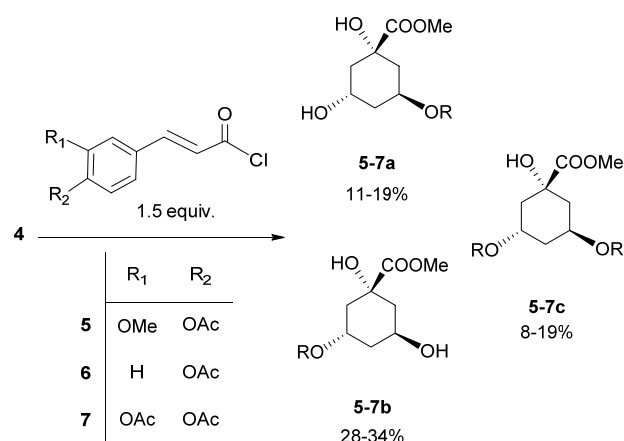
To extend our study with a second growth inhibition assay, different other structural parameters were addressed. As a very low activity was measured for methyl esters derivatives, only carboxylic acids would be included. First, some previously described but not assayed intermediates, **3a**, **3b**, **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

such as heterosubstitution in C-3 and C-5 positions and so the putative influence of the stereochemical position of each hydroxycinnamoyl group. To refine our previous results, some questions were addressed: are two caffeoyl or *p*-coumaroyl groups mandatory for such activity and if not, is their position in C-3 or C-5 determinant? We thus designed other diesters among which those featuring a single caffeoyl and/or a single *p*-coumaroyl residues. We could anticipate that such preparation would require a clear structural elucidation of defined intermediates to identify regioisomers. Natural caffeoyl-feruloyl quinic acids are interesting «hybrids» not well studied albeit their probable existence was first noted in 1965.²⁵ Characterization for such compounds were then however proposed by NMR^{26, 27, 28,29,30} or by LC-MSⁿ analysis of a methanolic coffee bean extract³¹ or of sweet potato *Ipomea batatas* from China.³² Synthesis of methyl *muco*-quinates, heterosubstituted in 1 and 3 positions, was reported by Jaiswal *et al.*³³ To the best of our knowledge, there were no reported synthesis for other 3,5-hetero diacylquinic acids. Here we describe our results on the preparation of novel heterocinnamoyl chlorogenic acid analogs : “hybrid diesters or heterodiesters” of 4-deoxy quinic acid **4** (Figure 1) were synthesized, carefully characterized and a complementary evaluation of the toxicity of eight compounds against the pea aphid *Acyrtosiphon pisum* is reported.

Results and discussion

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

Synthesis of monoesters



Scheme 1 : Synthesis of monoesters. Reagents and conditions. For **5** and **6** : Conditions A DMF/Pyridine 3/2, 0.4M at 45°C, 4h-6h : **5a** (15%); **5b** (33%) **5c** (18%); **6a** (19%); **6b** (28%); **6c** (19%); For **7** Conditions B CH₂Cl₂/Pyridine 5/1, DMAP 20 mol. %, 0.1M, -18°C-0°C to r.t, 4h: **7a** (11%); **7b** (34%); **7c** (8%).

To get an optimal conversion of **4** in reaction with acetylated feruloyl, *p*-coumaroyl or caffeoyl chloride into monoesters **5-7a/b** and to limit the formation of homodiesters **5-7c** resulted in reacting **4** with 1.5 equiv. acyl chloride under previously identified conditions.²⁴ A conversion rate of about 65% and a ratio monoesters/3,5-diester up to 2.7/1 could be reached. Best results were obtained under these conditions with feruloyl chloride and *p*-coumaroyl chloride (Scheme1). With caffeoyl chloride, a disappointing even distribution forced to switch to more usual conditions, in CH₂Cl₂/Pyridine/DMAP, with an addition of caffeoyl chloride at 0°C favouring **7b**, isolated with 34% yield on a 600 mg scale of **4** (details in Table S1).

NMR identification of the 3 and 5-substituted isomers

Despite moderate yields and selectivity, isolated monoesters **5-7a** and **5-7b** could be all isolated for characterization after the successful, albeit tedious, chromatographic separation of main products, diester, monoesters and unreacted triol **4** : the structural 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 heterodiesters.

The position of the esterification in monoesters **5a/5b**, **6a/6b** or **7a/7b** was determined using complete 1D-2D NMR analysis. Despite ^1H NMR spectra in CDCl_3 for **5a/5b** are very close (Figure 2, left) (similar analysis could be done for **6a/6b** and **7a/7b**, see supporting information), a slight discrimination could be however done in the 3.0-6.0 ppm region where could be found the respective signals for : H-3, H-5, OH-1, COOCH_3 and the unaffected OH in position 3 or 5 (Figure 2, right). Esterification of the OH-1, the 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 ppm for **4** to 5.3-5.6 ppm for **5a** or **5b**.

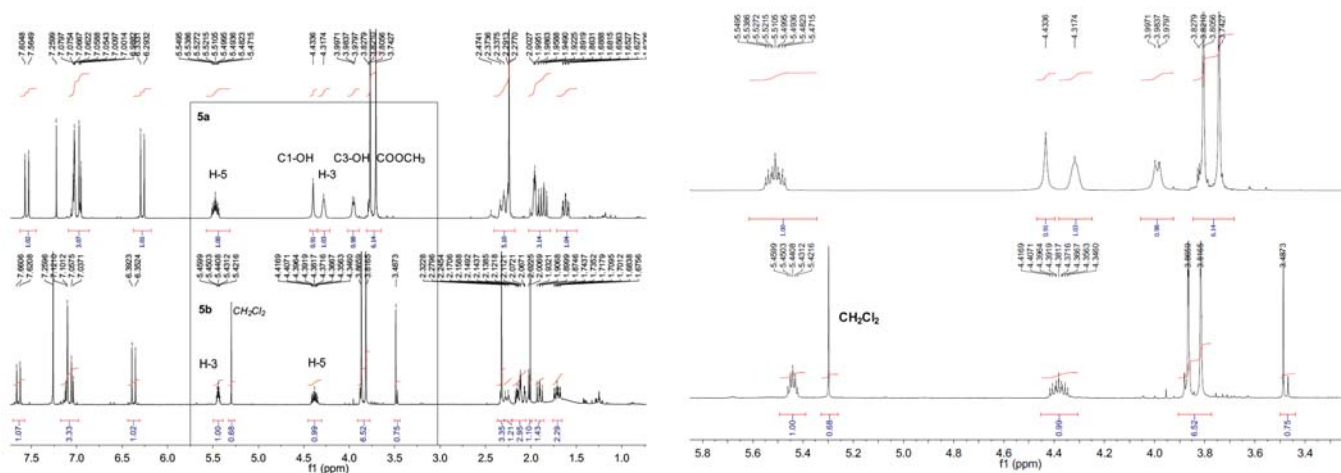
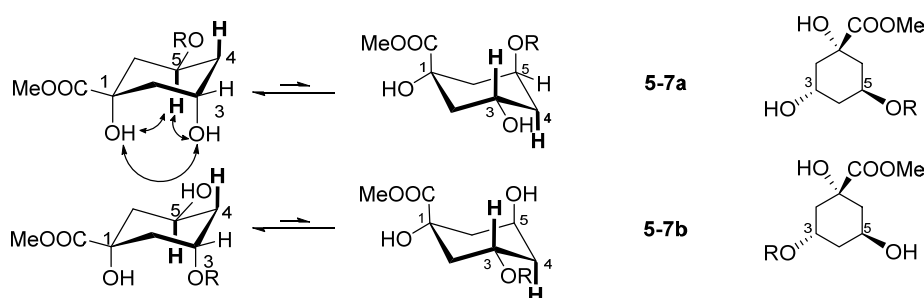


