

Revisiting Staudinger and Ruzicka's altered pyrethrolone: the cyclopentadienone dimers derived from pyrethrin I, cinerin I and jasmolin I

Oliver E. Hutt^A, Jamie A. Freemont^A, Stella Kyi^A, Stuart W. Littler^A, Ross P. McGeary^B, Peter J. Duggan^{A,C} , John Tsanaksidis^A, Helen F. Cole^D, Maurice G. Kerr^D, Elizabeth H. Krenske^B  and John H. Ryan^{A,*} 

For full list of author affiliations and declarations see end of paper

***Correspondence to:**

John H. Ryan
 CSIRO Manufacturing, Ian Wark Laboratory,
 Bayview Avenue, Clayton, Vic. 3168,
 Australia
 Email: jack.ryan@csiro.au

Handling Editor:

Craig Hutton

Received: 24 October 2023

Accepted: 14 February 2024

Published: 8 March 2024

Cite this: Hutt OE *et al.* (2024) Revisiting Staudinger and Ruzicka's altered pyrethrolone: the cyclopentadienone dimers derived from pyrethrin I, cinerin I and jasmolin I. *Australian Journal of Chemistry* **77**, CH23197. doi:10.1071/CH23197

© 2024 The Author(s) (or their employer(s)).
 Published by CSIRO Publishing.

This is an open access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License ([CC BY-NC-ND](https://creativecommons.org/licenses/by-nc-nd/4.0/))

OPEN ACCESS

ABSTRACT

The reactions of pyrethrin I, cinerin I and jasmolin I with sodium hydroxide in ethanol afforded an approximately 1:1 ratio of two respective cyclopentadienone dimers, isolated in good yield. A combination of one-dimensional and two-dimensional NMR spectroscopic studies allowed determination of the structure and stereochemistry of the dimers. The dimers are formed by cycloaddition reactions of the less substituted alkene of the cyclopentadienone, and by regioisomeric *endo* transition states. Density functional theory calculations were in accord with the experimental findings showing the products formed by ambimodal transition states. One such transition state led to two initial products with the less stable product undergoing facile conversion to the other more stable, experimentally observed product. These studies clarify the structures of the altered pyrethrolone reported by Staudinger and Ruzicka in 1924.

Keywords: altered pyrethrolone, biologically active molecules, cinerin I, cyclopentadienone, density functional calculations, dimerisation, electrocyclic reactions, elimination, jasmolin I, pyrethrin I.

Introduction

The Australian pyrethrum industry, based in Tasmania, has grown to be a major player in the natural insecticide market.¹ The industry contributes both to the agricultural sector through the growing of the pyrethrum daisy *Tanacetum cinerariifolium* and to the chemical sector through the production of commercial-grade refined pyrethrum extracts that in turn are the basis of a wide range of products. The active ingredients in the refined pyrethrum extracts, known as pyrethrins, are a series of six insecticidal compounds (Fig. 1).^{2,3} The pyrethrins continue to be a source of inspiration for the development of synthetic analogues referred to as pyrethroids.³ Despite the availability of a large array of synthetic analogues, the pyrethrins continue to find use in a range of human, pet and household applications where the very limited persistence and low mammalian toxicity of the natural compounds offers some advantage.³

The elucidation of the structures of the pyrethrins is intimately linked to the development of organic chemistry through the early to mid-20th century.^{2,3} The insecticidal principle was first recognised by Fujitani and Yamamoto as containing an ester residue,^{4–6} then by Staudinger and Ruzicka as comprising two compounds, designated as pyrethrin I and pyrethrin II (with correct molecular formula for pyrethrin I (**1a**) and pyrethrin II (**2a**), however assigned as isomeric structures with different positioning of the side chain double bonds).⁷ Subsequently, minor constituents were discovered, cinerin I (**1b**) and cinerin II (**2b**) by LaForge and Barthel,^{8–10} and jasmolin I (**1c**) and jasmolin II (**2c**) by Godin.¹¹ The determination of the absolute configuration of the pyrethrins involved significant endeavour, with the stereochemistry of the carboxyl residues first elucidated by Crombie and Inouye,^{12,13} and that of the alkoxy residues by Katsuda.¹⁴

