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^a Université Lyon 1, INSA Lyon, ICBMS Equipe Chimie Organique et Bioorganique, UMR 5246 CNRS, CPE-Lyon, Bâtiment Jules Verne, 20 Avenue Albert Einstein, F-69621 Villeurbanne Cedex, France; Tel : +33-(0)4 72 43 80 98 ; Fax : +33-(0)4 72 43 88 96; E-mail : sylvie.moebis@insa-lyon.fr

^b INSA Lyon, INRA BF2I UMR0203, Biologie Fonctionnelle Insectes et Interaction, Bâtiment Louis Pasteur, 20 Avenue Albert Einstein, F-69621 Villeurbanne Cedex, France; Tel : +33-(0)4 72 43 61 51; Fax : +33 (0)4 72 43 85 34 ; E-mail : pedro.da-silva@insa-lyon.fr

^c INRA Avignon, GAFL, Domaine St Maurice, 84143 Montfavet Cedex, France; E-mail : jean-luc.poessel@avignon.inra.fr

† Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: [Copies of ¹H and ¹³C NMR spectra for compounds **5-12**, ¹H NMR (CD₃OD) spectra of **4a** and **4d** after different times intervals, HPLC chromatograms and UV spectra for tested compounds, as well as complementary data on survival assays are given in the supplementary information file]. See DOI: 10.1039/x0xx00000x

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Synthesis of new dicinnamoyl 4-deoxy quinic acid and methyl ester derivatives and evaluation of the toxicity against the pea aphid *Acyrtosiphon pisum*

Xiubin Li,^a Lucie Grand,^a Thomas Pouleriguen,^a Yves Queneau,^a Pedro da Silva,^b Yvan Rahbé,^b Jean-Luc Poëssel,^c Sylvie Moebs-Sanchez,*^a

New dicinnamoyl (caffeoyl, feruloyl, *ortho* and *para*-coumaroyl) 4-deoxyquinic acid and esters were synthesized by using a new 4-deoxy quinic acid triol intermediate. The optimisation of both coupling and deprotection steps allowed the preparation in good yields of the target products either as the carboxylic acid or the methyl ester form. Eight new compounds were evaluated for their ability to influence the feeding behaviour of the pea aphid *Acyrtosiphon pisum*. Artificial diet bioassays showed that two compounds are toxic (mortality and growth inhibition) at lower concentrations than the reference 3,5-dicaffeoyl quinic acid.

Introduction

Chlorogenic acid, namely 5-*O*-caffeoyl quinic acid^{1,2} **1** is the parent component of a large family (CQA : Cinnamoyl Quinic Acids) of natural compounds formed by esterification of D-quinic acid **2** with one or several *trans*-cinnamic acids such as, most commonly, caffeic, *p*-coumaric or ferulic acids (Figure 1). Dimethoxycinnamic³ and sinapic acids⁴ can also be present in some species. These bioactive plant secondary metabolites are widely found in edible plants, isolated from various species^{5,6} and have been commonly used in traditional herbal medicines. Suspected to have many health benefits, they have been widely evaluated in different *in vitro* bioassays to confirm their potential biological activities, among antioxidant,⁷ antifungal,⁸ antiviral,⁹ renoprotective,¹⁰ neuroprotective,^{11,12} anti-atherosclerotic,¹³ or inhibitors of α -glucosidase.¹⁴ They have also been recently included in diverse cosmetic compositions.^{15,16}

Aphids are the major group of phloem feeding insects impairing seriously the production of agricultural and horticultural crops, causing significant yield losses and transmission of virus. Towards a more sustainable but efficient crop protection, which would prevent the development of insecticide resistance, the potential toxicity and environmental impact, alternative solutions to current pesticides are still investigated. Although host plant resistance to aphids mechanisms are not yet well understood, research for a biological mode of action could be an efficient alternative strategy.¹⁷ Indeed, the correlation between chlorogenic acids concentration and priming of plants¹⁸ was shown for the carrot fly larval damage¹⁹ then for fungal infection⁸ or for cultured tobacco cells²⁰ as examples.

Western flower thrips *Frankliniella occidentalis* were also reported.²² More recently, the cultivar Rubira peach tree, parent of a trait mapped to Rm2 gene²³ showed a strong induced resistance to *Myzus persicae*, the green peach aphid which represents a threat for many agro-industrial crops including potato, sugar beet, tobacco or horticultural crops or stone fruits.²⁴ In an early phenolic profiling study,²⁵ an accumulation of metabolite later identified as 3,5-dicaffeoyl quinic acid **3** had been detected in aphid-infested leaves, as was also later observed in a fungal-pear tree pathosystem.²⁶ In spite of the positive preliminary results of *in vitro* artificial diets assays adding **3** in nutritive medium for aphids,²⁷ the underlying biological mechanisms remain to be explored. A synthetic program was then initiated to prepare various dicinnamoyl quinic acid derivatives (DiCQA) and synthetic analogs to get insight into the pharmacophoric groups, into the mode of action of this phenolic compound onto putative specific aphicidal targets and/or to find more active compounds.

Due to known isomerization of **3** into the other 3,4 and 4,5 diCQ regioisomers under bioassay conditions,²⁷ in organic solvents,²⁸ or under very basic conditions,²⁹ questions about the stability of compounds to synthesise were addressed. We hypothesized that the synthesis of **4** and derivatives, as first part of our program, as analogues of **3** and other CQAs, featuring a 4-deoxy quinic acid nucleus (Figure 1), would prevent the easy isomerization of 3,5-derivatives. Here we wish to report our results on the first synthesis of new homo diesters **4** of 4-deoxy quinic acid, from the homo bis coupling of a new 4-deoxy triol with caffeic, coumaric and ferulic counterparts. The evaluation of the respective toxicity of 7 deoxy quinic acids or methyl esters derivatives against aphids was also carried out in comparison with the natural 3,5-diCQA derivative **3** and an analog prepared from isosorbide, a bicyclic diol.

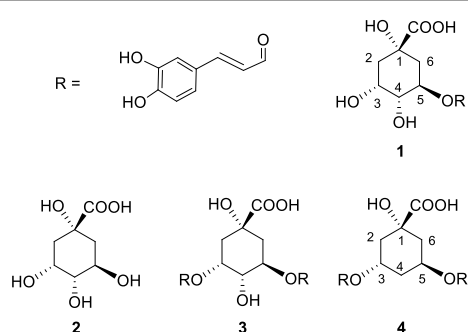


Figure 1 Representative structures of chlorogenic acid **1**, D-quinic acid **2**, dicaffeoyl quinic acid **3** and a deoxy analog **4**

The resistance of lettuce cultivars to *Pemphigus bursarius*²¹ or the negative effect of chlorogenic acid on

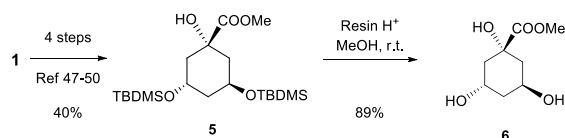
Results and discussion

Chemistry

Our retrosynthetic analysis was logically inspired by the previous syntheses of chlorogenic acids. Except for an elegant and original methodology using a Knoevenagel reaction,³⁰⁻³¹ most strategies rely on a coupling reaction between an acid chloride of a protected cinnamic acid and an appropriately protected derivative of quinic acid. Several reports disclosed the preparation of some cinnamoyl quinic acids or of the corresponding γ -quinides.^{32,33,34,35} Chemical syntheses for DiCQA derivatives have been nevertheless less reported than those for mono-^{14,36,37,38,39,40,41} or tri-substituted compounds.^{42,43,44} A great variability in the reaction conditions (solvent, catalyst, temperature) can be

observed.^{32,33,42,44,45} Phenol groups were most often protected as carbonates or naturally occurring methoxy,³² as acetates (despite some reported difficulties to remove them efficiently),³⁶ as methoxymethyl (MOM)³⁶ or as (3,4-(methylene-dioxy)).⁴³ Recently, Jaiswal *et al*⁴⁵ preferred using an alternative allyl ether protecting group for the successful access to 3-O-epimers of chlorogenic acids derivatives (*muco*). Activation of the cinnamic acid *via* carbonyldiimidazole¹⁴ or as an anhydride was also reported.^{37,46} Tertiary alcohol could also be protected albeit requiring additional steps.^{32,42}

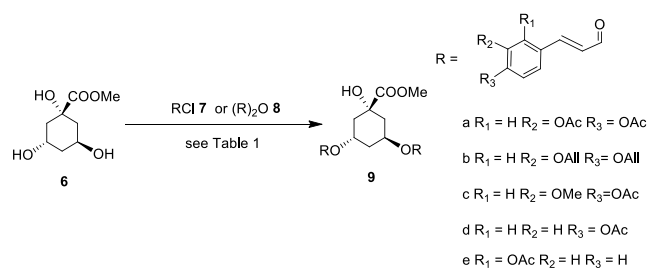
Aiming at a most atom-economic and direct approach, we chose to react the key triol **6** with various cinnamoyl chlorides. The synthesis of **6** was first optimized to the multi-gram scale from the known intermediate **5**^{47,48,49,50} obtained in four steps from D-quinic acid **1** in 40% overall yield (Scheme 1). Acidic hydrolysis was performed in the presence of a heterogeneous H⁺ resin in MeOH with an excellent 89% isolated yield.



Scheme 1 Synthesis of 4-deoxy methyl quinate

The coupling with the cinnamic counterpart turned out to be surprisingly challenging (Table 1). **6** was first reacted with known diacetylated caffeoylchloride **7a**⁴¹ under reported conditions : DMAP nucleophilic catalysis in pyridine or in DCM/pyridine varying concentration, stoichiometric ratio, temperature and/or reaction time led to very modest yields but above all to unrepeatable results (see Table1, entries 1-3 for selected experiments). Using anhydride **8a**⁴⁶ instead of caffeoyl chloride in pyridine as solvent/base was not more satisfactory even in a shorter reaction time (Entry 4). Analysis of the crude mixtures concluded to partial conversion and only mono-esterification of a secondary alcohol more than competitive 1-O-acylation was observed. Rather than adding protection/deprotection steps, we then decided to test DMF/pyridine as another Lewis base-solvent/auxiliary base system⁵¹ for the reaction of **6** with acid chlorides.⁵² Diesters could eventually be isolated with repeatability and reproducibility and fair good yields.⁵³ Bis diacetylated dicaffeate **9a** was indeed obtained with 76% yield after 1h at 45°C using an excess of **7a** (entry 5). During our work for optimization, we observed that better results could be obtained for total conversion by addition by portions of acyl chloride instead of increasing the number of molar equivalents leading to difficult purifications. 3 molar equivalents of acid chloride turned out to give the best results. With diallylated acid chloride **7b**, the same

improvement was observed compared to classical reported conditions albeit with only 59% yield (Entry 6 vs 7). The same procedure allowed to isolate diferulate **9c** (55%), di-*p*-coumarate **9d** (82%) and di-*o*-coumarate **9e** (62%) (Entries 8-10). Moreover our good results obtained in the regioselective monoesterification of quinic acid derivatives (unpublished data) led us to repeat some experiments at lower temperature, especially in the classical DCM/Pyridine/DMAP system in which reactions are usually reported at room^{32,33,38,41} or higher temperature.^{42,44,45} Two sets of optimized conditions were assayed (entries 11-12, 13-14, 15-16) giving **9a** with excellent 90 and 92% isolated yields.⁵⁴ Same or lower yield improvement was observed for **9c** and **9d** (entries 8 vs 13 and 9 vs 15) but an easier purification could be gained under these conditions, lowering the temperature minimizing potential acyl migration to OH-1. Complete conversions were in all cases observed within less than 4h.

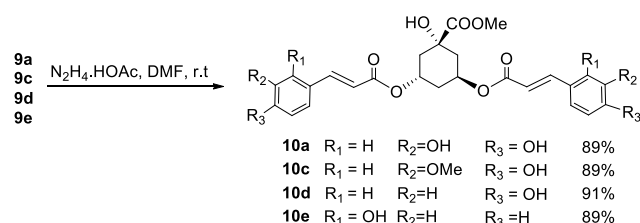
Table 1 Diesterification of 4-deoxy methyl quinate **6**

Entry	Acyating agent (molar equiv.)	Catalyst	Solvent	Concentration (M)	Temp.	Time	Product	Yield ^a
1	7a (3)	DMAP	Pyridine	0.7	rt	4 days	9a	<7%
2	7a (5)	DMAP	Pyridine	0.05	40°C	5h	9a	nd ^b
3	7a (6)	DMAP	DCM/Pyridine	0.05	rt	7 days	9a	40%
4	8a (3)		Pyridine	0.02	rt	4 days	9a	38%
5	7a (3)		DMF/Pyridine	0.4	45°C	1h	9a	76%
6	7b (5)	DMAP	DCM/Pyridine	0.1	rt	10 days	9b	Trace
7	7b (3)		DMF/Pyridine	0.4	45°C	1h30	9b	59%
8	7c (3)		DMF/Pyridine	0.4	45°C	1h	9c	55%
9	7d (3)		DMF/Pyridine	0.4	45°C	1h	9d	82% ^c
10	7e (3)		DMF/Pyridine	0.4	45°C	1h	9e	62%
11	7a (3)		DMF/Pyridine	0.4	0°C to rt	4h	9a	90%
12	7a (3)	DMAP	DCM/Pyridine	0.1	-18°C to rt	4h	9a	92%
13	7c (3)		DMF/Pyridine	0.4	0°C to rt	4h	9c	69%
14	7c (3)	DMAP	DCM/Pyridine	0.1	-18°C to rt	4h	9c	69%
15	7d (3)		DMF/Pyridine	0.4	0°C to rt	4h	9d	75%
16	7d (3)	DMAP	DCM/Pyridine	0.1	0°C to rt	4h	9d	<64% ^d

^a Isolated yield in 3,5-homodiester; ^b A monoester was detected but not quantified; ^c Triester was isolated with 7% yield; ^d Isolated product was contaminated with polar caffeic acid derivative.

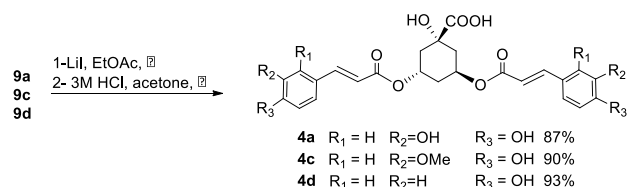
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To get deprotected methyl ester analogs, hydrolysis of **9a** under reported acidic conditions (HCl, in THF or acetone) was again inefficient. The alternative removal of aromatic allyl ethers from **9b** was then performed using Pd/C in the presence of *p*-TsOH in MeOH but in a disappointing yield lower than 56%. The hydrolysis of the aromatic acetates was actually successfully performed for **9a** with sodium acetate in ethanol/water⁵⁵ in 1h at reflux with 61% isolated yield giving **10a** without any hydrolysis of the aliphatic ester groups or any migration observed in the crude product. However, for the other cinnamoyl conjugates, the deprotection turned out to be incomplete under these conditions. With a mild method reported recently,⁵⁶ using hydrazine acetate in DMF at room temperature, all the derivatives could be obtained with very good isolated yields (89-91%) (Scheme 2).



Scheme 2 Deprotection of methyl ester analogs.

Betting for a better solubility of the carboxylic acid derivatives during bioassays and especially for **4a**, the main targeted analog of **3**, **9a** was first reacted with HCl in THF or acetone to remove both the aromatic acetates and the methyl ester.⁴⁰ But only a complex mixture was obtained after a long reaction time due to very slow conversion. Alternatively, removal of the methyl ester by Lil in EtOAc,⁵⁷ led to the intermediate carboxylic acid **11**, which was not isolated and directly submitted to acidic hydrolysis of acetyl groups with 3M HCl in acetone under reflux.^{46, 58} **4a** could be obtained with a very good 87% overall yield. The same sequence led to **4c** and **4d** with respective 90% and 93% yields (Scheme 3).



Scheme 3 Synthesis of carboxylic acids analogs

In the course of other ongoing projects around isosorbide, a more rigid bicyclic 1,4-diol, dicaffeoyl isosorbide **12** had also been prepared.⁵⁹ **12** was included in bioassays with the seven compounds **10a**, **10c**, **10d**, **10e**, **4a**, **4c**, **4d** for comparison (Figure 2). All the

intermediates were fully characterized. Higher order quantum effects are observed through the highly complex splitting pattern of signals in ¹H NMR spectra. The interesting pseudo-symmetry of these compounds make difficult to distinguish H-3 and H-5 signals but one H-4 signal is well-resolved in protected compounds **9**: the predominance of rapidly interconverted chair-like conformers is thus supported by a mean value of ³J coupling constant of 9-10 Hz between H-4axial and H-3/H-5. Preparative HPLC before bioassays confirmed the high purity of the different samples. ¹H NMR (CD₃OD) of **4a** and **4d** at different time intervals confirmed the stability of this compound at least over 60h compared to **3** (see Supplementary information).²⁸

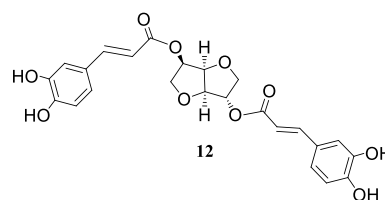


Figure 2 : Dicaffeoyl isosorbide 12

Insecticidal bioassays

10a, **10c**, **10d**, **10e**, **4a**, **4c**, **4d** and **12** were incorporated in culture media during nymphal development of the pea aphid *Acyrtosiphon pisum*. The natural compound **3** was used as control. This specialist and model aphid species (*A. pisum*) was indeed shown to be highly sensitive to **3**,²⁷ and was therefore selected for optimal suitability for growth-inhibition/ toxicity bioassays.

Bioassays were 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 500 μM gave the most discriminating analysis (likelihood ratio test with a χ^2 of 200.6, $p=4.8 \cdot 10^{-39}$), and we will only discuss this dose level, while growth-rate analyses will show all dose effects (Table 2). Table S3 in supplementary information displays all eight survival curves at dose 500 μM. Toxicity (mortality) features of the most active compounds **10a**, **10e**, **4a**, **4c**, **4d** are summarized in Figure 3 for a 500μM dose according to decreasing activities from **4a** to **10a**.

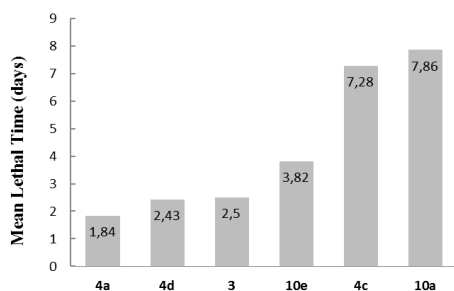


Figure 3 Survival analysis. LT50 mean values per active compound

Growth inhibition was measured by weighing and was analysed by a set of two one-way Anova (Table 2), comparing either the dose effects per compound (capital lettering) or the compound effect, dose per dose (small lettering). As five independent experiments were needed to score all compounds, a standard normalisation of data by the results of the control condition (diet alone) was

performed. Using this normalisation for weights resulted in a quite reproducible scoring of growth inhibition for the control natural molecule **3** used for every experimental batch: a two way Anova for dose/experiment, with interactions, resulted in a very significant “dose” effect ($p < 0.001$), a non-significant “experiment” effect ($p = 0.61$) and a non-significant interaction ($p = 0.24$). The effect of **3** was therefore represented in Table 2 by the global results of the 5 batches used for this molecule.

These growth inhibition analyses mainly underline the activity of two new molecules, superior or close to the one of the natural product **3**, namely **4a** and **4d**. **10d** showed no inhibitory effect on the growth of the pea aphid, while **12** displays a slight stimulatory effect at the highest 1 mM dose. As a result from all the “compound” factor ANOVAs (dose by dose), that read vertically in Table 2, one might rank the global toxicity index of compounds as: **4a** > **4d** > **3** ≈ **10e** > **4c** ≥ **10a** > **10d** ≈ **10c** > **12**.

Table 2 : Growth inhibition assay over nymphal development (7 days) of the pea aphid *Acyrtosiphon pisum*. Results are shown as means (% of control growth) ± SE, with ANOVA and mean comparisons (Tukey-Kramer HSD test) over lines (dose effect, capital lettering, →) and over columns (molecule effect, small lettering, ↓)

Compound	control	Dose (mM)					Anova	Experiment ^{iv}
	0	0.125	0.25	0.5	1	F-ratio	p	
3 ⁱ	1.00±0.04 →A,a↓	0.98±0.03 A,b	0.70±0.03 B,bc	0.36±0.04 C,d	0 ⁱⁱ -	35.3 (3df)	1.4 10 ⁻¹⁸	1-5
4a	1.00±0.03	0 ⁱⁱ	0 ⁱⁱ	0 ⁱⁱ	0 ⁱⁱ	na ⁱⁱⁱ	na ⁱⁱⁱ	2
10a	1.00±0.08 A,a	1.07±0.05 A,ab	1.03±0.06 A,a	0.96±0.10 A,a	0.53±0.04 B,c	6.8 (4 df)	6.5 10 ⁻⁵	3
10e	1.00±0.08 B,a	1.29±0.09 A,a	0.65±0.08 C,c	0.38±0.05 C,d	0 ⁱⁱ	21.3 (3 df)	2.0 10 ⁻¹⁰	3
4d	1.00±0.04 A,a	0.93±0.16 AB,ab	0.77±0.21 B,abc	0 ⁱⁱ	0 ⁱⁱ	4.3 (2 df)	2.5 10 ⁻²	4
10d	1.00±0.04 A,a	0.98±0.04 A,b	1.00±0.05 A,a	0.91±0.04 A,ab	0.89±0.04 A,b	1.28 (4df)	0.28 (ns)	4
4c	1.00±0.06 A,a	1.01±0.07 A,b	0.90±0.02 A,ab	0.67±0.05 B,bcd	0.57±0.08 B,bc	10.4 (4 df)	8.3 10 ⁻⁷	5
10c	1.00±0.06 A,a	1.03±0.04 AB,ab	0.86±0.05 AB,abc	0.87±0.05 AB,abc	0.75±0.06 B,bc	3.9 (4 df)	6.2 10 ⁻³	5
12	1.00±0.06 AB,a	0.92±0.05 B,b	0.94±0.06 B,ab	0.79±0.05 B,abc	1.22±0.10 A,a	5.4 (4 df)	4.6 10 ⁻⁴	1
Anova	na ⁱⁱⁱ	4.4	5.6	7.8	19.9			
F-ratio								
p	na ⁱⁱⁱ	1.4 10 ⁻⁴ (7 df)	6.2 10 ⁻⁶ (7 df)	3.8 10 ⁻⁷ (6 df)	3.5 10 ⁻¹³ (5 df)			

ⁱ: **3** was the repeated control condition for all experiments, presented data are that of all grouped experiments. See text for inter-experiment statistics.

ⁱⁱ: 0 is no survivor at day 7

ⁱⁱⁱ: not applicable

^{iv}: Five independent experiments were used (see text), and control data were checked for consistency (ANOVA ns on dose 0), and pooled after normalization

Experimental

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 peak⁶⁰ and coupling constants (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. 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 (ATRMiracle), 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 as 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 4).¹

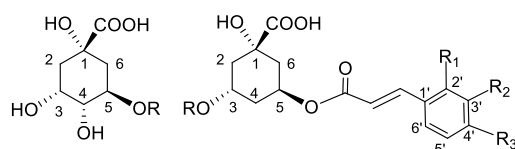


Figure 4 Numbering for CQA and deoxy analogs

Material and methods for bioassays

The natural compound **3** (3,5-dicaffeoyl quinic acid), was extracted with ethanol:water (70:30) from lyophilized non-tuberized roots of sweet potato *Ipomea batatas* and purified by semi-preparative HPLC on a Hibar® 250 mm x 25 mm column filled with Lichrospher® 100 RP18e 5 μm stationary phase. The compound was eluted with an acidified water/methanol gradient.²⁷

Compounds **10a**, **10c**, **10d**, **10e**, **4a**, **4c**, **4d** and **12** were administered pure by weighing after HPLC purification, solubilized at 1 mM in a standard AP3 artificial diet for the pea aphid *Acyrtosiphon pisum*,⁶¹ and diluted 3 times to obtain the experimental dose range (125 μM –1mM). Stability of compounds was checked by HPLC analysis in AP3 artificial diet samples after feeding bioassays. 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.⁶² 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 2). All analyses were made with JMP software, v11 (SAS Institute Cary USA, MacOS version).

Five separate experiments were needed to test all eight compounds (two-weeks apart each from the other), and the original compound **3** was used/repeated in each of the five tests. An ANOVA was performed on all dose 0 data and confirmed global inter-experiment consistency. All data (normalized on the respective dose 0 mean) from the 5 experiments were then used for the control compound **3** in the statistical analysis.

Chemistry

Methyl (3S,5S)-1,3,5-trihydroxycyclohexanecarboxylate or methyl 4-deoxy quinate 6. The disilylated compound **5** (106.7 mg, 0.25 mmol) was stirred in MeOH (2mL) with Amberlyst® A15 (H^+ form) at room temperature for 24h. After filtration and evaporation, the crude product was purified by flash chromatography (pentane/ethyl acetate 50/50 then ethyl acetate/methanol 90/10) to provide **6** (colorless oil then white solid on standing, 42.7 mg, 89%). $[\alpha]_D^{25} = -3.7$ (c 1.06, CH_3OH); IR (ATR) 3350, 2951, 2930, 2855, 1173, 1730, 1661, 1435, 1371, 1281, 1240, 1134, 1057, 1016 cm^{-1} ; ^1H NMR (400 MHz, 296K, CD_3OD) δ (ppm) = 4.24–4.16 (m, 2H, H_3 and H_5), 3.73 (s, 3H, OMe), 2.08 (dd, 1H, 2J 13.8 Hz, $^3J_{\text{H}_5/\text{H}_6}$ 3.3 Hz, H_6 or H_2), 2.00 (m, 2H, H_2 or H_6 and H_4), 1.88 (dd, 1H, 2J 12.8 Hz, $^3J_{\text{H}_2/\text{H}_3}$ 9.1 Hz, H_2 or H_6), 1.77 (dd, 1H, 2J 13.8 Hz, 3J 4.8 Hz, H_6 or H_2), 1.60 (ddd, 1H, 2J 12.7 Hz, $^3J_{\text{H}_{4a}/\text{H}_{3a}}$ ou $5a$ 9.2 Hz, $^3J_{\text{H}_{4a}/\text{H}_{3e}}$ ou H_{5e} 3.0 Hz, H_{4a}); ^{13}C NMR (CD_3OD , 295K, 100MHz) δ (ppm) 176.1 (COOMe), 76.8 (C_1), 67.8 (C_5 or C_3), 64.0 (C_3 or C_5), 52.8 (OMe), 43.8 (C_2 or C_6), 42.0 (C_4), 40.3 (C_6 or C_2). MS-ESI m/z $[\text{M}+\text{Na}]^+$ 213.1; HRMS-ESI m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_8\text{H}_{14}\text{NaO}_5$ 213.0733; found 213.0733.

General procedures for the synthesis of diesters **9** of deoxy methyl quinate.

Procedure A : To a solution of triol **6** in DMF / pyridine (v/v 3/2, $c = 0.4\text{M}$) under nitrogen was added the protected cinnamoyl chloride (3 equiv.) The mixture was stirred at 45°C until completion, in general after 1h. 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.

Procedure B : Similar to procedure A except that the mixture was stirred at 0°C until completion, in general after 4h.

Procedure C : To a solution of triol **6** in dichloromethane / pyridine (v/v 5/1, $c = 0.1\text{M}$) under nitrogen was added the protected cinnamoyl chloride (3 equiv.) and DMAP (20mol %). The mixture was stirred at -18°C to room temperature until completion, in general after 4h. Work-up as in procedures A and B.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(3,4-diacetoxyphenyl)-1-

oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9a. Synthesized according to the general procedure **B** using diacetylated caffeoyl chloride⁴¹ and methyl 4-deoxy quinate **6** (105 mg, 0.553 mmol). **9a** was obtained as a white solid (348 mg, yield: 92%) after purification by flash chromatography on silica using DCM/Et₂O 12/1 to 6/1. $[\alpha]_D^{25} = -46.9$ (c 1.215, CH₂Cl₂); m.p. = 93–94°C (CH₂Cl₂); IR(ATR) 2943, 2832, 1775, 1742, 1713, 1639, 1504, 1449, 1427, 1371, 1321, 1242, 1205, 1180, 1147, 1132, 1111, 1022 cm⁻¹; ¹H NMR (CDCl₃, 298K, 500MHz) δ (ppm) = 7.63 and 7.58 (2d, 2H, ³J 15.9 Hz, CH=CHCO), 7.39 and 7.38 (2dd, 2H, *J*_{ortho} 8.4Hz, *J*_{meta} 1.9 Hz, 2xH₆), 7.35 and 7.34 (2d, 2H, *J*_{meta} 1.9 Hz, 2x H₂), 7.20 (d, 2H, *J*_{ortho} 8.4 Hz, 2x H₅), 6.40 and 6.32 (2d, 2H, ³J 15.9 Hz, CH=CHCO), 5.51 (ddd, 1H, ²J 13.8 Hz, ³J 9.8 Hz, ³J 3.9 Hz, H_{3ax} ou _{5ax}), 5.46 (ddd, 1H, ³J=3.7 Hz, ³J 3.9 Hz, H_{3eq} ou _{5eq}), 3.76 (s, 1H, OH₁), 3.74 (s, 3H, COOMe), 2.28, 2.271 and 2.268 (3s, 12H, OCOCH₃), 2.32 (m, 1H, H₄), 2.23–2.18 (m, 2H, H₂ and H₆), 2.08–2.00 (m, 2H, H₂ and H₆), 1.87 (ddd, 1H, ²J 13.6 Hz, ³J 10.3 Hz, ³J 3.45 Hz, H_{4a}); ¹³C NMR (CDCl₃, 298K, 125 MHz) δ (ppm) = 175.0, 168.1(2) and 168.0(2) (4xOCOCH₃), 165.8 and 165.5 (2xCOO), 143.59 and 143.57 (C_q), 143.3 and 143.2 (CH=CHCO), 142.5 and 142.4 (C_q), 133.2 and 133.1(C_q), 126.5 and 126.4 (C₆), 124.0 and 123.9 (C₅), 122.9 and 122.8 (C₂), 119.4 and 119.2 (CH=CHCO), 74.7 (C₁), 68.9 (C₃ ou C₅), 66.9 (C₅ ou C₃), 53.1 (OMe), 39.7 (C₂ ou C₆), 36.7 (C₂ ou C₆), 35.0 (C₄), 20.7(2), 20.62 and 20.60 (4x OCOCH₃); HRMS-ESI m/z [M+Na]⁺ calcd for C₃₄H₃₄NaO₁₅ 705.1790; found 705.1780.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-di-(prop-2-en-1-yloxy)phenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate

9b. Synthesized according to the general procedure **A** using diallylated caffeoyl chloride⁴⁵ and **6** (102 mg, 0.537 mmol). Purification by flash chromatography on silica using petroleum ether/EtOAc 50/50, provided the triester (51mg, 10%) and diester **9b** (214 mg, 59%) as white solids. $[\alpha]_D^{25} = -140.8$ (c 0.86, CH₂Cl₂); m.p. 89–91°C; IR(ATR) 2922, 2827, 1706, 1631, 1597, 1510, 1456, 1423, 1362, 1335, 1304, 1246, 1223, 1165, 1134, 1090, 1067 cm⁻¹; ¹H NMR (CDCl₃, 298K, 300MHz) δ (ppm) = 7.63 and 7.58 (2d, 2H, ³J 15.9 Hz, CH=CHCO), 7.08 (m, 4H, CH_{Ar}), 6.87 (m, 2H, CH_{Ar}), 6.31 and 6.23 (2d, 2H, ³J 15.9 Hz, CH=CHCO), 6.07 (m, 4H, CH₂=CHCH₂O), 5.60–5.50 (m, 2H, H₃ and H₅), 5.42–5.39 (m, 2H, CH₂=CHCH₂O), 5.30 (m, 4H, CH₂=CHCH₂O), 4.64 (m, 8H, CH₂=CHCH₂O), 2.32 (m, 1H, H₂ or H₄ or H₆), 2.24–2.02 (m, 4H, H₂ or H₄ or H₆), 1.86 (ddd, 1H, *J* 13.7 Hz, *J* 10.4 Hz, *J* 3.4 Hz, H₂ or H₄ or H₆); ¹³C NMR (CDCl₃, 296K, 75 MHz) δ (ppm) = 175.1 (COOMe), 166.5 and 166.3 (OCO), 150.8 (2xC_q), 148.7 (2xC_q), 145.4 and 145.1(CH=CHCO), 133.2 133.1, 133.05 and 133.01 (4xCH₂=CHCH₂O), 127.64, 127.57 (2xC_q), 123.2 and 122.9 (2xCHAr), 118.15, 118.11, 118.1, 118.07 (4xCH₂=CHCH₂O), 115.88 and 115.84 (CH=CHCO), 113.50, 113.44, 112.7 and 112.5 (4xCHAr), 75.0 (C₁), 70.1, 70.0, and 69.8(2) (4xCH₂=CHCH₂O), 68.8 and 66.6 (C₃ and C₅), 53.2(OMe), 40.0, 36.9 and 35.2 (C₂, C₄ and C₆); HRMS-ESI m/z [M+Na]⁺ calcd for C₃₈H₄₂NaO₁₁ 697.2619; found 697.2615.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate

9c. Synthesized according to the general procedure **C** using acetylated feruloyl chloride and methyl 4-deoxy quinate **6** (117 mg, 0.616 mmol). **9c** was obtained as a white solid (266 mg, yield: 69%) after purification by flash chromatography on silica using DCM/Et₂O 10/1. $[\alpha]_D^{25} = -74.5$ (c 1.05, CH₂Cl₂); m.p. 90–92°C; IR(ATR) 1765, 1709, 1638, 1508, 1464, 1418, 1369, 1298, 1263, 1215, 1198, 1153, 1123, 1033, 1011 cm⁻¹; ¹H NMR (CDCl₃, 296K, 300MHz) δ (ppm) = 7.65 and 7.60 (2d, 2H, ³J 15.9 Hz, CH=CHCO), 7.12–7.02 (m, 6H,

CH_{Ar}), 6.41 and 6.33 (2d, 2H, ³J 15.9 Hz, CH=CHCO), 5.55 and 5.49 (2m, ³J 9.3 Hz, ³J 3.3 Hz, H₅ and H₃), 3.85 and 3.84 (2s, 2x3H, 2xOMe), 3.76 (s, 3H, COOMe), 2.30(s, 6H, 2xOAc), 2.28 (m, 1H, H_{4e}), 2.22–2.18 and 2.11–2.04(m, 2x2H, 2xH₆ and 2xH₂), 1.88 (ddd, 1H, ²J 13.6 Hz, ³J 10.4 Hz, ³J 3.4 Hz, H₄); ¹³C NMR (CDCl₃, 295K, 100 MHz) δ (ppm) = 175.0 (COOMe), 168.8 (2xOCOCH₃), 166.1 and 165.8 (COO), 151.4 (2xC_q), 144.6 and 144.4 (CH=CHCO), 141.54 and 141.51 (C_q), 133.34 and 133.30 (C_q), 123.33 and 123.25(CHAr), 121.6 and 121.3 (CHAr), 118.3 and 118.2 (CH=CHCO), 111.3 and 111.1 (CHAr), 74.8 (C₁), 68.9 (C₃ or C₅), 66.8 (C₅ or C₃), 56.0(2xOMe), 53.1 (COOMe), 39.8 and 36.8 (C₆ and C₂), 35.1 (C₄), 20.7 (2xOCOCH₃); HRMS-ESI m/z [M+Na]⁺ calcd for C₃₂H₃₄NaO₁₃ 649 649.1892; found 649.1865.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate

9d. Synthesized according to the general procedure **A** using acetylated *para*-coumaroyl chloride⁶³ and methyl 4-deoxy quinate **6** (58mg, 0.305 mmol). **9d** was obtained as a white solid (142 mg, yield: 82%) after purification by flash chromatography on silica using DCM/Et₂O 10/1. $[\alpha]_D^{25} = -79.4$ (c 0.83, CH₂Cl₂); m.p. 86–88°C; IR(ATR) 1765, 1736, 1709, 1638, 1601, 1506, 1418, 1369, 1312, 1265, 1202, 1163, 1140, 1086, 1063, 1011 cm⁻¹; ¹H NMR (CDCl₃, 295K, 400MHz) δ (ppm) = 7.67 and 7.62 (2d, 2H, ³J 16.0 Hz, CH=CHCO), 7.52 and 7.50 (2d, 4H, *J*_{ortho} 8.5 Hz, H₂), 7.10 (2d, 4H, *J*_{ortho} 8.5 Hz, H₃), 6.41 and 6.33 (2d, 2H, ³J 16.0 Hz, CH=CHCO), 5.53 and 5.48 (2 m, 2H, ³J 4.0 Hz, H₃ and H₅), 3.74 (s, 3H, COOMe), 2.27 (s, 6H, OAc), 2.24 (m, 1H, H₄), 2.23–2.19 (m, 2H, H₂ and H₆), 2.11–2.06 (m, 2H, H₂ and H₆), 1.88 (ddd, 1H, ²J 13.0 Hz, ³J 10.2 Hz, ³J 3.5 Hz, H₄); ¹³C NMR (CDCl₃, 295K, 100 MHz) δ (ppm) = 174.9 (COOMe), 169.2 (2xOCOCH₃), 166.1 and 165.8 (COO), 152.2 and 152.1 (C_q), 144.1 and 144.0 (CH=CHCO), 132.1 and 132.0 (2xCHAr), 129.4 and 129.3 (2xCHAr), 122.2 and 122.1 (C_q), 118.3 and 118.1 (CH=CHCO), 74.7 (C₁), 68.8 and 66.8 (C₃ and C₅), 53.0 (OMe), 39.7 and 36.8 (C₂ and C₆) 35.0 (C₄) 21.1 (2xCH₃); HRMS-ESI m/z [M+Na]⁺ calcd for C₃₀H₃₀NaO₁₁ 589.1680; found 589.1655.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(2-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate

9e. Synthesized according to the general procedure **A** using acetylated *ortho*-coumaroyl chloride and methyl 4-deoxy quinate **6** (82 mg, 0.432 mmol). Purification by flash chromatography (DCM/Et₂O 10/1) afforded **9e** as a white solid (152 mg, yield: 62%). $[\alpha]_D^{25} = -50.0$ (C 1.12, CH₂Cl₂); m.p. 87–90°C; IR(ATR) 1763, 1711, 1638, 1483, 1454, 1437, 1371, 1315, 1265, 1198, 1179, 1140, 1094, 1063, 1009 cm⁻¹; ¹H NMR (CDCl₃, 296K, 300MHz) δ (ppm) = 7.81 and 7.73 (2d, 2H, *J* 16.1 Hz, CH=CHCO), 7.63 (dd, 2H, *J* 7.9 Hz, H ortho), 7.40 (dd, 2H, *J* 7.40 Hz, H meta OAc), 7.25 (dd, 2H, *J* 7.6 Hz, H para OAc), 7.11 (d, 3H, *J* 8.1 Hz, H orthoOAc), 6.46 and 6.40 (2d, 2H, *J* 16.1 Hz, CH=CHCO), 5.53 (m, 2H, H₃ and H₅), 3.75 (s, 3H, COOMe), 2.40 and 2.38 (2s, 2x3H, 2xOAc), 2.29–2.19 (m, 3H, H-2, H-4, H-6), 2.13–2.02 (m, 2H, H-2, H-6), 1.90 (ddd, 1H, ²J 13.5 Hz, ³J 10.0 Hz, ³J 3.4 Hz, H-4); ¹³C NMR (CDCl₃, 295K, 100 MHz) δ (ppm) = 175.0 (COOMe), 169.45 and 169.40 (OCOCH₃), 165.8 and 165.6 (COO), 149.4(2xC_q), 138.56 and 138.50 (CH=CHCO), 131.34 and 131.30 (C_q), 127.6 and 127.5 (C₆), 127.1 and 127.0 (C_q), 126.44 and 126.41(C₅), 123.26 and 123.20 (C₃), 120.2 and 120.1 (CH=CHCO), 74.6 (C₁), 68.8 (C₃ or C₅), 67.0 (C₅ or C₃), 53.2 (COOMe), 39.7 and 36.9 (C₆ and C₂), 35.1 (C₄), 21.0 (2x OCOCH₃); HRMS-ESI m/z [M+Na]⁺ calcd for C₃₀H₃₀NaO₁₁ 589.1680; found 589.1669.

General procedure for the deprotection of aromatic acetates

Procedure D⁵⁵: To a solution of compound **9** in ethanol/water (2/1,

0.12M) was added hydrazine acetate (NaOAc, 20 eq). After stirring at reflux for 1 h, the mixture was diluted with EtOAc, washed with brine then the organic layer was dried over MgSO₄, concentrated and purified by flash chromatography.