Figure 2 Left : ^1H NMR spectra in CDCl_3 for isolated monoesters **5a/5b** ; **Right :** Zoom on the 3.0-6.0 ppm region

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-5 (about 3J 10.3-11.5 Hz for monoesters **5a/5b**) supports more favoured chair conformations of 3- and 5-cinnamoyl monoesters as depicted in Scheme 2 (H-4a and *trans*-diaxial configuration in bold). Moreover, the carboxyl or the carboxymethyl groups were found preferentially in an equatorial conformation in quinic derivatives.³⁴



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

First, according to the ^1H - ^{13}C HSQC 2D NMR spectrum of monoester **5a** (Figure 3, left), the signals at 5.51 ppm (3J 11.2 Hz and 3J 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 the other (H-5 or H-3) proton respectively. Then, thanks to ^1H - ^{13}C HMBC correlations (Figure 3, right), the signal at 4.43 ppm could be assigned to the tertiary hydroxyl group C1-OH and the one at 4.00 ppm to C3 or C5-OH.

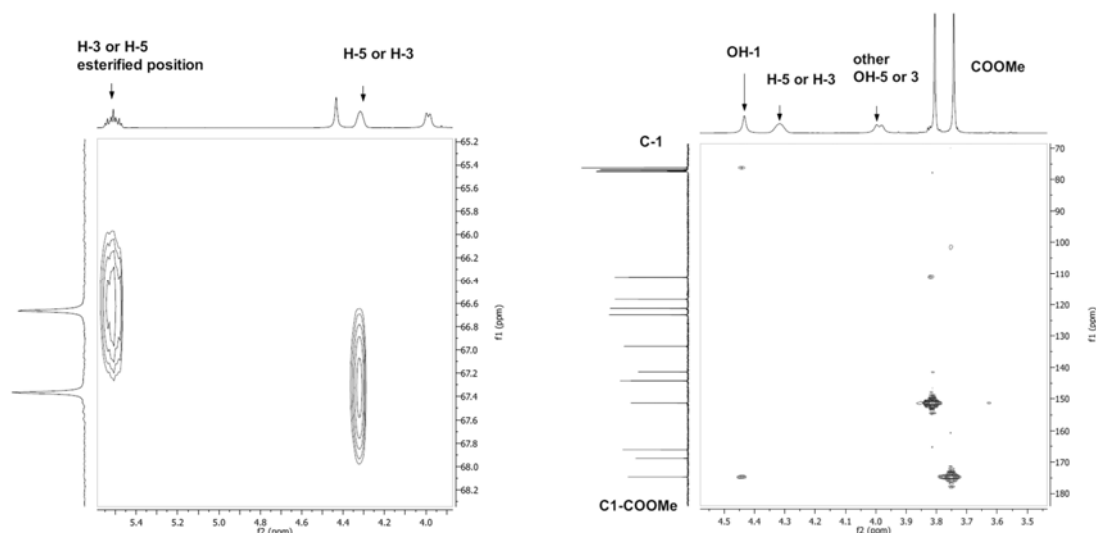


Figure 3 : 2D NMR analysis of **5a** (CDCl₃): Left: Partial ¹H-¹³C HSQC (CDCl₃); Right: Partial ¹H-¹³C HMBC (CDCl₃)

In ¹H-¹H NOESY spectrum (Figure 4), the two such assigned signals for hydroxyl groups C1-OH and C3 or C5-OH exhibit interactions with each other (rectangles in Figure 4) indicating their relative *cis* positions, which is only consistent with a mean conformation for 5-feruloyl monoester **5a** (Scheme 2). Additionally, the signal for an axial proton at 5.51 ppm is also correlated (circles in Figure 4) with these two signals for hydroxyl groups. **5a** corresponds to a monoester with a feruloyl group in position 5 with a predominant conformation with an equatorial methyl ester group in CDCl₃ and **5b** is the 3-*O*-isomer (Scheme 1). The acylation positions of *p*-coumaroyl and caffeoyl in other monoesters **6a/6b** and **7a/7b** were analogously confirmed.

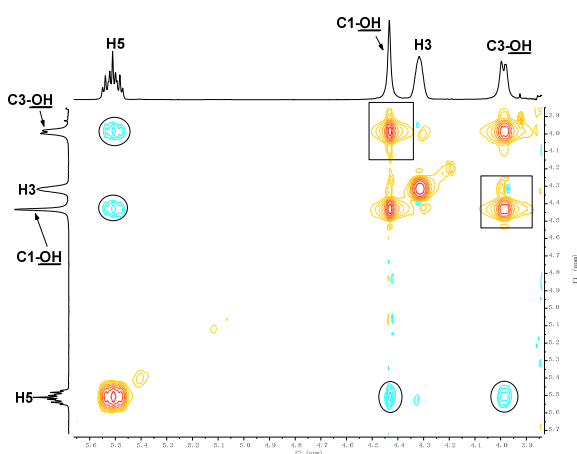
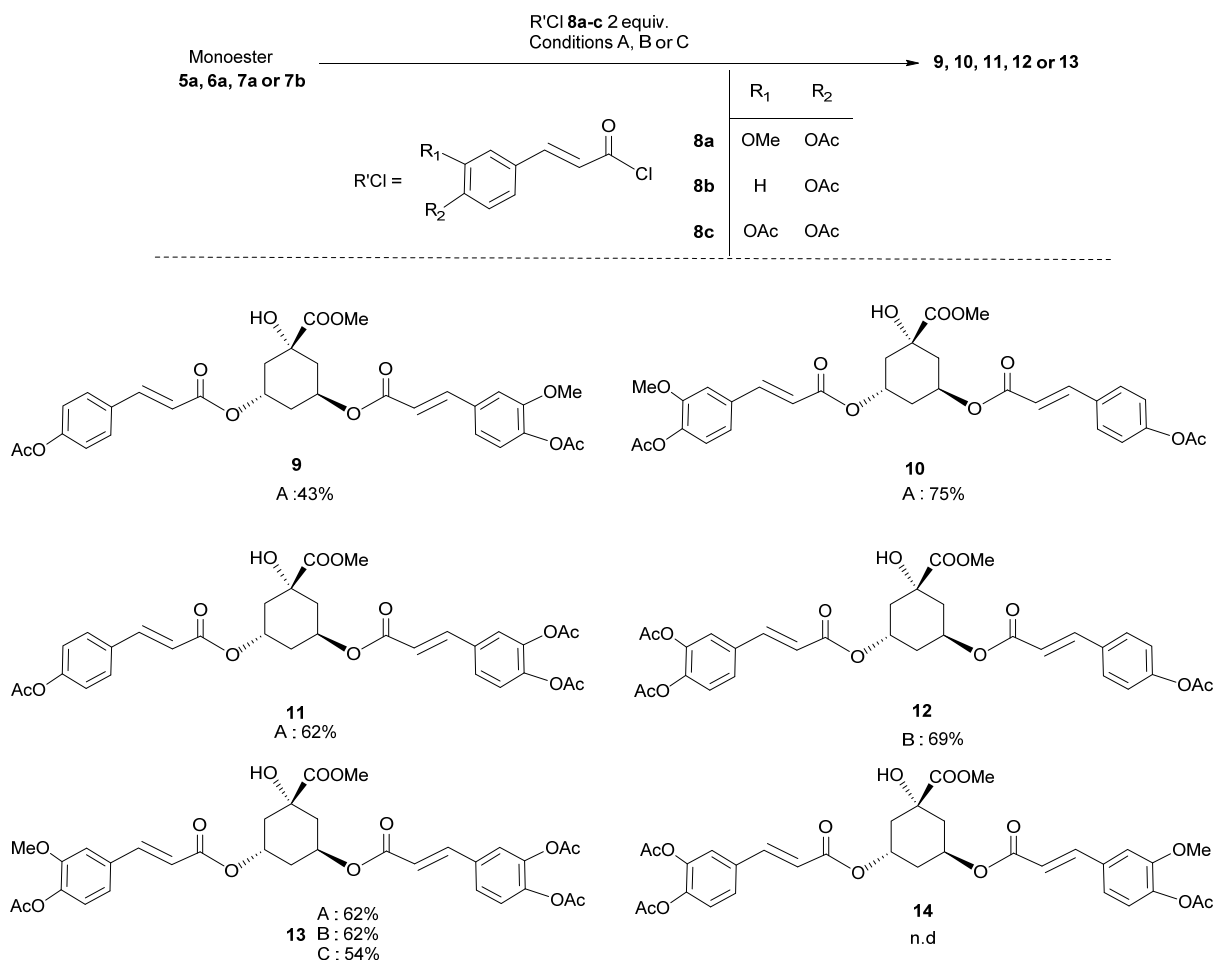