During the early studies of the chemistry of the pyrethrins, saponification reactions were performed (Scheme 1).^{2,15–17} Chrysanthemic acid (3) and chrysanthemic diacid (4) were recovered, representing the carboxyl residues of the pyrethrins. However, the alcohols (thought to be a single alcohol pyrethrolone (5)) were not obtained; instead, what was isolated was a material identified as altered pyrethrolone (7).^{2,15–17} It became accepted that hydrolysis of the natural pyrethrins is accompanied by competing elimination (E1cB) processes leading to cyclopentadienones 6, which are destabilised and highly reactive owing in part to their antiaromatic character, and undergo rapid Diels–Alder dimerisation.² A range of 2,3-disubstituted cyclopentadienones are known to exist as cyclopentadienone dimers.¹⁸ Therefore, it has been suggested that the altered pyrethrolone (7) is a mixture of cyclopentadienone dimers (Scheme 1).²

Although the processes involved in formation of the naturally derived cyclopentadienone dimers 7 are generally understood,^{2,19–22} the structures and stereochemistry of the dimers 7 have not been reported in the peer-reviewed chemical literature. The most closely related system studied

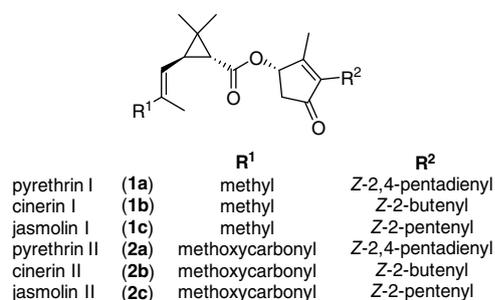
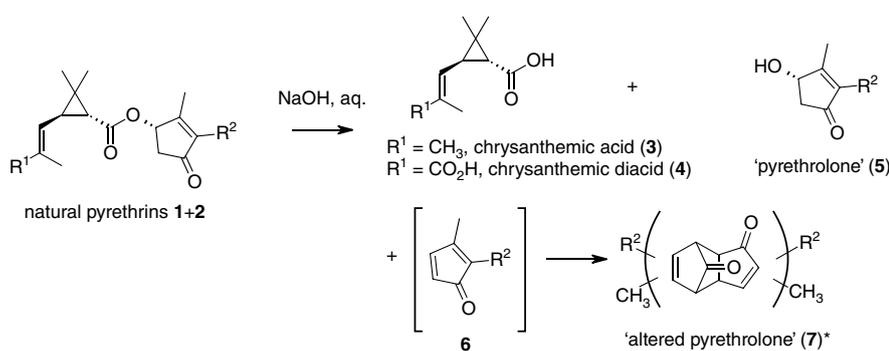
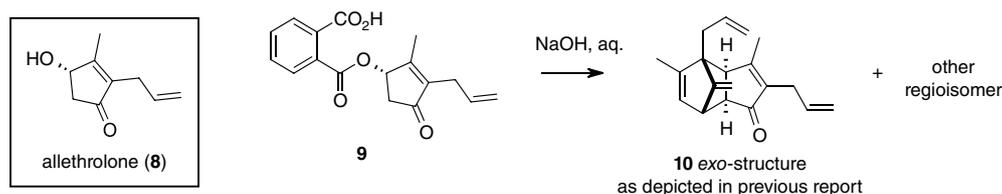


Fig. 1. The natural pyrethrins.



Scheme 1. Hydrolysis of the natural pyrethrins; regio- and stereo-chemistries (in 7) are not defined.^{2,15–17}



Scheme 2. The previously reported cyclopentadienone dimers derived from an allethrolone ester.¹⁹

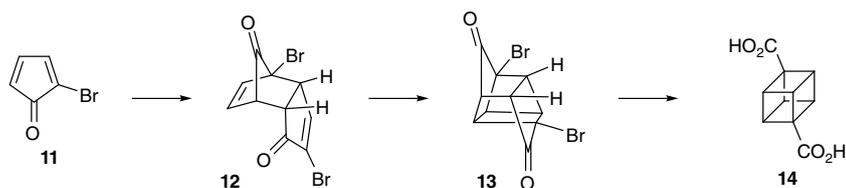
is an ester of allethrolone (8), a synthetic analogue of the pyrethrin-derived alcohols 5.¹⁹ Saponification of phthalate ester 9 produced two cyclopentadienone dimers, assigned as regioisomeric *exo* cycloadducts, with one depicted as regioisomer 10 (Scheme 2).¹⁹