Procedure E⁵⁶ : To a solution of compound **9** (a, c, d or e) in DMF (0.15M) was added hydrazine acetate (75 equiv.). After stirring at room temperature for 1 h, the mixture was diluted with EtOAc, washed with brine then the organic layer was dried over MgSO₄, concentrated and purified by flash chromatography.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10a. The general procedure **E** was performed with **9a** (116mg, 0.170 mmol) in DMF (0.9 mL) and hydrazine acetate (71 mg, 0.64 mmol) providing after purification **10a** as a colorless oil (78 mg, 89%). [α]_D²⁵ = -167.0 (c 0.64, CH₃OH); IR(ATR) 3323, 3304, 3285, 3275, 2949, 2835, 1680, 1630, 1599, 1516, 1443, 1373, 1256, 1159, 1140, 1119, 1067, 1016 cm⁻¹; ¹H NMR (CD₃OD, 298K, 500 MHz) : δ (ppm) = 7.58 and 7.52 (d, 2H, ³J 15.8 Hz, CH=CHCO), 7.06 (bs, 2H, Ar-H₂), 6.95 (dt, 2H, J_{ortho} = 8.1, J_{meta} 2.3 Hz, Ar-H₆), 6.80 (dd, 2H, J_{ortho} 8.2 Hz, J_{meta} 2.7 Hz, Ar-H₅), 6.28 and 6.19 (d, 2H, ³J 15.9 Hz, CH=CHCO), 5.42 (m, 2H, H₃ and H₅), 3.70 (s, 3H, OMe), 2.46 (dd, 1H, ²J 13.4 Hz, ³J 3.5 Hz, H₂ or H₆), 2.39 (dd, 1H, ²J 13.6 Hz, ³J 6.9 Hz, H₂ or H₆), 2.06 (m, 1H, H₄), 1.97 (m, 2H, H₄ and H₂ or H₆), 1.86 (dd, 1H, ²J 13.4 Hz, ³J 7.7 Hz, H₂ or H₆); ¹³C NMR (CD₃OD, 298K, 125 MHz) δ (ppm) = 175.7 (COOMe), 168.5 (OCO), 168.0 (OCO), 149.6 (C_q), 149.5 (C_q), 147.2 and 147.0 (CH=CHCO), 146.8 (C_q), 146.7(C_q), 127.7 (C_q), 127.6 (C_q), 123.04 and 123.00 (C₆'), 116.53 and 116.50 (C₅'), 115.4 and 115.1 (OCOCH=CH), 115.09 and 115.00 (C₂'), 75.0 (C₁'), 69.5 and 69.0 (C₃ and C₅), 53.0(OMe), 39.7, 39.3 and 35.9 (3xCH₂, C₂, C₆ and C₄); HRMS-ESI m/z [M+Na]⁺ calcd for C₂₆H₂₆NaO₁₁ 537.1367; found 537.1351.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[[(2E)- 3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10c. The general procedure **E** was performed with **9c** (65 mg, 0.104 mmol) in DMF (0.45 mL) and hydrazine acetate (43 mg, 0.47 mmol) providing after purification **10c** as a colorless oil (50 mg, 89%). [α]_D²⁵ = -170.0 (c 0.93, CH₃OH); IR(ATR) 3516, 3057, 2957, 2941, 1701, 1631, 1593, 1512, 1462, 1454, 1429, 1377, 1263, 1207, 1157, 1138, 1032, 1009 cm⁻¹; ¹H NMR (CD₃OD, 400 MHz) : δ ppm = 7.63 and 7.57 (d, 2H, ³J 15.9 Hz, CH=CHCO), 7.12 (bs, 2H, Ar-H), 7.07 (dd, 2H, J_{ortho} 8.2 Hz, J_{meta} 2.7 Hz, Ar-H), 6.81 (dd, 2H, J_{ortho} 8.2 Hz, J_{meta} 2.2 Hz, Ar-H), 6.38 and 6.29 (d, 2H, ³J 15.9 Hz, CH=CHCO), 5.432 (m, 2H, H₃ and H₅), 3.88 (s, 6H, 2x OMe), 3.70 (s, 3H, COOMe), 2.45 (dd, 1H, ²J 13.6 Hz, ³J 4.1 Hz, H₂ or H₆), 2.38 (dd, 1H, ²J 13.6 Hz, ³J 7.2 Hz, H₂ or H₆), 2.14-1.97 (m, 3H, 2x H₄ and H₂ or H₆), 1.88 (dd, 1H, ²J 13.6 Hz, ³J 7.5 Hz, H₂ or H₆); ¹³C NMR (CD₃OD, 100 MHz) δ (ppm) = 175.7 (COOMe), 168.4 and 168.0 (OCO), 150.7, 150.6, 149.4, 149.3 (C_q Ar), 147.1 and 147.0 (CH=CHCO), 127.7 and 127.5 (C_q Ar), 124.2 and 124.1 (CH_{Ar}), 116.5 and 116.4 (CH_{Ar}), 115.7 and 115.4 (OCOCH=CH), 111.6 (CH_{Ar}), 75.0 (C₁), 69.5 and 69.0 (C₅ or C₃), 56.4(2) (2xOCH₃), 53.0 (COOMe), 39.8 and 39.2 (C₂ or C₆), 35.9 (C₄); HRMS-ESI m/z [M+Na]⁺ calcd for C₂₈H₃₀NaO₁₁ 65.1680; found 565.1662.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10d. The general procedure **E** was performed with **9d** (80 mg, 0.14 mmol) in DMF (0.6 mL) and hydrazine acetate (59 mg, 0.64 mmol) providing after purification (CH₂Cl₂ / CH₃OH 40 / 1) **10d** as a colorless oil (62 mg, 91%). [α]_D²⁵ = -174.7 (c 0.95, CH₃OH); IR(ATR) 3325, 3308, 3279, 3267, 2947, 2832, 1688, 1632, 1603, 1587, 1514, 1441, 1371, 1325, 1307, 1254, 1202, 1165, 1144, 1103, 1065, 1018 cm⁻¹; ¹H NMR

(CD₃OD, 400 MHz) : δ (ppm) = 7.65 and 7.59 (2d, 2H, ³J 15.9 Hz, 2x CH=CHCO), 7.47 (d, 4H, J_{ortho} 8.6 Hz, Ar-H), 6.81 (dd, 4H, J_{ortho} 8.6 Hz, J_{meta} 1.8 Hz Ar-H), 6.34 and 6.26 (d, 2H, ³J 15.9 Hz, CH=CHCO), 5.43 (m, 2H, H₃ and H₅), 3.69 (s, 3H, OMe), 2.46 (dd, 1H, ²J 13.4 Hz, ³J 4.1 Hz, H₂, H₄ or H₆), 2.40 (dd, 1H, ²J 13.7 Hz, ³J 7.0 Hz, H₂, H₄ or H₆), 2.10-1.95 (m, 3H, H₂, H₄ or H₆), 1.87 (dd, 1H, ²J 13.4 Hz, ³J 7.6 Hz H₂, H₄ or H₆). ¹³C NMR (CD₃OD, 100 MHz) δ (ppm) = 175.7 (COOMe), 168.5(OCO), 168.0(OCO), 161.4 (C_q), 161.3 (C_q), 146.8 and 146.7 (2xCH=CHCO), 131.23 and 131.20 (2x2xCH), 127.2 and 127.0 (2xC_q), 116.9, 116.8 (2x2 CH), 115.5 and 115.1 (2x OCOCH=CH), 75.0 (C₁), 69.5, 69.0 (C₃ and C₅), 53.0 (OMe), 39.8, 39.3 and 35.9 (3xCH₂, C₂, C₆ and C₄). HRMS-ESI m/z [M+Na]⁺ calcd for C₂₆H₂₆NaO₉ 505.1469; found 505.1452.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(2-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10e. The general procedure **E** was performed with **9e** (118 mg, 0.21 mmol) in DMF (0.9 mL) and hydrazine acetate (88 mg, 0.96 mmol) providing after purification (CH₂Cl₂ / CH₃OH 40 / 1) **10e** as a colorless oil (89 mg, 89%). [α]_D²⁵ = -104.3 (c 1.00, CH₃OH); IR(ATR) 3337, 3298, 3283, 3256, 2945, 2835, 1688, 1626, 1603, 1499, 1458, 1369, 1317, 1294, 1254, 1169, 1146, 1113, 1067, 1018 cm⁻¹; ¹H NMR (CD₃OD, 400 MHz) : δ (ppm) = contaminated with chloroform at 7.90 ppm, 8.00 and 7.91 (2d, 2H, ³J 16.1 Hz, CH=CHCO), 7.48 (pseudo t, 2H, J_{ortho} 8.2 Hz Ar-H), 7.21 (pseudot, 2H, J_{ortho} 7.4 Hz Ar-H), 6.84 (m, 4H, Ar-H), 6.63 and 6.58 (d, 2H, ³J 16.1 Hz, CH=CHCO), 5.45 (m, 2H, H₃ and H₅), 3.72 (s, 3H, OMe), 2.49 (dd, 1H, ²J 13.4 Hz, ³J 3.6 Hz, H₂, H₄ or H₆), 2.43 (dd, 1H, ²J 13.8 Hz, ³J 6.8 Hz, H₂, H₄ or H₆), 2.15-2.09 (m, 1H, H₂, H₄ or H₆), 2.00-1.96 (m, 2H, H₂, H₄ or H₆), 1.86 (dd, 1H, ²J 13.3 Hz, ³J 7.9 Hz, H₂, H₄ or H₆). ¹³C NMR (CD₃OD, 100 MHz) δ (ppm) = contaminated with chloroform at 79.4 ppm; 175.7 (COOMe), 168.8(OCO), 168.4(OCO), 158.5 and 158.3 (2xC_q), 142.9 and 142.5 (2xCH=CHCO), 132.7, 132.6, 130.6, 130.2 (4xCH_{Ar}), 122.6, 122.5 (2xC_q), 120.8 (2xCH_{Ar}), 118.6, 118.5 (2x OCOCH=CH), 117.0 (2xCH_{Ar}), 79.4, 75.0 (C₁), 69.5, 69.1 (C₃ and C₅), 53.0 (OMe), 39.8, 39.4 and 35.9 (3xCH₂, C₂, C₆ and C₄). HRMS-ESI m/z [M+Na]⁺ calcd for C₂₆H₂₆NaO₉ 505.1469; found 505.1448.

(3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4a. Lil (143 mg, 1.07 mmol) was added to a solution of **9a** (146 mg, 0.214 mmol) in EtOAc (1.1 mL) then the mixture was heated under reflux overnight. After cooling down to room temperature, the mixture was diluted with EtOAc (30 mL), washed with 1M HCl (2x 10 mL) and extracted with EtOAc (3x30 mL). The organic layer was dried over MgSO₄, concentrated to give the crude (3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11a** (128 mg, crude yield: 90%), pure enough for characterization and used directly in the following step. IR(ATR) 3370, 2941, 2833, 1769, 1707, 1638, 1504, 1369, 1240, 1201, 1174, 1143, 1109, 1012 cm⁻¹; ¹H NMR (CD₃OD, 298K, 400 MHz) : δ (ppm) = 7.67 and 7.62 (2d, 2H, J 16.0 Hz, CH=CHCO), 7.50 (m, 2H, H₆'), 7.49 (m, 2H, H₂'), 7.24 (d, 2H, J_{ortho} 8.2 Hz, H₅'), 6.52 and 6.46 (2d, 2H, J 16.0 Hz, CH=CHCO), 5.46 (m, 2H, H₃ and H₅), 2.44-2.19 (m, 14H) and 2.06-1.90 (m, 4H, 3xCH₂ and 4xOCOCH₃); ¹³C NMR (CD₃OD, 298K, 100 MHz) δ (ppm) = 177.3 (COOH), 169.8 and 169.7 (4x OCOCH₃), 167.5 and 167.2 (2xOCO), 145.2 and 145.1 (2xC_q), 144.5 and 144.4 (2xCH=CHCO), 144.0 (2xC_q), 134.60 and 134.56 (2xC_q), 127.7 and 127.6 (2xC₆'), 125.13 and 125.11 (2xC₅'), 124.14 and 124.09 (C₂'), 120.45 and 120.13 (2x CH=CHCO), 75.0 (C₁'), 70.2, 69.2 (C₃ and C₅), 39.9, 38.7, 35.9 (C₂, C₄, C₆), 20.5 (4XOCOCH₃).

HRMS-ESI m/z $[M+H]^+$ calcd for $C_{33}H_{33}O_{15}$ 669.1814; found 669.1801.

To a solution of (3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11a** (208 mg) in acetone (4.8 mL) was added 3M HCl aqueous solution (2.0 mL) and the mixture was refluxed for 5h. After completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was concentrated to give the crude quantitatively as a pale solid **4a** (190 mg). $[\alpha]_D^{25} = -42.7$ (c 0.82, CH_3OH); IR(ATR) 3345, 3210, 1687, 1603, 1523, 1445, 1362, 1279, 1182, 1138, 1119 cm^{-1} ; 1H NMR (CD_3OD , 400 MHz, 295K) : δ (ppm) = 7.65 and 7.60 (2d, 2H, J 16.0 Hz, $CH=CHCO$), 7.45 (m, 4H, ArH), 6.81 (m, 4H, ArH), 6.34 and 6.27 (2d, 2H, J 16.0 Hz, $CH=CHCO$), 5.45 (m, 2H, H_3 and H_5), 2.41 (dd, 1H, 2J 14.0 Hz, 3J 3.8 Hz, H_2 , H_4 or H_6), 2.32 (dd, 1H, 2J 13.3 Hz, 3J 8.2 Hz, H_2 , H_4 or H_6), 2.06 (m, 3H, H_2 , H_4 or H_6), 1.93 (dd, 1H, 2J 13.8 Hz, 3J 6.5 Hz, H_2 , H_4 or H_6); ^{13}C NMR (CD_3OD , 100 MHz, 297K) δ (ppm) = 177.4 (COOH), 171.0 (2x C_q), 168.5 and 168.3 (2xOCO), 161.12 and 161.07 (2x C_q), 146.7 and 146.7 (2x $CH=CHCO$), 131.2, 131.1 (2x CH_{Ar}), 127.1 (2x C_q), 116.8 (4x CH_{Ar}), 115.5, 115.1 (2x $CH=CHCO$), 75.1 (C_1), 69.9, 68.7 (C_3 and C_5), 39.9, 38.6, 35.9 (C_2 , C_4 , C_6).

(3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4c. Lil (152 mg, 1.135 mmol) was added to a solution of **9c** (142 mg, 0.2274 mmol) in EtOAc (5.0 mL) then the mixture was heated under reflux 24h. After cooling down to room temperature, the mixture was diluted with EtOAc (25 mL), washed with 3M HCl (5 mL) and extracted with EtOAc (3x30mL). The organic layer was dried over $MgSO_4$, concentrated to give the crude (3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(4-acetoxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11c** (quantitative crude yield), pure enough for characterization and used directly in the following step. $[\alpha]_D^{25} = -97.5$ (c 0.96, CH_3OH); IR(ATR) 3466, 2941, 2833, 1763, 1705, 1599, 1508, 1464, 1454, 1418, 1369, 1256, 1215, 1177, 1152, 1063, 1020 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) : δ (ppm) = 7.66 and 7.61 (2d, 2H, 3J 15.9 Hz, $CH=CHCO$), 7.13-7.03 (2m, 6H, Ar-H), 6.41 and 6.34 (2d, 2H, 3J 15.9 Hz, $CH=CHCO$), 5.50 (m, 2H, H_3 and H_5), 3.87 and 3.85 (2s, 2x3H, 2xOMe), 2.33-1.83 (m, 12H, H_2 , H_4 , H_6 and 2x $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) = 176.7 (COOH), 169.04 and 169.02 (2x $OCOCH_3$), 166.1 and 166.0 (2xCOO), 151.53 and 151.50 (2x C_q), 145.3, 144.8 (2x $CH=CHCO$), 141.7, 141.6 (2x C_q), 133.3, 133.2 (2x C_q), 123.4 (2x CH_{Ar}), 121.8, 121.4 (2x $CH=CHCO$), 118.1, 117.9 (2x CH_{Ar}), 111.4, 111.3 (2x CH_{Ar}), 75.2 (C_1), 69.4, 66.5 (C_3 and C_5), 56.1, 56.0 (2xOMe), 39.3, 36.5, 34.9 (C_2 , C_4 , C_6), 20.8 (2x $OCOCH_3$); HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{31}H_{32}NaO_{13}$ 635.1735; found 635.1706.

To a solution of (3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(4-acetoxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11c** (176 mg) in acetone (3.0 mL) was added 3M HCl aqueous solution (1.5 mL) and the mixture was refluxed for 4h. After completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was concentrated then dissolved in MeOH/ H_2O (30/40 mL) and washed with pentane (2x 15mL). After concentration, the crude was obtained as a pale solid **4c** (150mg). $[\alpha]_D^{25} = -94.4$ (c 0.67, CH_3OH); IR(ATR) 3356, 3277, 1684, 1632, 1605, 1514, 1443, 1327, 1261, 1204, 1171, 1138, 1007 cm^{-1} ; 1H NMR (CD_3OD , 300 MHz, 297K) : δ (ppm) 7.65 and 7.60 (2d, 2H, J

15.9 Hz, $CH=CHCO$), 7.17 (m, 2H, ArH), 7.07 (m, 2H, ArH), 6.83 (d, 2H, J_{ortho} 8.1 Hz, ArH), 6.39 and 6.32 (2d, 2H, J 15.9 Hz, $CH=CHCO$), 5.47 (m, 2H, H_3 and H_5), 3.89 (s, 6H, 2xOMe), 2.42 (dd, 1H, 2J 13.9 Hz, 3J 4.0 Hz, H_2 , H_4 or H_6), 2.34 (dd, 1H, 2J 13.4 Hz, 3J 8.2 Hz, H_2 , H_4 or H_6), 2.00 (m, 4H, H_2 , H_4 or H_6); ^{13}C NMR (CD_3OD , 75 MHz, 297K) δ (ppm) = 177.4 (COOH), 170.9 (2x C_q), 168.5 and 168.2 (2xOCO), 150.44, 150.38 (2x C_q), 146.9 and 146.8 (2x $CH=CHCO$), 127.74 and 127.68 (2x C_q), 124.1, 124.0, 123.9, 116.4, 115.8, 115.5 (6x CH_{Ar}), 111.7 and 111.6 (2x $CH=CHCO$), 75.1 (C_1), 69.9, 68.7 (C_3 and C_5), 56.43 and 56.41 (2xOMe), 40.0, 38.7, 36.0 (C_2 , C_4 , C_6).

(3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4d. Lil (125 mg, 0.934 mmol) was added to a solution of **9d** (105 mg, 0.186 mmol) in EtOAc (4.0 mL) then the mixture was heated under reflux 24h. After cooling down to room temperature, the mixture was diluted with EtOAc (25 mL), washed with 3M HCl (5 mL) and extracted with EtOAc (3x30mL). The organic layer was dried over $MgSO_4$, concentrated to give the crude (3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11d** (quantitative crude yield), pure enough for characterization and used directly in the following step. $[\alpha]_D^{25} = -111.9$ (c 1.03, CH_3OH); IR(ATR) 3447, 3059, 2961, 1765, 1707, 1601, 1585, 1506, 1418, 1369, 1312, 1265, 1202, 1163, 1136, 1057, 1009 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) : δ (ppm) = 7.68 and 7.62 (2d, 2H, 3J 15.9 Hz, $CH=CHCO$), 7.52 (dd, 4H, J_{ortho} 8.6 Hz, J_{ortho} 6.8 Hz, Ar-H), 7.11 (dd, 4H, J_{ortho} 8.6 Hz, J_{meta} 2.0 Hz, Ar-H), 6.41 and 6.34 (2d, 2H, 3J 15.9 Hz, $CH=CHCO$), 5.49 (m, 2H, H_3 and H_5), 2.36-2.02 and 1.86 (2m, 11 and 1H, H_2 , H_4 , H_6 and 2x $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) = 177.0 (COOH), 169.41 and 169.39 (2x $OCOCH_3$), 166.2, 166.1 (2xCOO), 152.4, 152.3 (2x C_q), 144.9, 144.4 (2x $CH=CHCO$), 132.04, 132.0 (2x C_q), 129.6, 129.5 (4x CH_{Ar}), 122.3 (4x CH_{Ar}), 118.0, 117.9 (2x $CH=CHCO$), 75.2 (C_1), 69.4, 66.6 (C_3 and C_5), 39.3, 36.5, 34.9 (C_2 , C_4 and C_6), 21.3 (2x $OCOCH_3$); HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{29}H_{28}NaO_{11}$ 575.1524; found 575.1503.

To a solution of (3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11d** (196 mg) in acetone (4.0 mL) was added 3M HCl aqueous solution (2.0 mL) and the mixture was refluxed for 5h. After completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was concentrated, dissolved in MeOH/ H_2O (20/50 mL) and washed with pentane (2x 15mL). After concentration, the crude was obtained quantitatively as a pale solid **4d** (165 mg). $[\alpha]_D^{25} = -72.6$ (c 0.71, CH_3OH); IR (ATR) 3406, 2976, 2947, 1692, 1593, 1514, 1456, 1429, 1375, 1269, 1209, 1177, 1161, 1138, 1032 cm^{-1} ; 1H NMR (CD_3OD , 400 MHz, 295K) δ (ppm) = 7.59 and 7.54 (2d, 2H, J 16.0 Hz, $CH=CHCO$), 7.08 (m, 4H, ArH), 6.97-6.92 (m, 4H, ArH), 6.81 (m, 2H, ArH), 6.29 and 6.23 (2d, 2H, J 16.0 Hz, $CH=CHCO$), 5.44 (m, 2H, H_3 and H_5), 2.40 (dd, 1H, 2J 13.9 Hz, 3J 4.3 Hz, H_2 , H_4 or H_6), 2.32 (dd, 1H, 2J 13.4 Hz, 3J 8.2 Hz, H_2 , H_4 or H_6), 1.96 (m, 4H, H_2 , H_4 or H_6); ^{13}C NMR (CD_3OD , 100 MHz, 297K) δ (ppm) = 177.4 (COOH), 171.0 (2x C_q), 168.6 and 168.5 (2xOCO), 149.4, 149.3 (2x C_q), 147.1 and 146.9 (2x $CH=CHCO$), 127.74 and 127.68 (2x C_q), 123.1, 123.0, 116.5, 116.4 (x2), 115.4, 115.2, 115.11, 115.09, 115.0 (8x CH_{Ar} + 2x $CH=CHCO$), 75.0 (C_1), 69.9, 68.7 (C_3 and C_5), 39.9, 38.6, 35.9 (C_2 , C_4 , C_6).

Conclusions

In conclusion, new analogs of 3,5-dicaffeoyl quinic acid **3** were prepared from the previously unreported 4-deoxy triol intermediate **6**. Despite reported conditions for the synthesis of natural substrates, an optimization study was required to identify new conditions leading to an efficient and repeatable synthesis of seven new dicinnamoyl conjugates. Final deprotection steps were also investigated to provide robust access to both carboxylic acid and methyl ester series. Eight compounds were evaluated in toxicity bioassays against aphids. Two compounds turned out to be growth inhibitors at lower concentrations than the natural compound, when combining both the carboxylic acid function on a pseudo quinic core and either a 3,4-dihydroxyl substitution on the two cinnamic moieties or more unexpectedly a single *p*-hydroxyl group. Moreover, the amounts ingested during our assay per insect (1 μ l/larval life to 1 mg aphid) correspond to 250 ng, and concentrations of chlorogenic acid, the biosynthetic precursor of DiCQA, was found to be about 10 mM in peach-tree leaves for example,⁶⁴ therefore significantly higher than the active 500 μ M doses illustrated here. As perspectives to this work, more specific bioassays, such as behaviour-oriented short-term bioassays,²⁷ may be realized. Confirming the activity of the synthesized compounds on other aphid species of agronomic importance could also be performed. Moreover this work paves the way to more extensive structure-activity investigations using heterodiester or other series of adducts.

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Notes and references

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Synthesis of new dicinnamoyl 4-deoxy quinic acid and methyl ester derivatives and evaluation of the toxicity against the pea aphid *Acyrtosiphon pisum*

Xiubin Li,^a Lucie Grand,^a Thomas Pouleriguen,^a Yves Queneau,^a Pedro da Silva,^b Yvan Rahbe,^b Jean-Luc Poëssel,^c Sylvie Moebis-Sanchez,^{a*}

^a Université Lyon 1, INSA Lyon, ICBMS UMR 5246 CNRS, CPE-Lyon, Equipe Chimie Organique et Bioorganique, Bâtiment Jules Verne, 20 Avenue Albert Einstein, F-69621 Villeurbanne Cedex, France
Tel : +33-(0)4 72 43 80 98 Fax : +33-(0)4 72 43 88 96

^b INSA Lyon, INRA UMR0203 BF2I, Biologie Fonctionnelle Insectes et Interactions, Bâtiment Louis Pasteur, 20 Avenue Albert Einstein, F-69621 Villeurbanne Cedex, France Tel : +33-(0)4 72 43 61 51,
Fax : +33 (0)4 72 43 85 34.

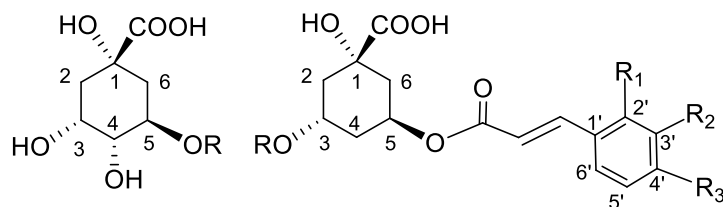
^c INRA Avignon, UR 1052, GAFL, Génétique et Amélioration des Fruits et Légumes, Domaine Saint Maurice, 67 allée des Chênes, CS 60094, 84143 Montfavet Cedex – France. Tel : +33-(0)4 32 72 26 78, Fax : +33 (0)4 32 72 27 02.

sylvie.moebis@insa-lyon.fr

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; ¹³C: 75 MHz), Bruker 400 (¹H: 400 MHz; ¹³C: 100 MHz), or Bruker 500 (¹H: 500 MHz; ¹³C: 125 MHz) spectrometers, at 295-298K, using CDCl₃ and CD₃OD as solvents. The chemical shifts (δ ppm) are referenced to the solvent residual peak and coupling constants (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. 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 as g/100 mL). Melting points were measured using Büchi apparatus B-540. Preparative HPLC was performed on Agilent equipment with a column Phenomenex C18: Jupiter® 5μm; 300 Å, LC Column 250 x 4.6mm, flow 1ml/min; Mobile phase 0 - 2min: 80% H₂O UHQ + TFA (A) / 20% CH₃CN + TFA (B); 22min: 40 % A / 60% B; 30min: 100% B; 33min: 80% A / 20% B. Samples were dissolved in MeOH (6mL) and 10μg were injected per sample.

All data for chlorogenic acids or related derivatives presented in this paper use the recommended IUPAC numbering system.¹ The assignment of NMR signals has been made according to the numbering shown in the general structure in the figure below. As much as possible an unambiguous designation of the corresponding atoms of the lateral chains has been preferred to a numbering using numerous «'» character or secondary indexation.



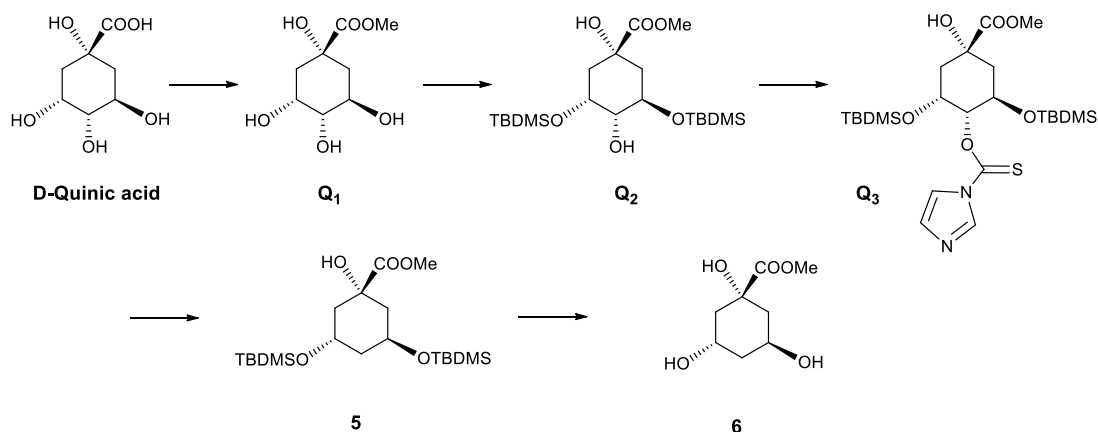
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Synthesis of compounds (4, 6, 9, 10, 11, 12)

Methyl (3S,5S)-1,3,5-trihydroxycyclohexanecarboxylate or methyl 4-deoxy quinate 6



Methyl (1S,3R,4S,5R)-1,3,4,5-tetrahydroxycyclohexanecarboxylate Q1²

Methyl (1S,3R,4S,5R)-1,4-dihydroxy-3,5-tert-butyldimethylsilyloxycyclohexanecarboxylate Q2³

Methyl (1S,3R,4S,5R)-1-hydroxy-4-[(1H-imidazol-1-ylcarbothioyl)oxy]-3,5-tert-butyldimethylsilyloxy cyclohexanecarboxylate Q3⁴

Q1, Q2, Q3 were prepared according reported procedures.

The disilylated compound **5**⁵ (106.7 mg, 0.25 mmol) was stirred in MeOH (2mL) with Amberlyst® A15 (H⁺ form) at room temperature for 24h. After filtration and evaporation, the crude product was purified by flash chromatography (pentane/ethyl acetate 50/50 then ethyl acetate/methanol 90/10) to provide **6** (colorless oil then white solid on standing, 42.7 mg, 89%). $[\alpha]_D^{25} - 3.7$ (c 1.06, CH₃OH); IR(ATR) 3350, 2951, 2930, 2855, 1173, 1730, 1661, 1435, 1371, 1281, 1240, 1134, 1057, 1016 cm⁻¹; ¹H NMR (400 MHz, 296K, CD₃OD) δ (ppm) = 4.24-4.16 (m, 2H, H₃ and H₅), 3.73 (s, 3H, OMe), 2.08 (dd, 1H, ²J 13.8 Hz, ³J_{H₅/H₆} 3.3 Hz, H₆ or H₂), 2.00 (m, 2H, H₂ or H₆ and H₄), 1.88 (dd, 1H, ²J 12.8 Hz, ³J 9.1 Hz, H₂ or H₆), 1.77 (dd, 1H, ²J 13.8 Hz, ³J 4.8 Hz, H₆ or H₂), 1.60 (ddd, 1H, ²J 12.7 Hz, ³J_{H_{4a}/H_{5a} ou 3a} 9.2 Hz, ³J_{H_{4a}/H_{3e} ou H_{5e}} 3.0 Hz, H_{4a}); ¹³C NMR (CD₃OD, 295K, 100MHz) δ (ppm) 176.1 (COOMe),

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76.8 (C₁), 67.8 (C₅ or C₃), 64.0 (C₃ or C₅), 52.8 (OMe), 43.8 (C₂ or C₆), 42.0 (C₄), 40.3 (C₆ or C₂). MS-ESI m/z [M+Na]⁺ 213.1; HRMS-ESI m/z [M+Na]⁺ calcd for C₈H₁₄NaO₅ 213.0733; found 213.0733.

General procedure for the synthesis of homodiesters of deoxy methyl quinate **9**

Procedure A :

To a solution of triol **6** in DMF / pyridine (v/v 3/2, c = 0.4M) under nitrogen was added the protected cinnamoyl chloride (3 equiv.) The mixture was stirred at 45°C until completion, in general after 1h. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated NaHCO₃ solution then with brine. The organic layer was dried over Na₂SO₄, concentrated and purified by flash chromatography on silica using the appropriate eluent.

Procedure B :

To a solution of triol **6** in DMF / pyridine (v/v 3/2, c = 0.4M) under nitrogen was added the protected cinnamoyl chloride (3 equiv.) The mixture was stirred at 0°C until completion, in general after 4h. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated NaHCO₃ solution then with brine. The organic layer was dried over Na₂SO₄, concentrated and purified by flash chromatography on silica using the appropriate eluent.

Procedure C :

To a solution of triol **6** in dichloromethane / pyridine (v/v 5/1, c = 0.1M) under nitrogen was added the protected cinnamoyl chloride (3 equiv.) and DMAP (20 mol%). The mixture was stirred at -18°C to room temperature until completion, in general after 4h. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated NaHCO₃ solution then with brine. The organic layer was dried over Na₂SO₄, concentrated and purified by flash chromatography on silica using the appropriate eluent.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate **9a**

Synthesized according to the general procedure B using diacetylated caffeoyl chloride⁶ and methyl 4-deoxy quinate **6** (105 mg, 0.553 mmol). **9a** was obtained as a white solid (348 mg, yield: 92%) after purification by flash chromatography on silica using DCM/Et₂O 12/1 to 6/1.

$[\alpha]_D^{25} = -46.9$ (c 1.215, CH₂Cl₂) ; m.p. = 92.8-94.1°C (CH₂Cl₂); IR(ATR) 2943, 2832, 1775, 1742, 1713, 1639, 1504, 1449, 1427, 1371, 1321, 1242, 1205, 1180, 1147, 1132, 1111, 1022 cm⁻¹; ¹H NMR (CDCl₃, 298K, 500MHz) δ (ppm) = 7.63 and 7.58 (2d, 2H, ³J 15.9 Hz, CH=CHCO), 7.39 and 7.38 (2dd, 2H, J_{ortho} 8.4Hz, J_{meta} 1.9 Hz, 2xH_{6'}), 7.35 and 7.34 (2d, 2H, J_{meta} 1.9 Hz, 2xH_{2'}), 7.20 (d, 2H, J_{ortho} 8.4 Hz, 2xH_{5'}), 6.40 and 6.32 (2d, 2H, ³J 15.9 Hz, CH=CHCO), 5.51 (ddd, 1H, ²J 13.8 Hz, ³J 9.8

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Hz, 3J 3.9 Hz, H₃ ou 5_{ax}), 5.46 (ddd, 1H, 3J 7.8 Hz, 3J 3.9 Hz, H_{3e} ou 5_e), 3.76 (s, 1H, OH₁), 3.74 (s, 3H, COOMe), 2.28, 2.271 and 2.268 (3s, 12H, OCOCH₃), 2.32 (m, 1H, H₄), 2.23-2.18 (m, 2H, H₂ and H₆), 2.08-2.00 (m, 2H, H₂ and H₆), 1.87 (ddd, 1H, 2J 13.6 Hz, 3J 10.3 Hz, 3J 3.45 Hz, H_{4a}); ^{13}C NMR (CDCl₃, 298K, 125 MHz) δ (ppm) = 175.0, 168.1(2) and 168.0(2) (4xOCOCH₃), 165.8 and 165.5 (2xCOO), 143.59 and 143.57 (C_q), 143.3 and 143.2 (CH=CHCO), 142.5 and 142.4 (C_q), 133.2 and 133.1(C_q), 126.5 and 126.4 (C_{6'}), 124.0 and 123.9 (C_{5'}), 122.9 and 122.8 (C_{2'}), 119.4 and 119.2 (CH=CHCO), 74.7 (C₁), 68.9 (C₃ ou C₅), 66.9 (C₅ ou C₃), 53.1 (OMe), 39.7 (C₂ ou C₆), 36.7 (C₂ ou C₆), 35.0 (C₄), 20.7(2), 20.62 and 20.60 (4x OCOCH₃); HRMS-ESI m/z [M+Na]⁺ calcd for C₃₄H₃₄NaO₁₅ 705.1790; found 705.1780.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-di-(prop-2-en-1-yloxy)phenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9b

Synthesized according to the general procedure A using diallylated caffeoyl chloride.⁷ and **6** (102 mg, 0.537 mmol) Purification by flash chromatography on silica using petroleum ether/EtOAc 50/50, providing the triester (51mg, 10%) and diester **9b** (214 mg, 59%) as white solids.

$[\alpha]_D^{25}$ - 140.8 (c 0.86, CH₂Cl₂); $[\alpha]_D^{23}$ m.p. 89-91°C; IR(ATR) 2922, 2827, 1706, 1631, 1597, 1510, 1456, 1423, 1362, 1335, 1304, 1246, 1223, 1165, 1134, 1090, 1067 cm⁻¹; 1H NMR (CDCl₃, 298K, 300MHz) δ (ppm) = 7.63 and 7.58 (2d, 2H, 3J 15.9 Hz, CH=CHCO), 7.08 (m, 4H, CH_{Ar}), 6.87 (m, 2H, CH_{Ar}), 6.31 and 6.23 (2d, 2H, 3J 15.9 Hz, CH=CHCO), 6.07 (m, 4H, CH₂=CHCH₂O), 5.60-5.50 (m, 2H, H₃ and H₅), 5.42-5.39 (m, 2H, CH₂anti=CHCH₂O), 5.30 (m, 4H, CH₂syn =CHCH₂O), 4.64 (m, 8H, CH₂=CHCH₂O), 2.32 (m, 1H, H₂ or H₄ or H₆), 2.24-2.02 (m, 4H, H₂ or H₄ or H₆), 1.86 (ddd, 1H, J 13.7 Hz, J 10.4 Hz, J 3.4 Hz, H₂ or H₄ or H₆); ^{13}C NMR (CDCl₃, 296K, 75 MHz) δ (ppm) = 175.1 (COOMe), 166.5 and 166.3 (OCO), 150.8 (2xC_q), 148.7 (2xC_q), 145.4 and 145.1(CH=CHCO), 133.2 133.1, 133.05 and 133.01 (4xCH₂=CHCH₂O), 127.64, 127.57 (2xC_q), 123.2 and 122.9 (2xCHAr), 118.15, 118.11, 118.1, 118.07 (4xCH₂=CHCH₂O), 115.88 and 115.84 (CH=CHCO), 113.50, 113.44, 112.7 and 112.5 (4xCHAr), 75.0 (C₁), 70.1, 70.0, and 69.8(2) (4xCH₂=CHCH₂O), 68.8 and 66.6 (C₃ and C₅), 53.2(OMe), 40.0, 36.9 and 35.2 (C₂, C₄ and C₆); HRMS-ESI m/z [M+Na]⁺ calcd for C₃₈H₄₂NaO₁₁ 697.2619; found 697.2615.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9c

Synthesized according to the general procedure C using acetylated feruloyl chloride and methyl 4-deoxy quinate **6** (117 mg, 0.616 mmol). **9c** was obtained as a white solid (266 mg, yield: 69%) after purification by flash chromatography on silica using DCM/Et₂O 10/1.

$[\alpha]_D^{25}$ = - 74.5 (c 1.05, CH₂Cl₂); $[\alpha]_D^{23}$ m.p. 90-92°C; IR(ATR) 1765, 1709, 1638, 1508, 1464, 1418, 1369, 1298, 1263, 1215, 1198, 1153, 1123, 1033, 1011 cm⁻¹; 1H NMR (CDCl₃, 296K, 300MHz) δ (ppm) = 7.65 and 7.60 (2d, 2H, 3J 15.9 Hz, CH=CHCO), 7.12-7.02 (m, 6H, CH_{Ar}), 6.41 and 6.33 (2d, 2H, 3J 15.9 Hz, CH=CHCO), 5.55 and 5.49 (2m, 3J 9.3 Hz, 3J 3.3 Hz, H₅ and H₃), 3.85 and 3.84 (2s, 2x3H, 2xOMe), 3.76 (s, 3H, COOMe), 2.30(s, 6H, 2xOAc), 2.28 (m, 1H, H_{4e}), 2.22-2.18 and 2.11-

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2.04(m, 2x2H, 2xH₆ and 2xH₂), 1.88 (ddd, 1H, ²J 13.6 Hz, ³J 10.4 Hz, ³J 3.4 Hz, H₄); ¹³C NMR (CDCl₃, 295K, 100 MHz) δ (ppm) = 175.0 (COOMe), 168.8 (2xOCOCH₃), 166.1 and 165.8 (COO), 151.4 (2xC_q), 144.6 and 144.4 (CH=CHCO), 141.54 and 141.51 (C_q), 133.34 and 133.30 (C_q), 123.33 and 123.25(CHAr), 121.6 and 121.3 (CHAr), 118.3 and 118.2 (CH=CHCO), 111.3 and 111.1 (CHAr), 74.8 (C₁), 68.9 (C₃ or C₅), 66.8 (C₅ or C₃), 56.0(2xOMe), 53.1 (COOMe), 39.8 and 36.8 (C₆ and C₂), 35.1 (C₄), 20.7 (2xOCOCH₃); HRMS-ESI m/z [M+Na]⁺ calcd for C₃₂H₃₄NaO₁₃ 649 649.1892; found 649.1865.

Methyl (3S,5S) 1-hydroxy-3,5 bis[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9d

Synthesized according to the general procedure A using acetylated *para*-coumaroyl chloride ⁸ and methyl 4-deoxy quinate **6** (58mg, 0.305 mmol). **9d** was obtained as a white solid (142 mg, yield: 82%) after purification by flash chromatography on silica using DCM/Et₂O 10/1. [α]_D²⁵ -79.4 (c 0.83, CH₂Cl₂); m.p. 86-88°C; IR(ATR) 1765, 1736, 1709, 1638, 1601, 1506, 1418, 1369, 1312, 1265, 1202, 1163, 1140, 1086, 1063, 1011 cm⁻¹; ¹H NMR (CDCl₃, 295K, 400MHz) δ (ppm) = 7.67 and 7.62 (2d, 2H, ³J 16.0 Hz, CH=CHCO), 7.52 and 7.50 (2d, 4H, *J*_{ortho} 8.5 Hz, H₂'), 7.10 (2d, 4H, *J*_{ortho} 8.5 Hz, H₃'), 6.41 and 6.33 (2d, 2H, ³J 16.0 Hz, CH=CHCO), 5.53 and 5.48 (2 m, 2H, ³J 4.0 Hz, H₃ and H₅), 3.74 (s, 3H, COOMe), 2.27 (s, 6H, OAc), 2.24 (m, 1H, H₄), 2.23-2.19 (m, 2H, H₂ and H₆), 2.11-2.06 (m, 2H, H₂ and H₆), 1.88 (ddd, 1H, ²J 13.0 Hz, ³J 10.2 Hz, ³J 3.5 Hz, H₄); ¹³C NMR (CDCl₃, 295K, 100 MHz) δ (ppm) = 174.9 (COOMe), 169.2 (2xOCOCH₃), 166.1 and 165.8 (COO), 152.2 and 152.1 (C_q), 144.1 and 144.0 (CH=CHCO), 132.1 and 132.0 (2xCHAr), 129.4 and 129.3 (2xCHAr), 122.2 and 122.1 (C_q), 118.3 and 118.1 (CH=CHCO), 74.7 (C₁), 68.8 and 66.8 (C₃ and C₅), 53.0 (OMe), 39.7 and 36.8 (C₂ and C₆) 35.0 (C₄) 21.1 (2xCH₃); HRMS-ESI m/z [M+Na]⁺ calcd for C₃₀H₃₀NaO₁₁ 589.1680; found 589.1655.

Methyl (3S,5S) 1-hydroxy-3,5 bis[(2E)-3-(2-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9e

Synthesized according to the general procedure A using acetylated *ortho*-coumaroyl chloride and methyl 4-deoxy quinate **6** (82 mg, 0.432 mmol). Purification by flash chromatography (DCM/Et₂O 10/1) afforded **9e** as a white solid (152 mg, yield: 62%)

[α]_D²⁵ - 50.0 (c 1.12, CH₂Cl₂); m.p. 87-90°C; IR(ATR) 1763, 1711, 1638, 1483, 1454, 1437, 1371, 1315, 1265, 1198, 1179, 1140, 1094, 1063, 1009 cm⁻¹; ¹H NMR (CDCl₃, 296K, 300MHz) δ (ppm) = 7.81 and 7.73 (2d, 2H, *J* 16.1 Hz, CH=CHCO), 7.63 (dd, 2H, *J* 7.9 Hz, H ortho), 7.40 (dd, 2H, *J* 7.40 Hz, H meta OAc), 7.25 (dd, 2H, *J* 7.6 Hz, H para OAc), 7.11 (d, 3H, *J* 8.1 Hz, H orthoOAc), 6.46 and 6.40 (2d, 2H, *J* 16.1 Hz, CH=CHCO), 5.53 (m, 2H, H₃ and H₅), 3.75 (s, 3H, COOMe), 2.40 and 2.38 (2s, 2x3H, 2xOAc), 2.29-2.19 (m, 3H, H-2, H-4, H₆), 2.13-2.02 (m, 2H, H-2, H-6), 1.90 (ddd, 1H, ²J 13.5 Hz, ³J 10.0 Hz, ³J 3.4 Hz, H-4); ¹³C NMR (CDCl₃, 295K, 100 MHz) δ (ppm) = 175.0 (COOMe), 169.45 and 169.40 (OCOCH₃), 165.8 and 165.6 (COO), 149.4(2xC_q), 138.56 and 138.50

⁸ R. F. Helm, J. Ralph and R. D. Hatfield, *Carbohydr. Res.*, 1992, **229**, 183-194.

($\underline{\text{C}}\text{H}=\text{CHCO}$), 131.34 and 131.30 ($\text{C}_{4'}$), 127.6 and 127.5 ($\text{C}_{6'}$), 127.1 and 127.0 (C_q), 126.44 and 126.41 ($\text{C}_{5'}$), 123.26 and 123.20 ($\text{C}_{3'}$), 120.2 and 120.1 ($\text{CH}=\underline{\text{C}}\text{HCO}$), 74.6 (C_1), 68.8 (C_3 or C_5), 67.0 (C_5 or C_3), 53.2 (COOMe), 39.7 and 36.9 (C_6 and C_2), 35.1 (C_4), 21.0 ($2 \times \text{OCOCH}_3$); HRMS-ESI m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{30}\text{H}_{30}\text{NaO}_{11}$ 589.1680; found 589.1669.

General procedure for the deprotection of aromatic acetates

Procedure D⁹ : To a solution of compound **9** (a, c, d or e) in ethanol/water (2/1, 0.12M) was added hydrazine acetate (NaOAc, 20 eq). After stirring at reflux for 1 h, the mixture was diluted with EtOAc, washed with brine then the organic layer was dried over MgSO_4 , concentrated and purified by flash chromatography.