Figure 4 : ¹H-¹H NOESY (in CDCl₃) of **5a**

Preparation of various heterodiesters

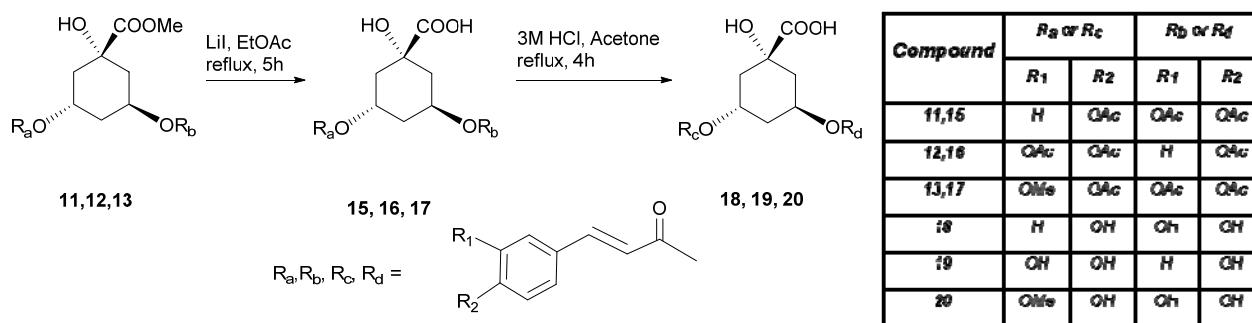
Compounds with various combinations of the three chosen hydroxycinnamoyl moieties were targeted: replacing one of active coumaroyl residue (from **2b**) by a feruloyl or caffeoyl one (Scheme 3, **9-12**), or a caffeoyl (from **2a**) by a feruloyl or coumaroyl residue (**11-14**). **9, 10, 11** could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



Scheme 3 : Synthesis of heterodiester. Reagents and conditions ^a 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-MSⁿ for monoacyl and diacyl chlorogenic acids³¹ or methyl esters³⁵ without the need to isolate the pure compounds. This identification method is based on the selective MSⁿ fragmentation pattern observed in tandem mass spectra of chlorogenic acids. Previous characterization of caffeoyl-feruloyl quinic acids³¹ and of 3,5- caffeoyl-*p*-coumaroyl quinic acids³⁶ showed that discrimination was possible between regioisomers according to MSⁿ spectra (n=2 to 3): m/z values for base peaks but also peak intensities for secondary ions already differ in MS² 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 MS² m/z 337 (first loss of caffeoyl in position 5) or m/z 353 (first loss of *p*-coumaroyl in position 5).³⁶

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. MS² 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.³¹ 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*

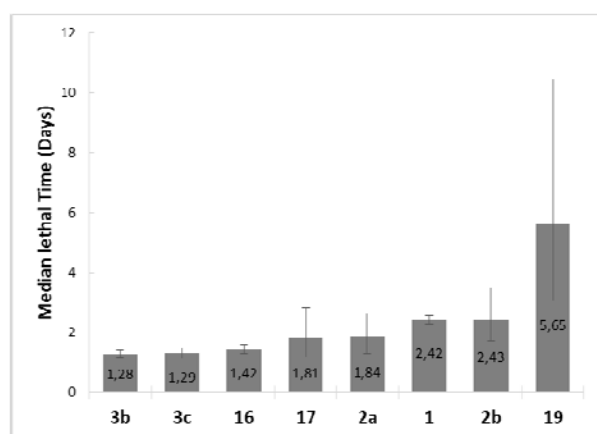


Figure 5 : Survival analysis. Lethal Time LT₅₀ mean values per active compound (0.5 mM)

3a, 18, 20 giving a mean LT₅₀ superior to 20 days are not represented

Together with the three acetylated homodiester **3a-3c**,²⁴ 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% (LT₅₀) 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 χ^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 LT₅₀, in days, and confidence interval under log-normal model, see supporting information). Results are summarized in Figure 5 (**3a, 18, 20** giving a mean LT₅₀ 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% (LT₅₀) 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.²⁴ 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 LT₅₀ 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
2 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 μ M, total inhibition had occurred over 7 days. A concentration of 250 μ 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 μ M and 500 μ 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		
1 [†]	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
3a	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
3b	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
3c	1.00 \pm 0.03 A	0 \ddagger -	0 \ddagger -	0 \ddagger -	0 \ddagger -	na [§]	na [§]	1
16	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
17	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
18	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
19	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
20	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
Anova	na [§]	12.0	27.6	26.5	22.8			
F-ratio	na [§]	12.0	27.6	26.5	22.8			
p	na [§]	1.6 e-12	7.2 e-19	2.9 e-20	1.1 e-10			

25 [†] **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 [‡] 0 is no survivor at day 7

28 [§] not applicable

29 Experimental

30 General

Reagents and solvents were supplied by Aldrich, Acros, Lancaster, Alfa Aesar, Fluka or TCI and purchased at the highest commercial quality to be used without further purification. NMR spectra were recorded on a Bruker 300 (^1H : 300 MHz; ^{13}C : 75 MHz), Bruker 400 (^1H : 400 MHz; ^{13}C : 100 MHz), or Bruker 500 (^1H : 500 MHz; ^{13}C : 125 MHz) spectrometers, at 295-298K, using CDCl_3 , CD_3OD or D_2O as solvents. The chemical shifts (δ ppm) are referenced to the solvent residual peak and coupling constants J in Hz are reported in the standard fashion. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, sext. = sextuplet, hept. = heptuplet, m = multiplet, br = broad; Ar is used for Aromatic and for the assignment of ^{13}C carbon signals : C_q = quaternary carbon. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on a Thermo Finnigan LCQ Advantage mass. High-resolution mass spectra (HRMS) were recorded on a Finnigan Mat 95xL mass spectrometer using electrospray. Analytical thin-layer chromatography was carried out on silica gel Merck 60 D254 (0.25 mm). Flash chromatography was performed on Merck Si 60 silica gel (40–63 μm). Infra-red (IR) spectra were recorded with a IRAffinity-1 Shimadzu spectrometer using Attenuated Total Reflectance (ATR-Miracle), and the wavenumbers are expressed in cm^{-1} . Optical rotations were measured on a Perkin Elmer 241 or Jasco P1010 polarimeter with a 10 cm cell (concentration c expressed in g/100 mL). Melting points were measured using Büchi apparatus B-540. All data for chlorogenic acids or related derivatives presented in this paper use the recommended IUPAC numbering system. The assignment of NMR signals has been made according to the numbering shown in the general structures below (Figure 6).³⁷