In contrast to the above results described by LaForge,¹⁹ other cyclopentadienone dimerisation reactions display a strong preference for the kinetically favoured *endo* cycloadducts.^{23–27} For example, 2-bromocyclopentadienone (11) dimerises to produce the *endo* cycloadduct 12 (Scheme 3).²⁸ The *endo* stereochemistry of 12 was elegantly confirmed by [2 + 2]-photocycloaddition of the diene 12 to give cage cyclobutane 13, which could only be achieved for the *endo* adduct. Then Favorskii ring-contraction of diketone 13 produced cubane-1,4-dicarboxylic acid 14, as part of the first synthesis of cubane (Scheme 3).²⁸

Given the ambiguities in the literature, we sought to fully characterise the cyclopentadienone dimers derived from the natural pyrethrins. A preliminary study of the cyclopentadienone dimers from pyrethrin I (1a) was communicated at a pyrethrum symposium,²⁹ and herein, we report the full study of the dimers resulting from pyrethrin I (1a), cinerin I (1b) and jasmolin I (1c).

Results and discussion

The base-promoted elimination of the natural pyrethrins 1 + 2 would lead to three cyclopentadienones 6, which in turn could lead to six Diels–Alder cycloaddition reactions, each of which could produce a number of regio- and stereoisomers. We reasoned that separation of such complex mixtures of dimers could be difficult, whereas separation of the



Scheme 3. An example of an *endo* selective cyclopentadienone dimerisation.²⁸

Table 1. UPLC (ultra performance liquid chromatography) analysis (percentage areas under the curve) of refined pyrethrum extract, before and after heat treatment.

Sample	1a	2a	1b	2b	1c	2c	Other
A	49.9	29.5	5.5	4.6	3.4	1.9	5.2
B	13.5 ^B	8.0 ^{A,B}	11.3 ^B	9.2 ^{A,B}	24.4 ^A	18.2	15.4
C	3.3 ^B	1.7 ^{A,B}	13.8 ^B	10.8 ^{A,B}	29.3 ^A	21.8 ^A	19.3

Sample A: refined pyrethrum extract prior to heat treatment. Sample B: after heating the extract at 230°C for 8 min. Sample C: after heating the extract at 230°C for 15 min. See Supplementary material for representative traces. Other refers to all other significant peaks.

^APeak shoulder.

^BPeak broadened and not baseline resolved.

products from base-promoted elimination of a single natural pyrethrin would be relatively straightforward. Additionally, we only needed access to one series of the natural pyrethrins to produce all three cyclopentadienones **6** and, therefore, we chose to isolate pyrethrin I (**1a**), cinerin I (**1b**) and jasmolin I (**1c**) from the natural source.

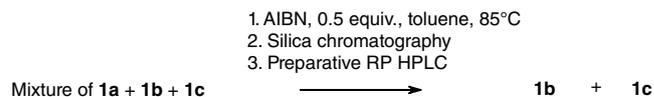
Isolation of pyrethrin I (**1a**), cinerin I (**1b**) and jasmolin I (**1c**)

A sample of pyrethrin I (**1a**) was obtained by repeated silica gel chromatography of a sample of refined pyrethrum extract. The first pass enabled separation of the fast-eluting **1a–c** from **2a** to **c** and the second pass enabled separation of major component **1a** from minor components **1b** and **1c**.

Although cinerin I (**1b**) and jasmolin I (**1c**) could be separated from the mixture on an analytical scale using normal or reverse-phase chromatography, preparative-scale chromatographic isolation was hampered by the similar retention times of all three components, compounded by the relatively minor amounts of these components compared with pyrethrin I (**1a**) (see Table 1, sample A).

It was thought that if pyrethrin I (**1a**) could be removed from the mixture of the three components, then it would be easier to separate the minor components chromatographically. We found that pyrethrin I/II (**1a/2a**) could be largely removed by heating samples of the pyrethrum extract containing the six esters at 230°C (Table 1, samples B and C). However, on inspection of the UPLC chromatograms of the heated samples, peak shoulders for the cinerin I/II (**1b/2b**) and jasmolin I/II (**1c/2c**) peaks were detected, indicating the formation of closely related impurities that would be very difficult to remove from the desired compounds.