Procedure E¹⁰ : To a solution of compound **9** (a, c, d or e) in DMF (0.15M) was added hydrazine acetate (75equiv.). After stirring at room temperature for 1 h, the mixture was diluted with EtOAc, washed with brine then the organic layer was dried over MgSO_4 , concentrated and purified by flash chromatography.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate **10a**

To a solution of **9a** (116mg, 0.170 mmol) in DMF (0.9 mL) was added hydrazine acetate (71 mg, 0.64 mmol). After stirring at room temperature for 1 h, the mixture was diluted with EtOAc (50 mL), washed with brine (30 mL x 3) then the organic layer was dried over MgSO_4 , concentrated and purified by flash chromatography (CH_2Cl_2 / CH_3OH 40 / 1) to provide **10a** as a colorless oil (78 mg, 89%). $[\alpha]_D^{25}$ - 167.0 (c 0.64, CH_3OH); IR(ATR) 3323, 3304, 3285, 3275, 2949, 2835, 1680, 1630,

1599, 1516, 1443, 1373, 1256, 1159, 1140, 1119, 1067, 1016 cm^{-1} ; ^1H NMR (CD_3OD , 298K, 500 MHz) : δ ppm = 7.58 and 7.52 (d, 2H, 3J 15.8 Hz, $\underline{\text{C}}\text{H}=\text{CHCO}$), 7.06 (bs, 2H, Ar- $\text{H}_{2'}$), 6.95 (dt, 2H, $J_{\text{ortho}} = 8.1$, $J_{\text{meta}} 2.3$ Hz, Ar- $\text{H}_{6'}$), 6.80 (dd, 2H, $J_{\text{ortho}} 8.2$ Hz, $J_{\text{meta}} 2.7$ Hz, Ar- $\text{H}_{5'}$), 6.28 and 6.19 (d, 2H, 3J 15.9 Hz, $\text{CH}=\underline{\text{C}}\text{HCO}$), 5.42 (m, 2H, H_3 and H_5), 3.70 (s, 3H, OMe), 2.46 (dd, 1H, 2J 13.4 Hz, 3J 3.5 Hz, H_2 or H_6), 2.39 (dd, 1H, 2J 13.6 Hz, 3J 6.9 Hz, H_2 or H_6), 2.06 (m, 1H, H_4), 1.97 (m, 2H, H_4 and H_2 or H_6), 1.86 (dd, 1H, 2J 13.4 Hz, 3J 7.7 Hz, H_2 or H_6); ^{13}C NMR (CD_3OD , 298K, 125 MHz) δ (ppm) = 175.7 (COOMe), 168.5 (OCO), 168.0 (OCO), 149.6 (C_q), 149.5 (C_q), 147.2 and 147.0 ($\underline{\text{C}}\text{H}=\text{CHCO}$), 146.8 (C_q), 146.7 (C_q), 127.7 (C_q), 127.6 (C_q), 123.04 and 123.00 ($\text{C}_{6'}$), 116.53 and 116.50 ($\text{C}_{5'}$), 115.4 and 115.1 ($\text{OCOCH}=\underline{\text{C}}\text{H}$), 115.09 and 115.00 ($\text{C}_{2'}$), 75.0 (C_1), 69.5 and 69.0 (C_3 and C_5), 53.0 (OMe), 39.7, 39.3 and 35.9 ($3 \times \text{CH}_2$, C_2 , C_6 and C_4); HRMS-ESI m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{26}\text{NaO}_{11}$ 537.1367; found 537.1351.

⁹ T. Narendar, K. P. Reddy and G. Madhur, *Synthetic Commun.*, 2009, **39**, 1949-1956.

¹⁰ Y. M. Zhu, M. Regner, F. C. Lu, H. Kim, A. Mohammadi, T. J. Pearson and J. Ralph, *RSC Adv.*, 2013, **3**, 21964.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[2E)- 3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10c

The general procedure E for the deprotection of aromatic acetates was performed with **9c** (65 mg, 0.104 mmol) in DMF (0.45 mL) and hydrazine acetate (43 mg, 0.47 mmol) providing after purification **10c** as a colorless oil (50 mg, 89%). $[\alpha]_D^{25}$ - 170.0 (*c* 0.93, CH₃OH); IR(ATR) 3516, 3057, 2957, 2941, 1701, 1631, 1593, 1512, 1462, 1454, 1429, 1377, 1263, 1207, 1157, 1138, 1032, 1009 cm⁻¹; ¹H NMR (CD₃OD, 400 MHz) : δ ppm = 7.63 and 7.57 (d, 2H, ³*J* 15.9 Hz, CH=CHCO), 7.12 (bs, 2H, Ar-H), 7.07 (dd, 2H, *J*_{ortho} 8,2 Hz, *J*_{meta} 2,7 Hz, Ar-H), 6.81 (dd, 2H, *J*_{ortho} 8,2 Hz, *J*_{meta} 2,2 Hz, Ar-H), 6.38 and 6.29 (d, 2H, ³*J* 15.9 Hz, CH=CHCO), 5.432 (m, 2H, H₃ and H₅), 3.88 (s, 6H, 2x OMe), 3.70 (s, 3H, COOMe), 2.45 (dd, 1H, ²*J* 13.6 Hz, ³*J* 4.1 Hz, H₂ or H₆), 2.38 (dd, 1H, ²*J* 13.6 Hz, ³*J* 7.2 Hz, H₂ or H₆), 2.14-1.97 (m, 3H, 2x H₄ and H₂ or H₆), 1.88 (dd, 1H, ²*J* 13.6 Hz, ³*J* 7.5 Hz, H₂ or H₆); ¹³C NMR (CD₃OD, 100 MHz) δ (ppm) = 175.7 ((COOMe), 168.4 and 168.0 (OCO), 150.7, 150.6, 149.4, 149.3 (C_q Ar), 147.1 and 147.0 (CH=CHCO), 127.7 and 127.5 (C_q Ar), 124.2 and 124.1 (CH_{Ar}), 116.5 and 116.4 (CH_{Ar}), 115.7 and 115.4 (OCOCH=CH), 111.6 (CH_{Ar}), 75.0 (C₁), 69.5 and 69.0 (C₅ or C₃), 56.4(2) (2xOCH₃), 53.0 (COOMe), 39.8 and 39.2 (C₂ or C₆), 35.9 (C₄); HRMS-ESI *m/z* [M+Na]⁺ calcd for C₂₈H₃₀NaO₁₁ 65.1680; found 65.1662.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10d

The general procedure E for the deprotection of aromatic acetates was performed with **9d** (80 mg, 0.14 mmol) in DMF (0.6 mL) and hydrazine acetate (59 mg, 0.64 mmol) providing after purification (CH₂Cl₂ / CH₃OH 40 / 1) a colorless oil (62 mg, 91%). $[\alpha]_D^{25}$ - 174.7 (*c* 0.95, CH₃OH); IR(ATR) 3325, 3308, 3279, 3267, 2947, 2832, 1688, 1632, 1603, 1587, 1514, 1441, 1371, 1325, 1307, 1254, 1202, 1165, 1144, 1103, 1065, 1018 cm⁻¹; ¹H NMR (CD₃OD, 400 MHz) : δ (ppm) = 7.65 and 7.59 (2d, 2H, ³*J* 15.9 Hz, 2x CH=CHCO), 7.47 (d, 4H, *J*_{ortho} 8.6 Hz, Ar-H), 6.81 (dd, 4H, *J*_{ortho} 8.6 Hz, *J*_{meta} 1.8 Hz Ar-H), 6.34 and 6.26 (d, 2H, ³*J* 15.9 Hz, CH=CHCO), 5.43 (m, 2H, H₃ and H₅), 3.69 (s, 3H, OMe), 2.46 (dd, 1H, ²*J* 13.4 Hz, ³*J* 4.1 Hz, H₂, H₄ or H₆), 2.40 (dd, 1H, ²*J* 13.7 Hz, ³*J* 7.0 Hz, H₂, H₄ or H₆), 2.10-1.95 (m, 3H, H₂, H₄ or H₆), 1.87 (dd, 1H, ²*J* 13.4 Hz, ³*J* 7.6 Hz H₂, H₄ or H₆). ¹³C NMR (CD₃OD, 100 MHz) δ (ppm) = 175.7 (COOMe), 168.5(OCO), 168.0(OCO), 161.4 (C_q), 161.3 (C_q), 146.8 and 146.7 (2xCH=CHCO), 131.23 and 131.20 (2x2xCH), 127.2 and 127.0 (2xC_q), 116.9, 116.8 (2x2 CH), 115.5 and 115.1 (2x OCOCH=CH), 75.0 (C₁), 69.5, 69.0 (C₃ and C₅), 53.0 (OMe), 39.8, 39.3 and 35.9 (3xCH₂, C₂, C₆ and C₄). HRMS-ESI *m/z* [M+Na]⁺ calcd for C₂₆H₂₆NaO₉ 505.1469; found 505.1452.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[2E)-3-(2-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10e

The general procedure E for the deprotection of aromatic acetates was performed with **9e** (118 mg, 0.21 mmol) in DMF (0.9 mL) and hydrazine acetate (88 mg, 0.96 mmol) providing after purification (CH₂Cl₂ / CH₃OH 40 / 1) a colorless oil (89 mg, 89%). $[\alpha]_D^{25}$ - 104.3 (*c* 1.00, CH₃OH); IR(ATR) 3337, 3298, 3283, 3256, 2945, 2835, 1688, 1626, 1603, 1499, 1458, 1369, 1317, 1294, 1254, 1169, 1146, 1113, 1067, 1018 cm⁻¹; ¹H NMR (CD₃OD, 400 MHz) : δ ppm = contaminated with chloroform at 7.90 ppm, 8.00 and 7.91 (2d, 2H, ³*J* 16.1 Hz, CH=CHCO), 7.48 (pseudo t, 2H, *J*_{ortho} 8,2 Hz Ar-H),

7.21 (pseudot, 2H, J_{ortho} 7.4 Hz Ar-H), 6.84 (m, 4H, Ar-H), 6.63 and 6.58 (d, 2H, 3J 16.1 Hz, CH=CHCO), 5.45 (m, 2H, H₃ and H₅), 3.72 (s, 3H, OMe), 2.49 (dd, 1H, 2J 13.4 Hz, 3J 3.6 Hz, H₂, H₄ or H₆), 2.43 (dd, 1H, 2J 13.8 Hz, 3J 6.8 Hz, H₂, H₄ or H₆), 2.15-2.09 (m, 1H, H₂, H₄ or H₆), 2.00-1.96 (m, 2H, H₂, H₄ or H₆), 1.86 (dd, 1H, 2J 13.3 Hz, 3J 7.9 Hz, H₂, H₄ or H₆). ¹³C NMR (CD₃OD, 100 MHz) δ (ppm) = contaminated with chloroform at 79.4 ppm; 175.7 (COOMe), 168.8(OCO), 168.4(OCO), 158.5 and 158.3 (2xC_q), 142.9 and 142.5 (2xCH=CHCO), 132.7, 132.6, 130.6, 130.2 (4xCH_{Ar}), 122.6, 122.5 (2xC_q), 120.8 (2xCH_{Ar}), 118.6, 118.5 (2x OCOCH=CH), 117.0 (2xCH_{Ar}), 79.4, 75.0 (C₁), 69.5, 69.1 (C₃ and C₅), 53.0 (OMe), 39.8, 39.4 and 35.9 (3xCH₂, C₂, C₆ and C₄). HRMS-ESI m/z [M+Na]⁺ calcd for C₂₆H₂₆NaO₉ 505.1469; found 505.1448.

(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4a

LiI (143 mg, 1.07 mmol) was added to a solution of **9a** (146 mg, 0.214 mmol) in EtOAc (1.1 mL) then the mixture was heated under reflux overnight. After cooling down to room temperature, the mixture was diluted with EtOAc (30 mL), washed with 1M HCl (2x 10 mL) and extracted with EtOAc (3x30mL). The organic layer was dried over MgSO₄, concentrated to give the crude (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11a** (128 mg, crude yield: 90%), pure enough for characterization and used directly in the following step. IR(ATR) 3370, 2941, 2833, 1769, 1707, 1638, 1504, 1369, 1240, 1201, 1174, 1143, 1109, 1012 cm⁻¹; ¹H NMR (CD₃OD, 298K, 400 MHz) : δ ppm = 7.67 and 7.62 (2d, 2H, J 16.0 Hz, CH=CHCO), 7.50 (m, 2H, H₆'), 7.49 (m, 2H, H₂'), 7.24 (d, 2H, J_{ortho} 8.2 Hz, H₅'), 6.52 and 6.46 (2d, 2H, J 16.0 Hz, CH=CHCO), 5.46 (m, 2H, H₃ and H₅), 2.44-2.19 (m, 14H) and 2.06-1.90 (m, 4H, 3xCH₂ and 4xOCOCH₃); ¹³C NMR (CD₃OD, 298K, 100 MHz) δ (ppm) = 177.3 (COOH), 169.8 and 169.7 (4x OCOCH₃), 167.5 and 167.2 (2xOCO), 145.2 and 145.1 (2xC_q), 144.5 and 144.4 (2xCH=CHCO), 144.0 (2xC_q), 134.60 and 134.56 (2xC_q), 127.7 and 127.6 (2xC₆'), 125.13 and 125.11 (2xC₅'), 124.14 and 124.09 (C₂'), 120.45 and 120.13 (2x CH=CHCO), 75.0 (C₁), 70.2, 69.2 (C₃ and C₅), 39.9, 38.7, 35.9 (C₂, C₄, C₆), 20.5 (4XOCOCH₃). HRMS-ESI m/z [M+H]⁺ calcd for C₃₃H₃₃O₁₅ 669.1814; found 669.1801.

To a solution of (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11a** (208 mg) in acetone (4.08 mL) was added 3M HCl aqueous solution (2.0mL) and the mixture was refluxed for 5h. After completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was concentrated to give the crude quantitatively as a pale solid **4a** (190 mg).

$[\alpha]_D^{25}$ - 42.7 (c 0.82, CH₃OH); ¹H NMR (CD₃OD, 400 MHz, 295K) : IR(ATR) 3345, 3210, 1687, 1603, 1523, 1445, 1362, 1279, 1182, 1138, 1119 cm⁻¹; δ (ppm) = 7.65 and 7.60 (2d, 2H, J 16.0 Hz, CH=CHCO), 7.45 (m, 4H, ArH), 6.81 (m, 4H, ArH), 6.34 and 6.27 (2d, 2H, J 16.0 Hz, CH=CHCO), 5.45 (m, 2H, H₃ and H₅), 2.41 (dd, 1H, 2J 14.0 Hz, 3J 3.8 Hz, H₂, H₄ or H₆), 2.32 (dd, 1H, 2J 13.3 Hz, 3J 8.2 Hz, H₂, H₄ or H₆), 2.06 (m, 3H, H₂, H₄ or H₆), 1.93 (dd, 1H, 2J 13.8 Hz, 3J 6.5 Hz, H₂, H₄ or H₆); ¹³C NMR (CD₃OD, 100 MHz, 297K) δ (ppm) = 177.4 (COOH), 171.0 (2xC_q), 168.5 and 168.3 (2xOCO), 161.12 and 161.07 (2xC_q), 146.7 and 146.7 (2xCH=CHCO), 131.2, 131.1 (2xCH_{Ar}), 127.1

(2xC_q), 116.8 (4xCH_{Ar}), 115.5, 115.1 (2x CH=CHCO), 75.1 (C₁), 69.9, 68.7 (C₃ and C₅), 39.9, 38.6, 35.9 (C₂, C₄, C₆).

(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **4c**

LiI (152 mg, 1.135 mmol) was added to a solution of **9c** (142 mg, 0.2274 mmol) in EtOAc (5.0 mL) then the mixture was heated under reflux 24h. After cooling down to room temperature, the mixture was diluted with EtOAc (25 mL), washed with 3M HCl (5 mL) and extracted with EtOAc (3x30mL). The organic layer was dried over MgSO₄, concentrated to give the crude (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11c** (quantitative crude yield), pure enough for characterization and used directly in the following step.

[α]_D²⁵ - 97.5 (c 0.96, CH₃OH); IR(ATR) 3466, 2941, 2833, 1763, 1705, 1599, 1508, 1464, 1454, 1418, 1369, 1256, 1215, 1177, 1152, 1063, 1020 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) : δ (ppm) = 7.66 and 7.61 (2d, 2H, ³J 15.9 Hz, CH=CHCO), 7.13-7.03 (2m, 6H, Ar-H), 6.41 and 6.34 (2d, 2H, ³J 15.9 Hz, CH=CHCO), 5.50 (m, 2H, H₃ and H₅), 3.87 and 3.85 (2s, 2x3H, 2xOMe), 2.33-1.83 (m, 12H, H₂, H₄, H₆ and 2xOCOCH₃); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) = 176.7 (COOH), 169.04 and 169.02 (2xOCOCH₃), 166.1 and 166.0 (2xCOO), 151.53 and 151.50 (2xC_q), 145.3, 144.8 (2xCH=CHCO), 141.7, 141.6 (2xC_q), 133.3, 133.2 (2xC_q), 123.4 (2xCH_{Ar}), 121.8, 121.4 (2x CH=CHCO), 118.1, 117.9 (2xCH_{Ar}), 111.4, 111.3(2xCH_{Ar}), 75.2(C₁), 69.4, 66.5 (C₃ and C₅), 56.1, 56.0 (2xOMe), 39.3, 36.5, 34.9 (C₂, C₄, C₆), 20.8 (2xOCOCH₃); HRMS-ESI m/z [M+Na]⁺ calcd for C₃₁H₃₂NaO₁₃ 635.1735; found 635.1706.

To a solution of (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11c** (176 mg) in acetone (3.0 mL) was added 3M HCl aqueous solution (1.5 mL) and the mixture was refluxed for 4h. After completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was concentrated then dissolved in MeOH/H₂O (30/40 mL) and washed with pentane (2x 15mL). After concentration, the crude was obtained as a pale solid **4c** (150mg).

[α]_D²⁵ - 94.4 (c 0.67, CH₃OH); IR(ATR) 3356, 3277, 1684, 1632, 1605, 1514, 1443, 1327, 1261, 1204, 1171, 1138, 1007 cm⁻¹; ¹H NMR (CD₃OD, 300 MHz, 297K) : δ (ppm) 7.65 and 7.60 (2d, 2H, J 15.9 Hz, CH=CHCO), 7.17 (m, 2H, ArH), 7.07 (m, 2H, ArH), 6.83 (d, 2H, J_{ortho} 8.1 Hz, ArH), 6.39 and 6.32 (2d, 2H, J 15.9 Hz, CH=CHCO), 5.47 (m, 2H, H₃ and H₅), 3.89 (s, 6H, 2xOMe), 2.42 (dd, 1H, ²J 13.9 Hz, ³J 4.0 Hz, H₂, H₄ or H₆), 2.34 (dd, 1H, ²J 13.4 Hz, ³J 8.2 Hz, H₂, H₄ or H₆), 2.00 (m, 4H, H₂, H₄ or H₆); ¹³C NMR (CD₃OD, 75 MHz, 297K) δ (ppm) = 177.4 (COOH), 170.9 (2xC_q), 168.5 and 168.2 (2xOCO), 150.44, 150.38 (2xC_q), 146.9 and 146.8 (2xCH=CHCO), 127.74 and 127.68 (2xC_q), 124.1, 124.0, 123.9, 116.4, 115.8, 115.5 (6x CH_{Ar}), 111.7 and 111.6 (2x CH=CHCO), 75.1 (C₁), 69.9, 68.7 (C₃ and C₅), 56.43 and 56.41 (2xOMe), 40.0, 38.7, 36.0 (C₂, C₄, C₆).

(3S,5S) 1-hydroxy-3,5 bis[[2(E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4d

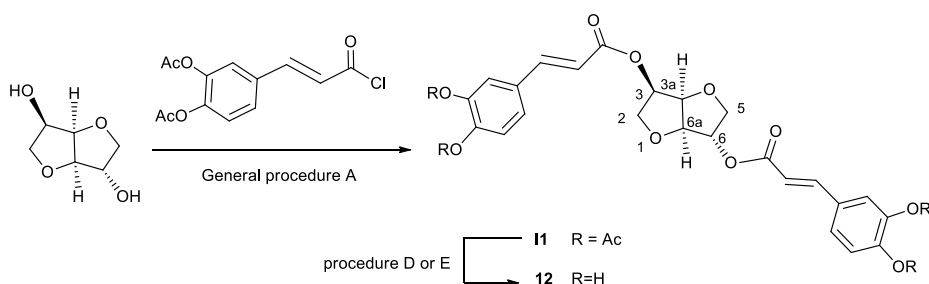
LiI (125 mg, 0.934 mmol) was added to a solution of **9d** (105 mg, 0.186 mmol) in EtOAc (4.0 mL) then the mixture was heated under reflux 24h. After cooling down to room temperature, the mixture was diluted with EtOAc (25 mL), washed with 3M HCl (5 mL) and extracted with EtOAc (3x30mL). The organic layer was dried over MgSO₄, concentrated to give the crude (3S,5S) 1-hydroxy-3,5 bis[[2(E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11d** (quantitative crude yield), pure enough for characterization and used directly in the following step. $[\alpha]_D^{25}$ - 111.9 (c 1.03, CH₃OH); IR(ATR) 3447, 3059, 2961, 1765, 1707, 1601, 1585, 1506, 1418, 1369, 1312, 1265, 1202, 1163, 1136, 1057, 1009 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) : δ ppm = 7.68 and 7.62 (2d, 2H, ³J 15.9 Hz, CH=CHCO), 7.52 (dd, 4H, *J*_{ortho} 8,6 Hz, *J*_{ortho} 6.8 Hz, Ar-H), 7.11 (dd, 4H, *J*_{ortho} 8,6 Hz, *J*_{meta} 2.0 Hz, Ar-H), 6.41 and 6.34 (2d, 2H, ³J 15.9 Hz, CH=CHCO), 5.49 (m, 2H, H₃ and H₅), 2.36-2.02 and 1.86 (2m, 11 and 1H, H₂, H₄, H₆ and 2xOCOCH₃); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) = 177.0 (COOH), 169.41 and 169.39 (2xOCOCH₃), 166.2, 166.1 (2xCOO), 152.4, 152.3 (2xC_q), 144.9, 144.4 (2xCH=CHCO), 132.04, 132.0 (2xC_q), 129.6, 129.5 (4xCH_{Ar}), 122.3 (4xCH_{Ar}), 118.0, 117.9 (2xCH=CHCO), 75.2 (C₁), 69.4, 66.6 (C₃ and C₅), 39.3, 36.5, 34.9 (C₂, C₄ and C₆), 21.3 (2x OCOCH₃); HRMS-ESI m/z [M+Na]⁺ calcd for C₂₉H₂₈NaO₁₁ 575.1524; found 575.1503.

To a solution of (3S,5S) 1-hydroxy-3,5 bis[[2(E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11d** (196 mg) in acetone (4.0 mL) was added 3M HCl aqueous solution (2.0 mL) and the mixture was refluxed for 5h. After completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was concentrated, dissolved in MeOH/H₂O (20/50 mL) and washed with pentane (2x 15mL). After concentration, the crude quantitatively as a pale solid **4d** (165 mg).

$[\alpha]_D^{25}$ - 72.6 (c 0.71, CH₃OH); IR (ATR) 3406, 2976, 2947, 1692, 1593, 1514, 1456, 1429, 1375, 1269, 1209, 1177, 1161, 1138, 1032 cm⁻¹; ¹H NMR (CD₃OD, 400 MHz, 295K) δ (ppm) = 7.59 and 7.54 (2d, 2H, *J* 16.0 Hz, CH=CHCO), 7.08 (m, 4H, ArH), 6.97-6.92 (m, 4H, ArH), 6.81 (m, 2H, ArH), 6.29 and 6.23 (2d, 2H, *J* 16.0 Hz, CH=CHCO), 5.44 (m, 2H, H₃ and H₅), 2.40 (dd, 1H, ²J 13.9 Hz, ³J 4.3 Hz, H₂, H₄ or H₆), 2.32 (dd, 1H, ²J 13.4 Hz, ³J 8.2 Hz, H₂, H₄ or H₆), 1.96 (m, 4H, H₂, H₄ or H₆); ¹³C NMR (CD₃OD, 100 MHz, 297K) δ (ppm) = 177.4 (COOH), 171.0 (2xC_q), 168.6 and 168.5 (2xOCO), 149.4, 149.3 (2xC_q), 147.1 and 146.9 (2xCH=CHCO), 127.74 and 127.68 (2xC_q), 123.1, 123.0, 116.5, 116.4 (x2), 115.4, 115.2, 115.11, 115.09, 115.0 (8x CH_{Ar} + 2x CH=CHCO), 75.0 (C₁), 69.9, 68.7 (C₃ and C₅), 39.9, 38.6, 35.9 (C₂, C₄, C₆).

Synthesis of (3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3-yl (2E)-3-(3,4-dihydroxyphenyl)prop-2-enoate (12)¹¹

¹¹ To the best of our knowledge, the only reported syntheses of this family of compounds (dicinnamate and di (p-coumarate) isosorbide) used DCC/DMAP methodology. W. Huang, Y. B. Cao, X. G. Zhang, F. S. Li and H. Yang, *Chin. Chem. Lett.*, 2009, **20**, 873-876 ; A. Y. Bobrovsky, N. I. Boiko and V. P. Shibaev, *Mol. Cryst. Liq. Cryst.*, 2001, **363**, 35-50.



Isosorbide dicafeate was also synthesized in our lab using the general procedure A with isosorbide (300 mg, 2.05 mmol) in anhydrous pyridine (2.1 mL) and DMF (3.2 mL) and diacetylaccaffeylchloride (1.51 g, 5.36 mmol, 2.6 eq.). (3R, 3aR, 6S, 6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl (2E,2'E)-bis-[3,4-bis(acetyloxy)phenyl]prop-2-enoate **11** was obtained as a white solid (414mg, 32%) was obtained after purification by flash chromatography (pentane/EtOAc 6/4).

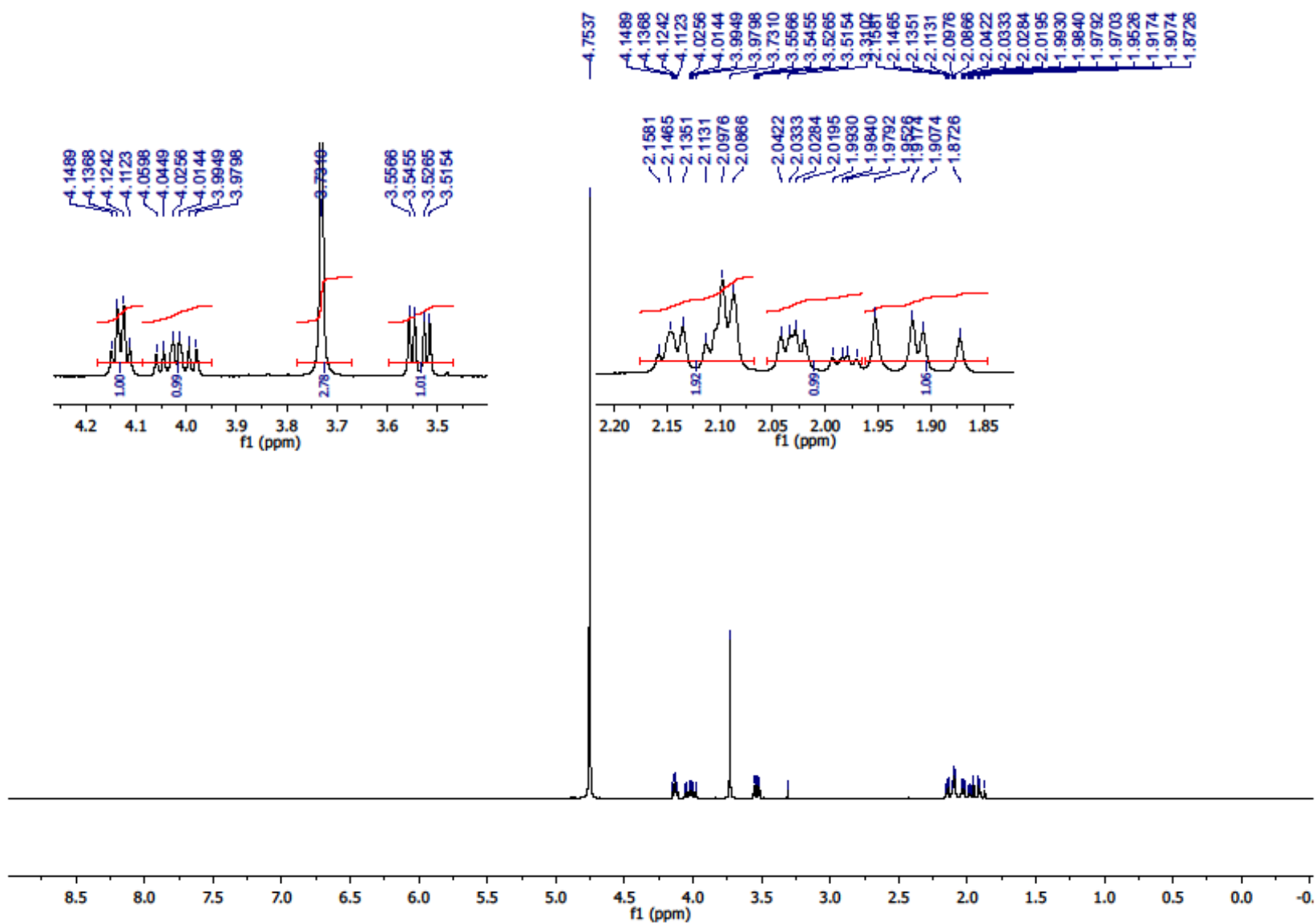
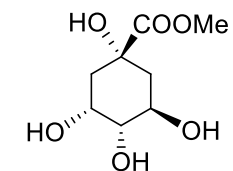
$[\alpha]_D^{25}$ -59 (c 1.00, CH₂Cl₂); m.p.69-70°C (CH₂Cl₂); IR (ATR) cm⁻¹ 1767, 1707, 1638, 1502, 1242, 1204, 1168, 1110; ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.67 and 7.63 (2d, 2H, ³J 16.0 Hz, CH=CHCO), 7.40-7.35 (m, 4H, ArH), 7.26-7.21 (m, 2H, ArH), 6.44 and 6.36 (2d, 2H, ³J 16.0 Hz, CH=CHCO), 5.35 (bs, 1H, H₆), 5.29 (q, 1H, $J_{H_3/H_2} \approx J_{H_{3a}/H_3} \approx 5.5$ Hz, H₃), 4.94 (dd, 1H, $J_{H_{3a}/H_{6a}} \approx J_{H_{3a}/H_3}$ 4.6 Hz, H_{3a}), 4.59 (d, 1H, $J_{H_{3a}/H_{6a}}$ 4.6 Hz, H_{6a}), 4.06 (m, 2H, 2xH₅), 4.03 (dd, 1H, ²J 9.9 and ³J 6.0 Hz, H₂), 3.90 (dd, 1H, ²J 9.8 and ³J 5.4 Hz, H₂), 2.292, 2.294, 2.298, 2.302 (4s, 12H, 3xCH₃); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 168.15 and 168.06 (4 COCH₃), 165.9 and 165.6 (2 COO), 144.03 and 143.98 (2 CH=CH), 143.82 and 143.77 (2 C_q Ar), 142.5 (2 C_q Ar), 133.1 and 133.0 (2 C_q Ar), 126.6, 124.1, and 123.0 (6 CH_{Ar}), 118.5 and 118.4 (2 CH=CH), 86.1 (C_{6a}), 81.1 (C_{3a}), 78.3 (C₆), 74.3 (C₃), 73.6 (C₅), 70.5 (C₂), 20.8 and 20.7 (4 COCH₃); HRMS (ESI) calcd for C₃₂H₃₀NaO₁₄ [M+Na]⁺ 661.1528, found 661.1537.

11 was submitted to general procedure D for deprotection : **11** (144 mg, 0.225 mmol) in ethanol (1.2 mL) with NaOAc (377 mg, 20 eq) in water (600 μL). **12** was obtained as a white solid (74 mg, 72%) after purification by flash chromatography (CH₂Cl₂/MeOH 97/3-95/5).

$[\alpha]_D^{25}$ -191 (c 0.99, CH₂Cl₂); m.p. 192-193°C (MeOH) ; IR (ATR) cm⁻¹ 3670,3660, 2986, 2972, 2901, 2370, 2322, 1688, 1601, 1379, 1049; ¹H NMR (300 MHz, CD₃OD) δ (ppm) = 7.58 and 7.55 (2d, ³J 15.9 Hz, CH=CHCO), 7.05 (dd, 2H, J 6.1 Hz, J 2.0 Hz, ArH); 6.94 (m, 2H, ArH), 6.77 (dd, 2H, J 8.1 Hz, J 3.1 Hz, ArH), 6.29 and 6.24 (2d, 2H, ³J 15.9 Hz, CH=CHCO), 5.26 (m, 2H, H₃, H₆), 4.92 (dd, 1H, $J_{H_{3a}/H_{6a}} \approx J_{H_{3a}/H_3}$ 5.0 Hz, H_{3a}), 4.53 (d, 1H, $J_{H_{3a}/H_{6a}}$ 5.0 Hz, H_{6a}), 3.95 (m, 4H, H₂, H₅) ; ¹³C NMR (75 MHz, CD₃OD) δ (ppm) = 168.4, 168.1, 149.71, 149.66, 147.7, 147.5, 146.8, 127.6, 127.5, 123.2, 123.1, 116.5, 115.2, 114.4, 87.3, 82.6, 79.2, 75.5, 74.2, 71.8; HRMS (ESI) calcd for C₂₄H₂₂NaO₁₀ [M+Na]⁺ 493.1105, found 493.1087.

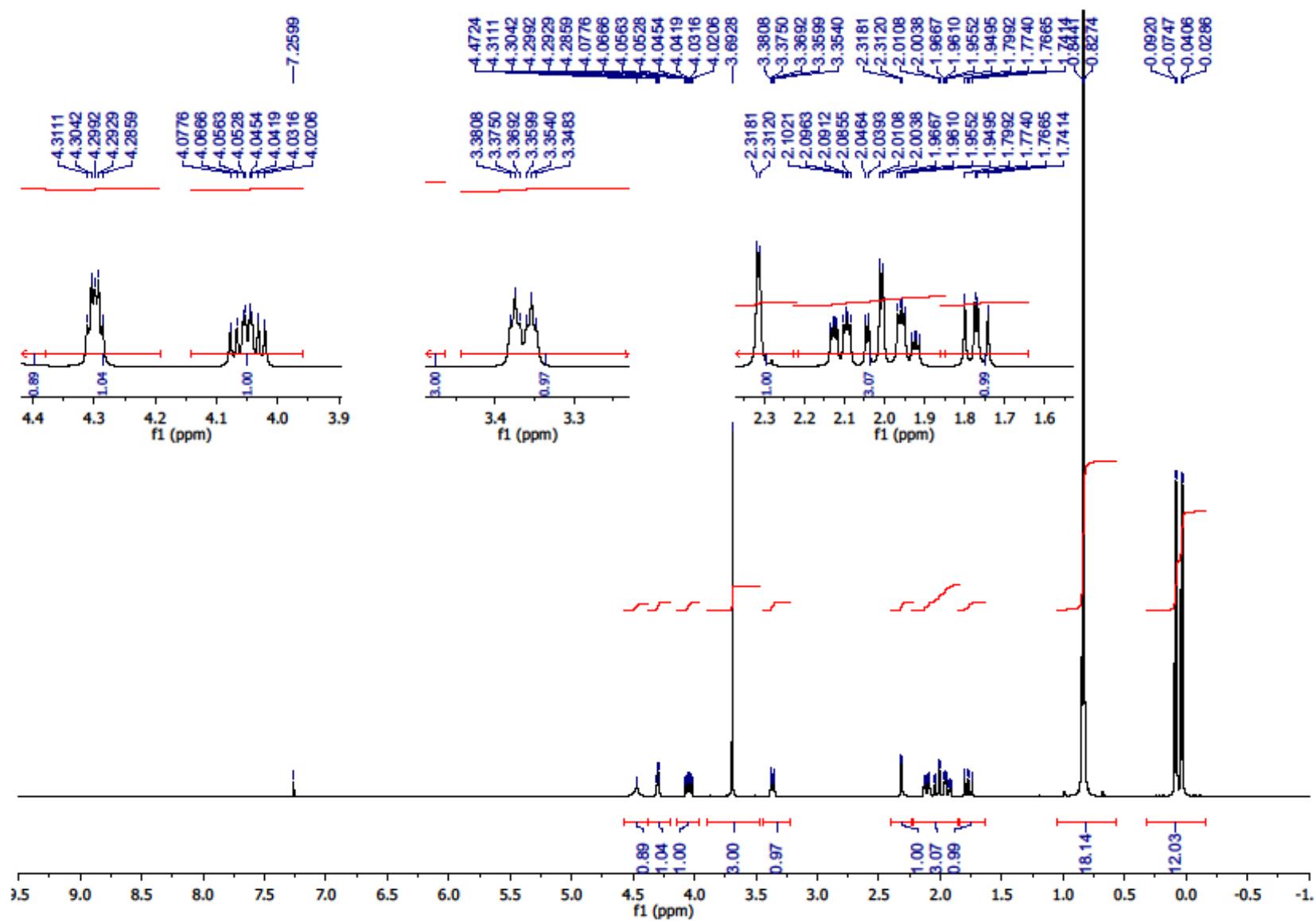
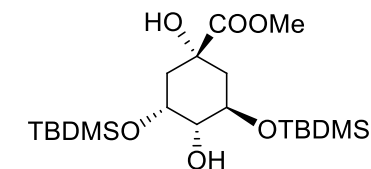
Methyl (3R, 5R)-1,3,4,5-tetrahydroxycyclohexanecarboxylate Q1

^1H NMR (300MHz, CD_3OD , 300K)

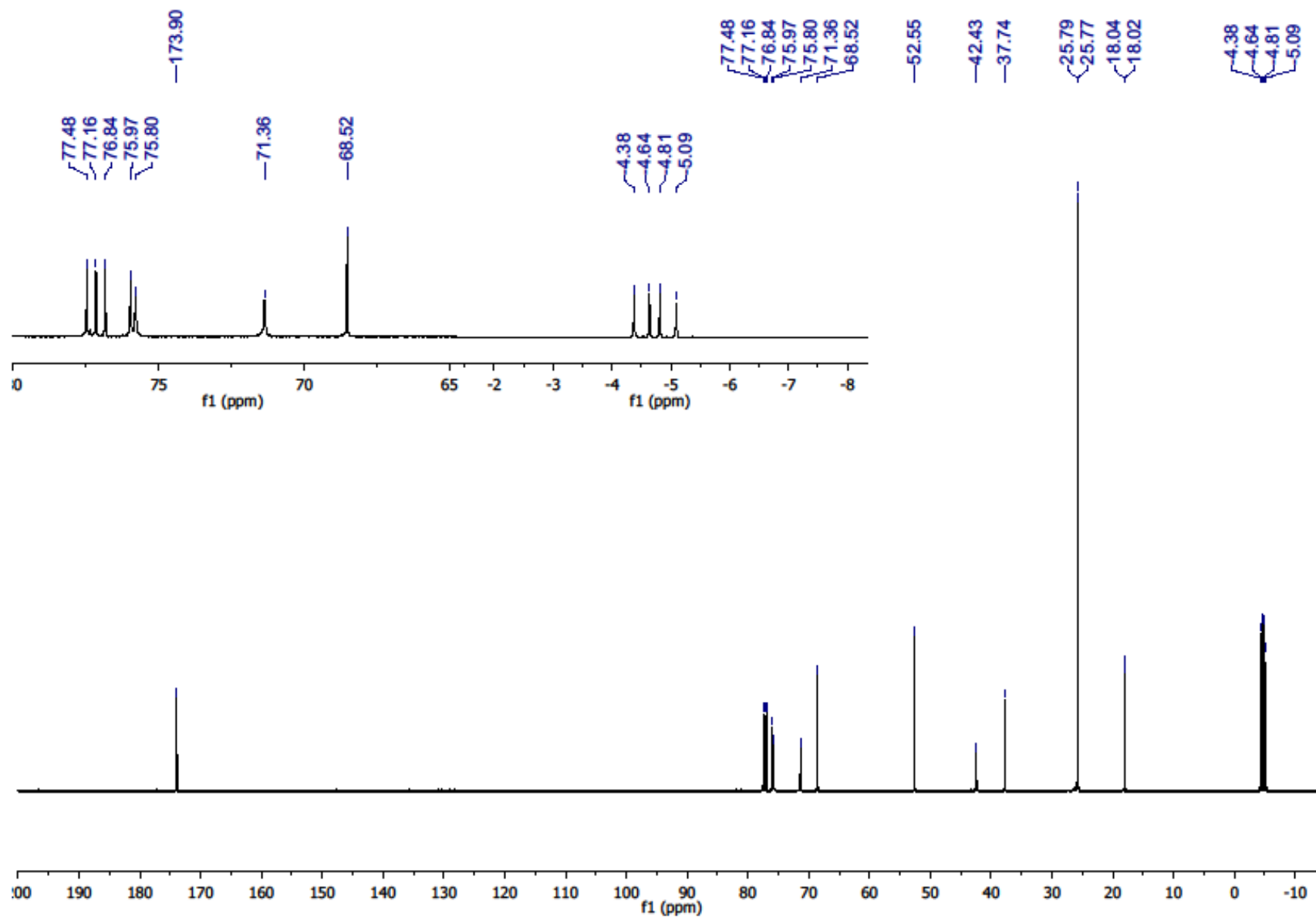


Methyl (3*R*,5*R*)-1,4-dihydroxy-3,5-tert-butyltrimethylsilyloxycyclohexanecarboxylate Q2

¹H NMR (300MHz, CDCl₃, 293K)

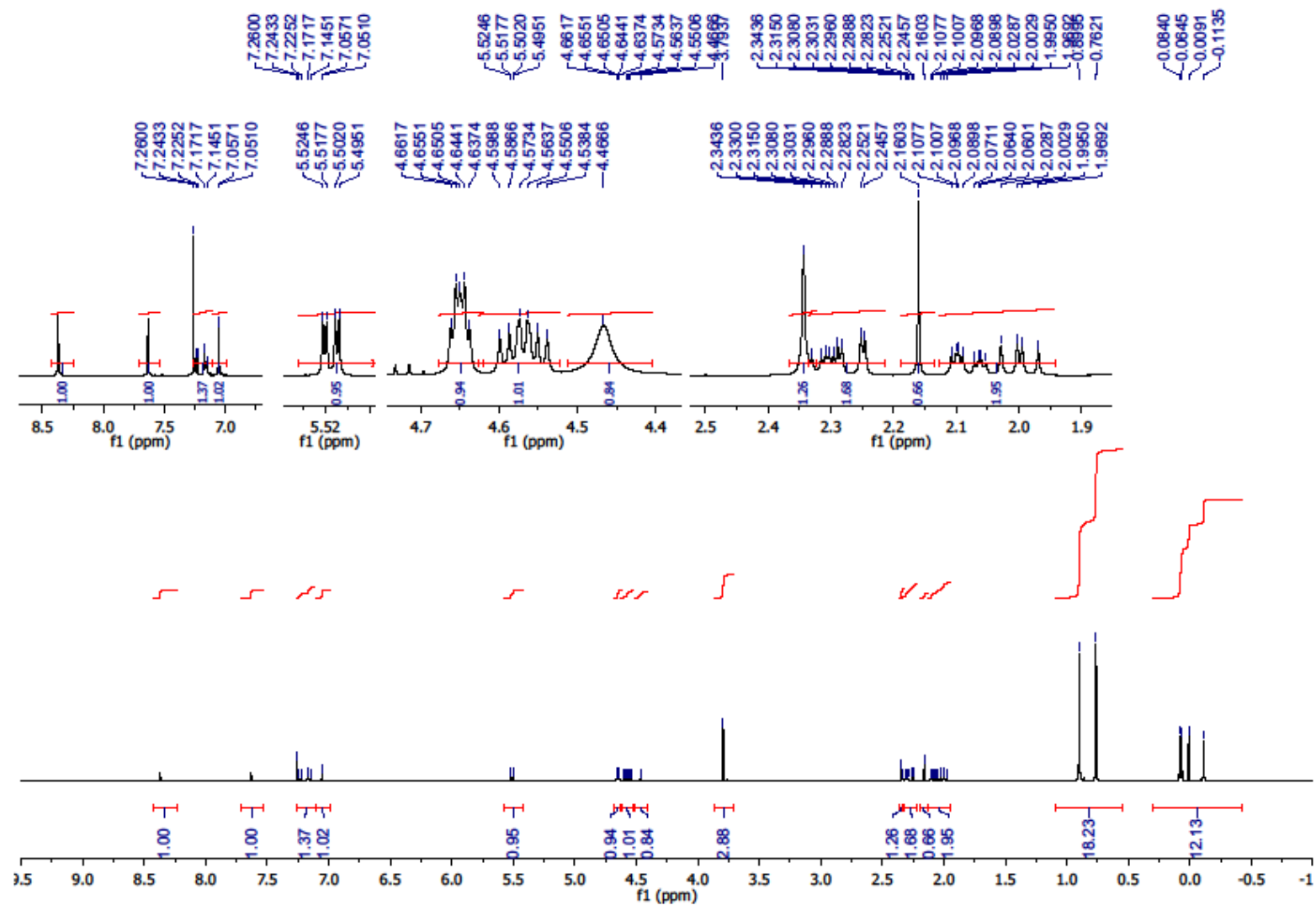
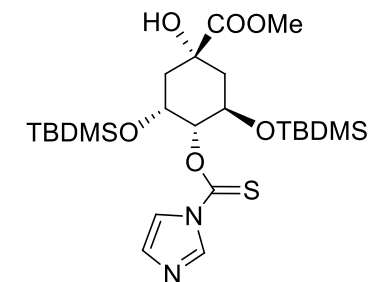