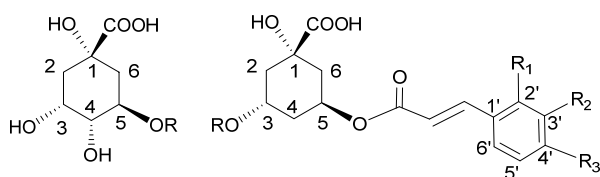


Figure 6 : Numbering for CQA and deoxy analogs

Synthetic procedures

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

Conditions A : To a solution of triol **4**²⁴ in DMF / pyridine (v/v 3/2, $c = 0.4\text{M}$) under nitrogen, was added the appropriate acetylated hydroxycinnamoyl chloride (1.5 equiv.) and the mixture was heated at 45°C under stirring until a maximum of conversion was reached. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated NaHCO_3 solution then with brine. The organic layer was dried over Na_2SO_4 , concentrated and purified by flash chromatography on silica using the appropriate eluent.

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

5a (EtOAc / petroleum ether = 1/1 to 3/1, second fraction, light yellow oil, 15%), $[\alpha]_D^{25} - 5.8$ (c 0.89 in CH_2Cl_2); IR(ATR) 2934, 1763, 1736, 1707, 1638, 1601, 1508, 1456 cm^{-1} ; ^1H NMR (400 MHz, 298K, CDCl_3) δ 7.58 (d, 1H, 3J 16.0 Hz, $\text{CH}=\text{CHCO}$), 7.08 – 7.05 (m, 2H, H_{Ar}), 7.00 (d, 1H, J_{ortho} 8.6 Hz, H_{Ar}), 6.31 (d, 1H, 3J 16.0 Hz, $\text{CH}=\text{CHCO}$), 5.51 (tt, 1H, 3J 11.2 Hz, 3J 4.4 Hz, H_5), 4.43 (s, 1H, OH_1), 4.32 (m, 1H, H_3), 3.98 (m, 1H, OH_3), 3.82 (s, 3H, COOCH_3), 3.74 (s, 3H, OCH_3), 2.47 – 2.29 (m, 2H, H_4 and H_6), 2.27 (s, 3H, OCOCH_3), 2.04 – 1.99 (m, 2H, $2x\text{H}_2$), 1.91 (dd, 1H, 2J 12.6 Hz, 3J 11.2 Hz, H_{6a}), 1.65 (ddd, 1H, 2J 12.7 Hz, 3J 11.5 Hz, 3J 3.0 Hz, H_{4a}); ^{13}C NMR (100 MHz, 298K, CDCl_3) δ = 174.7 (COOCH_3), 168.8 (OCOCH_3), 166.0 ($\text{CH}=\text{CHCO}$), 151.4 ($\text{C}_q \text{Ar}$), 144.3 ($\text{CH}=\text{CHCO}$), 141.4 ($\text{C}_q \text{Ar}$), 133.3 ($\text{C}_q \text{Ar}$), 123.2 (CH_{Ar}), 121.2 (CH_{Ar}), 118.3 ($\text{CH}=\text{CHCO}$), 111.3 (CH_{Ar}), 76.2 (C_1), 67.4 (C_3), 66.7 (C_5), 55.9 (OCH_3), 53.0 (COOCH_3), 39.7 (C_6), 38.1 (C_4), 38.0 (C_2), 20.6 (OCOCH_3); HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{24}\text{NaO}_9$ [$\text{M} + \text{Na}^+$]: 431.1313, found: 431.1332.