The fast degradation of pyrethrin I/II (**1a/2a**) at such elevated temperatures was thought to be due to free radical



Scheme 4. Method for isolation of gram quantities of **1b** and **1c**.

reactions of the diene sidechain of **1a/2a**. To test this hypothesis, we investigated the effect of adding a free radical initiator to a mixture of pyrethrin I (**1a**), cinerin I (**1b**) and jasmolin I (**1c**), readily obtained by column chromatography of the pyrethrum extract on silica gel. Addition of minor amounts of azobis(isobutyronitrile) (AIBN) to the mixture in toluene at 85°C resulted in a slight reduction in the levels of pyrethrin I (**1a**). Addition of further quantities of AIBN (up to ~0.50 mol equiv.) resulted in complete reaction of pyrethrin I (**1a**). The levels of cinerin I (**1b**) and jasmolin I (**1c**) did not appear to be affected by this process. The pyrethrin I (**1a**)–AIBN derived products could be readily separated by chromatography on silica gel, affording a mixture of cinerin I (**1b**) and jasmolin I (**1c**). This mixture of **1b** and **1c** was readily separated by preparative reverse-phase HPLC, which allowed isolation of cinerin I (**1b**) and jasmolin I (**1c**) in gram quantities with purity of greater than 95% by UPLC (Scheme 4).

Hydrolysis of pyrethrin I (**1a**), cinerin I (**1b**) and jasmolin I (**1c**)

A sample of pyrethrin I (**1a**) was exposed to sodium hydroxide in ethanol and after consumption of the starting material, the reaction mixture was worked up, yielding a mixture of two major products. The products were readily separated by flash column chromatography on silica, resulting in 30 and 38% yields of the respective faster-eluting and slower-eluting products (Table 2; percentage yields calculated

Table 2. Percentage yields of products obtained from the hydrolysis of **1a**, **1b** and **1c**.

Starting material	High R_F dimer 21	Low R_F dimer 22
1a	21a : 30%	22a : 38%
1b	21b : 26%	22b : 31%
1c	21c : 24%	22c : 27%

Conditions: NaOH, 2 equiv., ethanol, 25°C, 30 min.

assuming the products are the expected dimers). The treatment of cinerin I (**1b**) and jasmolin I (**1c**) under the same conditions also each afforded two products, isolated in similar yields, with the slower-eluting product isolated in slightly higher yield than the faster-eluting product (Table 2).

Structural elucidation of the cyclopentadienone dimers

The products from the hydrolysis of pyrethrin I (**1a**) were shown to be *endo* cyclopentadienone dimers. For both products, the high-resolution electrospray ionisation mass spectrum (positive ion mode) contained a peak at m/z 343.1657 assigned to the $[M + Na^+]$ ion, supporting a molecular formula of $C_{22}H_{24}O_2$. The infrared spectrum of the higher R_F product showed strong absorption bands at ν_{max} 1775 and 1692 cm^{-1} assigned to bridged ketone and enone carbonyl groups respectively, whereas for the lower R_F product, the corresponding bands were observed at ν_{max} 1775 and 1695 cm^{-1} . The ^{13}C NMR spectrum of the higher R_F product contained resonances at δ 204.7 and 201.3 ppm, assigned to the two carbonyl carbons, and at δ 16.2 and 15.8 ppm assigned to the two methyl groups, whereas for the lower R_F product, the corresponding resonances occurred at δ 205.2, 201.1, 17.3 and 15.8 ppm. For the higher R_F product, the two methyl groups exhibited resonances at δ 1.95 and 1.65 ppm in the 1H NMR spectrum, whereas for the lower R_F product, these resonances occurred at δ 2.05 and 1.62 ppm. For both products, the 1H and ^{13}C NMR spectra contained two distinct sets of signals assigned to the two diene side chains.