^{13}C NMR (100MHz, CDCl_3 , 293K)



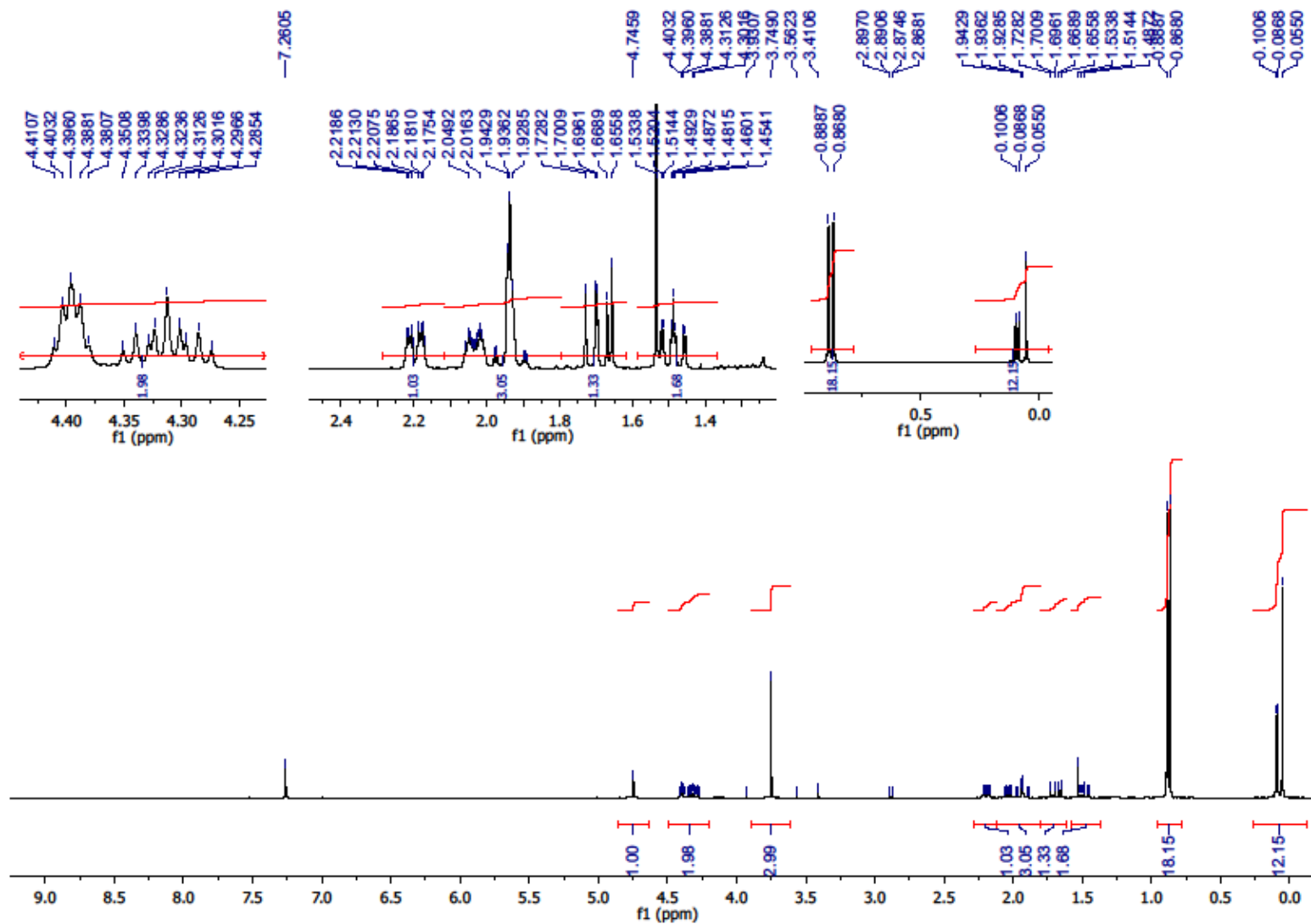
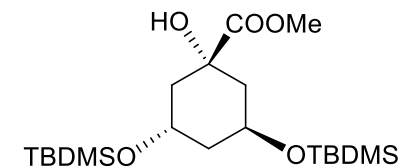
Methyl (3*R*,5*R*)-1-hydroxy-4-[(1*H*-imidazol-1-ylcarbothioyl)oxy]-3,5-*tert*-butyldimethylsilyloxy cyclohexanecarboxylate Q3

¹H NMR (400MHz, CDCl₃, 296K)

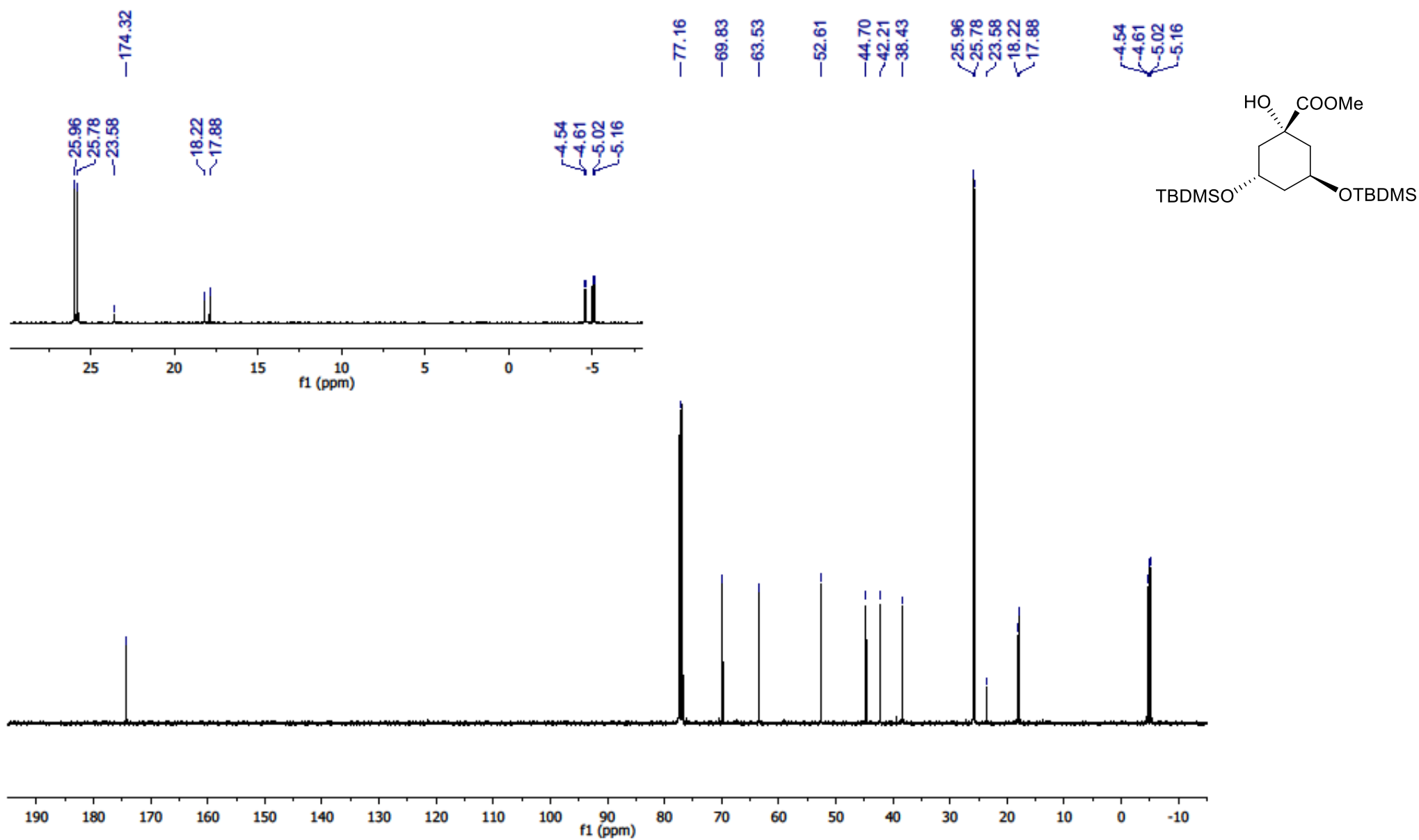


Methyl (3*S*,5*S*)-1-hydroxy-3,5- *tert*-butyldimethylsilyloxy cyclohexanecarboxylate 5

¹H NMR (400MHz, CDCl₃, 296K)

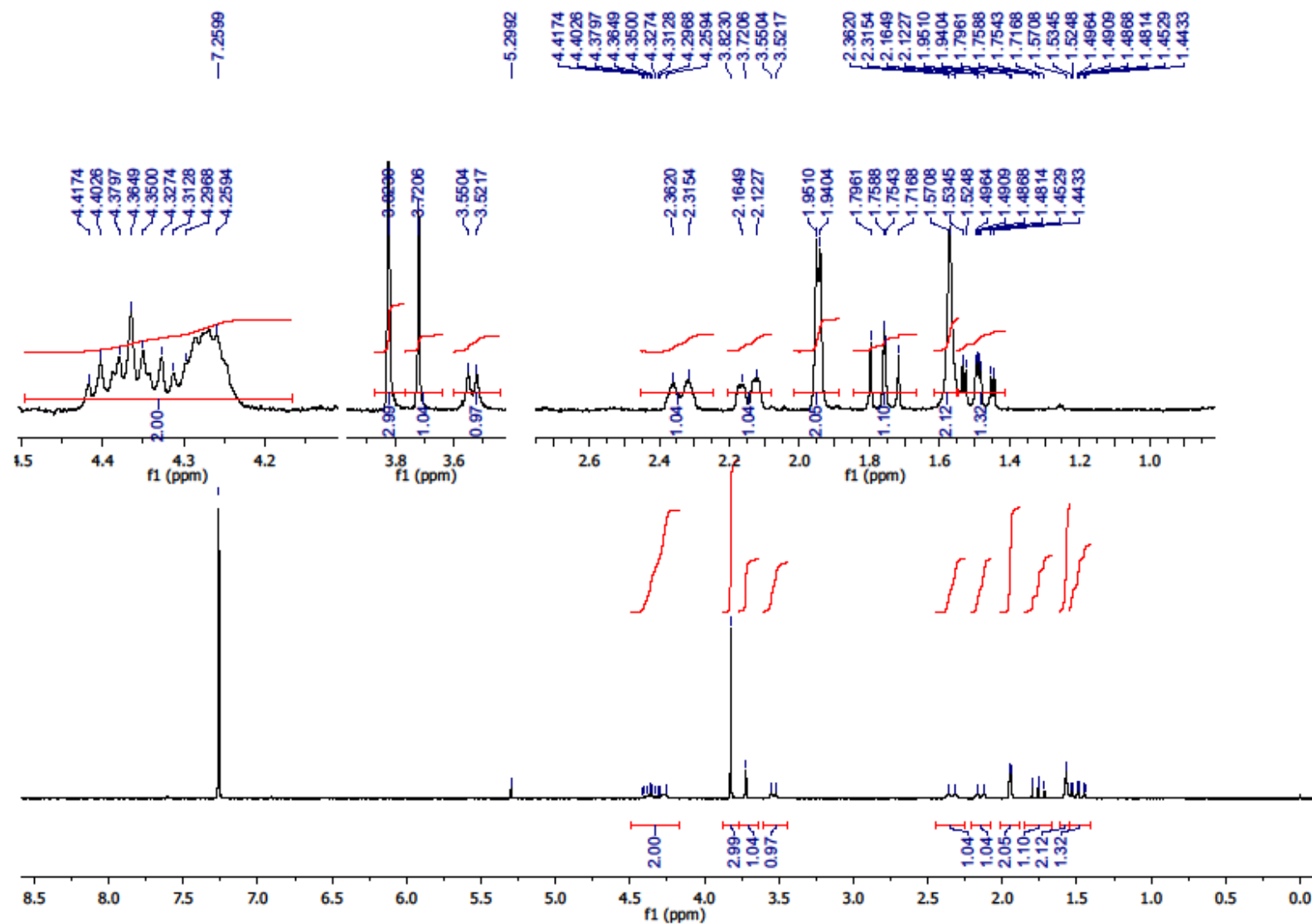
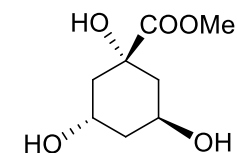


¹³C NMR (100MHz, CDCl₃, 297K)

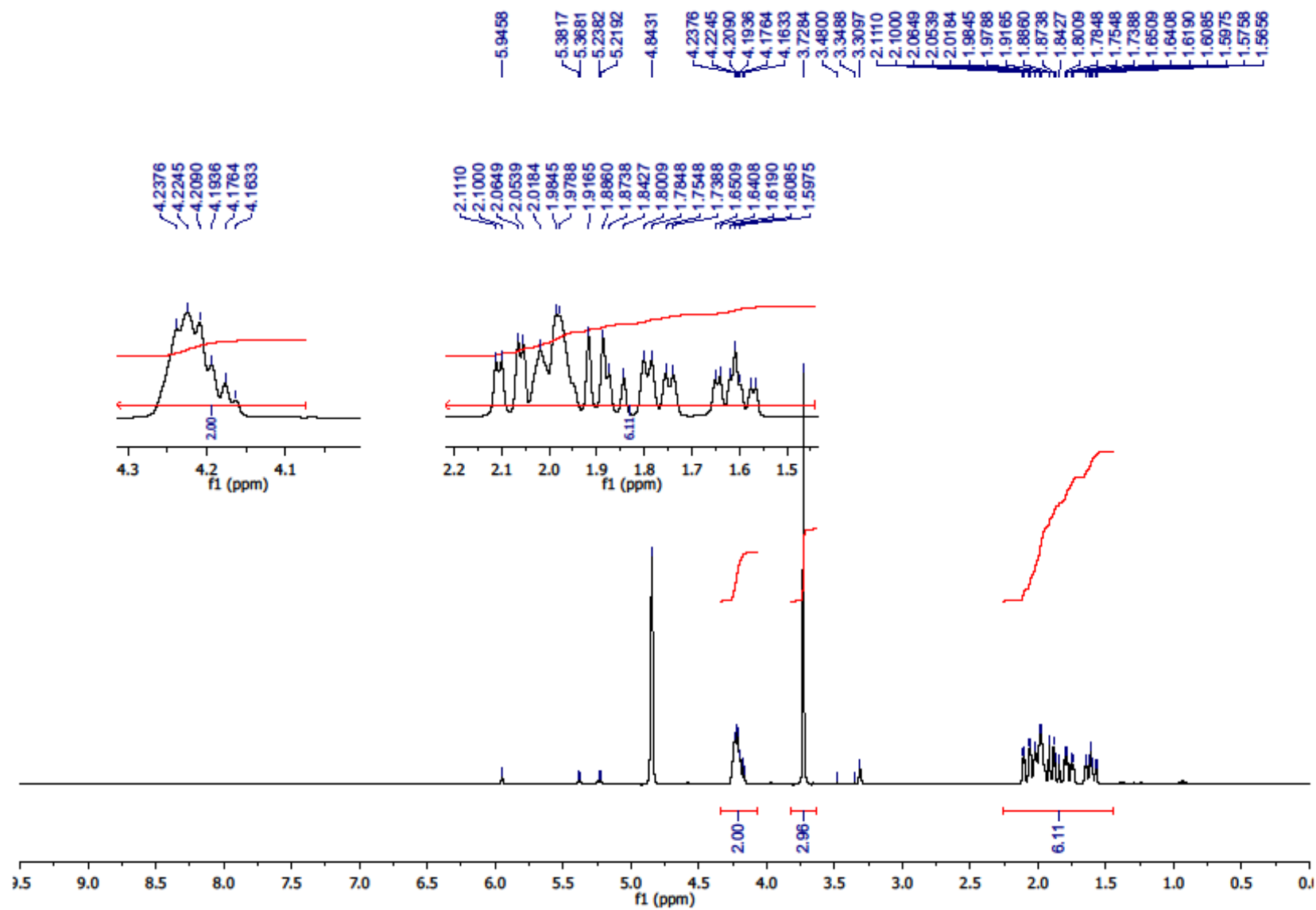
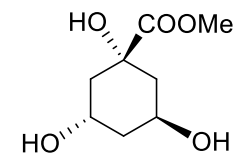


Methyl (3*S*,5*S*)-1,3,5-trihydroxy cyclohexanecarboxylate 6

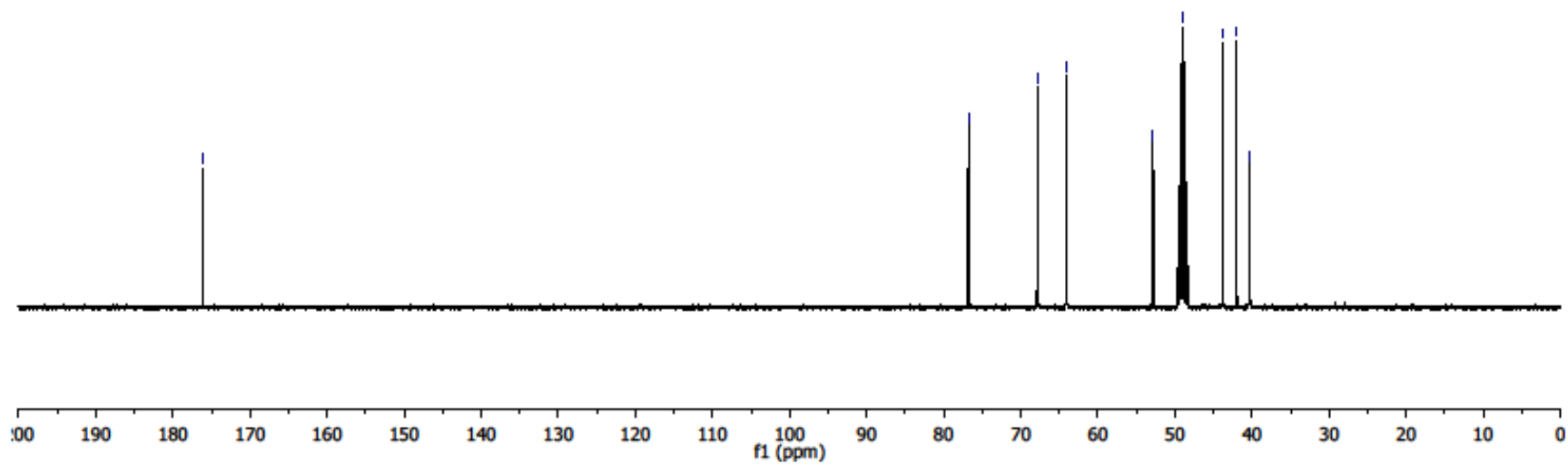
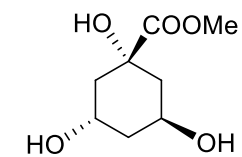
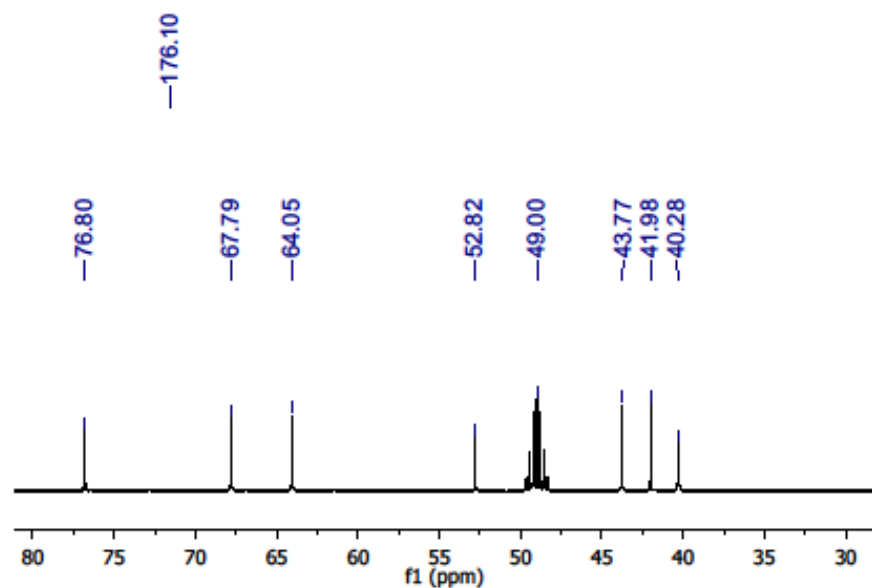
¹H NMR (300MHz, CDCl₃, 296K)



¹H NMR (400MHz, CD₃OD, 296K)

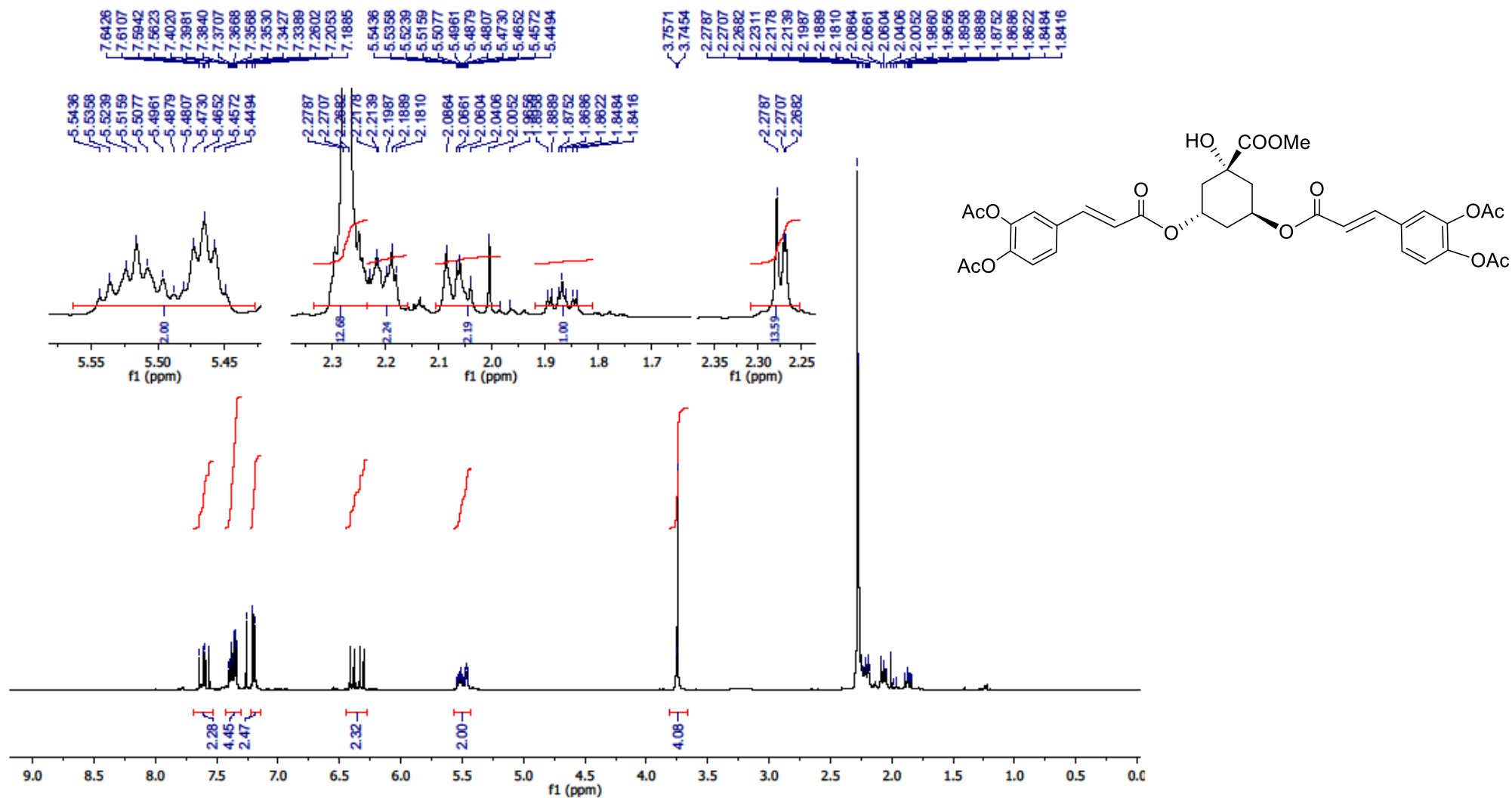


¹³C NMR (100MHz, CD₃OD, 295K)

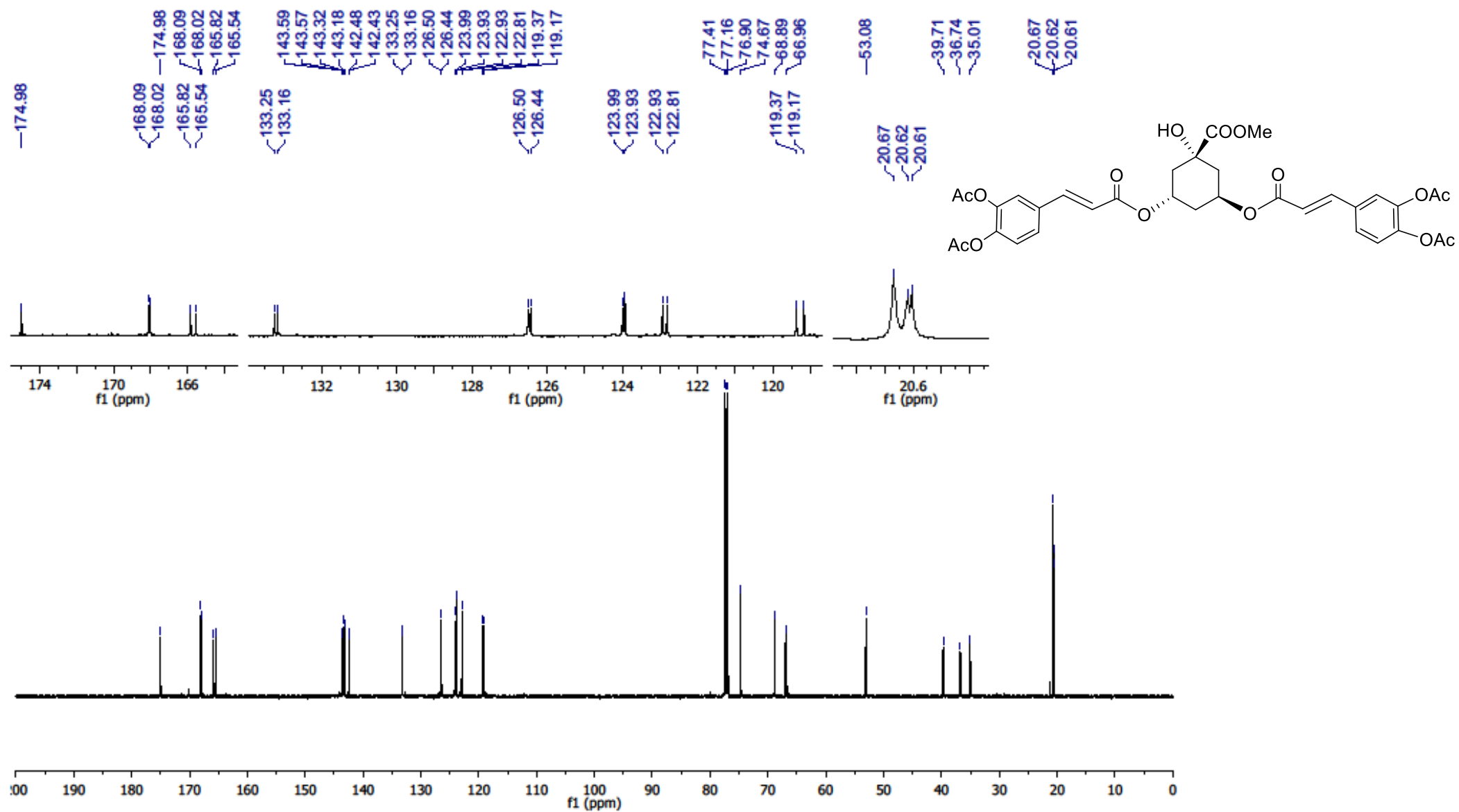


Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9a

¹H NMR (500MHz, CDCl₃, 297K)

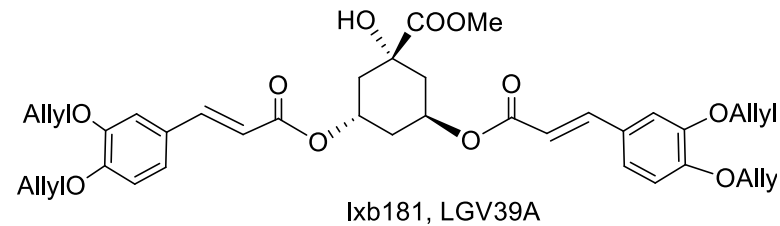
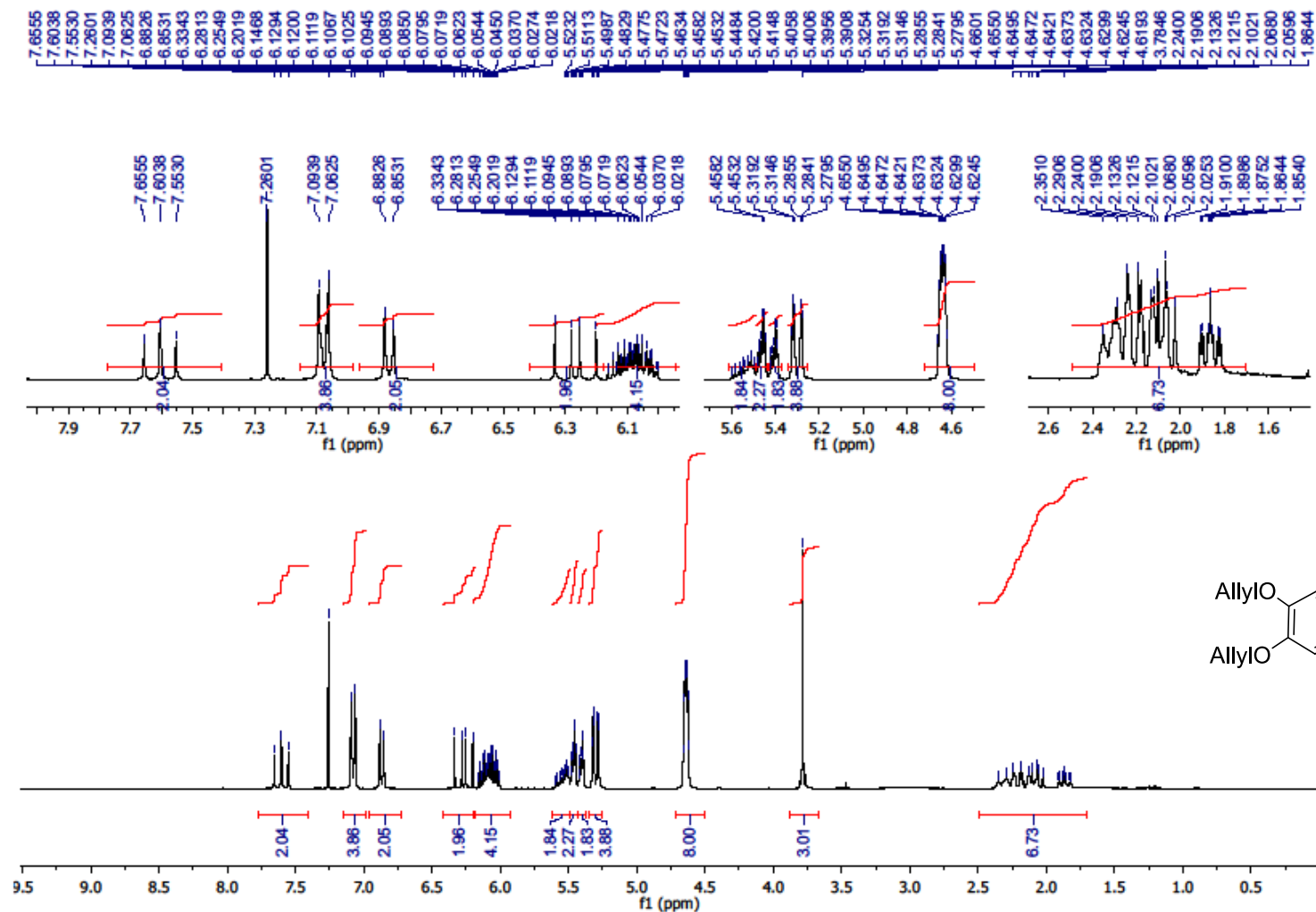


¹³C NMR (125MHz, CD₃OD, 295K)

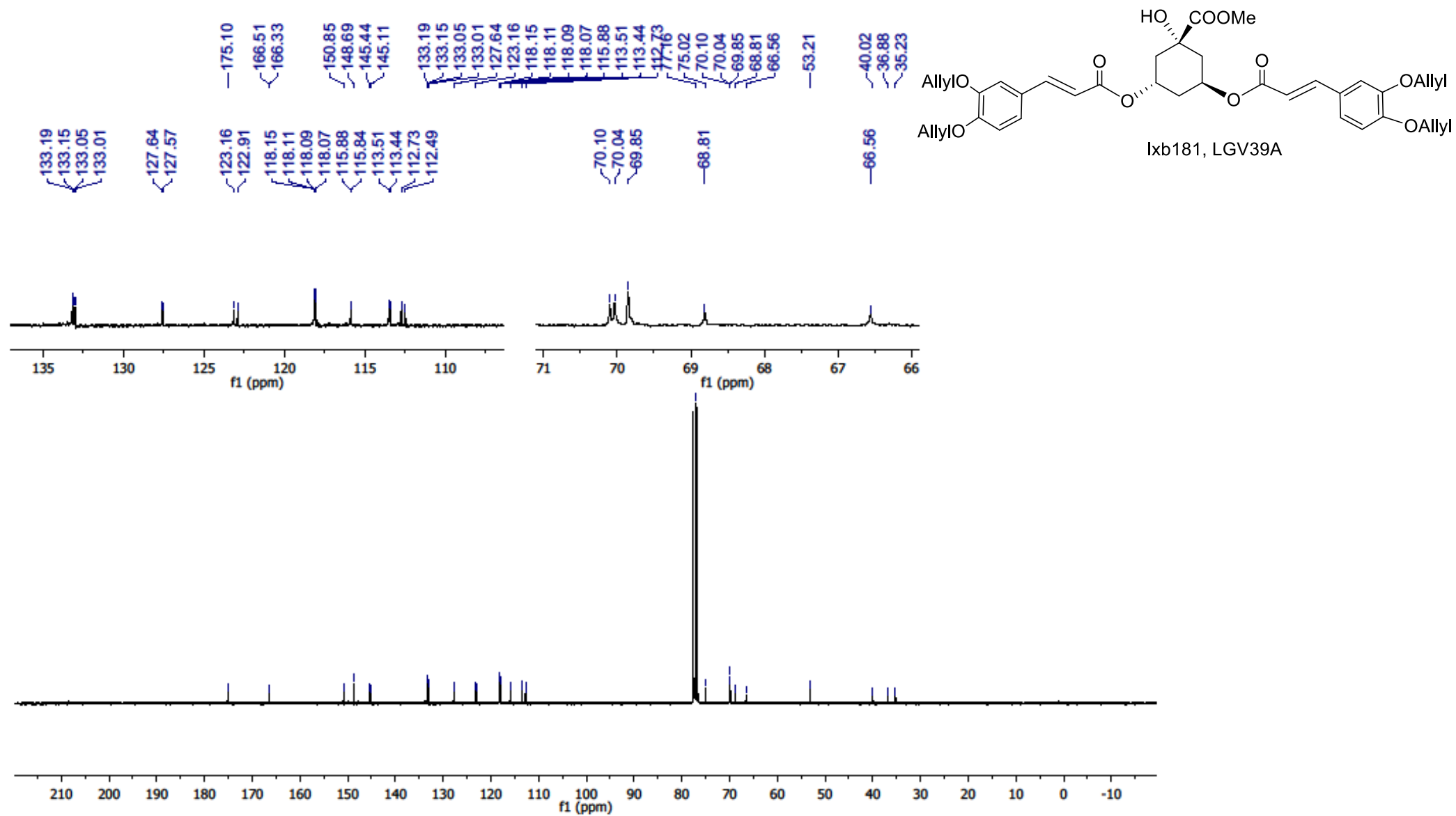


Methyl (3S,5S) 1-hydroxy-3,5 bis[[*(2E)*-3-(3,4-di-(prop-2-en-1-yloxy)phenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9b

¹H NMR (300MHz, CDCl₃, 296K)

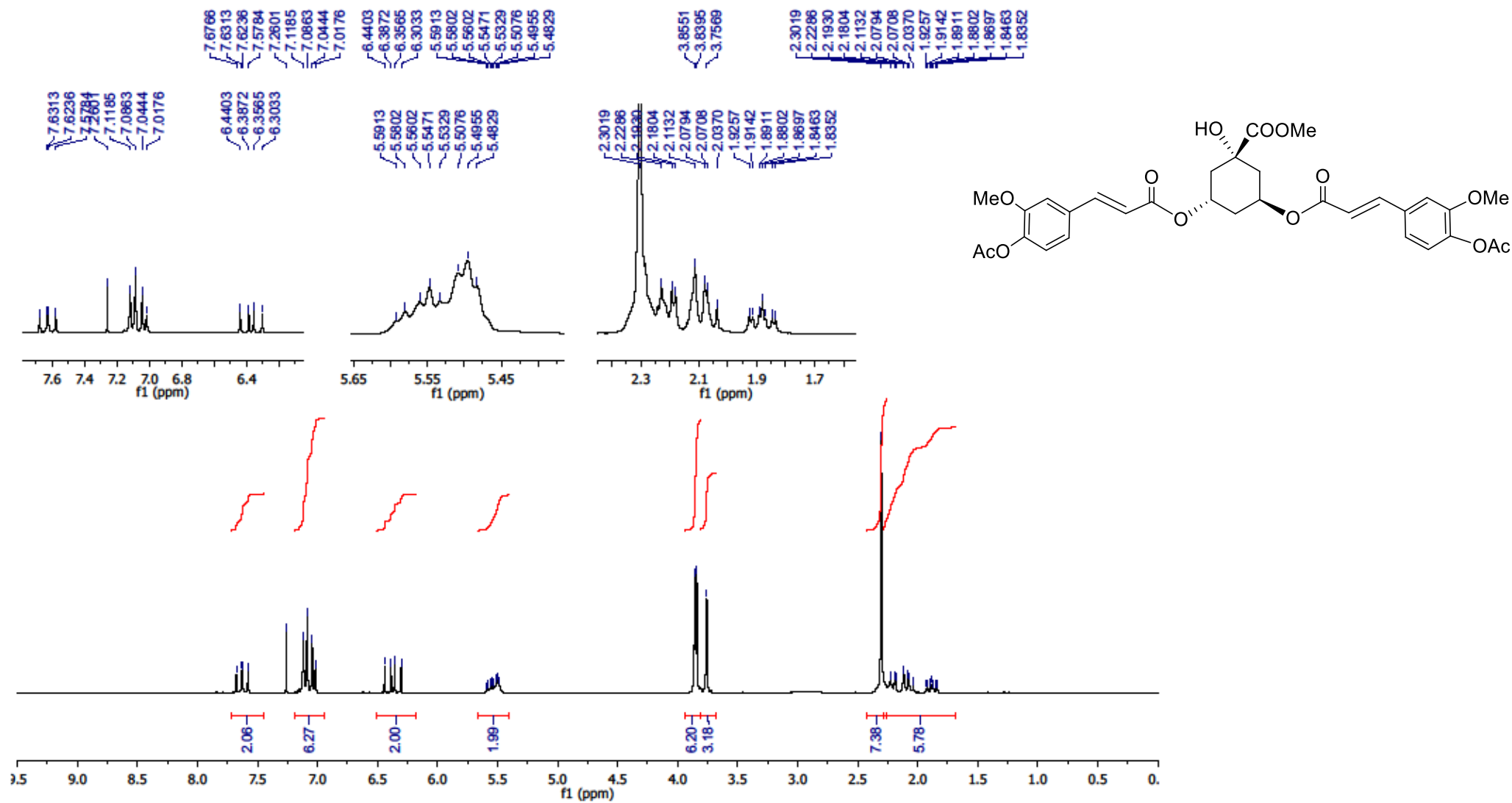


¹³C NMR (75MHz, CDCl₃, 296K)

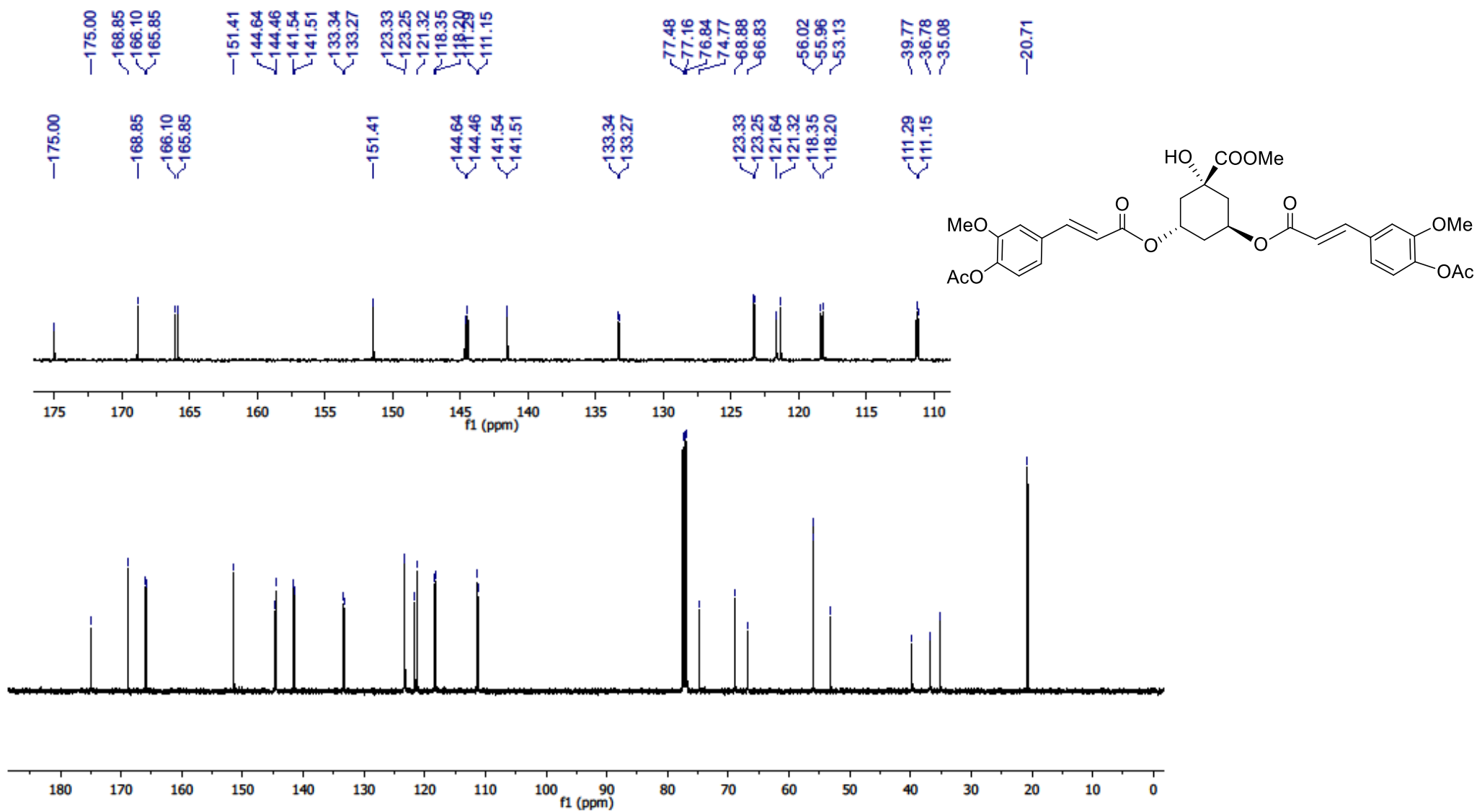


Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9c

^1H NMR (300MHz, CDCl_3 , 296K)