5b (EtOAc / petroleum ether = 1/1 to 3/1, light yellow oil, 33%), $[\alpha]_D^{25} + 3.3$ (c 0.81 in CH_3OH); IR(ATR) 3443, 2951, 2926, 1763, 1732, 1705, 1634, 1599, 1510, 1454 cm^{-1} ; ^1H NMR (400 MHz, 298K, CDCl_3) δ 7.64 (d, 1H, 3J 15.9 Hz, $\text{CH}=\text{CHCO}$), 7.12 – 7.04 (m, 3H, H_{Ar}), 6.37 (d, 1H, 3J 16.0 Hz, $\text{CH}=\text{CHCO}$), 5.44 (m, 1H, 3J 3.9 Hz, H_3), 4.38 (tt, 1H, 3J 10.2 Hz, 3J 4.1 Hz, H_5), 3.87 (s, 3H, OCH_3), 3.82 (s, 3H, COOCH_3), 2.32 (s, 3H, OCOCH_3), 2.26 (m, 1H, H_4), 2.15 – 2.07 (m, 2H, H_2 and H_6), 2.02 (m, 1H, H_2), 1.90 (dd, 1H, 2J 12.9 Hz, 3J 10.1 Hz, H_{6a}), 1.71 (ddd, 1H, 2J 13.6 Hz, 3J 10.3 Hz, 3J 3.4 Hz, H_{4a}); ^{13}C NMR (100 MHz, 298K, CDCl_3) δ = 175.8 (COOCH_3), 168.9 (OCOCH_3), 166.1 ($\text{CH}=\text{CHCO}$), 151.5 ($\text{C}_q \text{Ar}$), 144.7 ($\text{CH}=\text{CHCO}$), 141.6 ($\text{C}_q \text{Ar}$), 133.4 ($\text{C}_q \text{Ar}$), 123.4 (CH_{Ar}), 121.6 (CH_{Ar}), 118.4 ($\text{CH}=\text{CHCO}$), 111.3 (CH_{Ar}), 75.2 (C_1), 69.5 (C_3), 63.5 (C_5), 56.1 (OCH_3), 53.4 (COOCH_3), 43.1 (C_6), 38.5 (C_4), 37.1 (C_2), 20.7 (OCOCH_3); HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{24}\text{NaO}_9$ [$\text{M} + \text{Na}^+$]: 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 CH₂Cl₂); IR(ATR) 1765, 1736, 1709, 1638,
2 1506, 1435 cm⁻¹; ¹H NMR (400 MHz, 298K, CDCl₃) δ 7.63 (d, 1H, ³J 16.0 Hz, CH=CHCO), 7.51 and 7.01 (2d, 2x2H, ³J 8.0 Hz,
3 H_{Ar}), 6.33 (d, 1H, ³J 16.0 Hz, CH=CHCO), 5.53 (tt, 1H, ²J 11.3 Hz, ³J 4.4 Hz, H₅), 4.33 (m, 1H, ³J 3.3 Hz, H₃), 3.84 (s, 1H, OH), 3.78
4 (s, 3H, COOCH₃), 2.36 (m, 2H, H₄ and H₆), 2.29, (s, 3H, OCOCH₃), 2.00 (m, 2H, H₂), 1.90 (dd, 1H, ²J \approx ³J 11.5 Hz, H_{6a}), 1.67 (ddd,
5 1H, ²J 13.6 Hz, ³J 10.3 Hz, ³J 3.4 Hz, H_{4a}); ¹³C NMR (100 MHz, 298K, CDCl₃) with traces of **6b** or **6c** δ 175.0 (COOCH₃), 169.3
6 (OCOCH₃), 166.1 (CH=CHCO), 152.2 (C_q Ar), 144.0 (CH=CHCO), 132.1 (C_q Ar), 129.3 (CH_{Ar}), 122.2 (CH_{Ar}), 118.3 (CH=CHCO),
7 76.3 (C_i), 67.5 (C₃), 66.6 (C₅), 53.2 (COOCH₃), 39.8 (C₆), 38.2 (C₄), 38.0 (C₂), 21.2 (OCOCH₃); HRMS (ESI): calcd for C₁₉H₂₂NaO₈
8 [M + Na⁺]: 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, CH₂Cl₂); IR(ATR) 3406, 2947, 1759, 1724,
10 1680, 1634, 1601, 1508, 1446 cm⁻¹; ¹H NMR (400 MHz, 295K, CDCl₃) δ = 7.65 (d, 1H, ³J 16.0 Hz, CH=CHCO), 7.52 and 7.11 (2d,
11 2x2H, ³J 8.0 Hz, H_{Ar}), 6.37 (d, 1H, ³J 16.0 Hz, CH=CHCO), 5.42 (m, 1H, ³J 3.9 Hz, H₃), 4.36 (tt, 1H, ³J 10.1 Hz, ³J 4.0 Hz, H₅), 3.80
12 (s, 3H, COOCH₃), 2.30 (s, 3H, OCOCH₃), 2.22 (m, 1H, H₄), 2.16 – 2.00 (m, 3H, 2xH₂ and H₆), 1.90 (dd, 1H, ²J 13.0 Hz, ³J 9.9 Hz,
13 H_{6a}), 1.71 (ddd, 1H, ²J 13.6 Hz, ³J 10.2 Hz, ³J 3.4 Hz, H₄); ¹³C NMR (100 MHz, 295K, CDCl₃) δ = 175.8 (COOCH₃), 169.3
14 (OCOCH₃), 166.2 (CH=CHCO), 152.2 (C_q Ar), 144.2 (CH=CHCO), 132.1 (C_q Ar), 129.4 (CH_{Ar}), 122.2 (CH_{Ar}), 118.4 (CH=CHCO),
15 75.2 (C_i), 69.5 (C₃), 63.4 (C₅), 53.3 (COOCH₃), 43.0 (C₆), 38.4 (C₄), 37.1 (C₂), 21.3 (OCOCH₃); HRMS (ESI): calcd for C₁₉H₂₂NaO₈
16 [M + Na⁺]: 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 CH₂Cl₂); IR(ATR) 1770, 1736, 1711,
18 1639, 1504 cm⁻¹; ¹H NMR (400 MHz, 296K, CDCl₃) δ 7.58 (d, 1H, ³J 16.0 Hz, CH=CHCO), 7.39 – 7.33 (m, 2H, H_{Ar}), 7.19 (d, 1H,
19 *J*_{ortho} 8.3 Hz, H_{Ar}), 6.32 (d, 1H, ³J 16.0 Hz, CH=CHCO), 5.51 (tt, ³J 11.4 Hz, ³J 4.4 Hz, 1H, H₅), 4.32 (s, 1H, H₃), 4.32 and 3.88 (2m,
20 2H, OH₁ and OH₃), 3.77 (s, 3H, COOCH₃), 2.39-2.27 (m, 8H, H₄, H₆ and 2xOCOCH₃), 2.00 (m, 2H, 2xH₂), 1.88 (dd, 1H, ²J \approx ³J 11.5
21 Hz, H_{6a}), 1.65 (ddd, 1H, ²J 13.6 Hz, ³J 10.2 Hz, ³J 3.4 Hz, H₄); ¹³C NMR (100 MHz, 297K, CDCl₃) δ 174.9 (COOCH₃), 168.2 and
22 168.1 (2xOCOCH₃), 165.9 (CH=CHCO), 143.6 (C_q Ar), 143.1 (CH=CHCO), 142.5 and 133.3 (C_q Ar), 126.5, 124.0 and 122.8 (CH_{Ar}),
23 119.3 (CH=CHCO), 76.3 (C_i), 67.5 (C₃), 66.8 (C₅), 53.2 (COOCH₃), 39.7 (C₆), 38.1 (C₄), 38.0 (C₂), 20.71 (2xOCOCH₃); HRMS
24 (ESI): calcd for C₂₁H₂₄NaO₁₀ [M + Na⁺]: 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 CH₂Cl₂); IR(ATR) 1773, 1732, 1707,
26 1639, 1504 cm⁻¹; ¹H NMR (400 MHz, 296K, CDCl₃) probably contaminated with **7a** and **7c** δ 7.60 (d, 1H, ³J 16.0 Hz, CH=CHCO),
27 7.41 – 7.34 (m, 2H, H_{Ar}), 7.20 (d, 1H, *J*_{ortho} 8.3 Hz, H_{Ar}), 6.36 (d, 1H, ³J 16.0 Hz, CH=CHCO), 5.40 (m, 1H, ³J 3.9 Hz, H₃), 4.34 (m,
28 1H, H₅), 3.78 (s, 3H, COOCH₃), 3.23 (m, 1H, OH-1 or OH-5), 2.29 and 2.28 (2s, 6H, 2xOCOCH₃), 2.22 – 1.98 (m, 4H, H₂, H₄ and/or
29 H₆), 1.89 (dd, 1H, ²J 12.9 Hz, ³J 10.0 Hz, H_{6a}), 1.69 (ddd, 1H, ²J 13.6 Hz, ³J 10.2 Hz, ³J 3.3 Hz, H_{4a}); ¹³C NMR (100 MHz, 297K,
30 CDCl₃) δ 175.7 (COOCH₃), 168.2 and 168.1 (2xOCOCH₃), 165.9 (CH=CHCO), 143.5 (C_q Ar), 143.3 (CH=CHCO), 142.4 (C_q Ar),
31 133.2 (C_q Ar), 126.5 (CH_{Ar}), 124.0 (CH_{Ar}), 122.9 (CH_{Ar}), 119.4 (CH=CHCO), 75.1 (C_i), 69.5 (C₃), 63.2 (C₅), 53.1 (COOCH₃), 42.8
32 (C₆), 38.2 (C₄), 36.9 (C₂), 20.7 (2xOCOCH₃); HRMS (ESI): calcd for C₂₁H₂₄NaO₁₀ [M + Na⁺]: 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 CH₂Cl₂); IR(ATR) 1765, 1732, 1709,
39 1638, 1601, 1506 cm⁻¹; ¹H NMR (400 MHz, 295K, CDCl₃) δ 7.69 and 7.62 (2d, 2H, ³J 16.0 Hz, CH=CHCO), 7.55 (d, 2H, *J*_{ortho} 8.3
40 Hz, H_{Ar}), 7.14 – 7.04 (m, 5H, H_{Ar}), 6.42 and 6.34 (2d, ²H, ³J 16.0 Hz, CH=CHCO), 5.58 – 5.50 (m, 2H, H₃ and H₅), 3.86 (s, 3H,
41 OCH₃), 3.77 (s, 3H, COOCH₃), 2.32 and 2.30 (2s, 6H, 2xOCOCH₃), 2.37 – 2.04 (m, 5H, H₂, H₆ and H₄), 1.89 (ddd, 1H, ²J 13.6 Hz,
42 ³J 10.3 Hz, ³J 3.4 Hz, H₄); ¹³C NMR (100 MHz, 295K, CDCl₃) δ 175.1 (COOCH₃), 169.3 and 168.9 (2xOCOCH₃), 166.2 and 165.9
43 (2xCH=CHCO), 152.2 and 151.5 (C_q Ar), 144.5 and 144.3 (CH=CHCO), 141.6, 133.3 and 132.2 (C_q Ar), 129.7, 129.5, 123.4, 122.4,
44 122.2 and 121.4 (CH_{Ar}), 118.4 and 118.3 (CH=CHCO), 111.3 (CH_{Ar}), 74.8 (COOCH₃), 68.9 and 66.9 (C₃, C₅), 56.0 (OCH₃), 53.2
45 (COOCH₃), 39.9 and 36.8 (C₂, C₆), 35.1 (C₄), 21.3 and 20.8 (2xOCOCH₃); HRMS (ESI): calcd for C₃₁H₃₂NaO₁₂ [M + Na⁺]:
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, CH₂Cl₂); IR(ATR) 1762, 1736, 1705,
48 1636, 1601, 1506 cm⁻¹; ¹H NMR (400 MHz, 295K, CDCl₃) δ 7.64 and 7.62 (2d, 2H, ³J 16.0 Hz, CH=CHCO), 7.52 (d, 2H, *J*_{ortho} 8.3
49 Hz, H_{Ar}), 7.10 (m, 4H, H_{Ar}), 7.03 (d, 1H, *J*_{ortho} 8.3 Hz, H_{Ar}), 6.41 and 6.33 (2d, ²H, ³J 16.0 Hz, CH=CHCO), 5.58 – 5.47 (m, 2H, H₃
50 and H₅), 3.85 (s, 3H, OCH₃), 3.76 (s, 3H, COOCH₃), 2.30 and 2.29 (2s, 6H, 2xOCOCH₃), 2.37 – 2.03 (m, 5H, H₂, H₆ and H₄), 1.87
51 (ddd, 1H, ²J 13.6 Hz, ³J 10.3 Hz, ³J 3.4 Hz, H₄); ¹³C NMR (100 MHz, 295K, CDCl₃) δ 175.0 (COOCH₃), 169.2 and 168.8