The cyclopentadienone **6a** derived from pyrethrin I (**1a**) could dimerise by addition of the diene of one molecule to either double bond of the other, by either *endo* or *exo* transition states and by two regioisomeric orientations, so, in principle, eight isomers could be formed (Fig. 2). Analysis of the NMR spectra of the isolated dimers confirmed cycloaddition to the unsubstituted alkene of the cyclopentadienone moiety of **6a**. In the 1H NMR spectra of the higher R_F dimer and lower R_F dimer, the respective methine signals at δ_H 3.14 and 2.64 ppm, and δ_H 3.09 and \sim 2.85 ppm are assigned to the bridgehead protons H3a and H7a (see Fig. 3). If cycloaddition had occurred at the substituted alkene of cyclopentadienone **6a**, these signals would not be apparent and instead additional signals due to two olefinic protons would be present. This analysis allows exclusion of structures **15a–18a**.

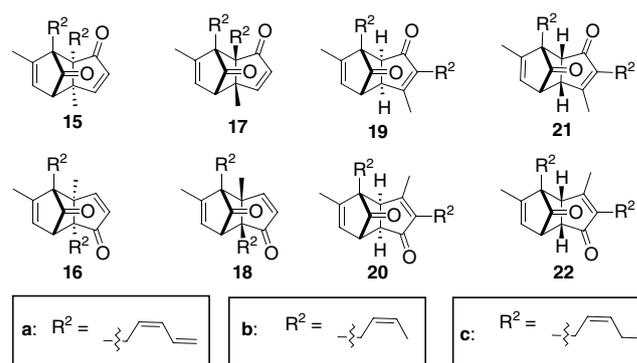


Fig. 2. The structural formulae of the eight potential cyclopentadienone dimers derived from pyrethrin I (**1a**), cinerin I (**1b**) or jasmolin I (**1c**).

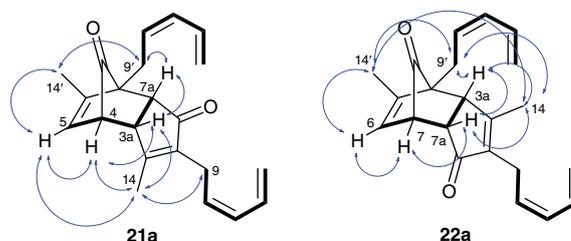


Fig. 3. 1H - 1H COSY (bold) and NOE correlations (arrows) for higher R_F dimer **21a** and lower R_F dimer **22a** (COSY, correlation spectroscopy).

A range of NMR experiments allowed full assignment of all 1H and ^{13}C resonances (see Supplementary materials) and assignment of the higher R_F dimer as **21a** and lower R_F dimer as **22a**. As shown in Fig. 3, the 1H - 1H correlation spectroscopy (1H - 1H COSY) spectrum of the higher R_F dimer indicated the presence of the partial structures depicted in bold. Next, the relative stereochemistry of the higher R_F dimer was characterised by a nuclear Overhauser enhancement (nOe) spectroscopy (NOESY) experiment, which showed nOe correlations between the signals due to the following protons: H3a with H7a, H14 and H4, H4 with H3a, H14 and H5, H5 with H4, H14' with H9' and H5, and H9' with H7a. In particular, the nOe correlation between the signals due to H5 and H14 could only be achieved with the depicted regio- and stereo-chemistry of **21a**. For the alternative stereoisomeric *exo* structure **19a**, H5 and H14 would be too distant to exhibit a nOe correlation. For the lower R_F dimer, the 1H - 1H COSY spectrum again allowed assignment of partial structures depicted in bold. The NOESY spectrum showed several correlations consistent with the assigned structure. In particular, the correlation between the signals of H14 and H14' is only possible for the depicted regio- and stereo-chemistry of **22a**.

The cyclopentadienone dimers derived from cinerin I (**1b**) and jasmolin I (**1c**) were assigned in an analogous fashion, with the higher R_F dimers being assigned structures **21b** and **21c** respectively and the lower R_F dimers being