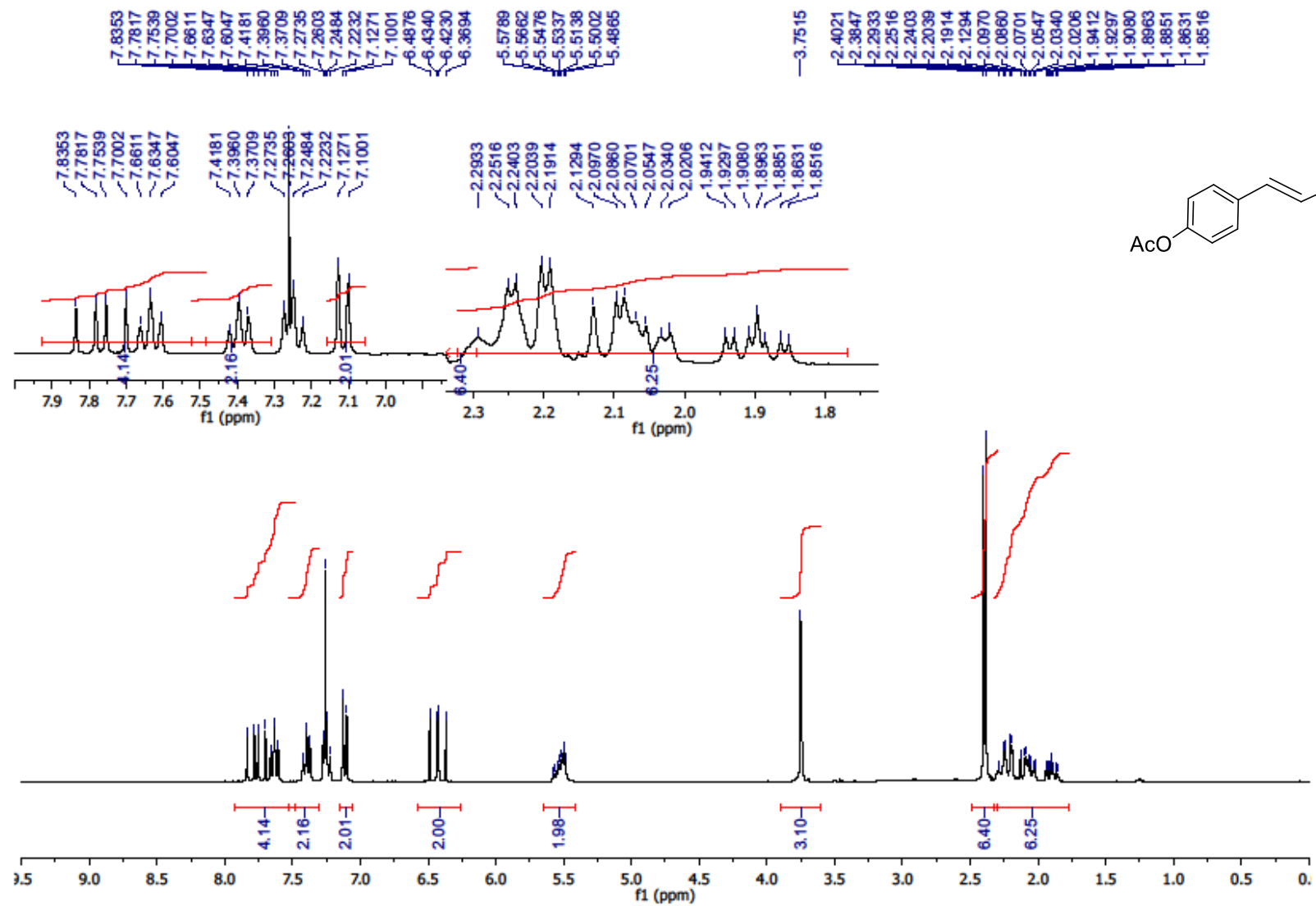


¹³C NMR (100MHz, CDCl₃, 295K)

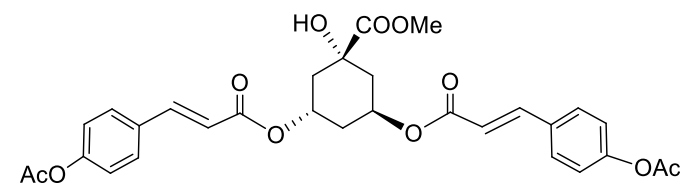
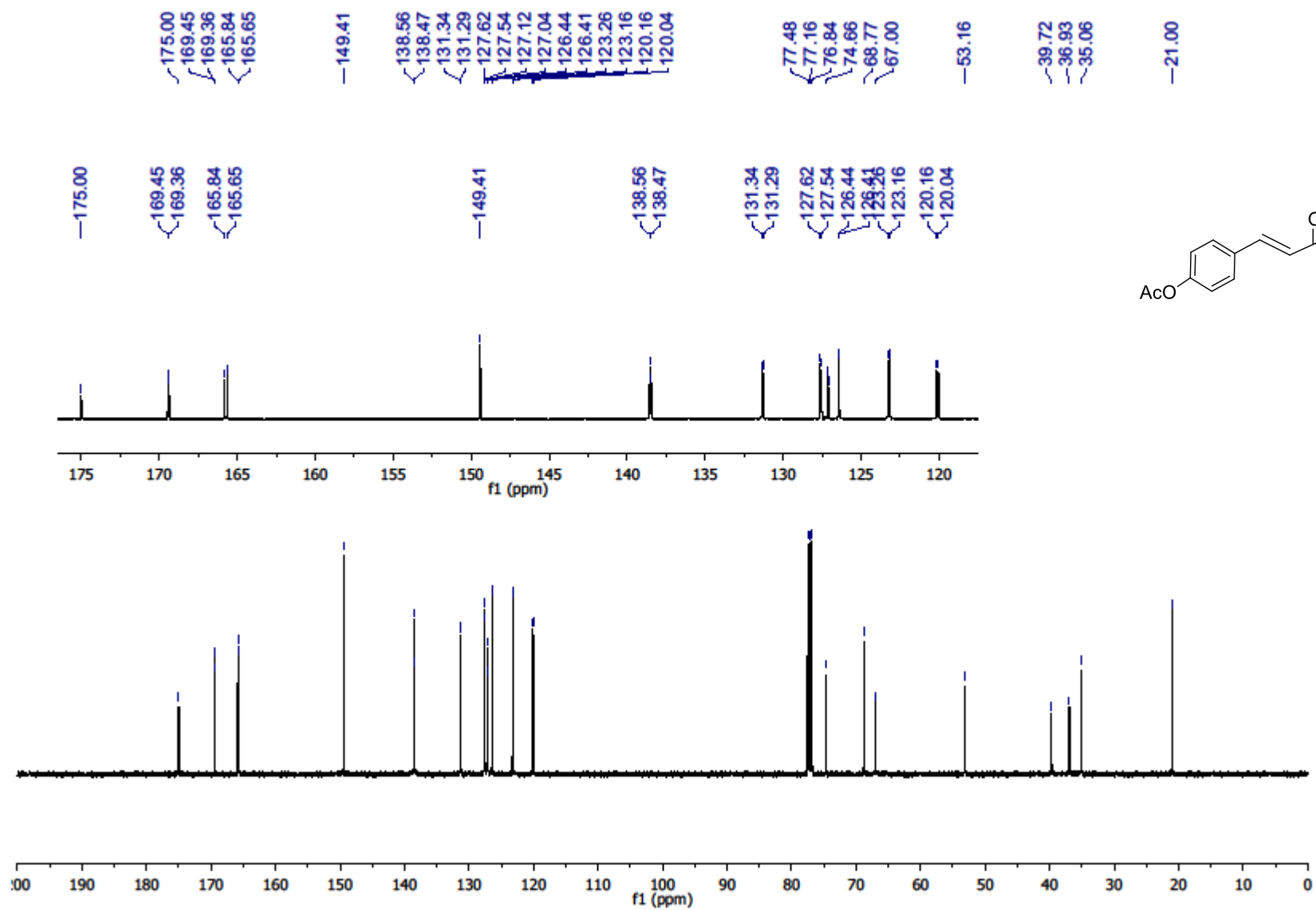


Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9d

^1H NMR (300MHz, CDCl_3 , 296K)

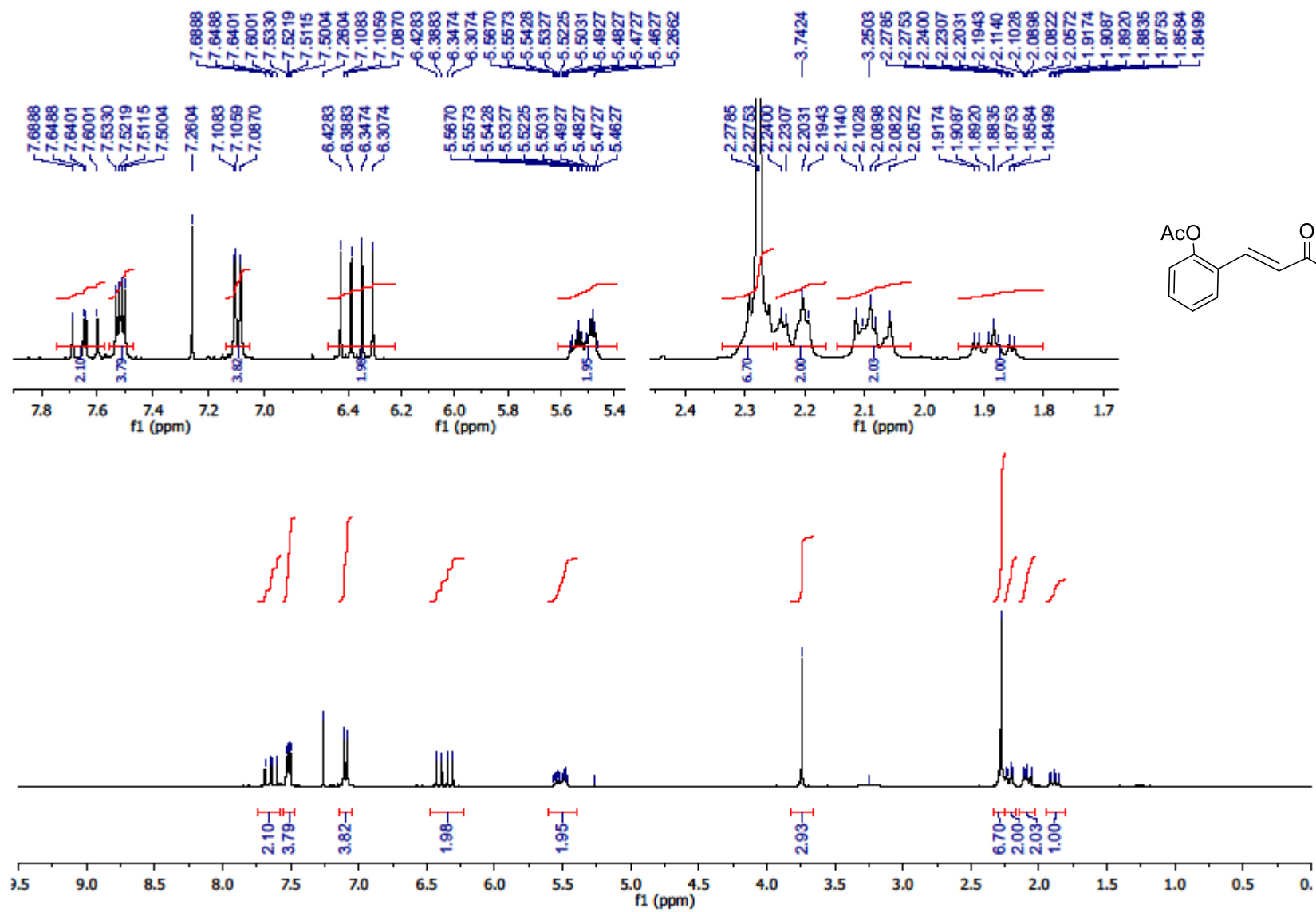


^{13}C NMR (100MHz, CDCl_3 , 295K)

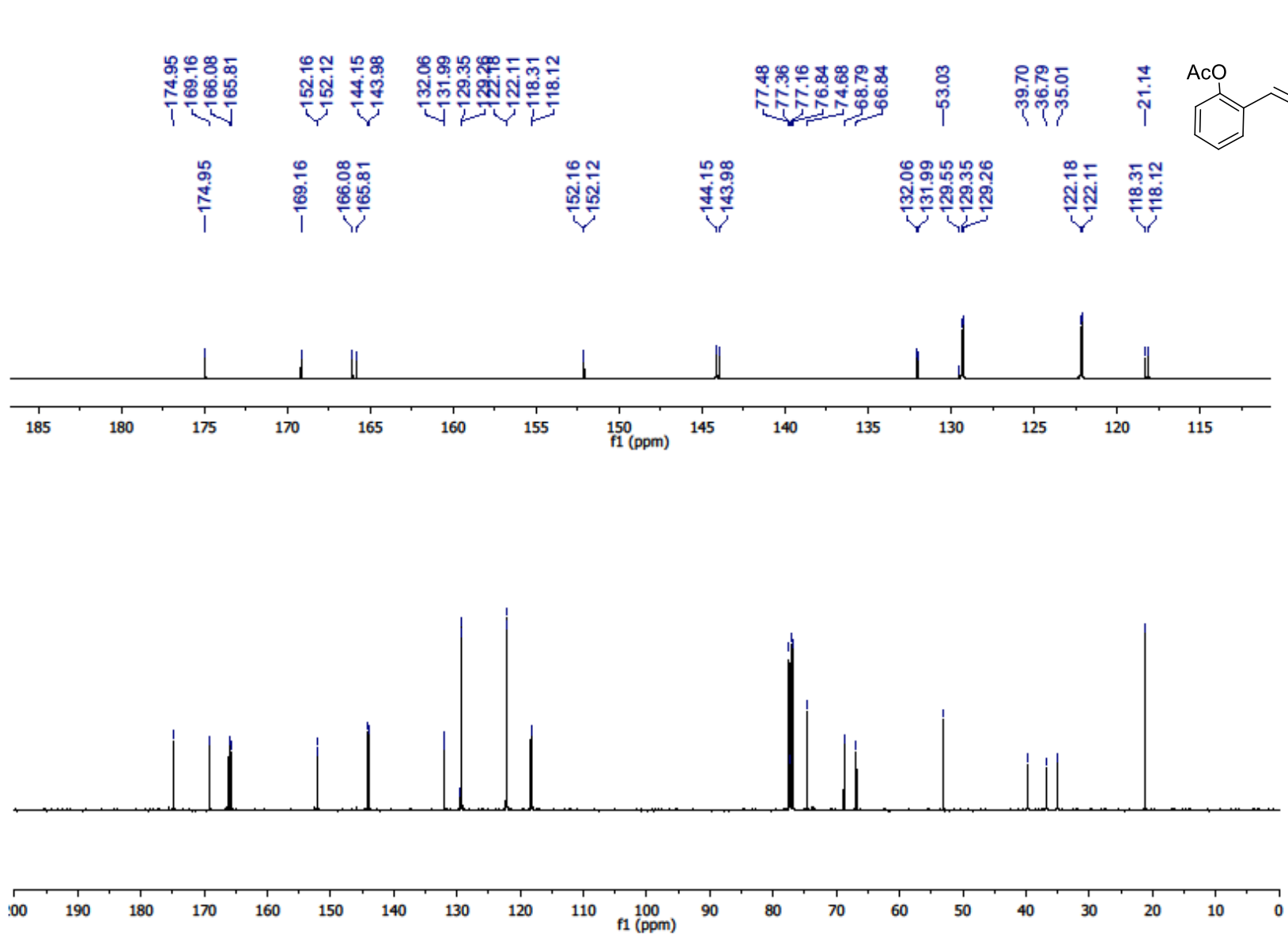


Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9e

^1H NMR (400MHz, CDCl_3 , 295K)

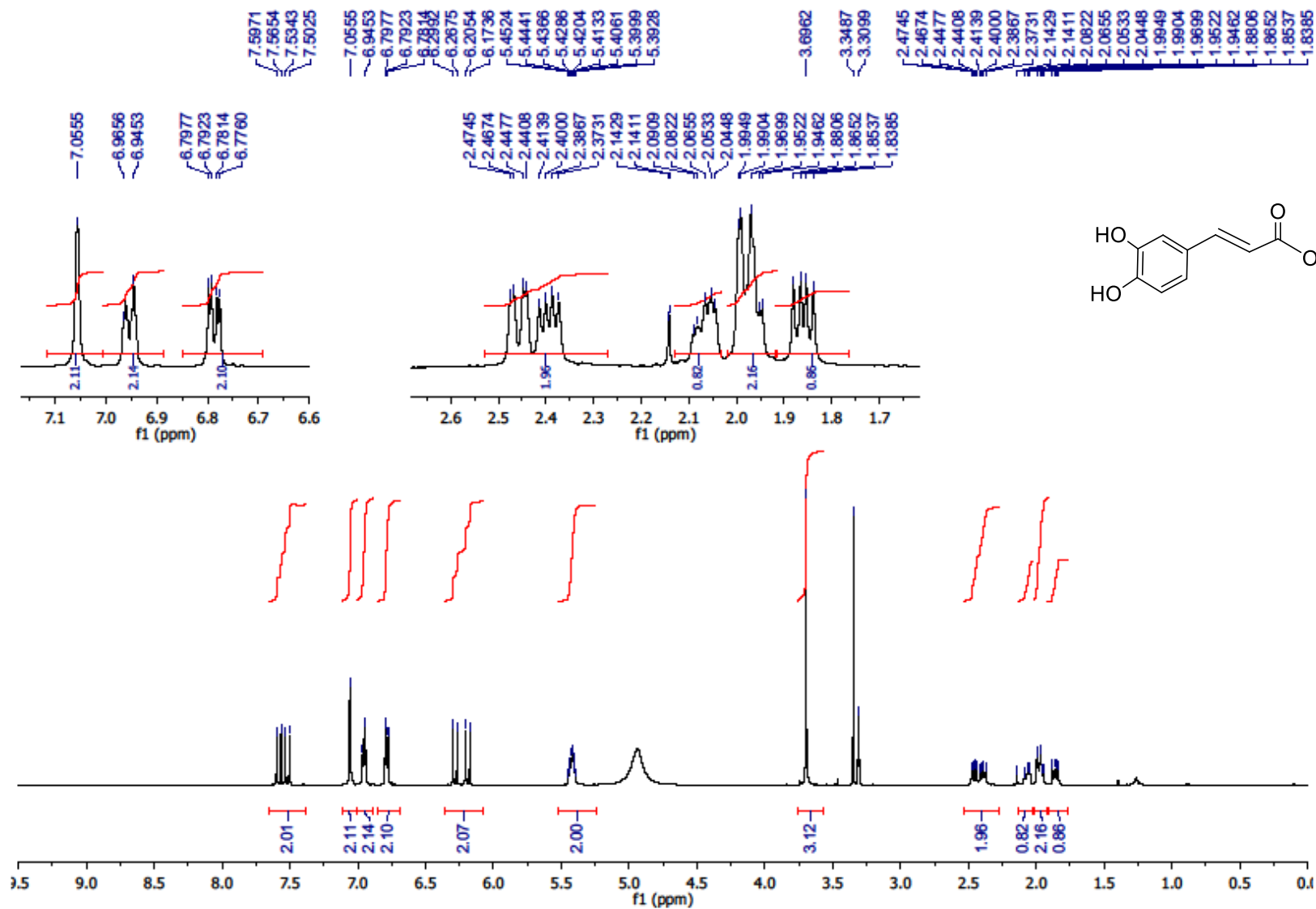


¹³C NMR (100MHz, CD₃OD, 295K)

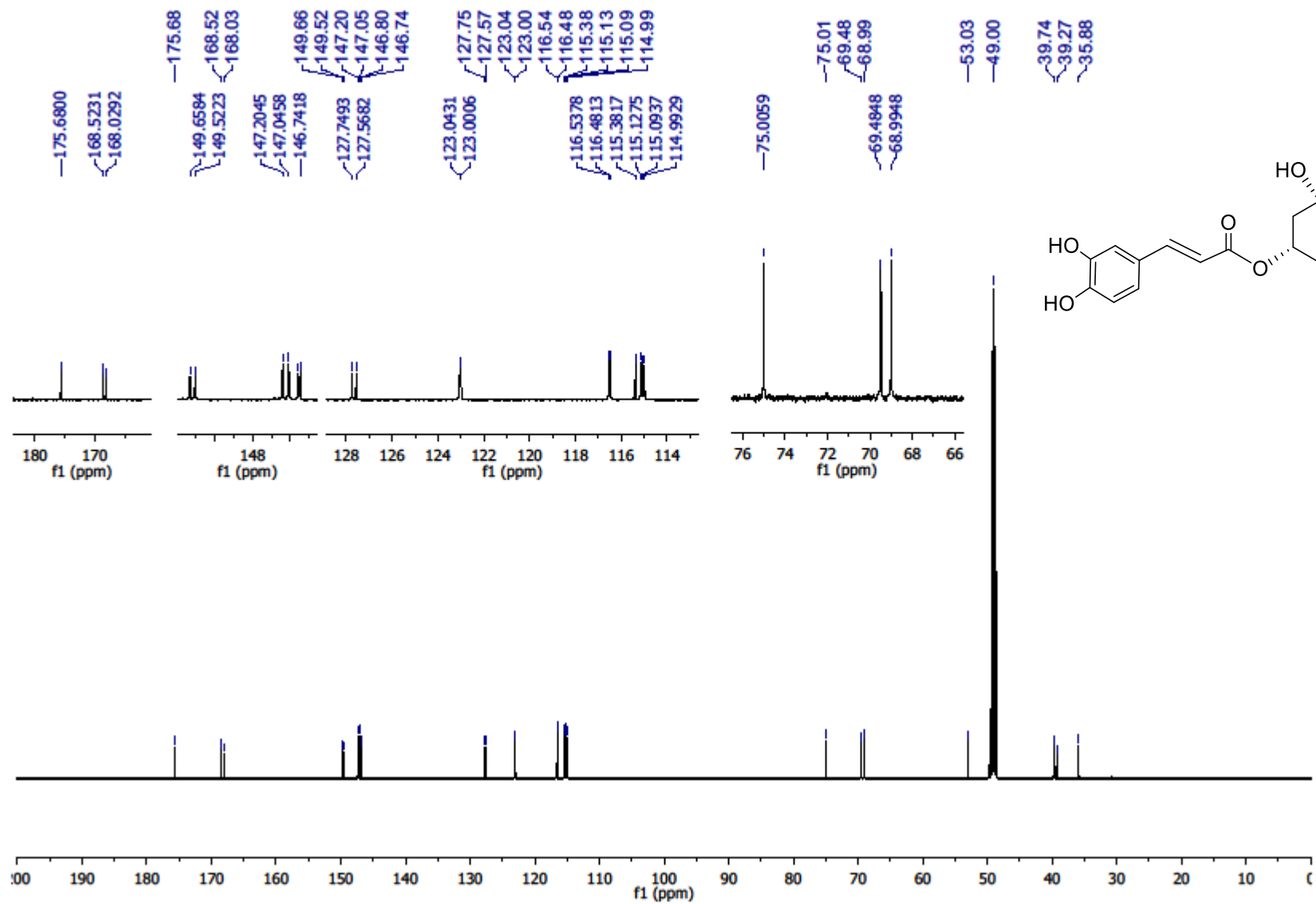


Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10a

¹H NMR (500MHz, CD₃OD, 298K)

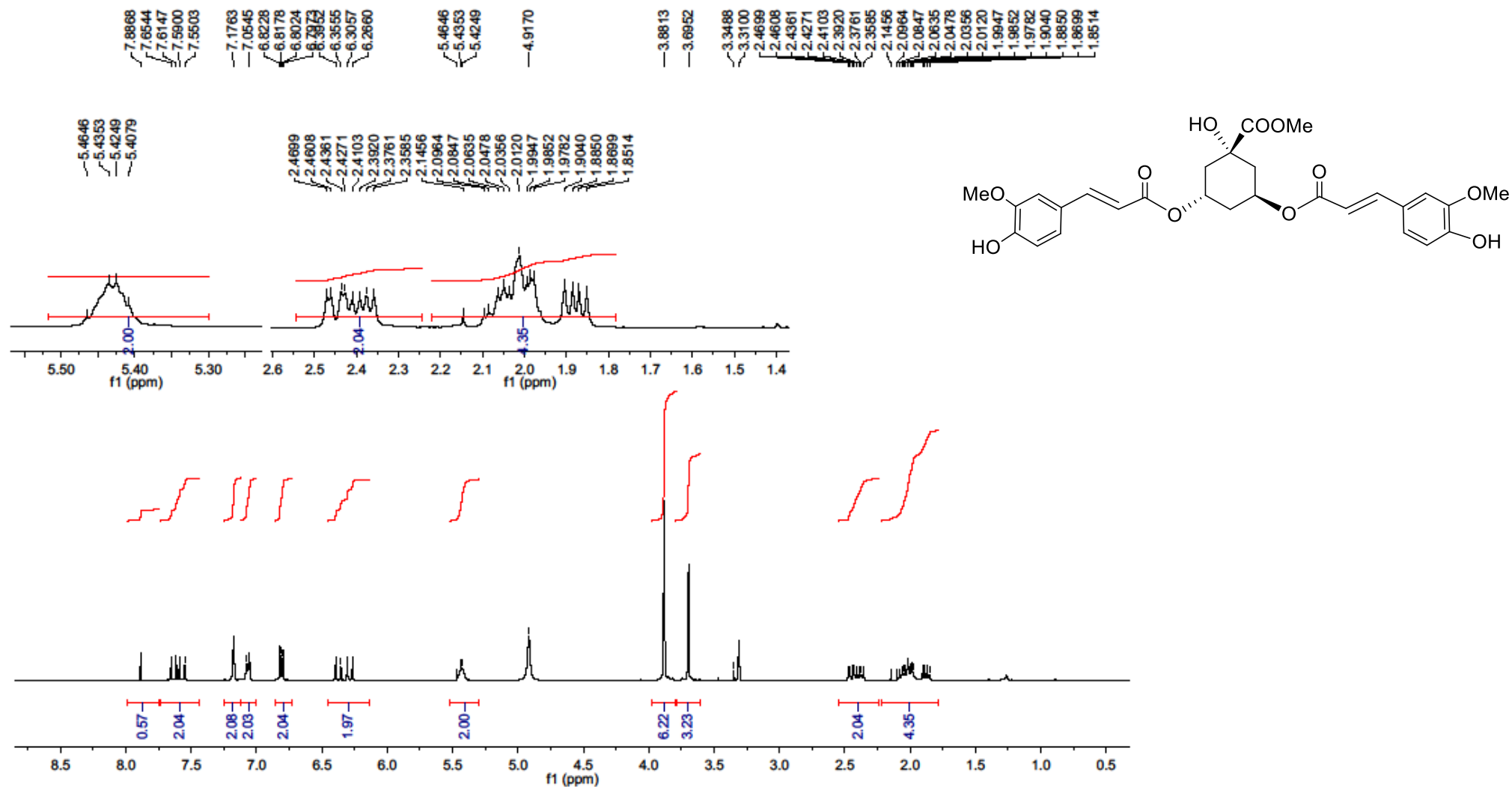


^{13}C NMR (125MHz, CD_3OD , 297K)

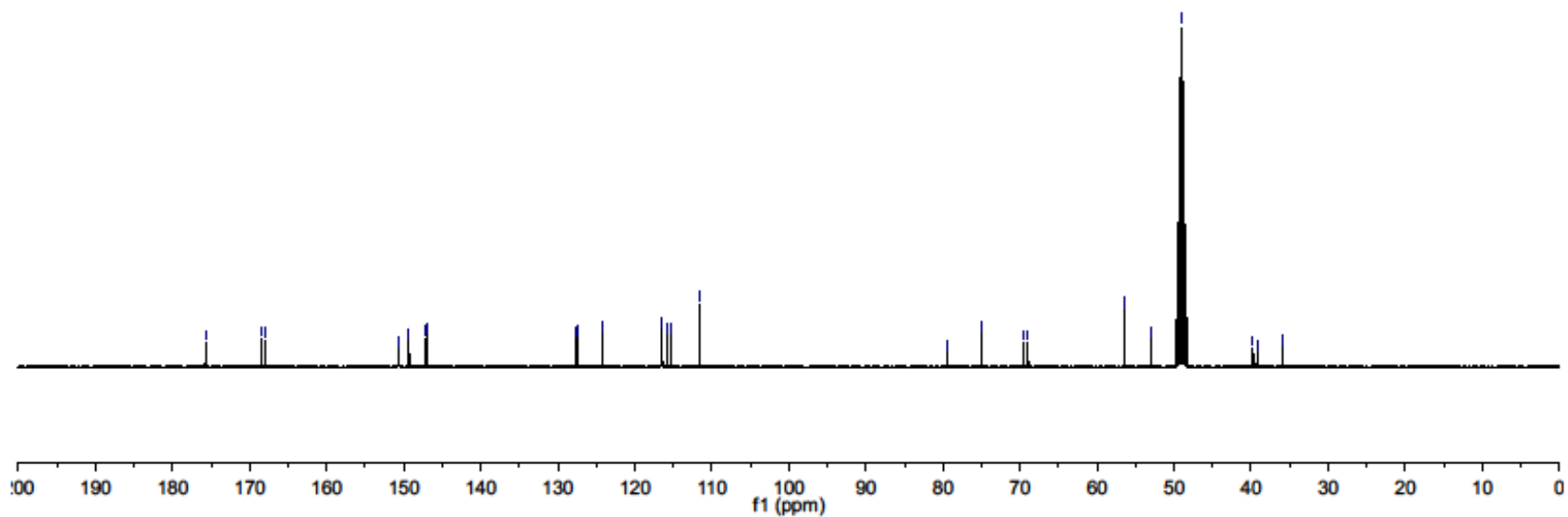
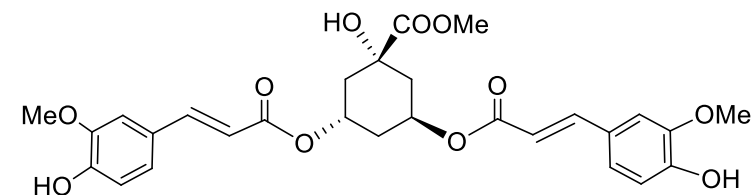
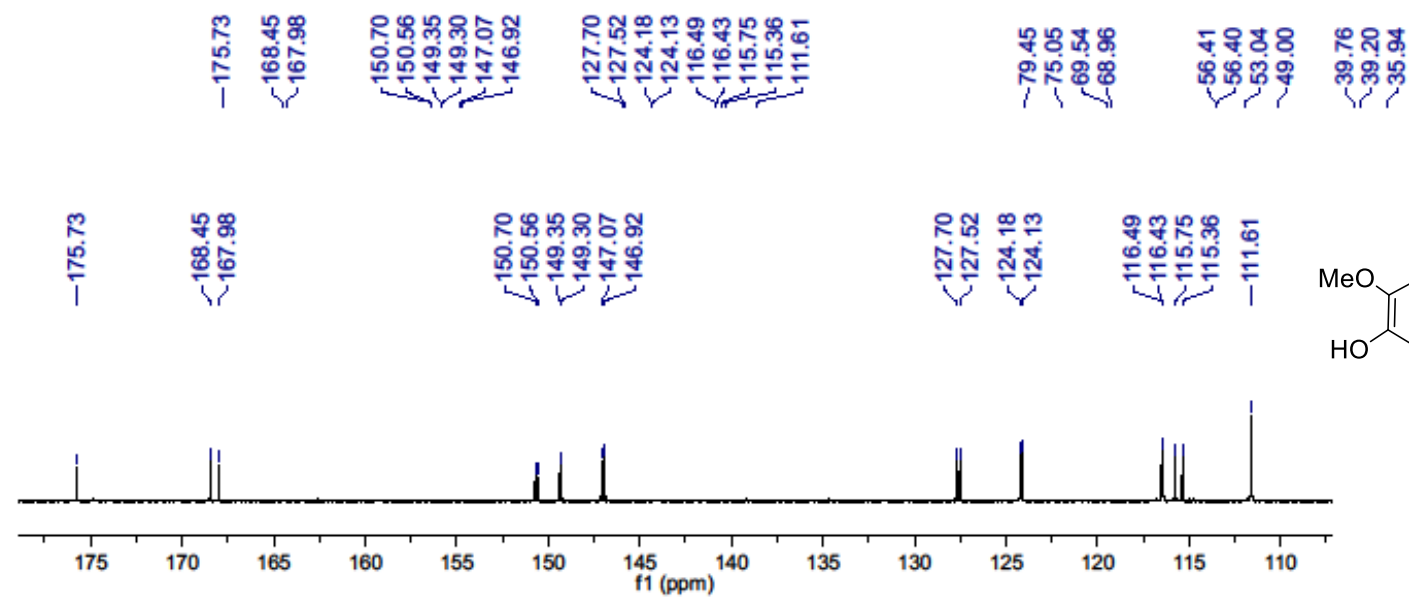


Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)- 3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10c

^1H NMR (400MHz, CD_3OD , 295K)

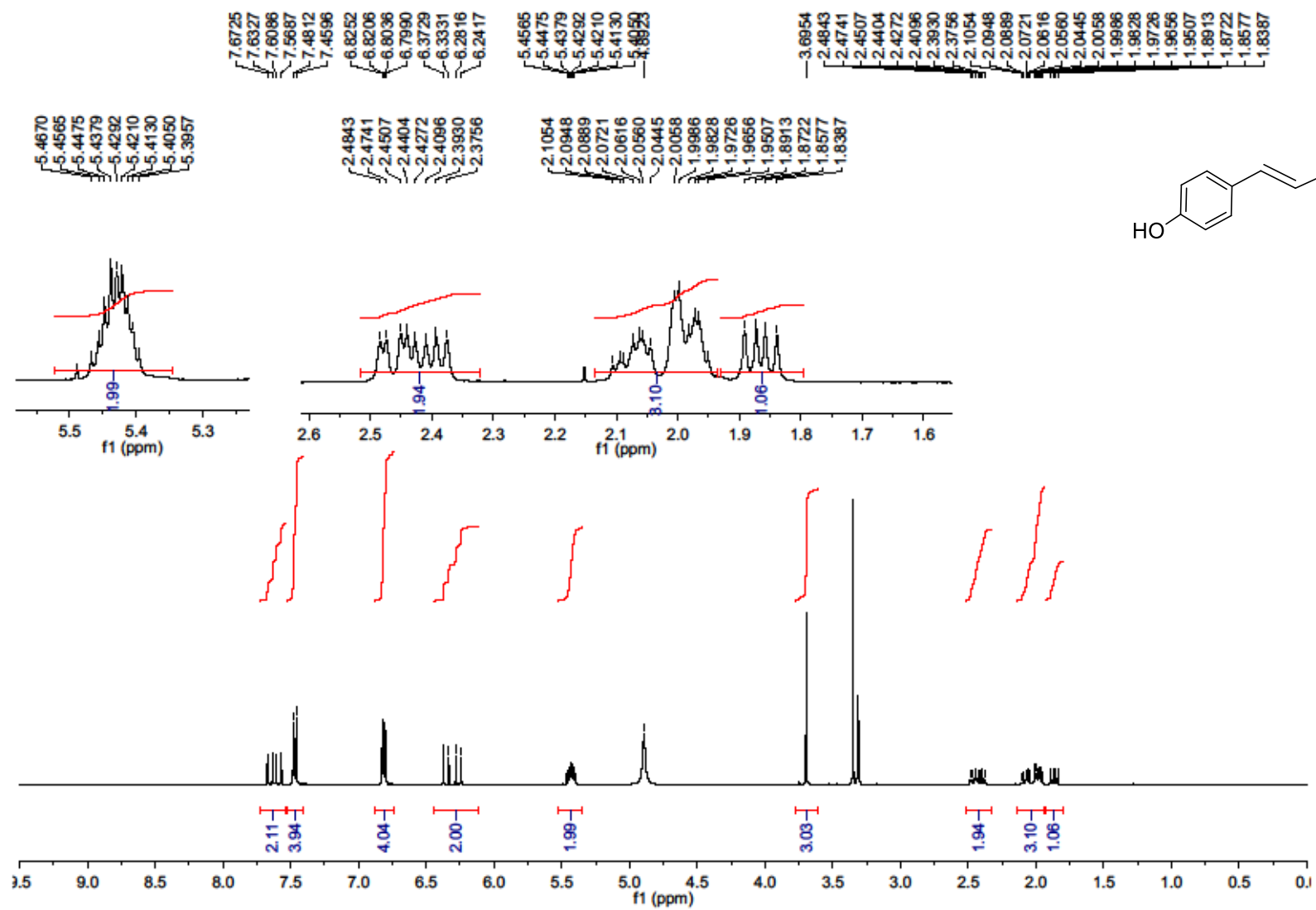


¹³C NMR (100MHz, CD₃OD, 295K)

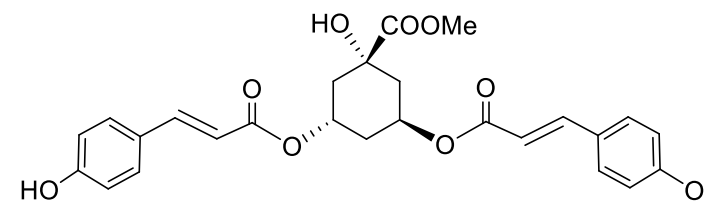
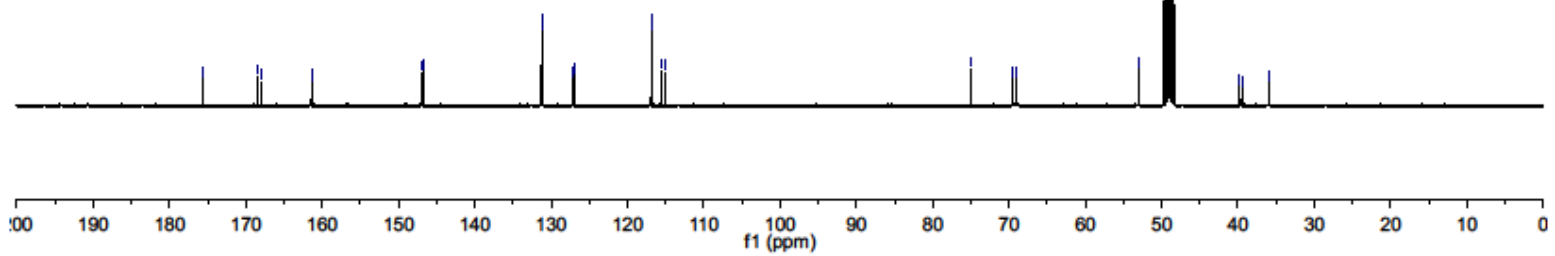
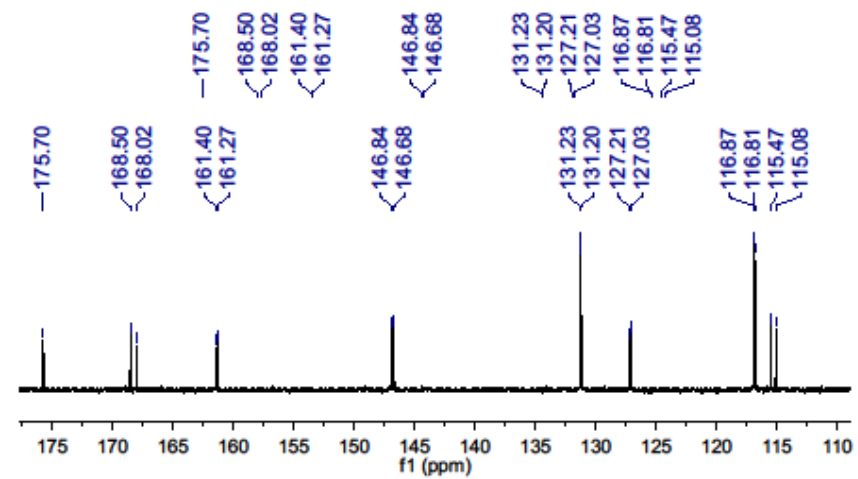


Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10d

^1H NMR (400MHz, CD_3OD , 295K)

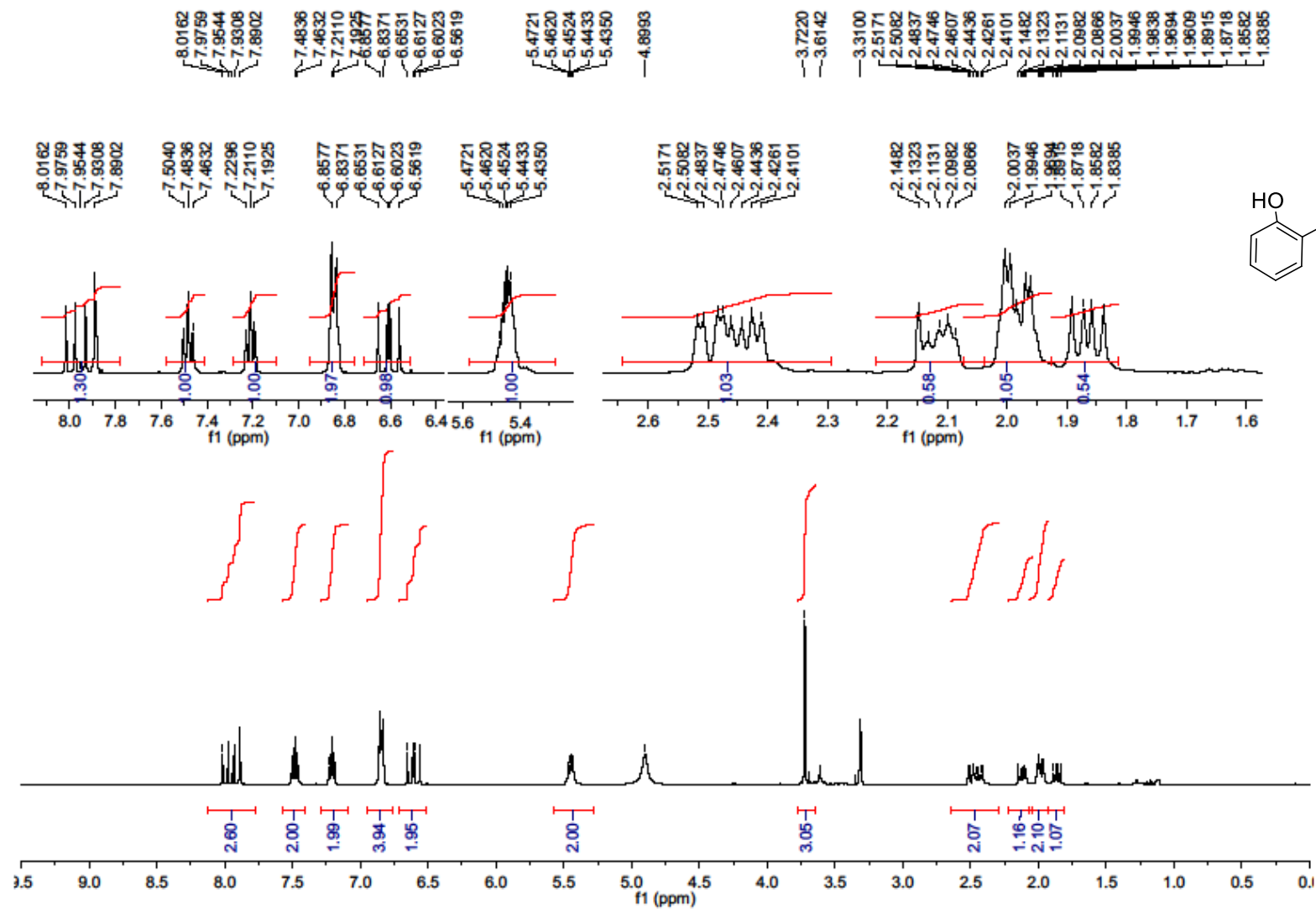


¹³C NMR (100MHz, CD₃OD, 295K)