1 (2xO $\underline{\text{C}}\text{OCH}_3$), 166.1 and 165.9 (2xCH=CH $\underline{\text{C}}\text{O}$), 152.2 and 151.4 (C $_{\text{q Ar}}$), 144.6 and 144.0 (2x $\underline{\text{C}}\text{H}=\text{CHCO}$), 141.5, 133.3 and 132.0 (C $_{\text{Ar}}$), 129.3(2), 123.2, 122.2(2) and 121.6 (CH $_{\text{Ar}}$), 118.3 and 118.1 (CH=CHCO), 111.1 (CH $_{\text{Ar}}$), 74.8 (C $_{\text{I}}$), 68.9 and 66.8 (C $_{\text{3}}$, C $_{\text{5}}$), 56.0
2 (O $\underline{\text{C}}\text{H}_3$), 53.1 (COO $\underline{\text{C}}\text{H}_3$), 39.8 and 36.8 (C $_{\text{2}}$, C $_{\text{6}}$), 35.1 (C $_{\text{4}}$), 21.2 and 20.7 (2xOCO $\underline{\text{C}}\text{H}_3$); HRMS (ESI): calcd for C $_{31}\text{H}_{33}\text{O}_{12}$ [M + H $^{+}$]:
3 597.1967, found: 597.1944.

5 **11** (EtOAc/ Pentane = 1/1 to 2/1, white solid, 62%), mp 87 - 89 °C, [α] $_{\text{D}}^{25}$ - 67.5 (c 1.05, CH $_2\text{Cl}_2$); IR(ATR) 1767, 1734, 1709,
6 1638, 1504 cm $^{-1}$; ^1H NMR (400 MHz, 295K, CDCl $_3$) with CH $_2\text{Cl}_2$ δ 7.70 and 7.61 (2d, 2H, 3J 16.0 Hz, CH=CHCO), 7.57, 7.40, 7.26
7 (3m, 6H, H $_{\text{Ar}}$), 7.14 (d, 1H, J_{ortho} 8.4 Hz, H $_{\text{Ar}}$), 6.44 and 6.35 (d, 1H, 3J 16.0 Hz, CH=CHCO), 5.59 - 5.51 (m, 2H, H $_{\text{3}}$ and H $_{\text{5}}$), 3.77 (s,
8 3H, COO $\underline{\text{C}}\text{H}_3$), 2.34 - 2.05 (m, 14H, 3xOCOCH $_3$, H $_{\text{4}}$, H $_{\text{6}}$ and H $_{\text{2}}$), 1.90 (ddd, 1H, 2J 13.6 Hz, 3J 10.3 Hz, 3J 3.4 Hz, H $_{\text{4}}$); ^{13}C NMR
9 (100 MHz, 295K, CDCl $_3$) with CH $_2\text{Cl}_2$ δ 175.1 (COOCH $_3$), 169.2, 168.3 and 168.0 (3xOCOCH $_3$), 166.1 and 165.6 (2xCH=CHCO),
10 152.2 (C $_{\text{q Ar}}$), 144.3 (CH=CHCO), 143.7 (C $_{\text{q Ar}}$), 143.2 (CH=CHCO), 142.6, 133.3 and 132.2 (C $_{\text{q Ar}}$), 129.4(2), 126.5, 124.1, 122.9 and
11 122.2 (CH $_{\text{Ar}}$), 119.3 and 118.4 (2xCH=CHCO), 74.8 (C $_{\text{I}}$), 68.9 and 67.0 (C $_{\text{3}}$, C $_{\text{5}}$), 53.2 (COO $\underline{\text{C}}\text{H}_3$), 39.9 and 36.8 (C $_{\text{2}}$, C $_{\text{6}}$), 35.1 (C $_{\text{4}}$),
12 21.24, 20.75 and 20.7 (3xOCOCH $_3$); HRMS (ESI): calcd for C $_{32}\text{H}_{32}\text{NaO}_{13}$ [M + Na $^{+}$]: 647.1735, found: 647.1707.

13 **12** (EtOAc/ Pentane = 1/2 to 1/1, white solid, 69%), mp 87 - 89 °C, [α] $_{\text{D}}^{25}$ -75.0 (c 1.04, CH $_2\text{Cl}_2$); IR(ATR) 1767, 1738, 1707, 1638,
14 1504 cm $^{-1}$; ^1H NMR (400 MHz, 295K, CDCl $_3$) δ 7.63 and 7.62 (2d, 2H, 3J 16.0 Hz, CH=CHCO), 7.52 (d, 2H, J_{ortho} 8.4 Hz, H $_{\text{Ar}}$), 7.41-
15 7.36 (m, 2H, H $_{\text{Ar}}$), 7.20 and 7.10 (2d, 1H+2H, J_{ortho} = 8.4 Hz, H $_{\text{Ar}}$), 6.40 and 6.33 (2d, 2H, 3J 16.0 Hz, CH=CHCO), 5.56 - 5.45 (m,
16 2H, H $_{\text{3}}$ and H $_{\text{5}}$), 3.75 (s, 3H, COOCH $_3$), 3.24 (m, 1H, OH-1), 2.29, 2.29, and 2.27 (3s, 9H, 3xOCOCH $_3$), 2.27 - 2.05 (m, 5H, H $_{\text{4}}$, H $_{\text{6}}$
17 and H $_{\text{2}}$), 1.88 (ddd, 1H, 2J 13.6 Hz, 3J 10.3 Hz, 3J 3.4 Hz, H $_{\text{4a}}$); ^{13}C NMR (100 MHz, 295K, CDCl $_3$) δ 175.0 (COOCH $_3$), 169.2, 168.1
18 and 168.0 (3xOCOCH $_3$), 165.9 (2xCH=CHCO), 152.2 (C $_{\text{q Ar}}$), 144.0 (CH=CHCO), 143.6 (C $_{\text{q Ar}}$), 143.4 (CH=CHCO), 142.4, 133.3
19 and 132.0 (C $_{\text{q Ar}}$), 129.3(2), 126.5, 124.0, 123.0, and 122.2(2) (CH $_{\text{Ar}}$), 119.4 and 118.2 (2xCH=CHCO), 74.7 (C $_{\text{I}}$), 68.9 and 66.8 (C $_{\text{3}}$,
20 C $_{\text{5}}$), 53.1 (COO $\underline{\text{C}}\text{H}_3$), 39.8 and 36.8 (C $_{\text{2}}$, C $_{\text{6}}$), 35.0 (C $_{\text{4}}$), 21.2, 20.7 and 20.6 (3xOCOCH $_3$); HRMS (ESI): calcd for C $_{32}\text{H}_{32}\text{NaO}_{13}$ [M +
21 Na $^{+}$]: 647.1735, found: 647.1704.