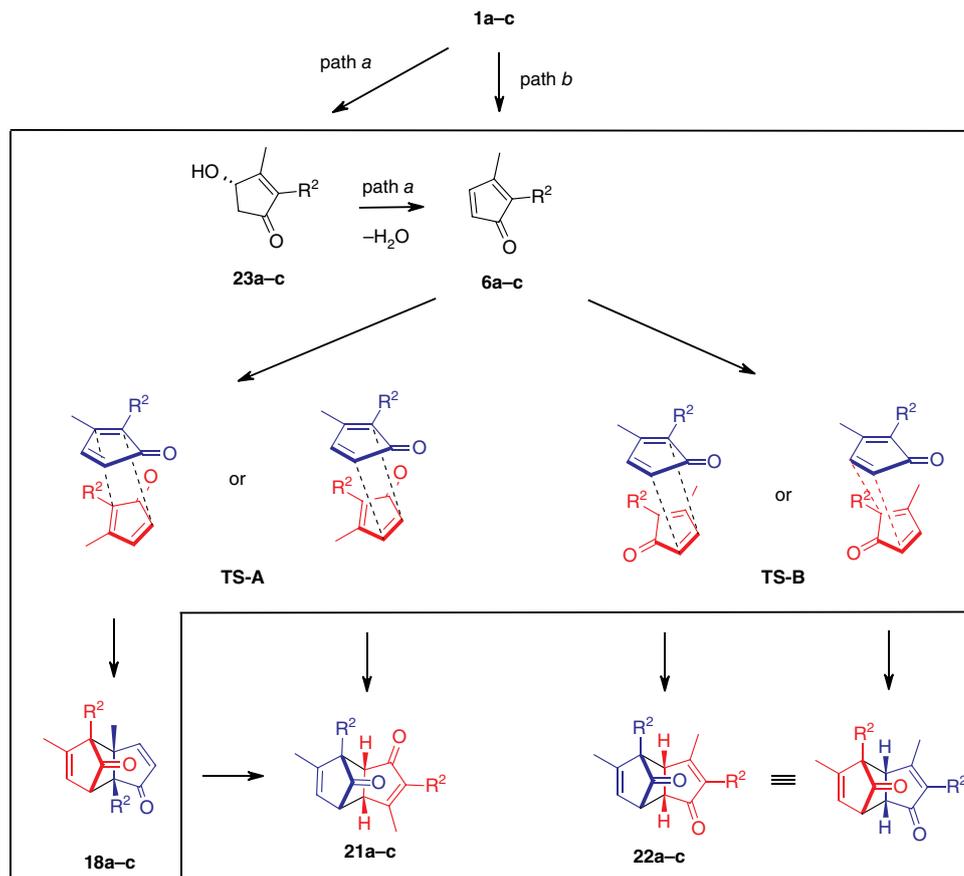
assigned structures **22b** and **22c** respectively. Diagnostically, the ^1H and ^{13}C NMR resonances for the protons and carbons of the cyclic core were very similar within the series of the higher or the lower R_F dimers. For example, for the higher R_F dimers derived from **1a**, **1b** and **1c**, respective resonances at δ_{H} 5.68, 5.67 and 5.67 ppm were assigned to the ring vinyl proton H5 of **21a**, **21b** and **21c**. Similarly, for the lower R_F dimers from **1a**, **1b** and **1c**, the respective resonances at δ_{H} 5.92, 5.91 and 5.91 ppm were assigned to the ring vinyl proton H6 of **22a**, **22b** and **22c**.

A proposed pathway for the formation of the respective cyclopentadienone dimers **21a–c** and **22a–c** from the natural pyrethrins **1a–c** is shown in Scheme 5. Thus, reaction of natural pyrethrins (**1a–c**) with sodium hydroxide could result in ester hydrolysis to give the sodium salt of chrysanthemic acid (**3**) and pyrethrolones **23a–c**. The latter could undergo E1cB reaction to give the transient cyclopentadienones **6a–c** (path a). Alternatively, the cyclopentadienones **6a–c** could form directly from E1cB elimination of chrysanthemic acid (**3**) from natural pyrethrins **1a–c** (path b).^{19,22} Diels–Alder dimerisation of the cyclopentadienones **6a–c** would then occur by *endo* transition state **TS-A** leading to compounds **21a–c** or by regioisomeric *endo* transition state **TS-B** leading to compound **22a–c**. The comparable yields obtained for the regioisomeric *endo* dimers

imply that the regioisomeric *endo* transition states **TS-A** and **TS-B** are of similar energy.