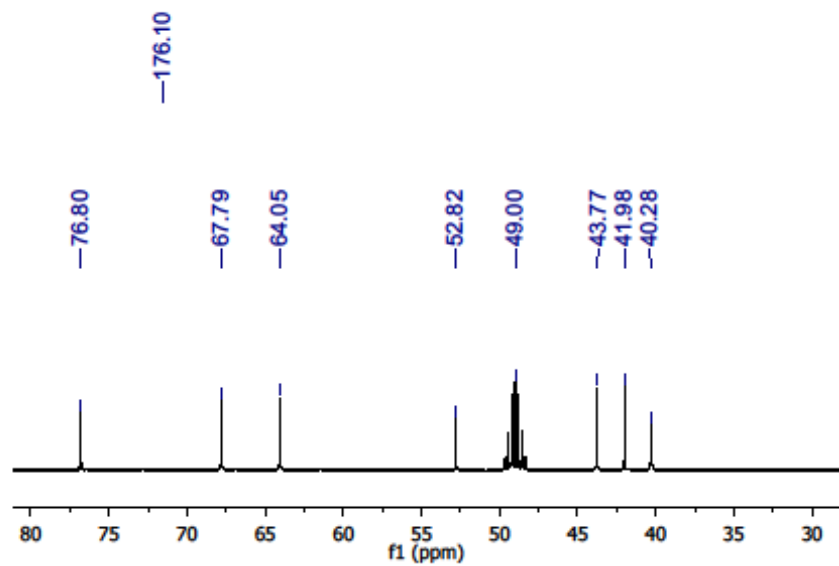


Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(2-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10e

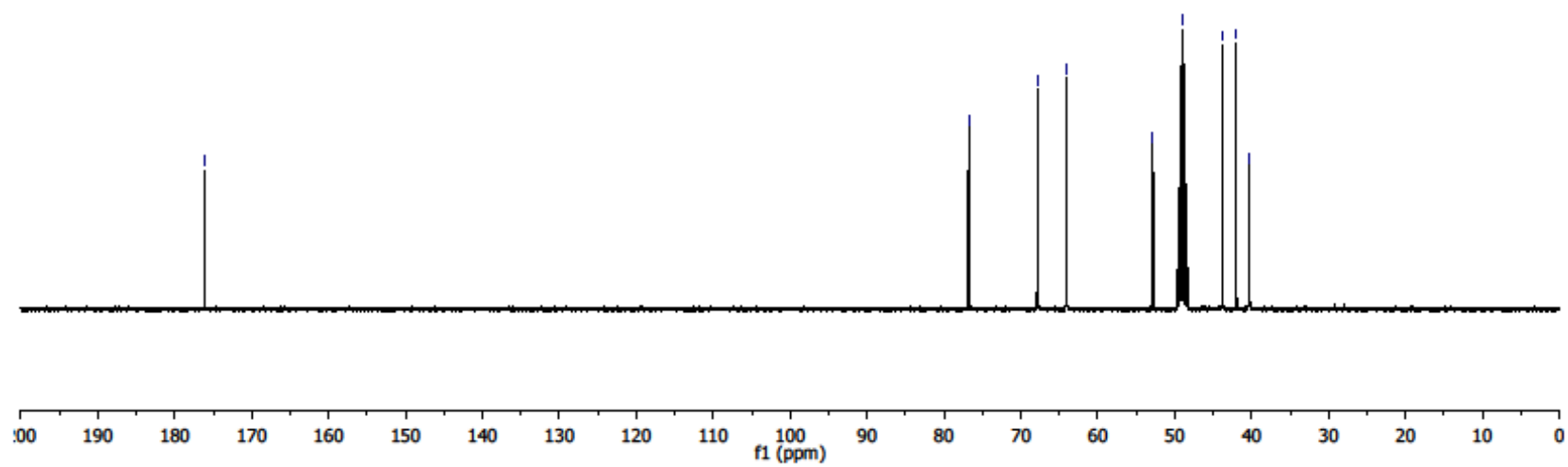
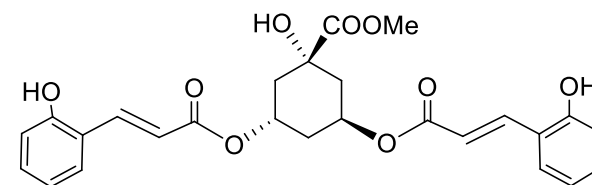
¹H NMR (400MHz, CD₃OD, 295K)



^{13}C NMR (100MHz, CD_3OD , 295K)

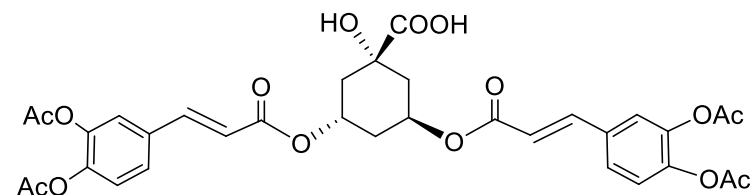
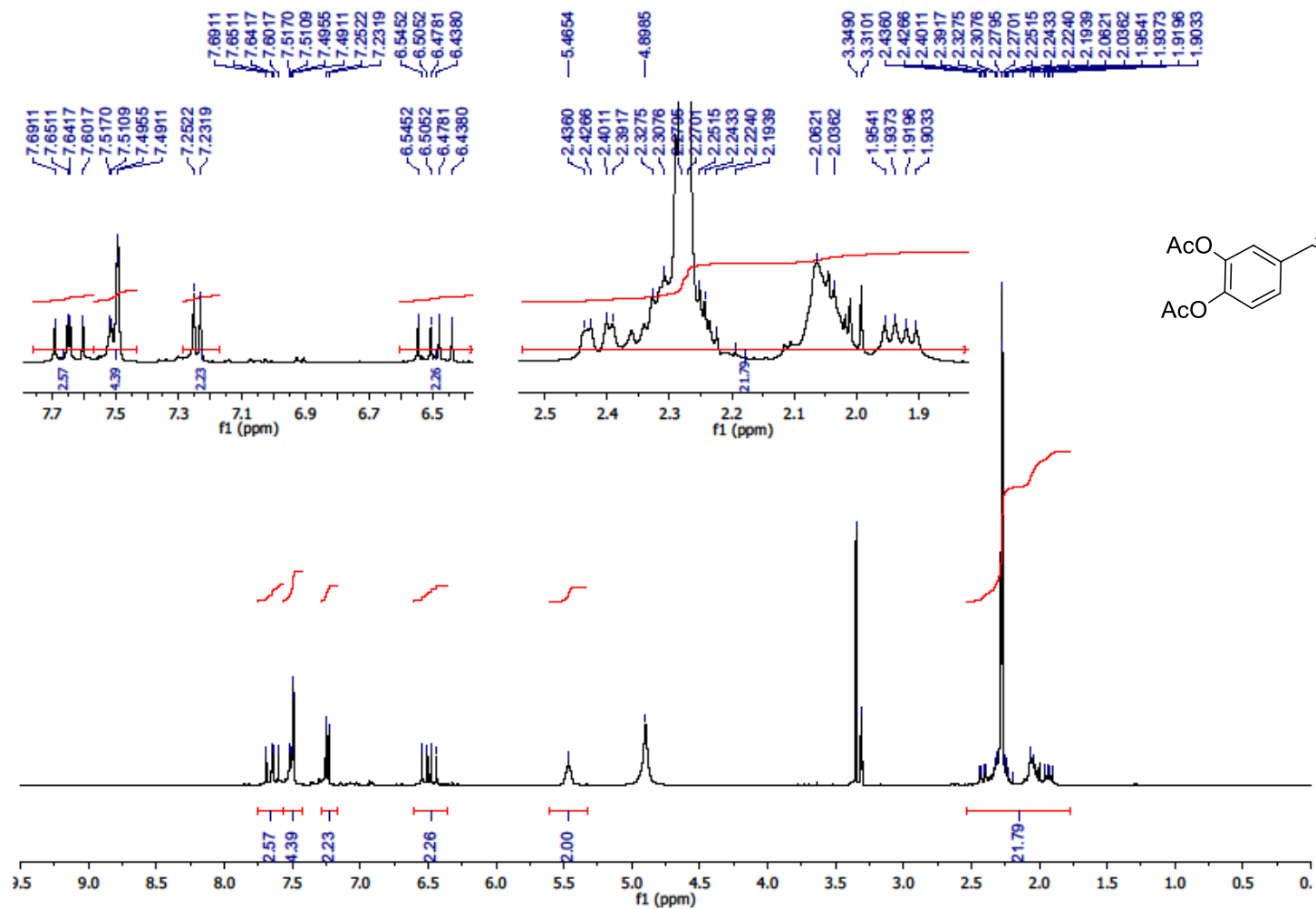


76.80
67.79
64.05
52.82
49.00
43.77
41.98
40.28

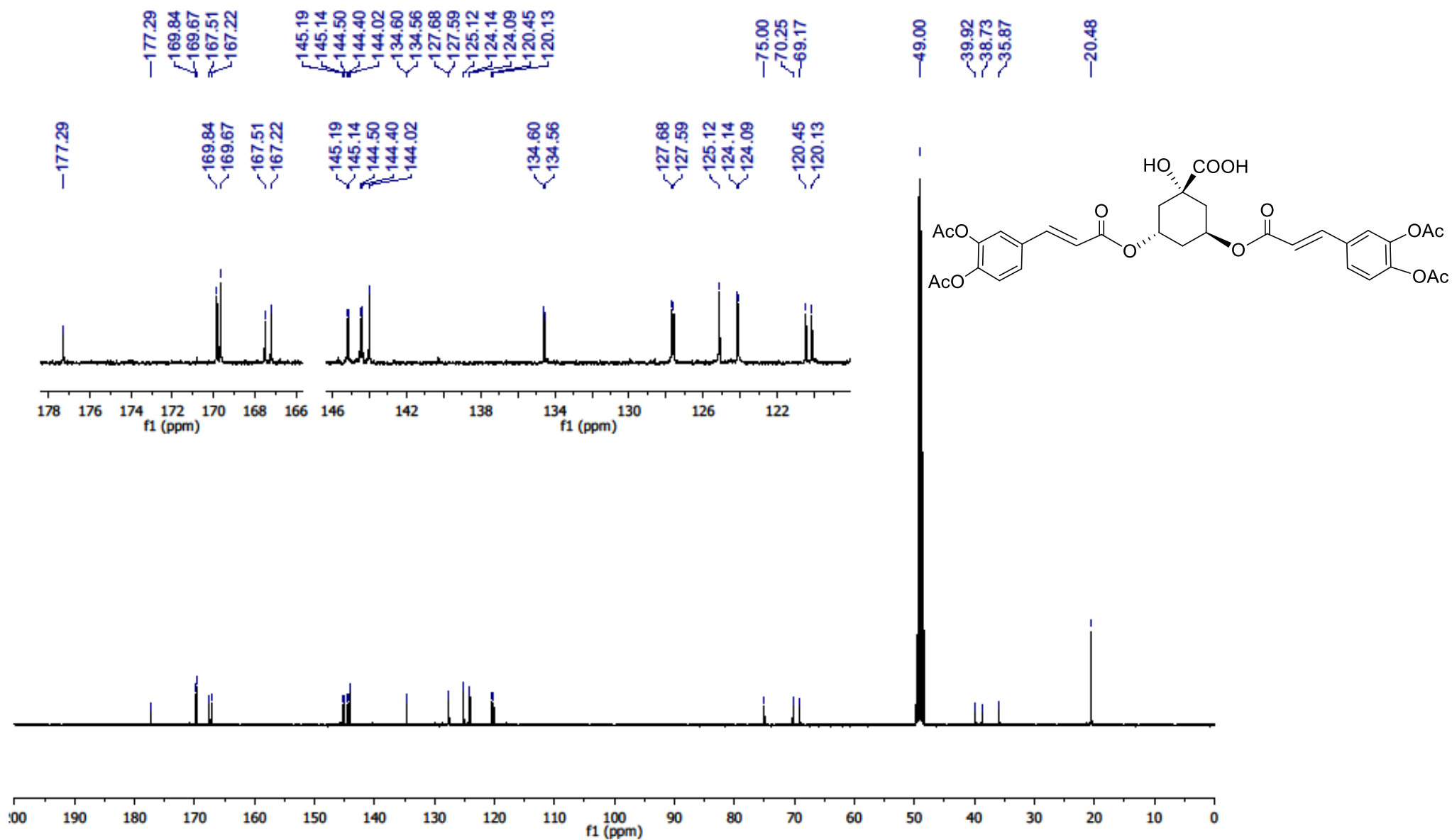


(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 11a

^1H NMR (400MHz, CD_3OD , 298K)

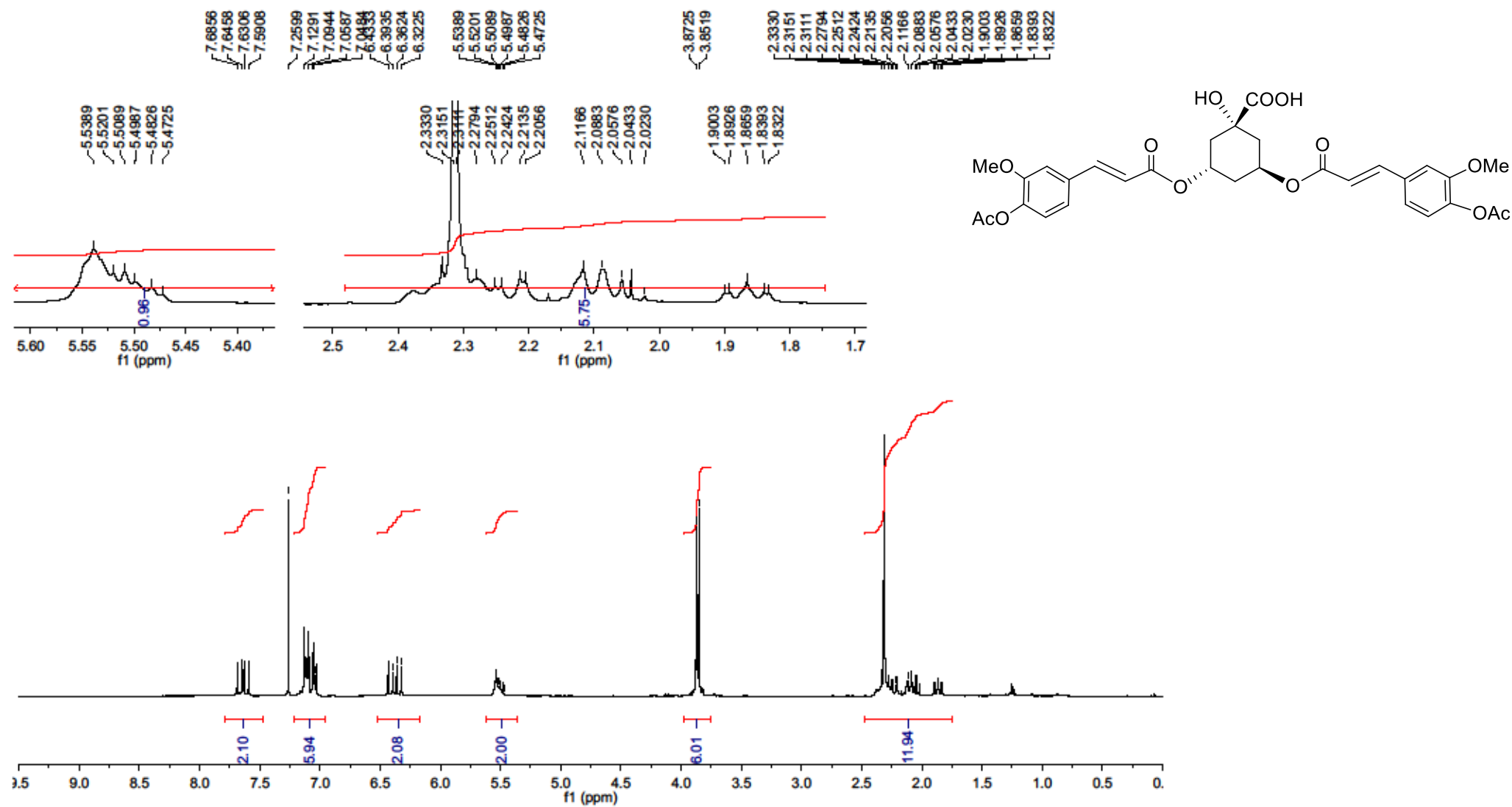


¹³C NMR (100MHz, CD₃OD, 298K)

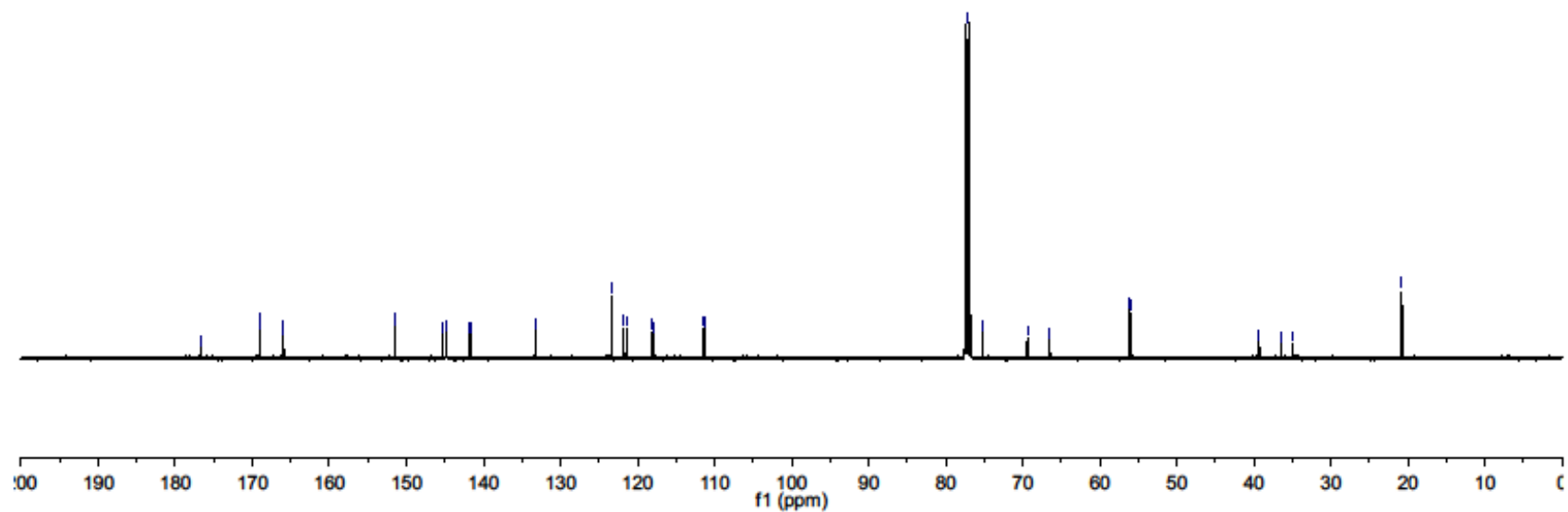
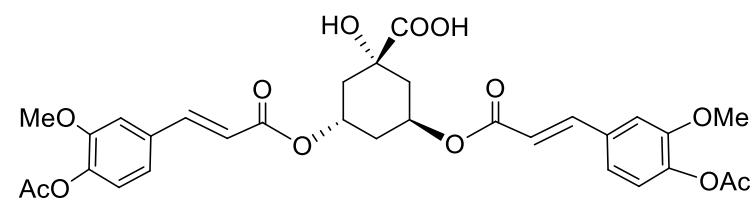
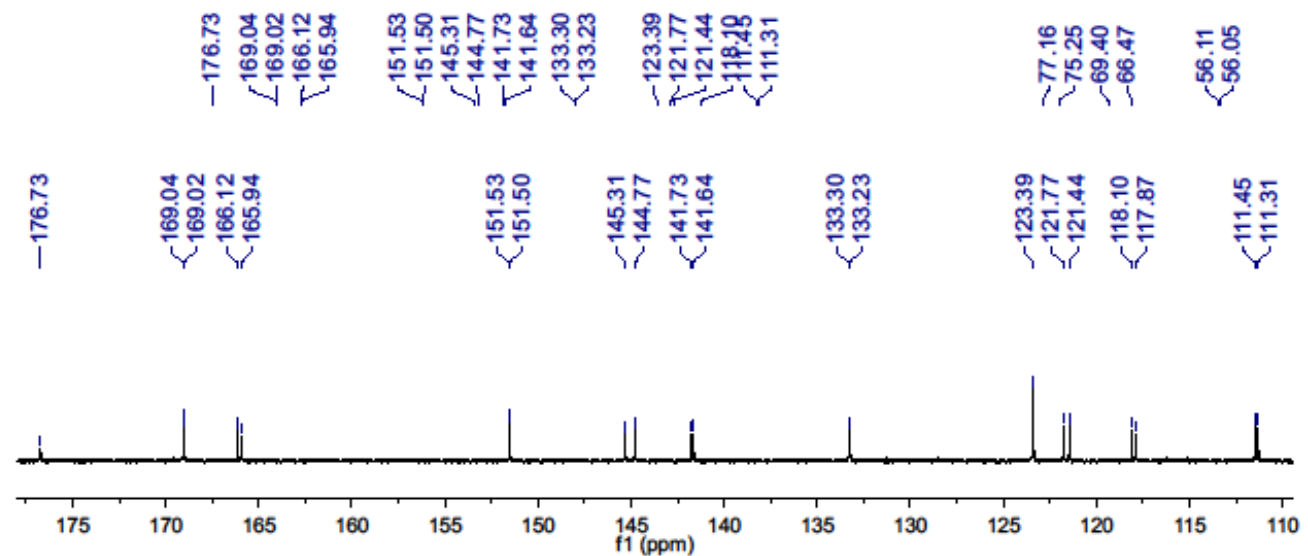


(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 11c

^1H NMR (400MHz, CDCl_3 , 295K)

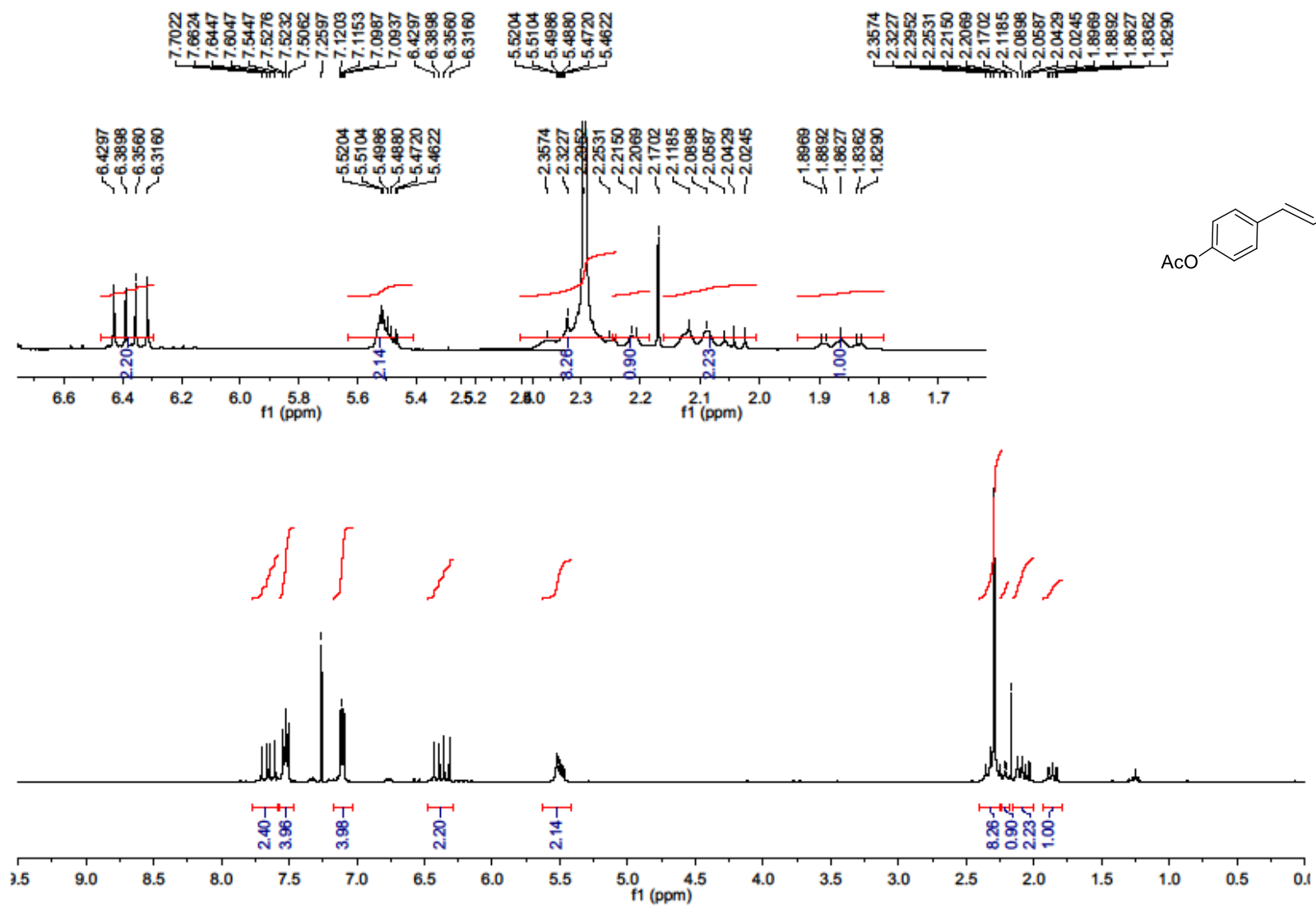


¹³C NMR (100MHz, CD₃OD, 295K)

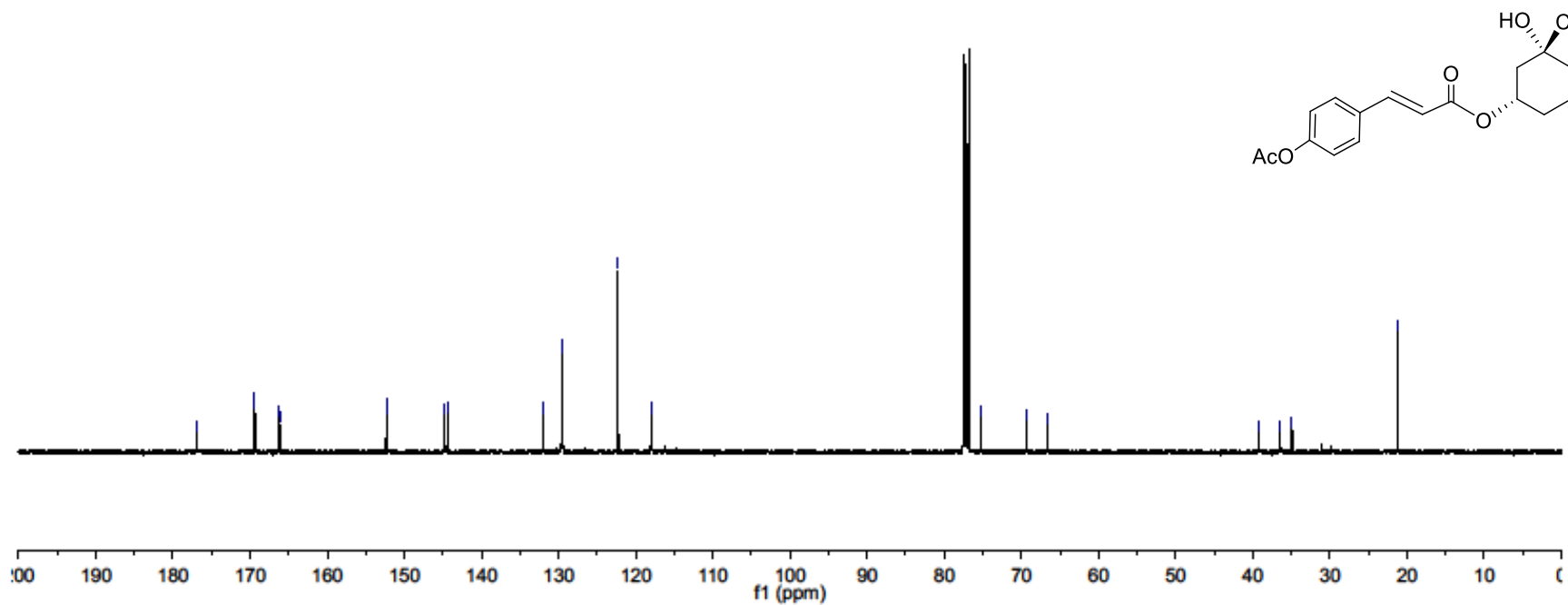
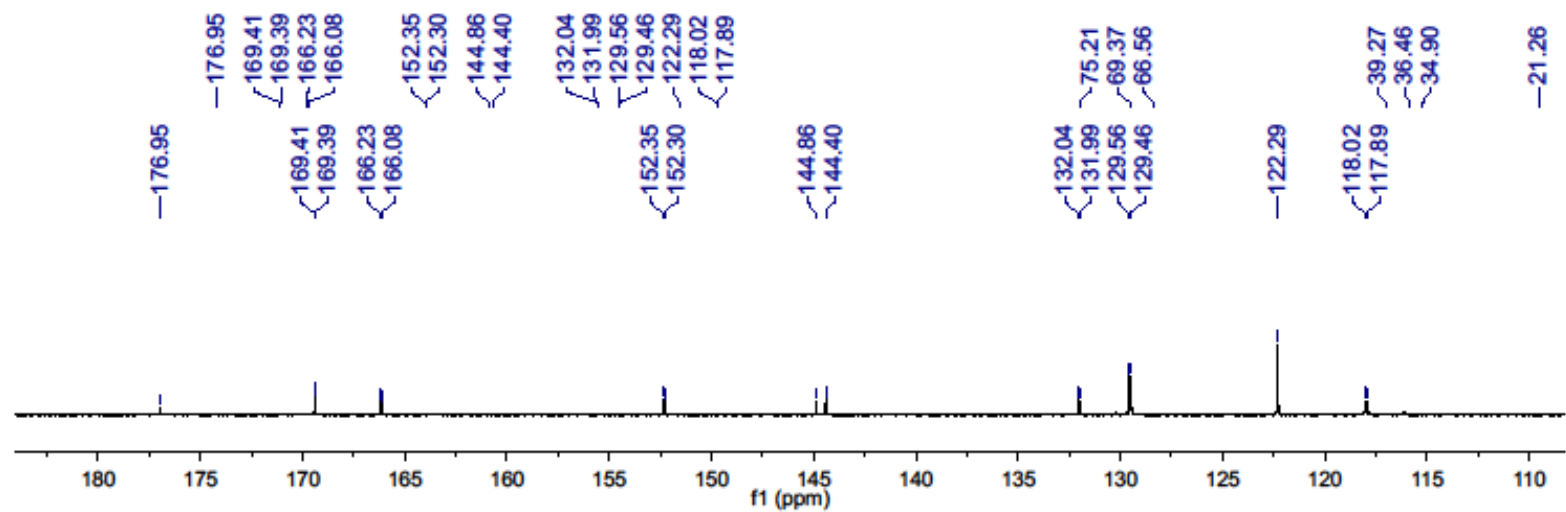


(3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 11d

¹H NMR (400MHz, CDCl₃, 295K)

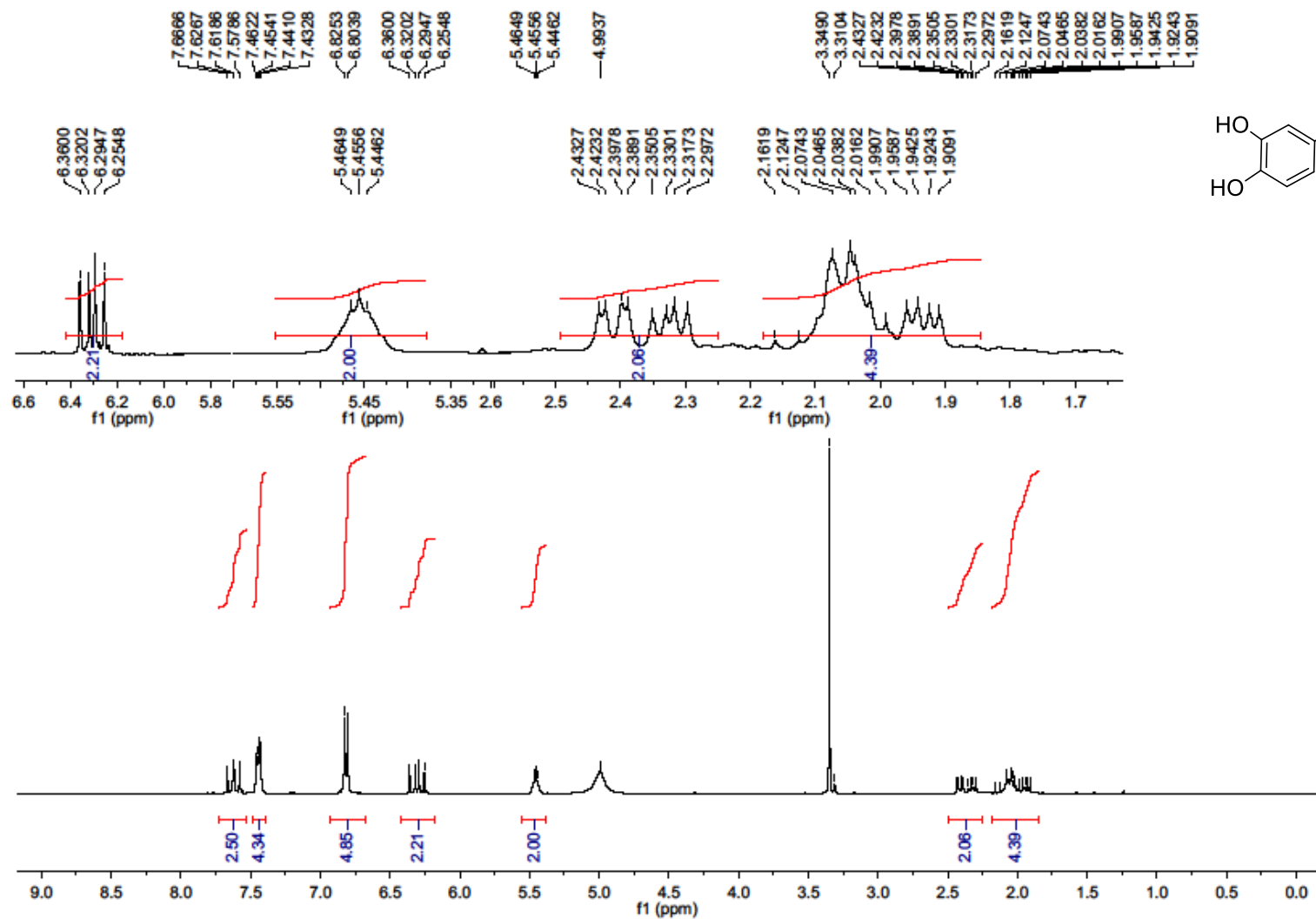


¹³C NMR (100MHz, CD₃OD, 295K)

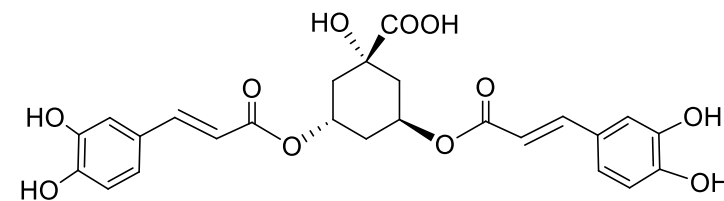
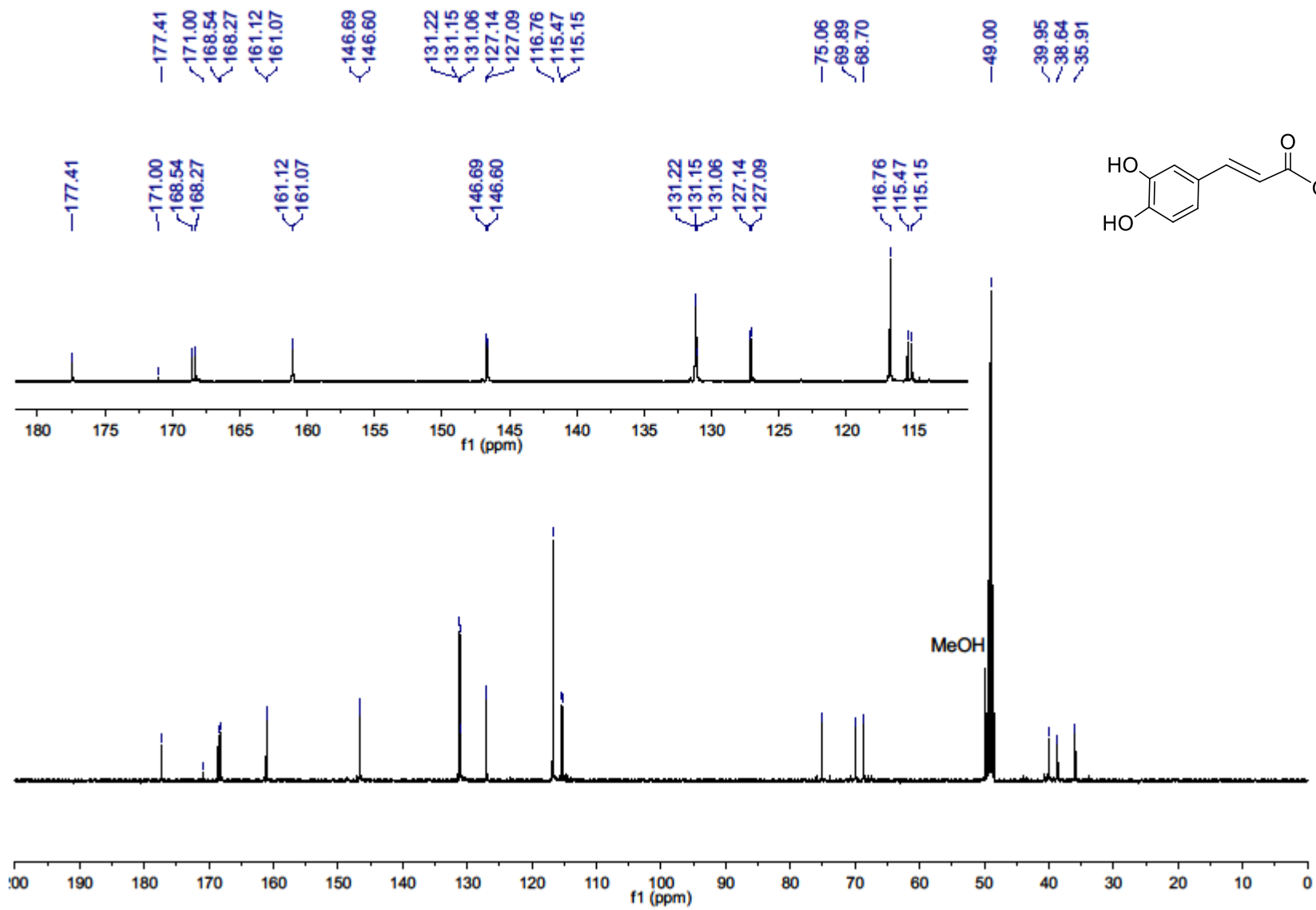


(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4a

^1H NMR (400MHz, CDCl_3 , 295K)

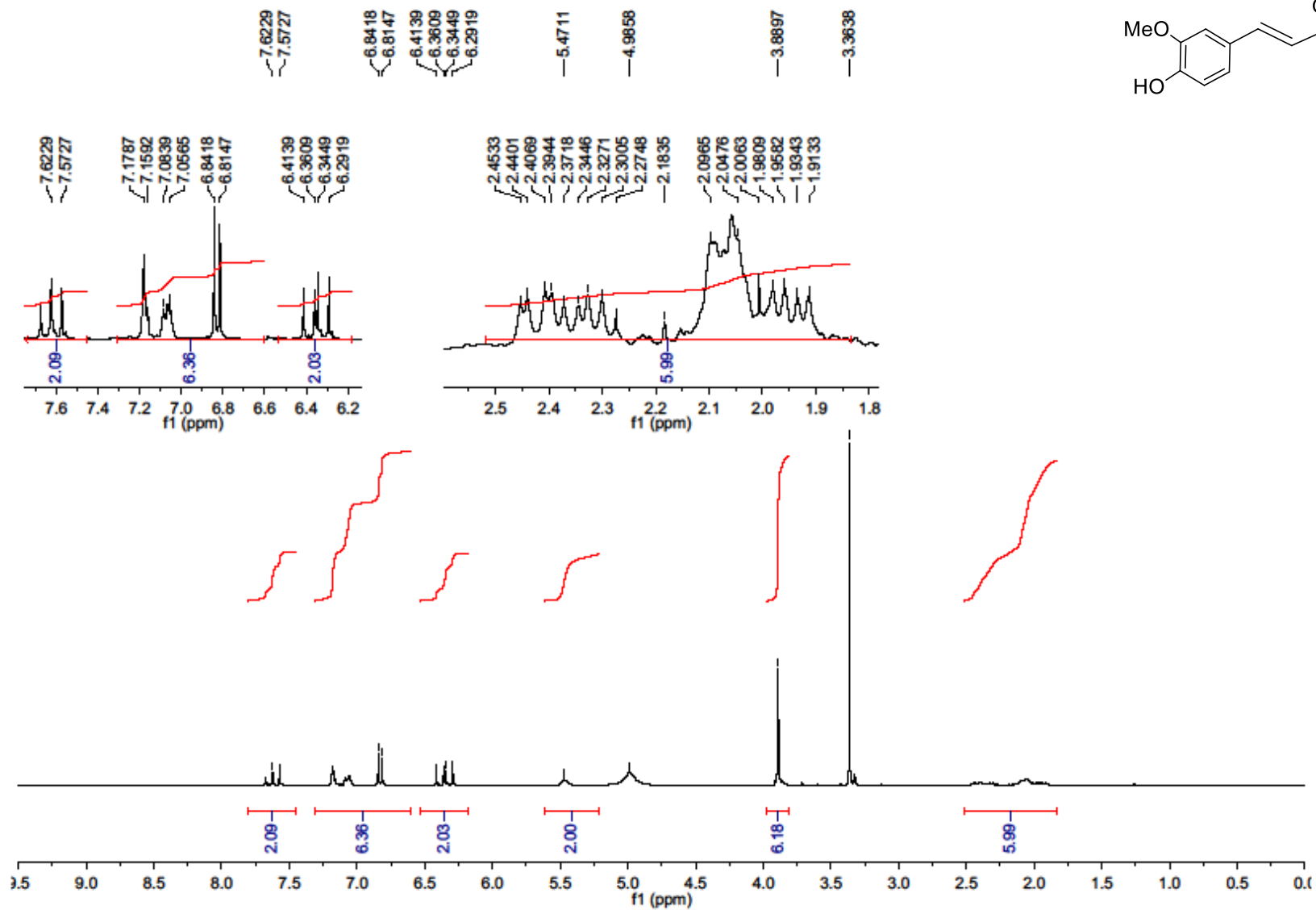
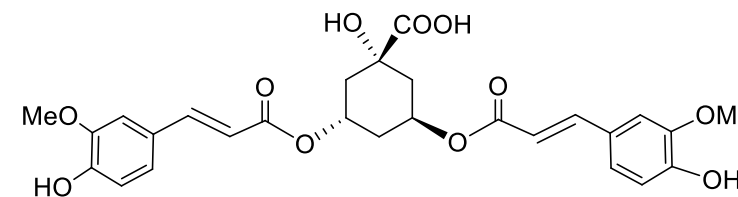