22 **13** (diethyl ether / dichloromethane = 1/15 to 1/6, white solid, 54-62%), mp 80 - 82 °C, [α] $_{\text{D}}^{25}$ - 83.5 (c 1.04, CH $_2\text{Cl}_2$); IR(ATR)
23 1767, 1709, 1639, 1506 cm $^{-1}$; ^1H NMR (400 MHz, 296K, CDCl $_3$) δ 7.64 and 7.58 (2d, 2H, 3J 16.0 Hz, CH=CHCO), 7.39 - 7.34 (m,
24 2H, H $_{\text{Ar}}$), 7.19 (d, 1H, J_{ortho} = 8.4 Hz, H $_{\text{Ar}}$), 7.11 - 7.01 (m, 3H, H $_{\text{Ar}}$), 6.40 and 6.32 (d, 1H, 3J 16.0 Hz, CH=CHCO), 5.56 - 5.47 (m,
25 2H, H $_{\text{3}}$ and H $_{\text{5}}$), 3.85 (s, 3H, OCH $_3$), 3.75 (s, 3H, COOCH $_3$), 3.30 (s, 1H, OH), 2.30, 2.28 and 2.27 (3s, 9H, 3x OCOCH $_3$), 2.27-1.92
26 (m, 5H, H $_{\text{4}}$, H $_{\text{2}}$ and H $_{\text{6}}$), 1.86 (ddd, 1H, 2J 13.6 Hz, 3J 10.4, 3J 3.5 Hz, H $_{\text{4}}$); ^{13}C NMR (100 MHz, 297K, CDCl $_3$) δ 175.0 (COOCH $_3$),
27 168.8, 168.1 and 168.0 (3xOCOCH $_3$), 166.1 and 165.6 (2xCH=CHCO), 151.4 (C $_{\text{q Ar}}$), 144.6 (CH=CHCO), 143.6 (C $_{\text{q Ar}}$), 143.2
28 (CH=CHCO), 142.5, 141.5, 133.3 and 133.1 (C $_{\text{q Ar}}$), 126.4, 124.0, 123.2, 122.8 and 121.5 (CH $_{\text{Ar}}$), 119.1 and 118.4 (2xCH=CHCO),
29 111.2 (CH $_{\text{Ar}}$), 74.7 (C $_{\text{I}}$), 68.8 and 66.9 (C $_{\text{3}}$, C $_{\text{5}}$), 56.0 (CH $_3$), 53.1 (COOCH $_3$), 39.7 and 36.7 (C $_{\text{2}}$, C $_{\text{6}}$), 35.0 (C $_{\text{4}}$), 20.7 (3xOCOCH $_3$);
30 HRMS (ESI): calcd for C $_{33}\text{H}_{34}\text{NaO}_{14}$ [M + Na $^{+}$]: 677.1841, found: 677.1830.

31 **General procedure for the cleavage of methyl ester.** Lil (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 $_4$, 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); ^1H NMR (400 MHz, 295K, CD $_3\text{OD}$) δ 7.70 (d, 2H, 3J 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 $_{\text{Ar}}$), 6.52 and 6.45 (2d, 2H, 3J 16.0 Hz,
37 CH=CHCO), 5.47 (m, 2H, H $_{\text{3}}$ and H $_{\text{5}}$), 2.42 (dd, 1H, 2J 13.7 Hz, 3J 3.8 Hz, H $_{\text{2}}$, H $_{\text{4}}$ or H $_{\text{6}}$), 2.36 - 2.20 (m, 1H, H $_{\text{2}}$, H $_{\text{4}}$ or H $_{\text{6}}$), 2.28, 2.27
38 (2s, 9H, 3xOCOCH $_3$), 2.11 - 2.00 (m, 3H, H $_{\text{2}}$, H $_{\text{4}}$ and/or H $_{\text{6}}$), 1.94 (dd, 1H, 2J 13.7 Hz, 3J 6.4 Hz, H $_{\text{2}}$, H $_{\text{4}}$ or H $_{\text{6}}$); ^{13}C NMR (100 MHz,
39 295K, CD $_3\text{OD}$) δ 177.3 (COOH), 170.8, 169.8, and 169.6 (3xOCOCH $_3$), 167.7 and 167.2 (2xCH=CHCO), 153.7 (C $_{\text{q Ar}}$), 145.2
40 (CH=CHCO), 145.1 (C $_{\text{q Ar}}$), 144.5 (CH=CHCO), 144.0, 134.5 and 133.4 (C $_{\text{q Ar}}$), 130.4 (2), 127.7, 125.1, 124.1 and 123.4 (CH $_{\text{Ar}}$),
41 120.1 (2xCH=CHCO), 119.4 (2xCH=CHCO), 75.0 (C $_{\text{I}}$), 70.1 and 69.2 (C $_{\text{3}}$, C $_{\text{5}}$), 39.9, 38.7, 35.9 (C $_{\text{2}}$, C $_{\text{4}}$, C $_{\text{6}}$), 20.9, 20.5(2)
42 (3xOCOCH $_3$); HRMS (ESI): calcd for C $_{31}\text{H}_{30}\text{NaO}_{13}$ [M + Na $^{+}$]: 663.1579, found: 663.1581.

43 **16** (63 mg, quantitative crude yield, light yellow oil), [α] $_{\text{D}}^{32}$ - 80.3 (c 1.15 in MeOH) IR(ATR) 2930, 1765, 1705, 1635, 1504 cm $^{-1}$;
44 ^1H NMR (400 MHz, 295K, CD $_3\text{OD}$) δ 7.68-7.62 (m, 4H, H $_{\text{Ar}}$ + 2xCH=CHCO), 7.49, 7.24 and 7.13 (3m, 2+1+2H, ArH), 6.52 and
45 6.45 (2d, 2x1H, 3J 16.0 Hz, 2xCH=CHCO), 5.47 (m, 2H, H $_{\text{3}}$ and H $_{\text{5}}$), 2.42 (dd, 1H, 2J 13.7 Hz, 3J 3.8 Hz, H $_{\text{2}}$, H $_{\text{4}}$ or H $_{\text{6}}$), 2.34 - 2.30
46 (m, 1H, H $_{\text{2}}$, H $_{\text{4}}$ or H $_{\text{6}}$), 2.28, 2.27 (2s, 9H, 3xOCOCH $_3$), 2.12 - 2.00 (m, 3H, H $_{\text{2}}$, H $_{\text{4}}$ and/or H $_{\text{6}}$), 1.94 (dd, 1H, 2J 13.7 Hz, 3J 6.4 Hz,
47 H $_{\text{2}}$, H $_{\text{4}}$ or H $_{\text{6}}$); ^{13}C NMR (100 MHz, 295K, CD $_3\text{OD}$) δ 177.4 (COOH), 170.8, 169.8, and 169.7 (3xOCOCH $_3$), 167.5 (2xCH=CHCO),
48 153.8 (C $_{\text{q Ar}}$), 145.3 (CH=CHCO), 145.1 (C $_{\text{q Ar}}$), 144.4 (CH=CHCO), 144.0 (C $_{\text{q Ar}}$), 134.6 and 133.4 (C $_{\text{q Ar}}$), 130.5 (2), 127.6, 125.1,
49 124.1 and 123.3(2) (CH $_{\text{Ar}}$), 120.5 and 119.1 (2xCH=CHCO), 75.1 (C $_{\text{I}}$), 70.3 and 69.0 (C $_{\text{3}}$, C $_{\text{5}}$), 40.0, 38.6, 35.9 (C $_{\text{2}}$, C $_{\text{4}}$, C $_{\text{6}}$), 20.9,
50 20.5 (2) (3xOCOCH $_3$); HRMS (ESI): calcd for C $_{31}\text{H}_{30}\text{NaO}_{13}$ [M + Na $^{+}$]: 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 cm^{-1} ; ^1H NMR (400 MHz, 298K, CD_3OD) δ 7.66 and 7.59 (2d, 2H, 3J 16.0 Hz, $2x\text{CH}=\text{CHCO}$), 7.49 – 7.43, 7.29 –
3 7.12 and 7.03 (3m, $2H+3H+1H$, H_{Ar}), 6.52 and 6.43 (2d, 2H, 3J 16.0 Hz, $2x\text{CH}=\text{CHCO}$), 5.47 (m, 2H, H_3 and H_5), 3.80 (s, 3H,
4 OCH_3), 2.41 (dd, 1H, 2J 13.7 Hz, 3J 3.8 Hz, H_2 , H_4 or H_6), 2.36 – 2.20 (m, 1H, H_2 , H_4 or H_6), 2.27, 2.26, and 2.25 (3s, 9H,
5 $3x\text{OCOCH}_3$), 2.05 (m, 3H, H_2 , H_4 and/or H_6), 1.94 (dd, 1H, 2J 13.7 Hz, 3J 6.4 Hz, H_2 , H_4 or H_6); ^{13}C NMR (100 MHz, 295K, CD_3OD)
6 δ 177.3 (COOCH_3), 170.4, 169.8, and 169.7 (OCOCH_3), 167.7 ($\text{CH}=\text{CHCO}$), 167.2 ($\text{CH}=\text{CHCO}$), 152.8 ($\text{C}_{\text{q Ar}}$), 145.6 ($\text{CH}=\text{CHCO}$),
7 145.1 ($\text{C}_{\text{q Ar}}$), 144.4 ($\text{CH}=\text{CHCO}$), 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 (CH_{Ar}), 125.1 (CH_{Ar}), 124.2 (CH_{Ar}),
8 124.1 (CH_{Ar}), 122.4 (CH_{Ar}), 120.1 ($\text{CH}=\text{CHCO}$), 119.5 ($\text{CH}=\text{CHCO}$), 112.6 (CH_{Ar}), 75.0 (C_1), 70.1 (C_3 or C_5), 69.1 (C_3 or C_5), 56.5
9 (PhOCOCH_3), 39.9 (C_2 or C_4 or C_6), 38.7 (C_2 or C_4 or C_6), 35.89 (C_2 or C_4 or C_6), 20.8, 20.7, and 20.50 (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 cm^{-1} ; ^1H NMR (400 MHz, 295K, CD_3OD) δ 7.66 and 7.54 (2d, $2x1H$, 3J 16.0 Hz, $2x\text{CH}=\text{CHCO}$), 7.47-6.78 (m, 7H, H_{Ar}), 6.35 and
18 6.23 (2d, $2x1H$, 3J 16.0 Hz, $2x\text{CH}=\text{CHCO}$), 5.45 (m, 2H, H_3 and H_5), 2.43-2.29 and 2.11-1.90 (2m, $2H+4H$, H_2, H_4 and H_6); ^{13}C NMR
19 (100 MHz, 295K, CD_3OD) δ 177.5 (COOH), 168.6 ($\text{CH}=\text{CHCO}$), 168.3 ($\text{CH}=\text{CHCO}$), 161.2(2) and 149.5 ($\text{C}_{\text{q Ar}}$), 147.1 and 146.7
20 ($\text{CH}=\text{CHCO}$), 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 (CH_{Ar}), 115.5 ($\text{CH}=\text{CHCO}$), 115.2 ($\text{CH}=\text{CHCO}$),
21 75.1 (C_1), 70.0 and 68.7 (C_3, 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 CH_3OH), IR(ATR) 3320, 2359, 1688, 1603, 1514 cm^{-1} ; ^1H
24 NMR (400 MHz, 298K, CD_3OD) δ 7.60 and 7.58 (2d, 2H, 3J 15.9 Hz, $2x\text{CH}=\text{CHCO}$), 7.46 (m, 2H, H_{Ar}), 7.07-6.78 (m, 5H, H_{Ar}),
25 6.29 and 6.28 (2d, 2H, 3J 15.9 Hz, $2x\text{CH}=\text{CHCO}$), 5.45 (m, 2H, H_3 and H_5), 2.40-2.30 and 2.06-1.89 (2m, $2H+4H$, $\text{H}_2, \text{H}_4, \text{H}_6$); ^{13}C
26 NMR (100 MHz, 298K, CD_3OD) δ 177.6 (COOH), 168.6 and 168.3 ($\text{CH}=\text{CHCO}$), 161.3(2) and 149.5 ($\text{C}_{\text{q Ar}}$), 147.0 and 146.7
27 ($2x\text{CH}=\text{CHCO}$), 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 (CH_{Ar}), 115.2 and 115.1
28 ($2x\text{CH}=\text{CHCO}$), 75.1 (C_1), 70.0 and 68.8 (C_3, 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), $[\alpha]_D^{25}$ - 77.6 (*c* 0.98 in MeOH), IR(ATR) 3393, 2950, 2360, 1680, 1654, 1629, 1603
31 cm^{-1} ; ^1H NMR (400 MHz, 298K, CD_3OD) δ 7.64 and 7.53 (2d, 2H, 3J 15.9 Hz, $2x\text{CH}=\text{CHCO}$), 7.19-6.78 (m, 7H, H_{Ar}), 6.38 and 6.22
32 (2d, 2H, 3J 15.9 Hz, $2x\text{CH}=\text{CHCO}$), 5.45 (m, 2H, H_3 and H_5), 3.89 (s, 3H, 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}C NMR (100 MHz, 298K, CD_3OD) δ 177.4 (COOH), 168.5 and 168.3 ($2x\text{CH}=\text{CHCO}$), 150.4, 149.5, 149.3 ($\text{C}_{\text{q Ar}}$), 147.1 and 146.9
34 ($2x\text{CH}=\text{CHCO}$), 146.7, 127.8, 127.7 ($\text{C}_{\text{q Ar}}$), 124.1, 123.1, 116.5 and 116.4 (CH_{Ar}), 115.9 and 115.20 ($\text{CH}=\text{CHCO}$), 115.18 and 111.6
35 (CH_{Ar}), 75.1 (C_1), 70.0 and 68.7 (C_3, C_5), 56.4 (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 μm) 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 μm stationary phase. The compound was eluted with an acidified water/methanol gradient.²² 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*,³⁸ and diluted 3 times to obtain the experimental dose range (125 μM -1mM). Toxicity was evaluated by scoring

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

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

Conclusions

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

Conflicts of interest

There are no conflict to declare.

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

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