¹³C NMR (100MHz, CD₃OD, 295K)

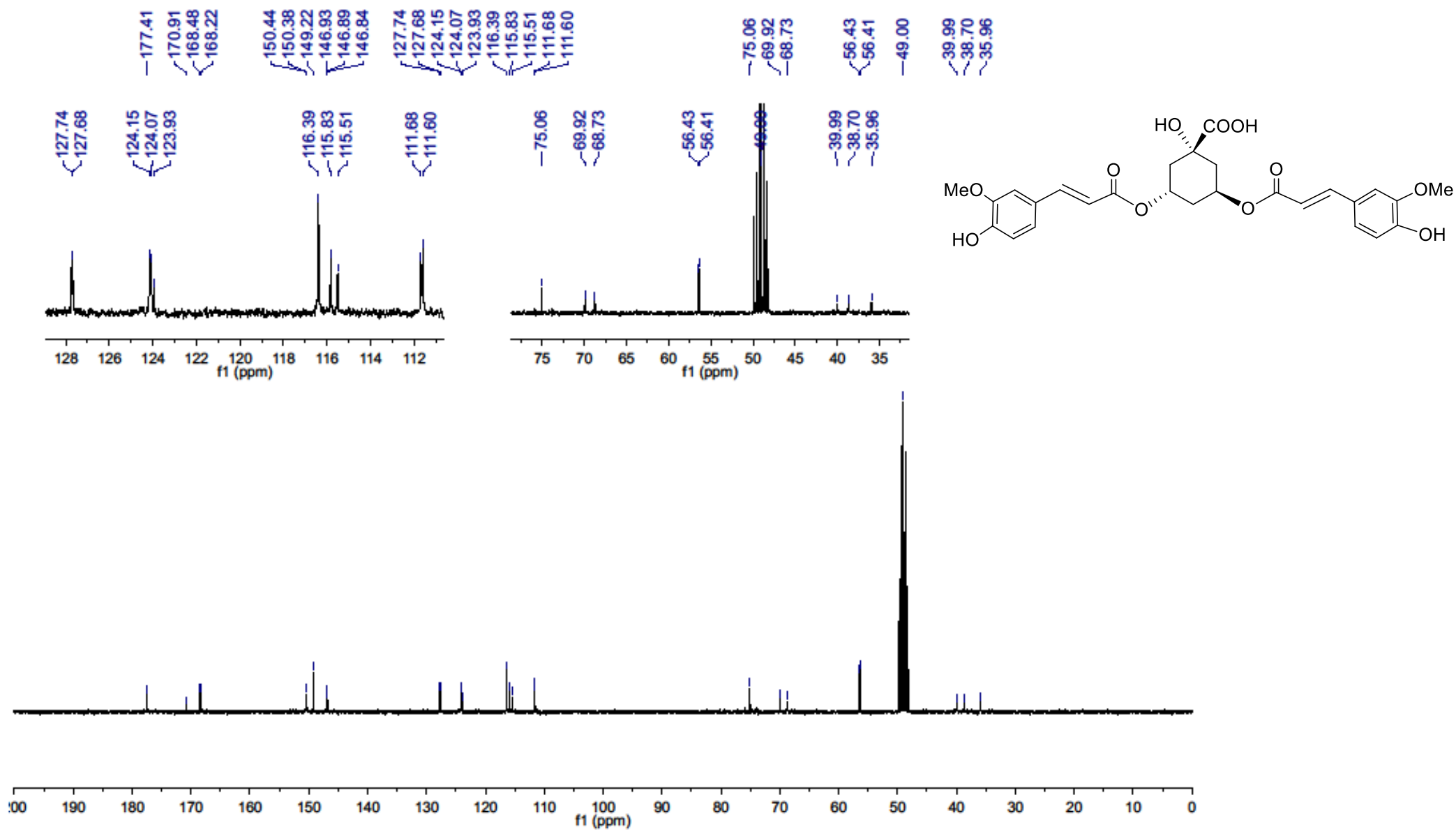


(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4c

¹H NMR (400MHz, CD₃OD, 297K)

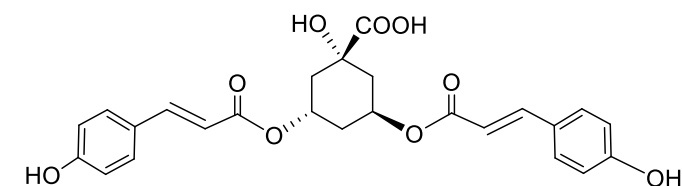
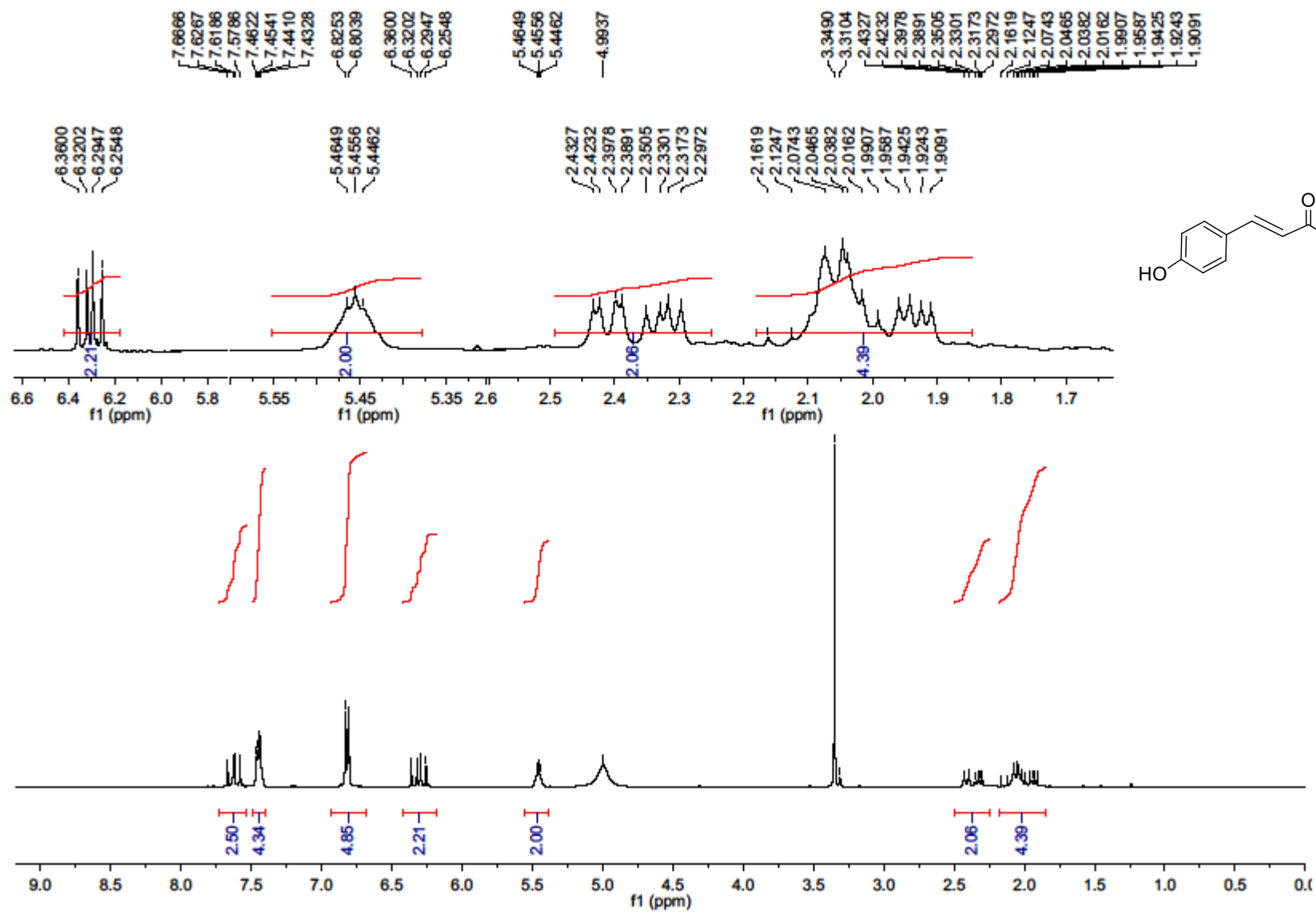


¹³C NMR (100MHz, CD₃OD, 297K)

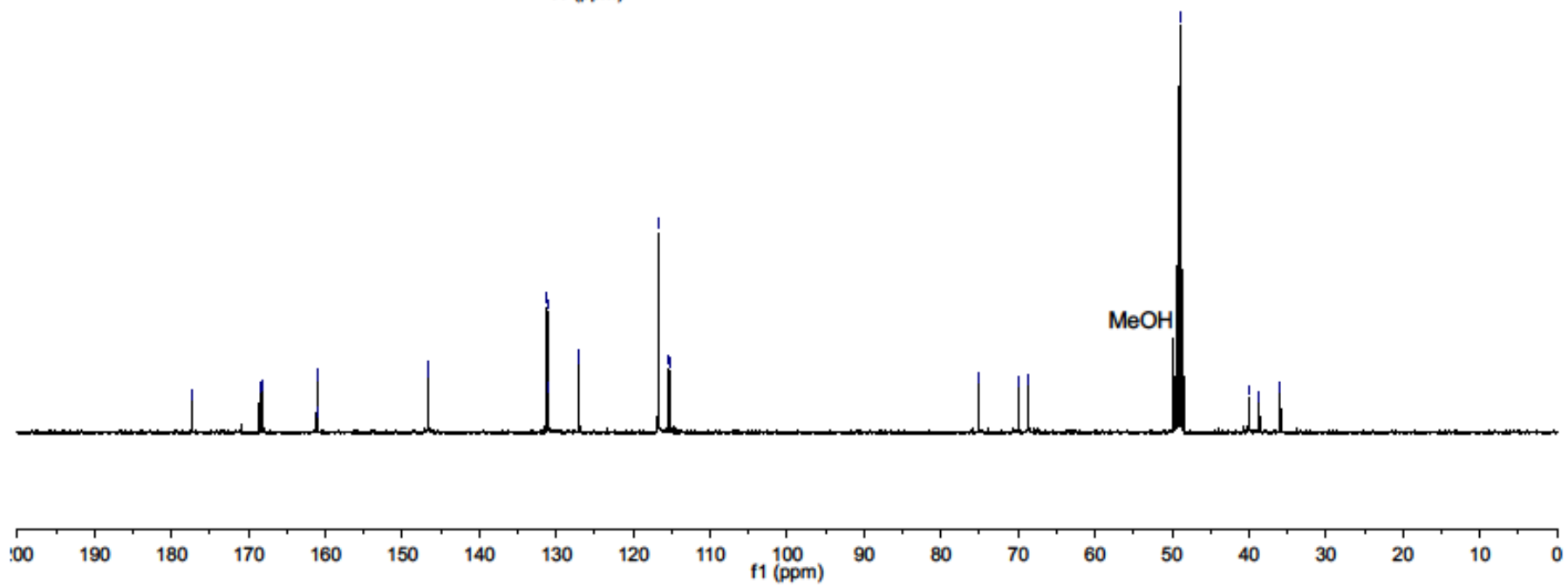
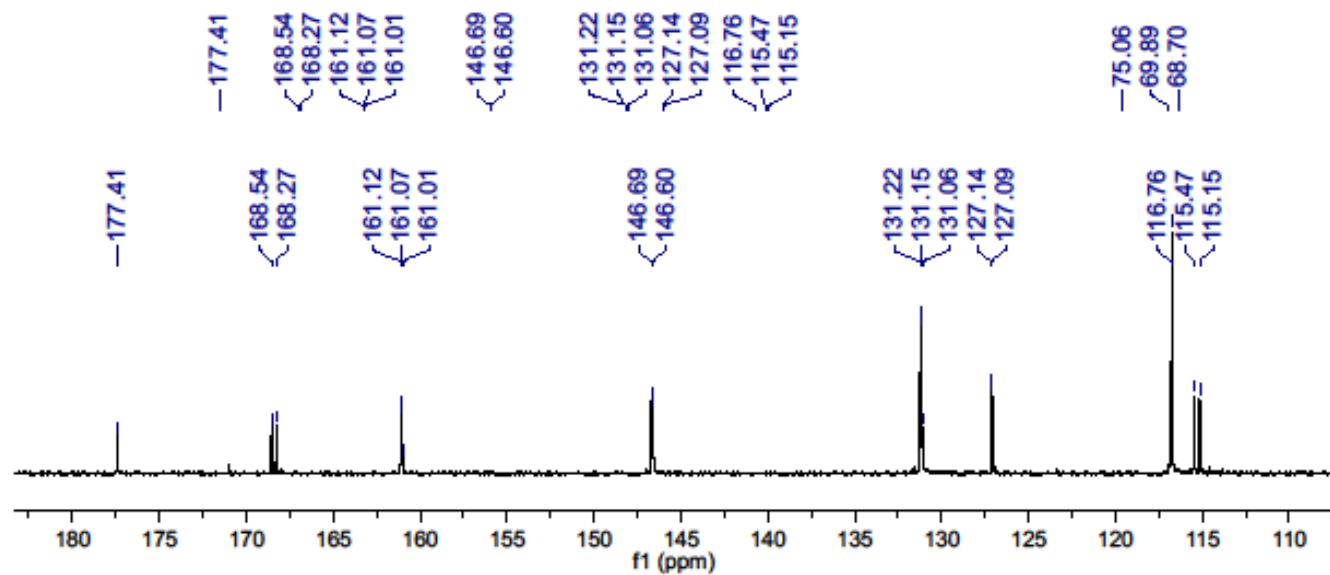


(3S,5S) 1-hydroxy-3,5 bis[[[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4d

¹H NMR (400MHz, CDCl₃, 295K)

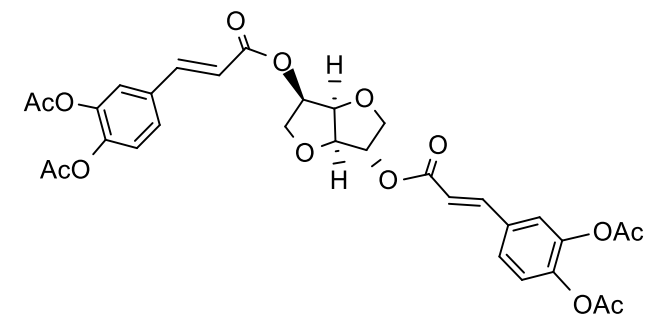
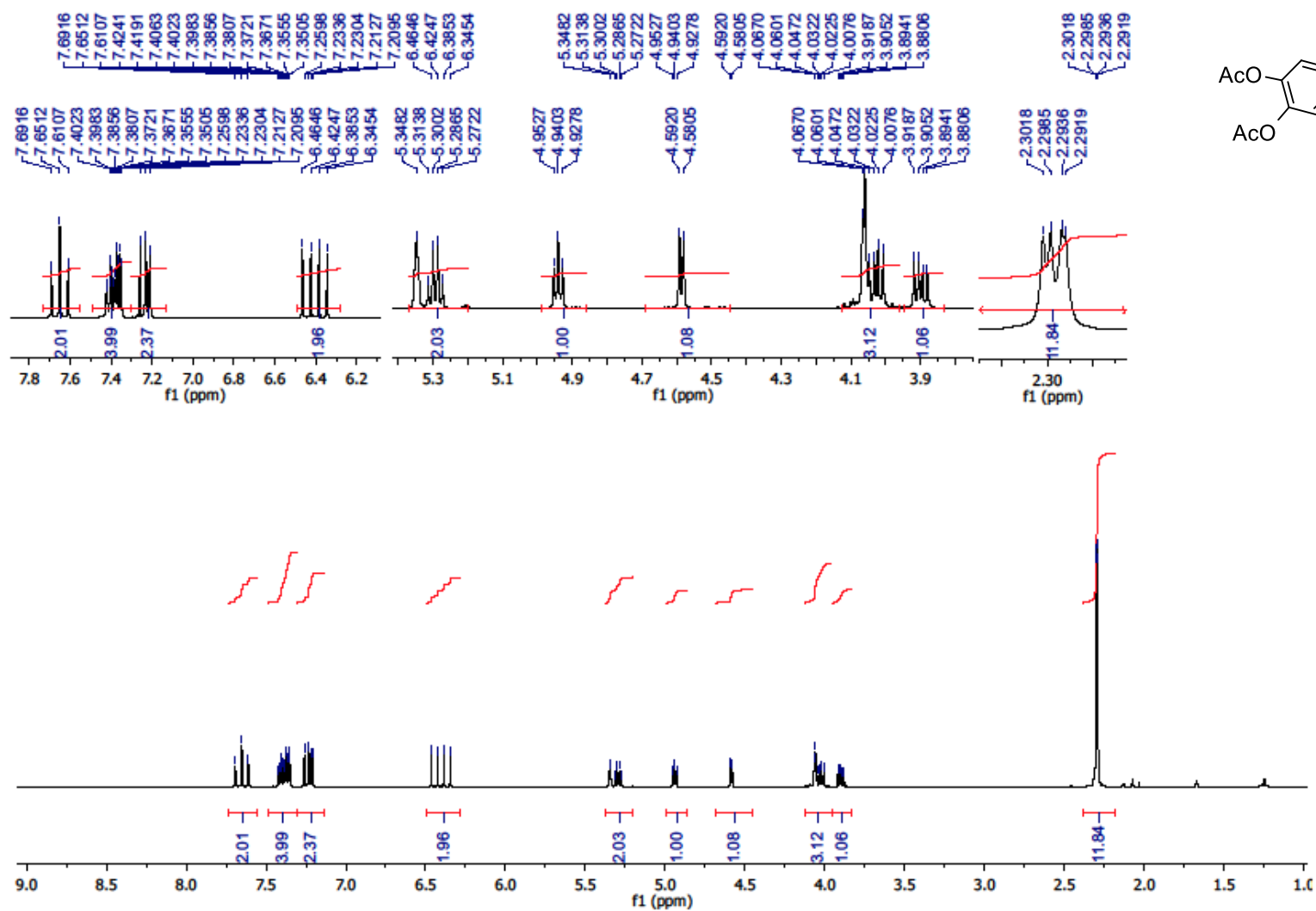


¹³C NMR (100MHz, CD₃OD, 295K)

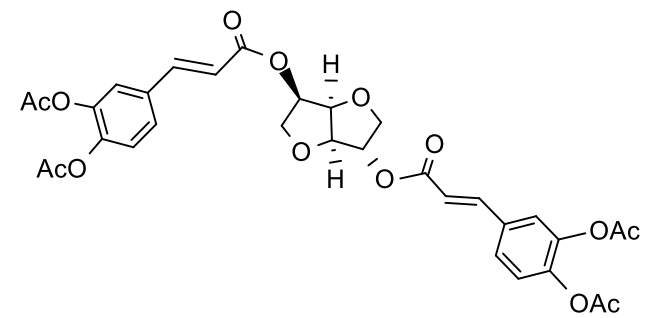
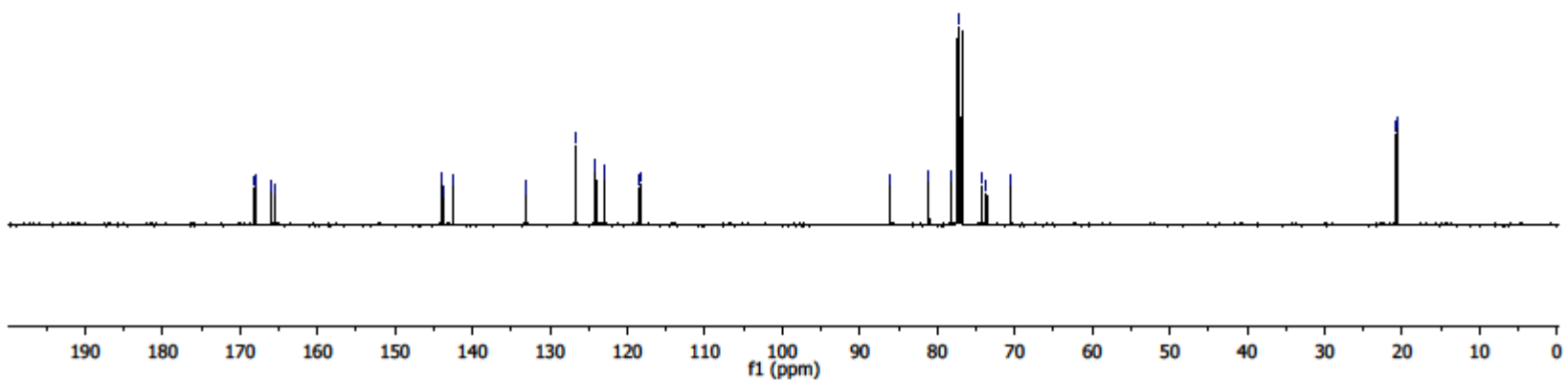
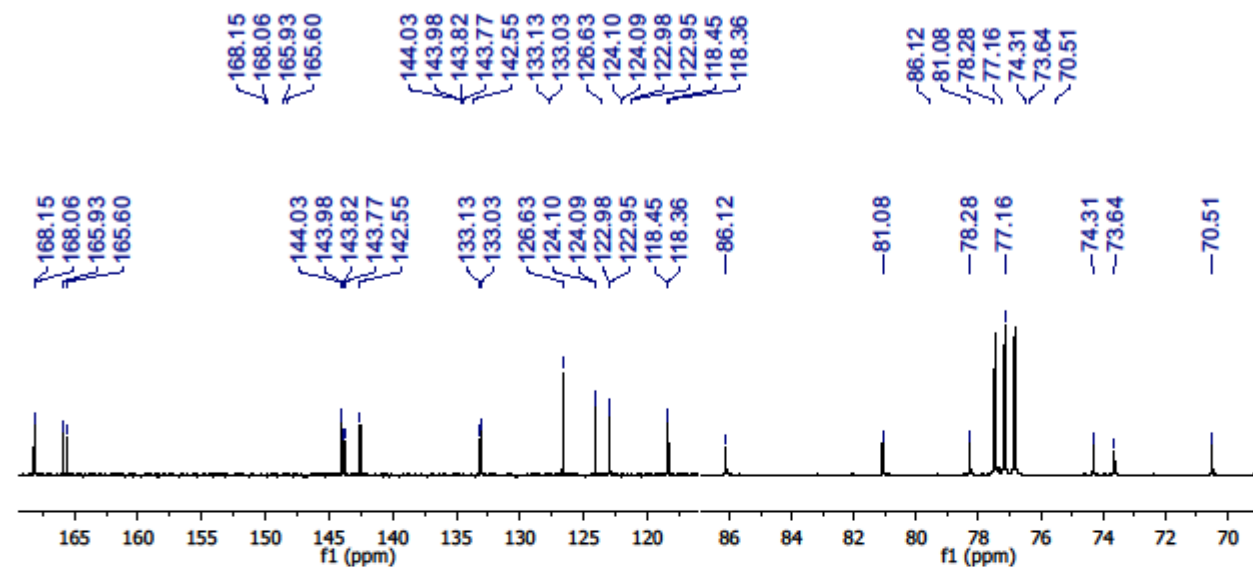


(3R, 3aR, 6S, 6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl (2E,2'E)bis--[4-(acetyloxy)-3-methoxyphenyl]prop-2-enoate II

NMR ¹H (400 MHz, CDCl₃, 295 K)

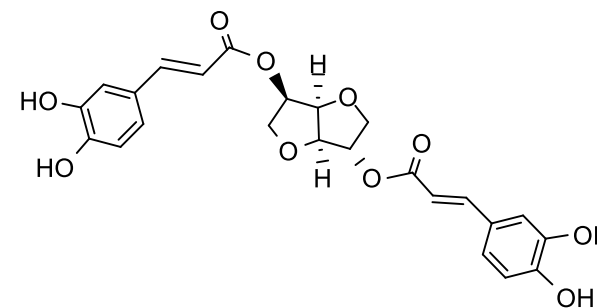
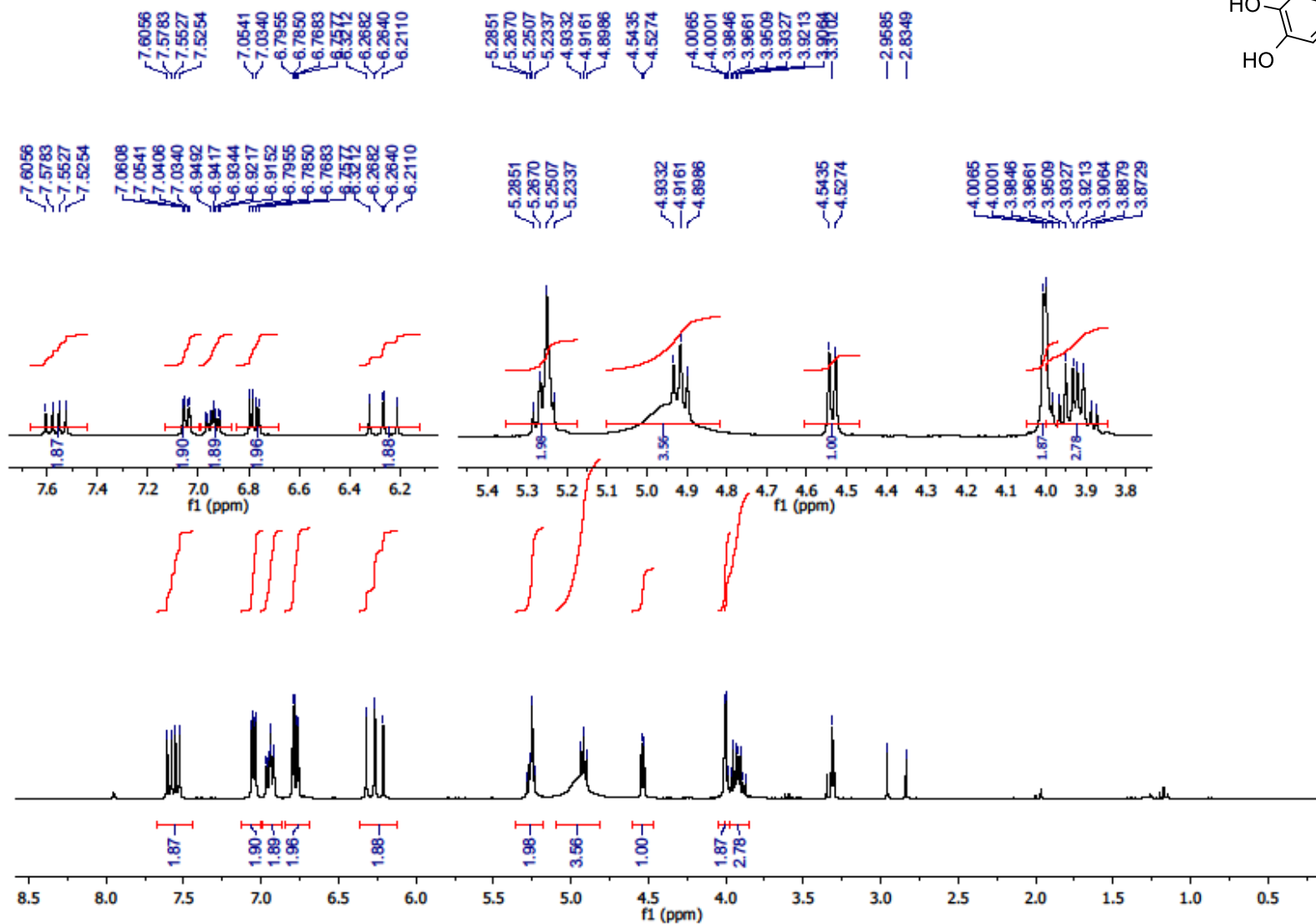


NMR ^{13}C (100 MHz, CDCl_3)

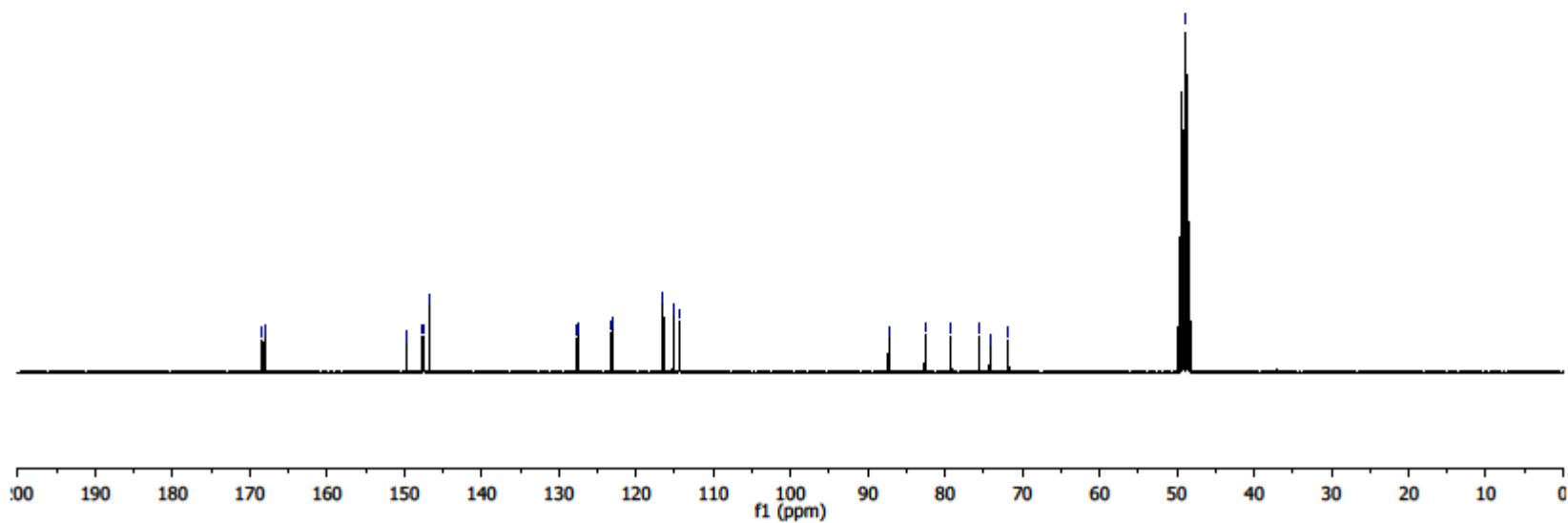
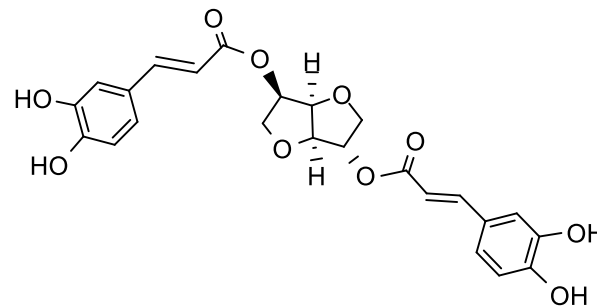
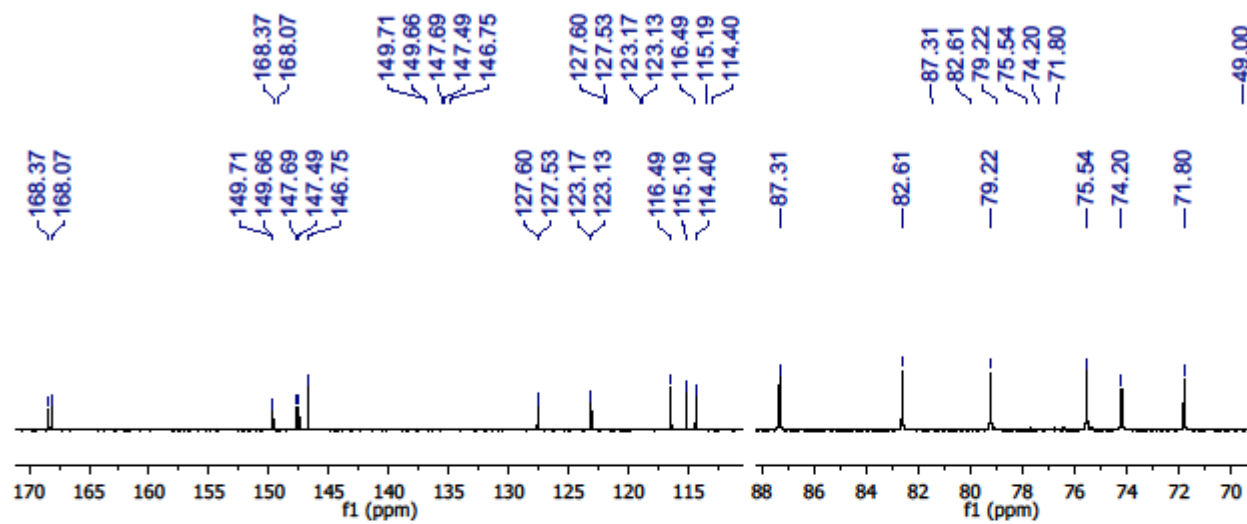


(3*R*,3*aR*,6*S*,6*aR*)-hexahydrofuro[3,2-*b*]furan-3-yl (2*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoate 12

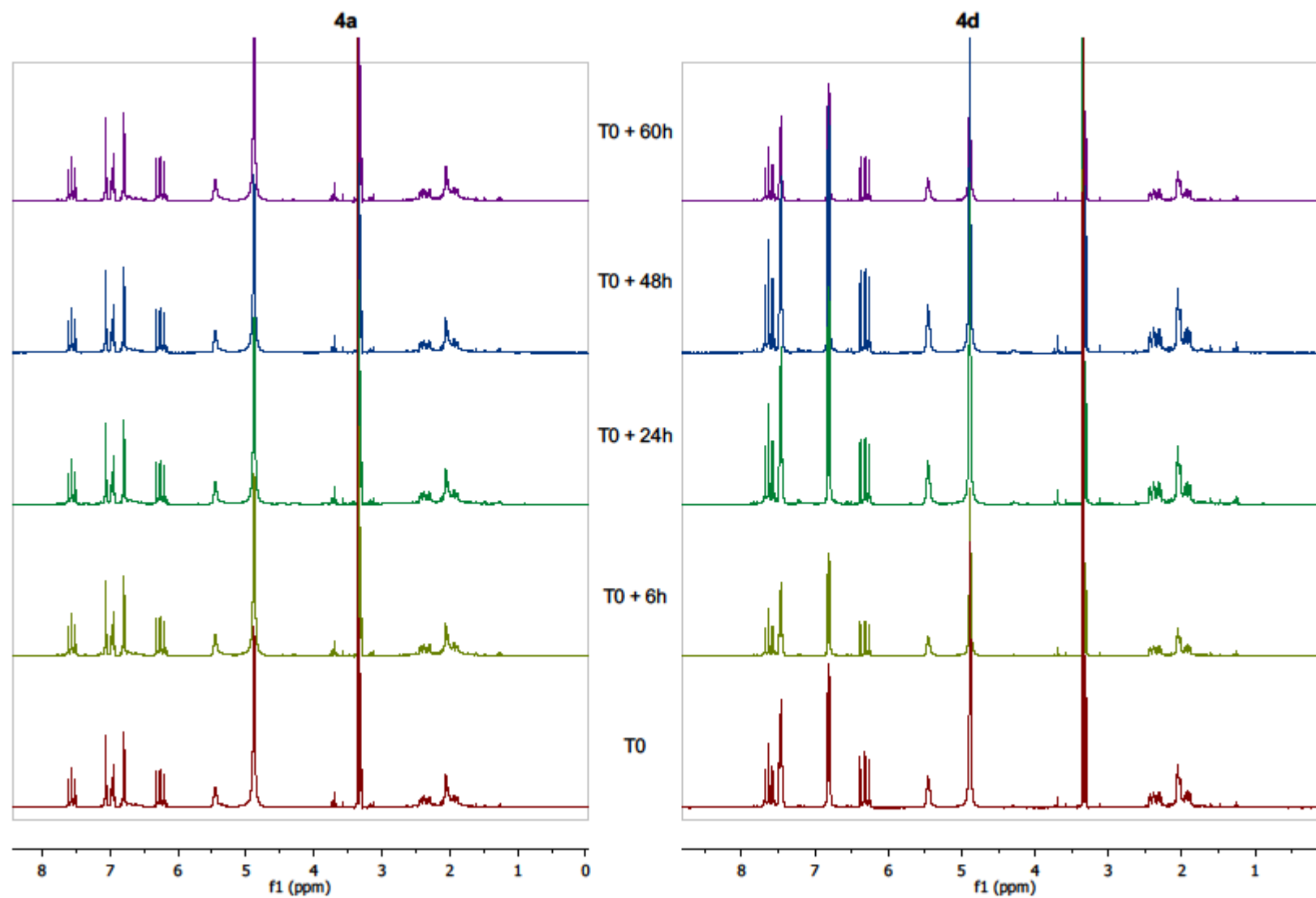
NMR ¹H (300 MHz, CD₃OD)



NMR ^{13}C (75 MHz, CD_3OD)



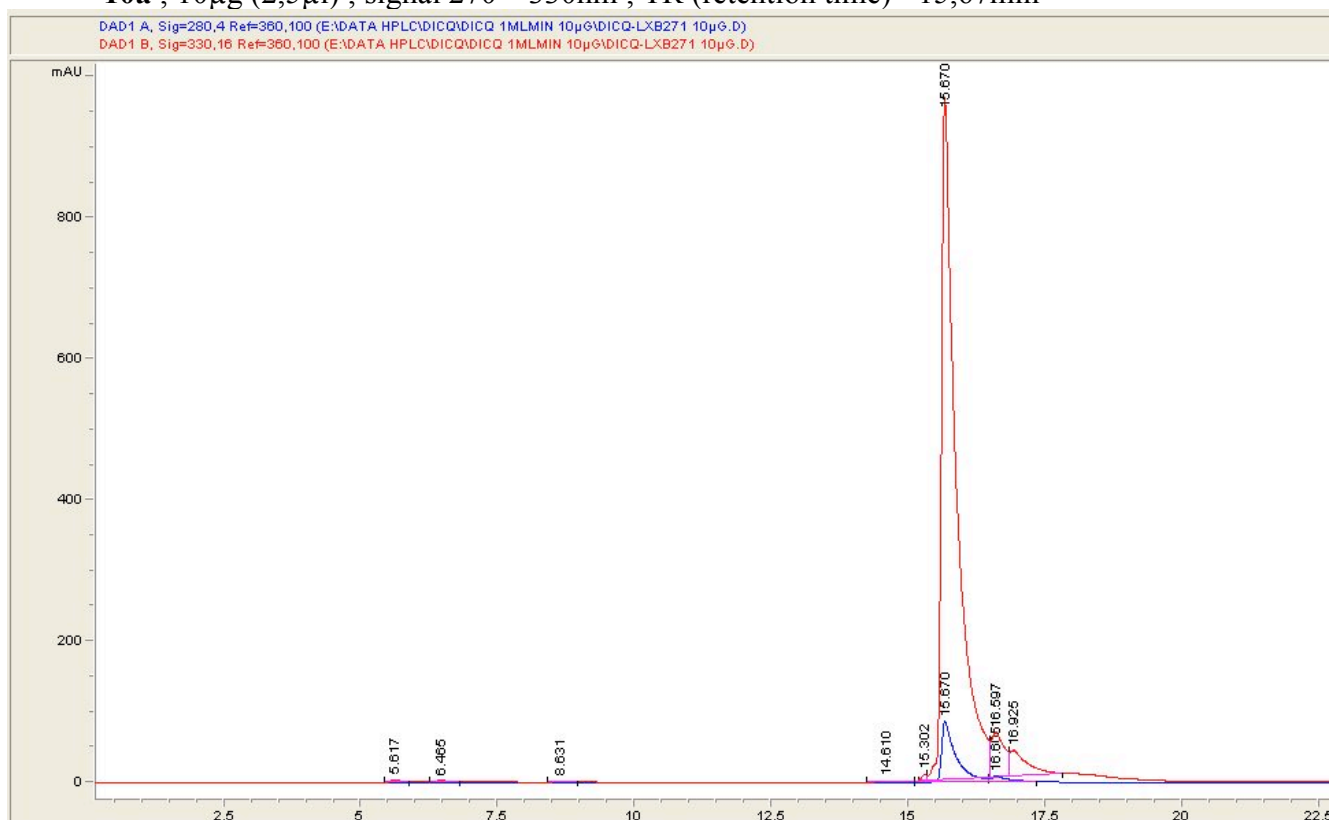
^1H NMR Spectra of 4a and 4d in CD_3OD at 296,5 K at different time intervals ($t_0 + 6\text{h}$, $t_0 + 24\text{h}$, $t_0 + 48\text{h}$, $t_0 + 60\text{h}$)



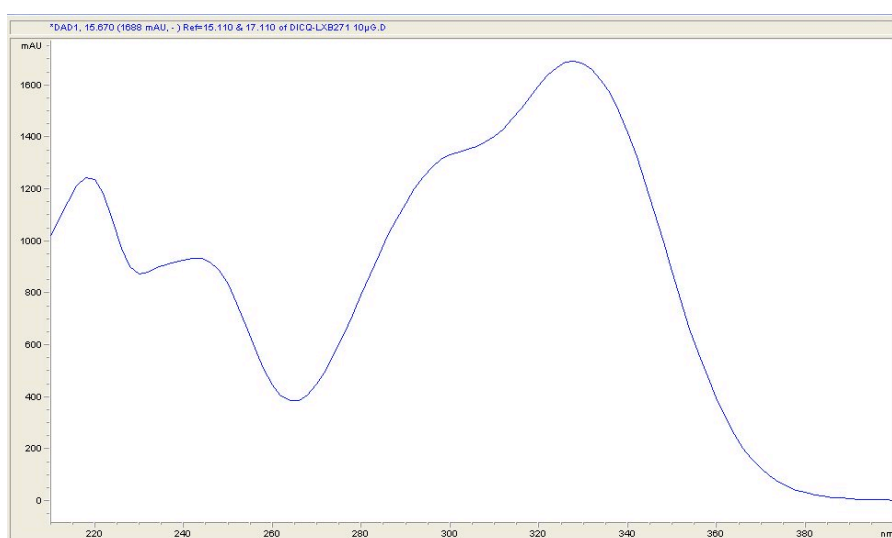
HPLC analysis and UV spectra for compounds 10a, 10c, 10d, 10e, 4a, 4c, 4d, 12

HPLC conditions : Agilent equipment, Column phenomenex C18: Jupiter® 5µm; 300 Å, LC Column 250 x 4.6mm, flow **1ml/min**; Mobile phase 0 - 2min: 80% H₂O UHQ + TFA (A) / 20% CH₃CN + TFA (B); 22min: 40 % A / 60% B; 30min: 100% ACN + TFA; 33min: 80% A/ 20% B. Samples were dissolved in MeOH (6mL) and 10µg were injected per sample

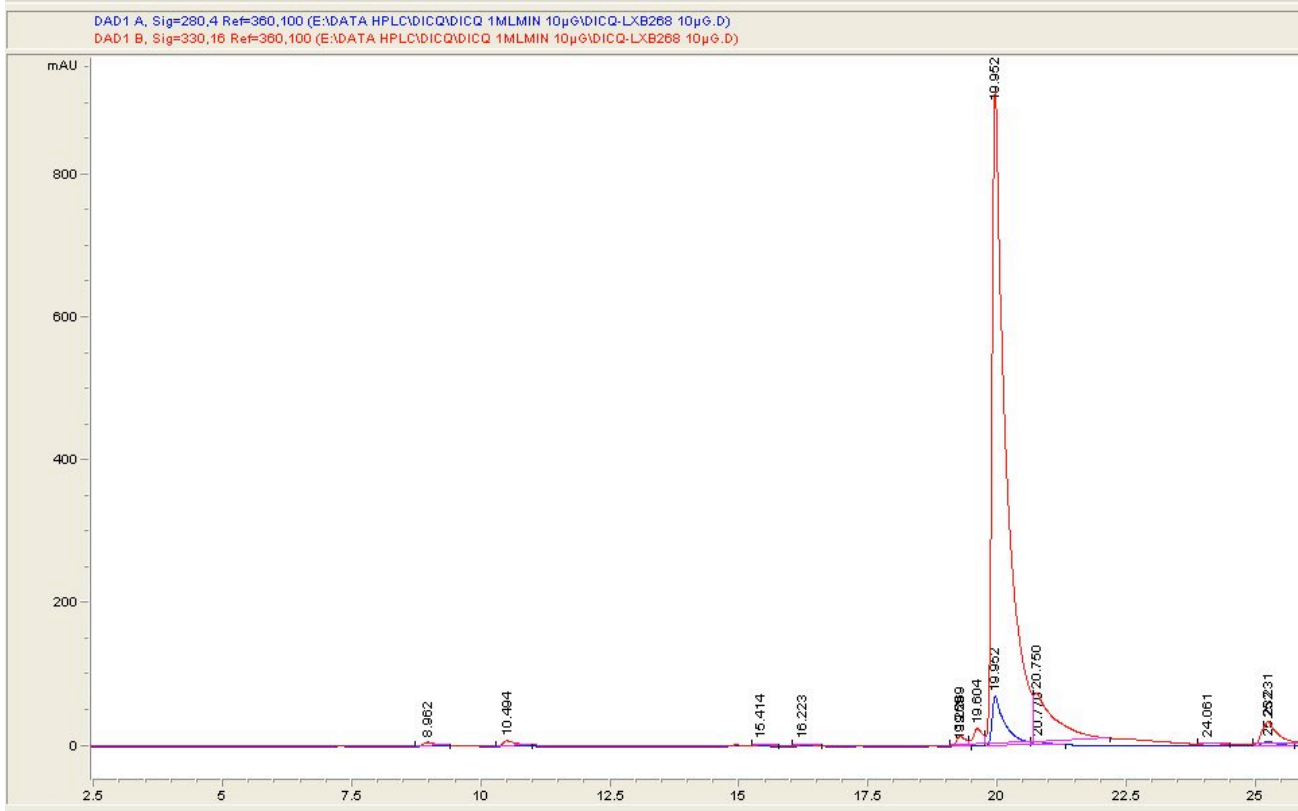
- **10a** ; 10µg (2,5µl) ; signal 270 – 330nm ; TR (retention time) =15,67min



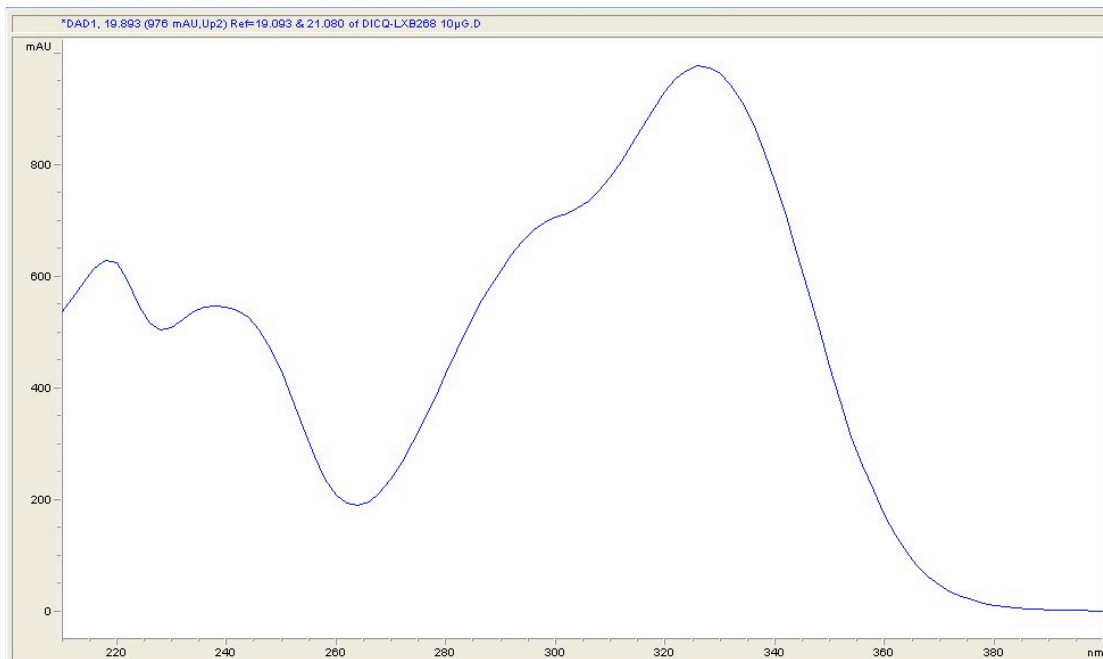
UV spectrum (210 – 400nm) à 15,670min (signal 330nm)



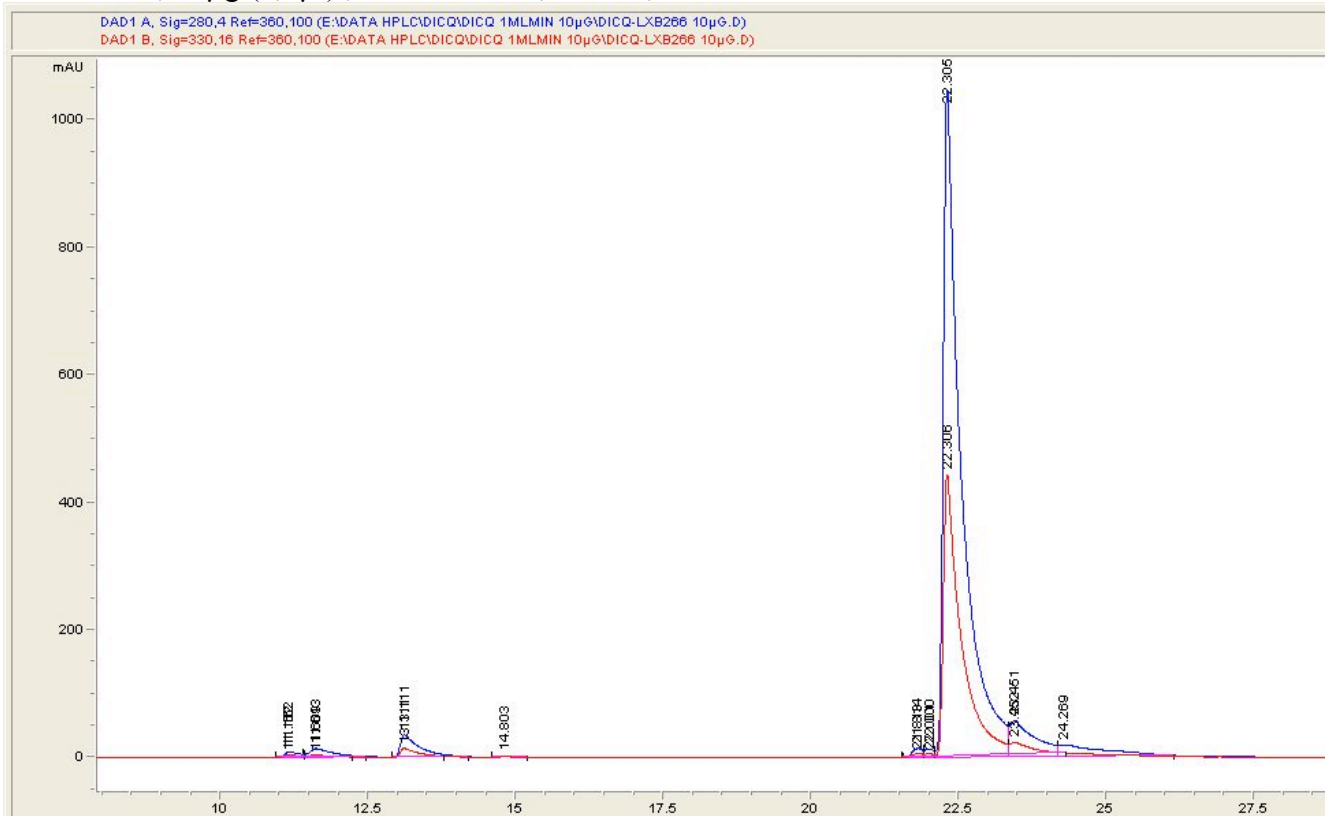
- **10c** 10µg (4µl) ; 270 – 330nm ; TR=19,95min



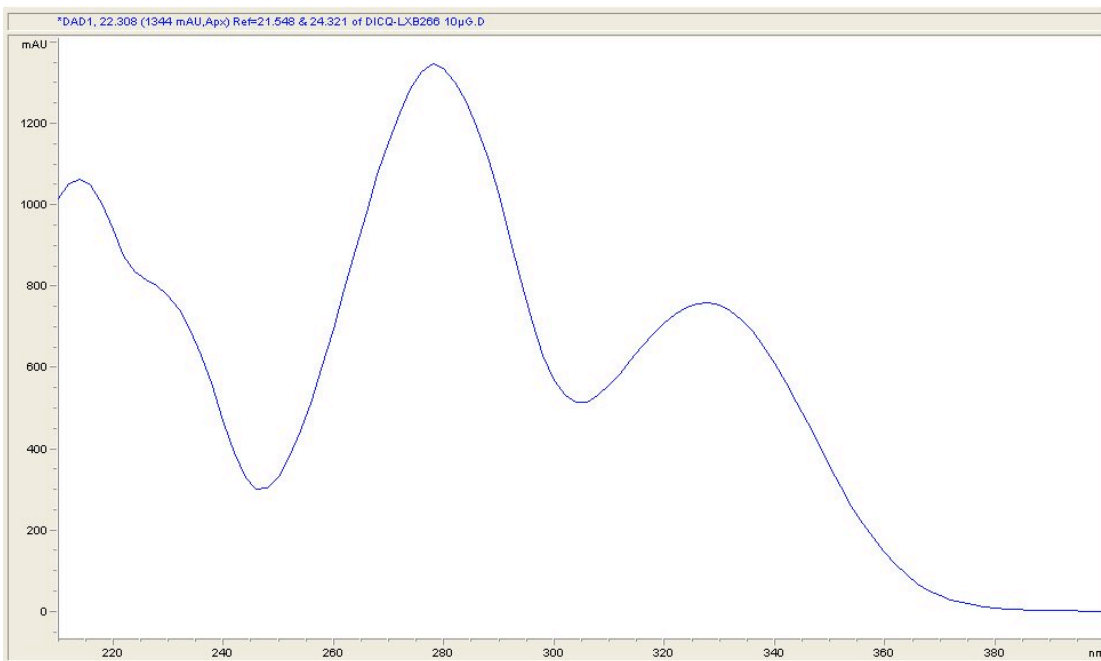
Spectre UV (210 – 400nm) à 19,893min (signal 330nm)



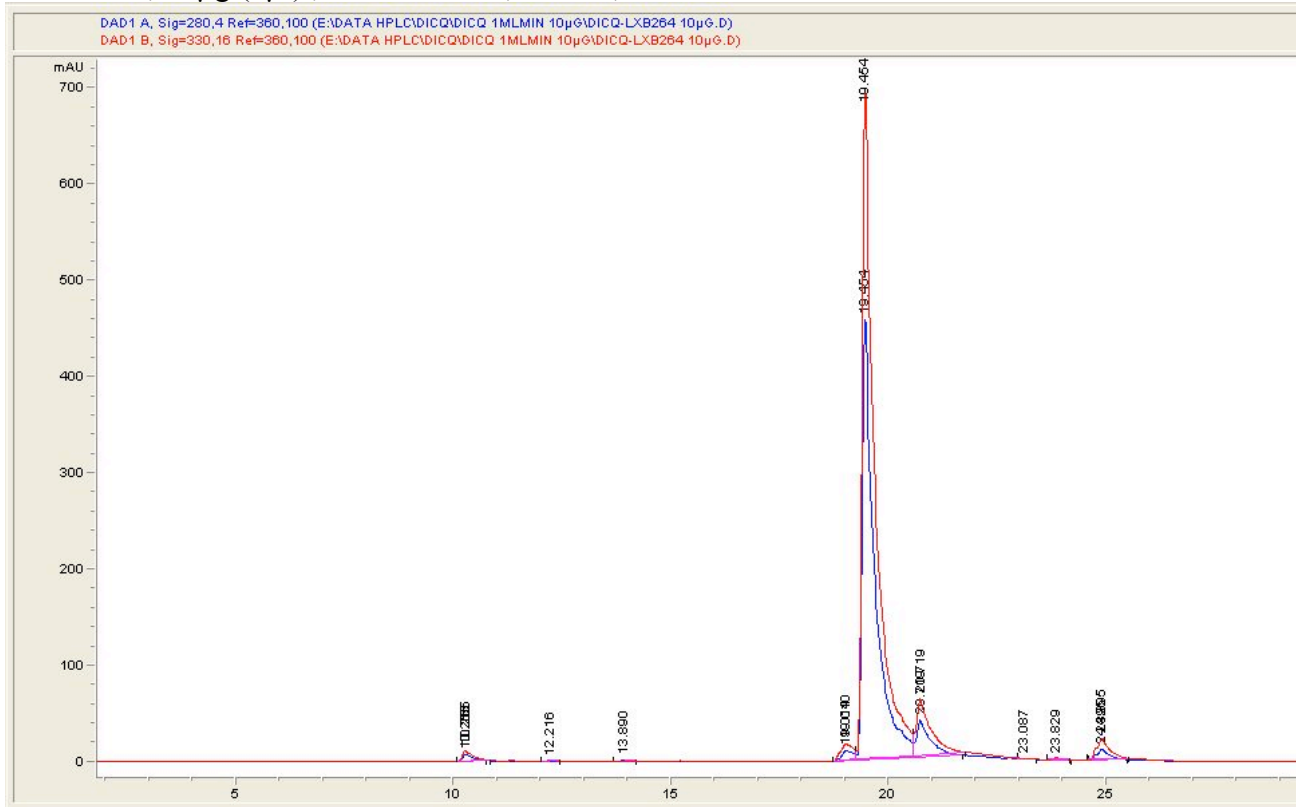
- **10d** ; 10µg (8,5µl) ; 270 – 330nm ; TR=22,3min



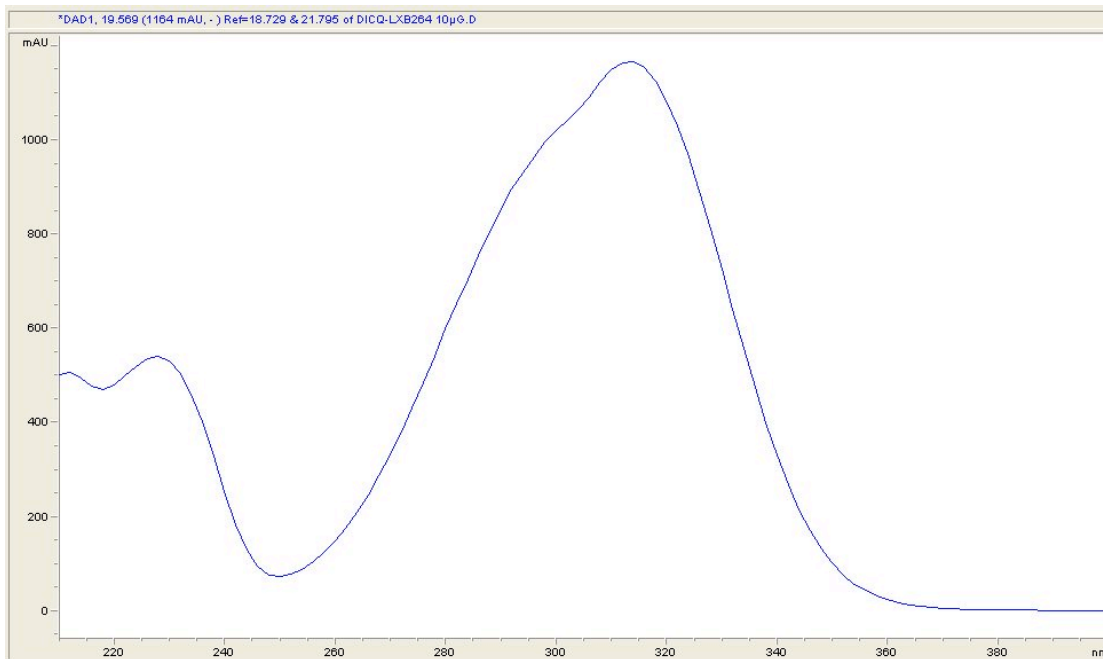
Spectre UV (210 – 400nm) à 22,308min (signal 330nm)



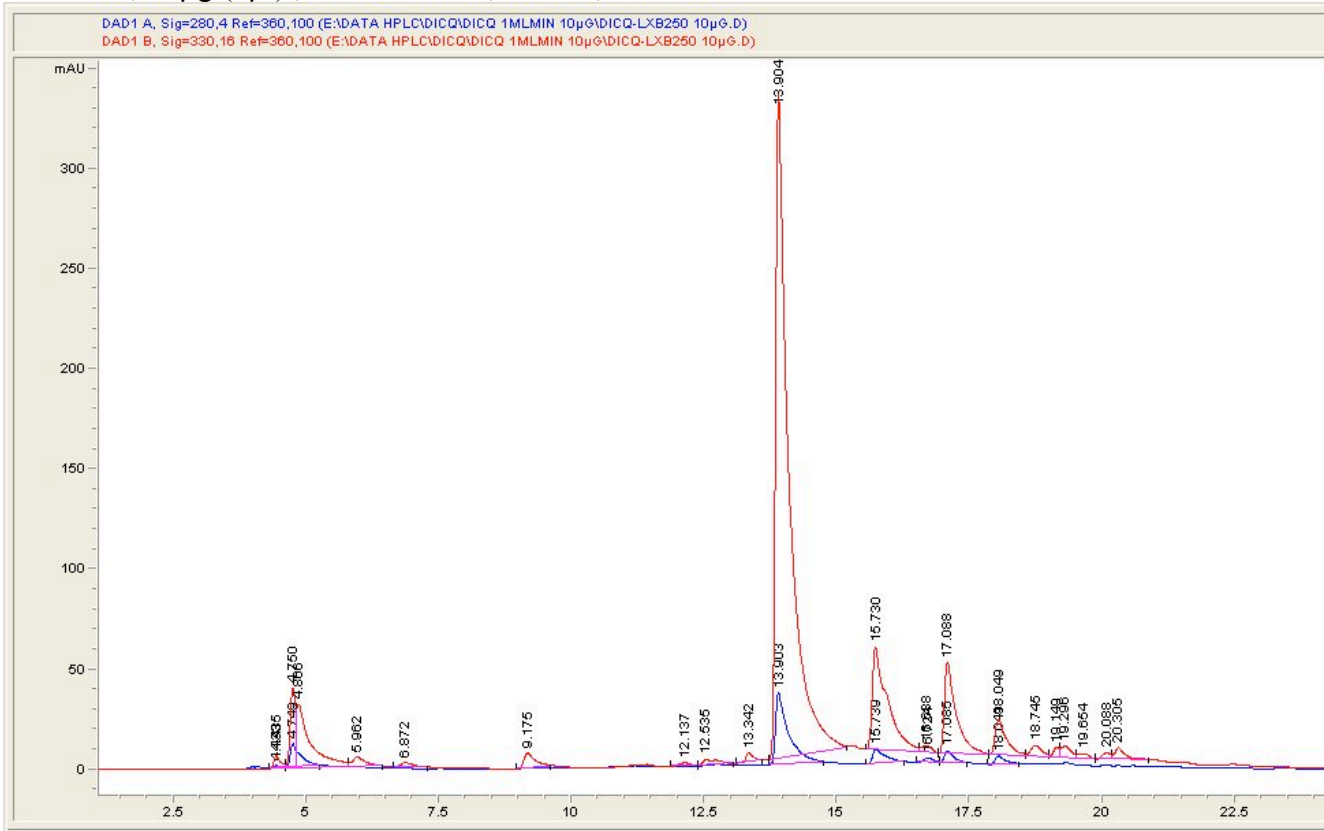
- 10e; 10µg (3µl) ; 270 – 330nm ; TR=19,4min



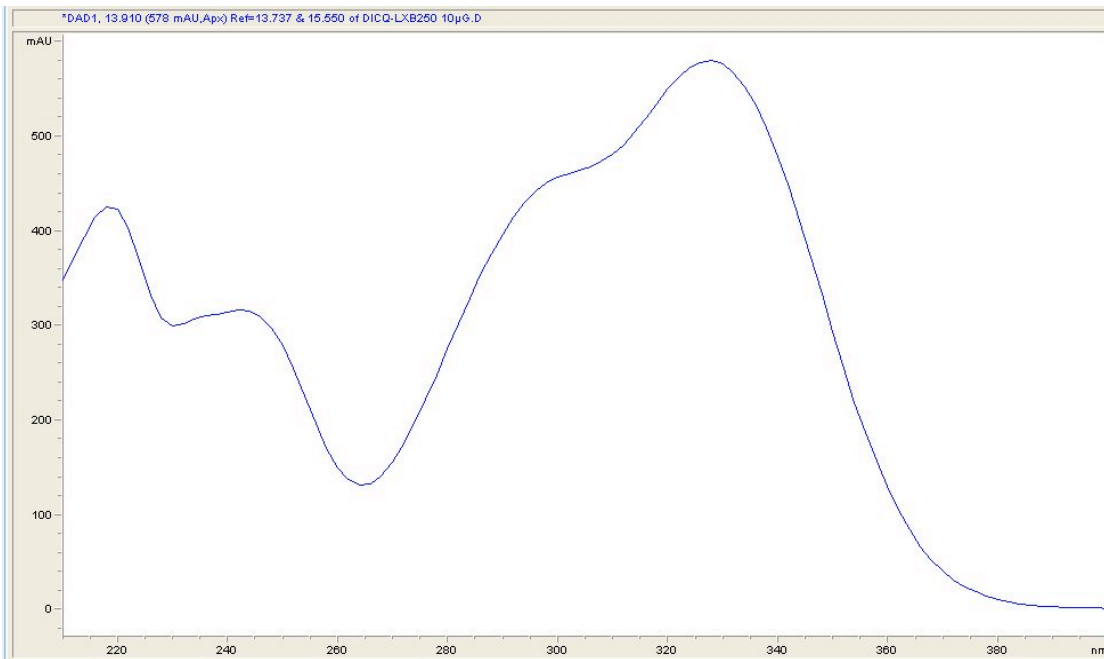
Spectre UV (210 – 400nm) à 19,569min (signal 330nm)



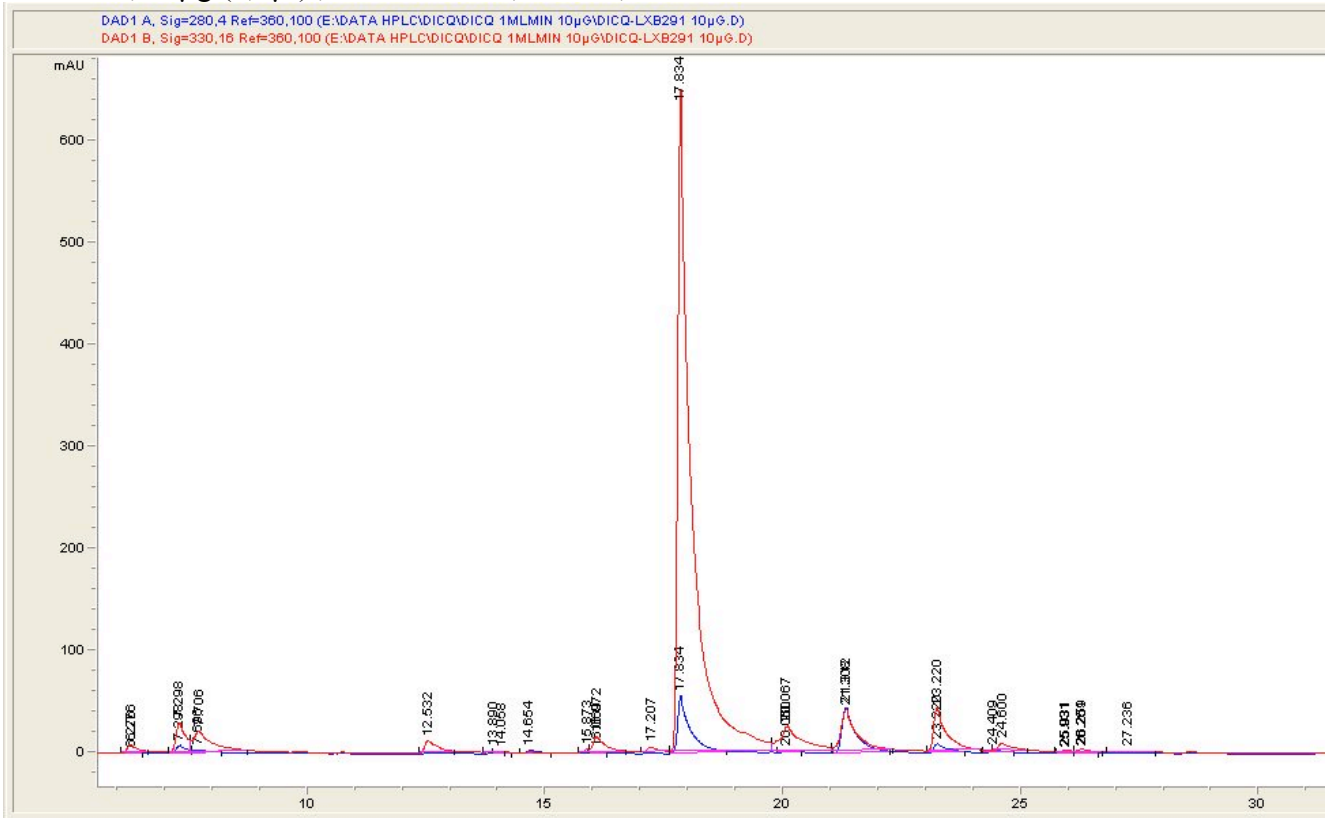
- **4a**; 10 μ g (3 μ l) ; 270 – 330nm ; TR=13,9min



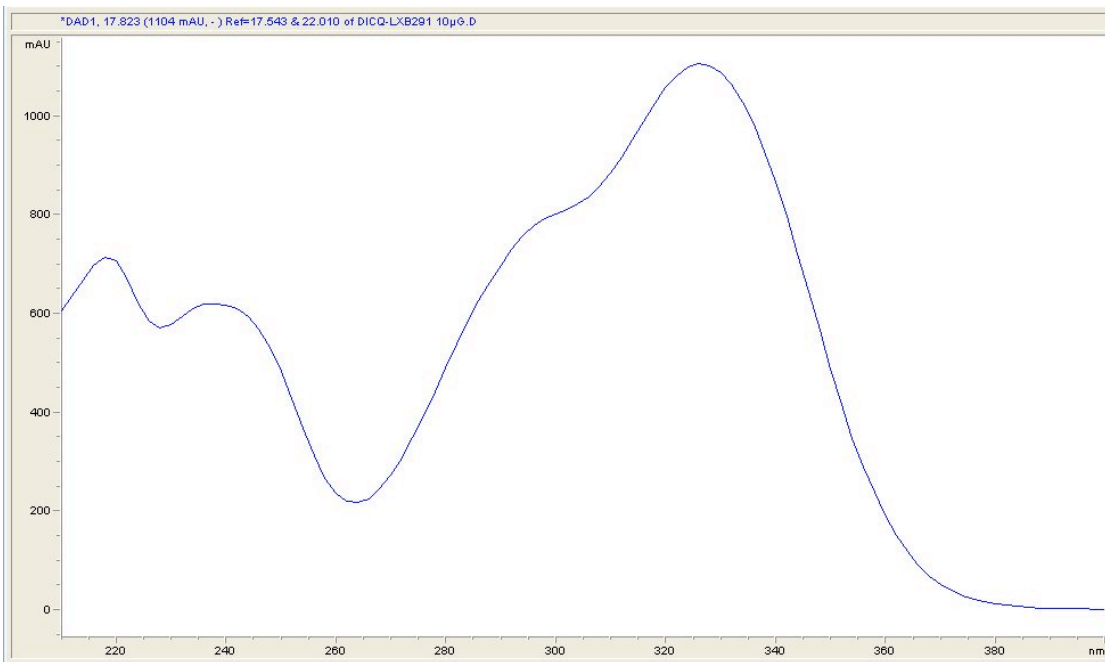
Spectre UV (210 – 400nm) à 13,910min (signal 330nm)



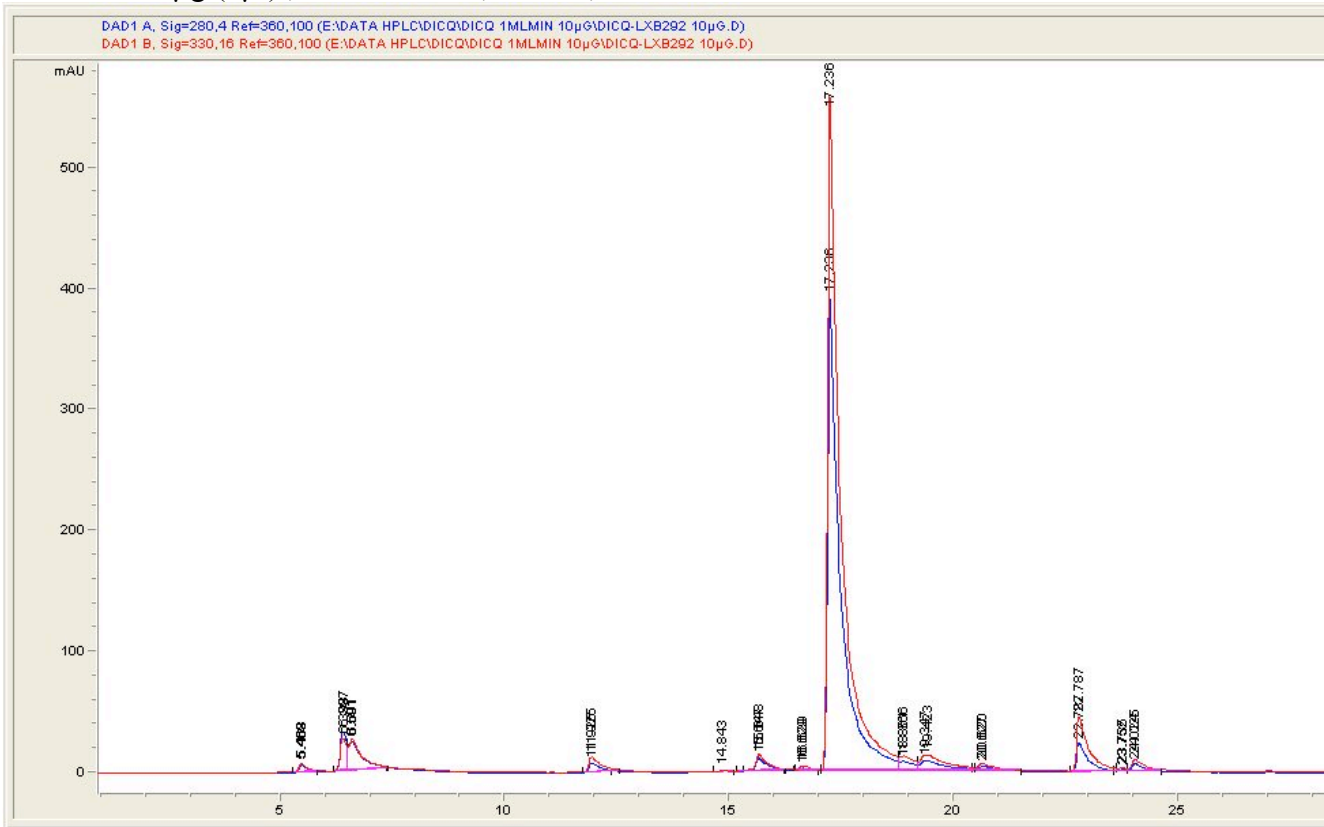
- 4c; 10µg (3,5µl) ; 270 – 330nm ; TR=17,8min



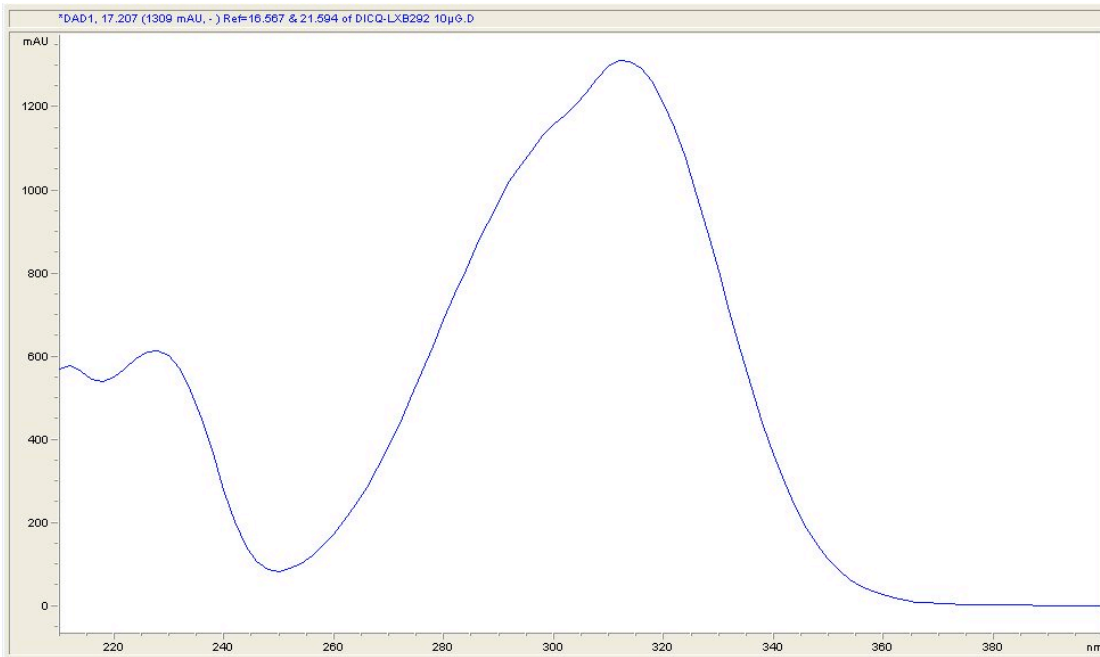
Spectre UV (210 – 400nm) à 17,823min (signal 330nm)



- 4d 10µg (4µl) ; 270 – 330nm ; TR=17,2min

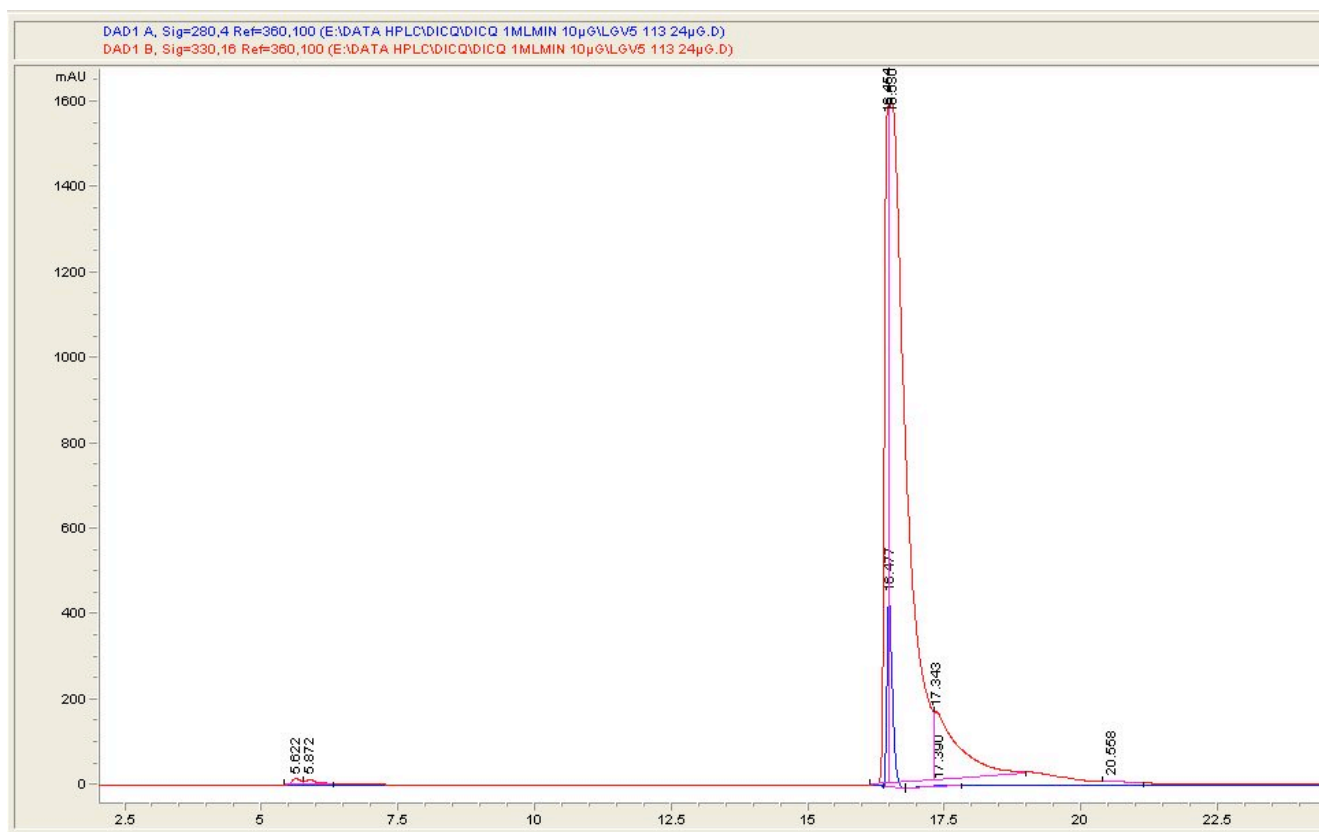


Spectre UV (210 – 400nm) à 17,207min (signal 330nm)



12 : (dissolved in 1,5ml MeOH); 24µg injected (2µl) ;

280 – 330nm ; TR=16,5min



Spectre UV (210 – 400nm) à 16,374min (signal 330nm)

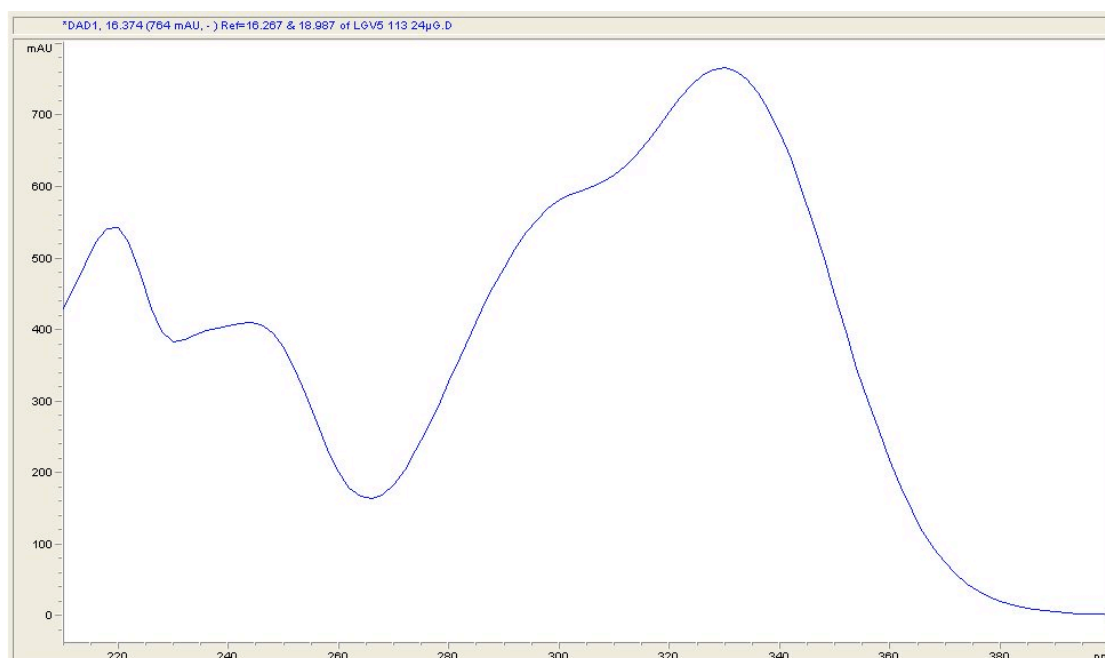
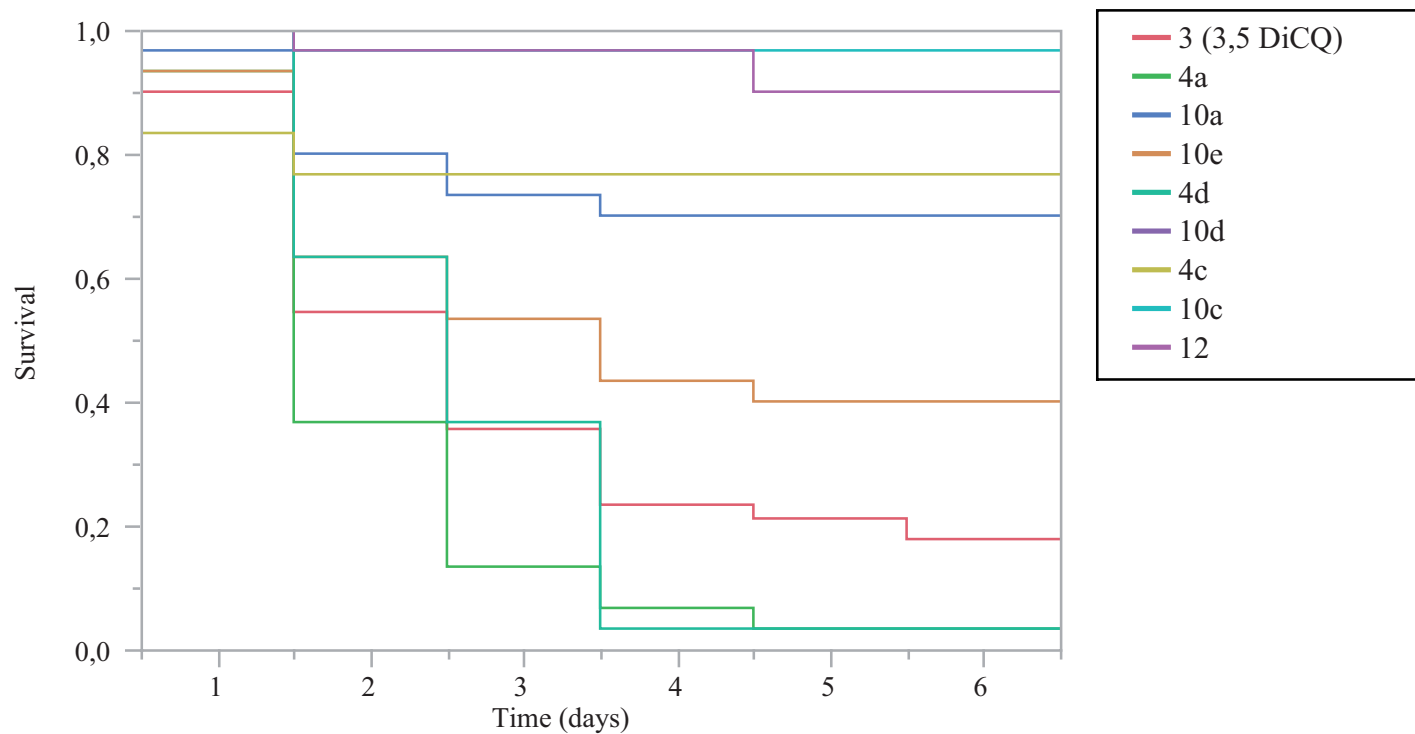


Table S3 Survival analysis^a



Compound	4a	4d	3	10e	4c	10a	10d, 10c, 12
Mean LT50 ^b	1.84	2.43	2.50	3.82	7.28	7.86	>20
IC ^c	[1.29-2.62]	[1.71-3.48]	[2.03-3.09]	[2.62-5.57]	[4.7-11.2]	[5.1-12.1]	

^a Detailed mortality curves upon ingestion of synthesized compounds **10a** to **12**, incorporated in artificial diet of the pea aphid *Acyrtosiphon pisum* at 0.5 mM; ^bin days; ^c confidence intervals (at 95% confidence levels) of mean LT50 under log-normal survival model.