Density functional theory calculations were performed to explore the *endo* and *exo* selectivities of the Diels–Alder dimerisations (Fig. 4). The calculations modelled the cyclopentadienones **6a–c** as the methyl derivative **6d** ($R^2 = \text{Me}$) and were performed with B3LYP-D3(BJ)/6-311+G(d,p) using the solvent model based on solute electron density (SMD) of ethanol. In agreement with the experiment, the two *endo* transition states (TSs, labelled as **21d-TS** and **22d-TS** in Fig. 4) are strongly favoured, lying 10–12 kcal mol⁻¹ (1 kcal mol⁻¹ = 4.186 kJ mol⁻¹) lower in energy than the corresponding *exo* transition states **19d-TS** and **20d-TS**. The two *endo* TSs differ in energy by 1 kcal mol⁻¹, with **22d-TS** being favoured, consistent with the small selectivity for **22** relative to **21** observed in experiments. The two *endo* cycloadditions have very small barriers (3–4 kcal mol⁻¹), consistent with the antiaromaticity of the reacting cyclopentadienones, and lead to cycloadducts that are 22 kcal mol⁻¹ more stable than the reactants.

A distortion–interaction analysis³⁰ was performed to explore the origin of the *endo* selectivity (Fig. 4). The diene and dienophile were found to undergo a similar amount of distortion, or even a few kilocalories per mole more distortion, when forming the *endo* TSs compared with



Scheme 5. Mechanism for formation of cyclopentadienone dimers **21a–c** and **22a–c**.

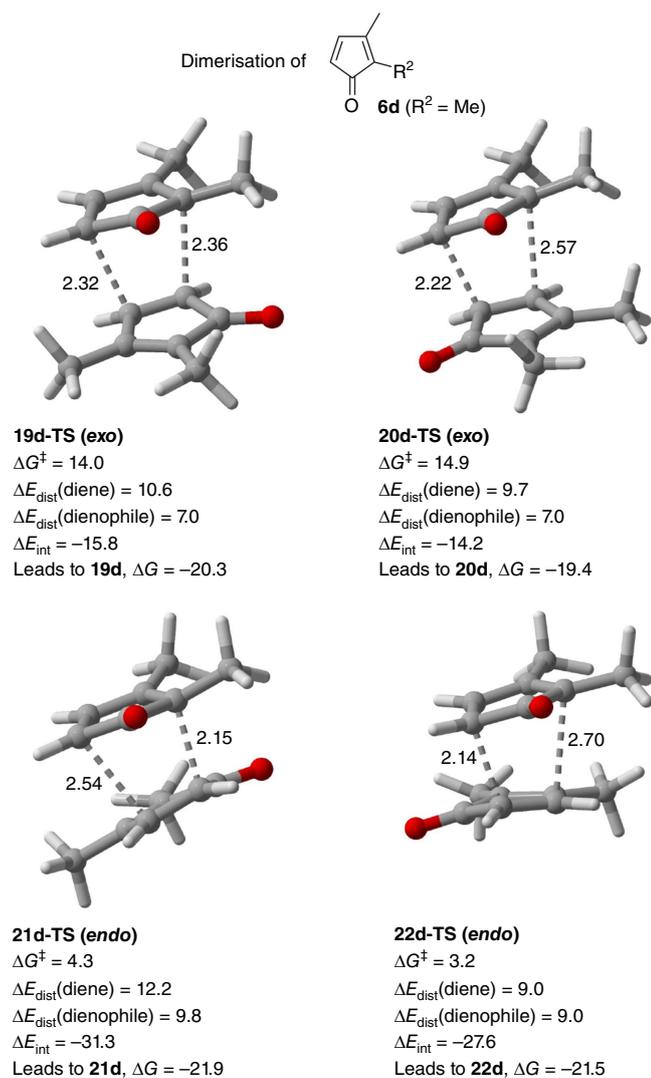


Fig. 4. Calculated transition structures for Diels–Alder dimerisations of cyclopentadienone **6d** ($R^2 = \text{Me}$) leading to **19d**, **20d**, **21d** and **22d**, calculated with B3LYP-D3(BJ)/6-311+G(d,p) in SMD implicit ethanol. The standard atom colouring scheme has been used (red is O). ΔG^\ddagger , change in Gibbs energy of activation; ΔE_{dist} , change in energy of distortion; ΔE_{int} , change in energy of interaction. Distances (dashed lines) in Ångströms, energies in kilocalories per mole.

the *exo* TSs, but the interaction between the diene and dienophile is much stronger (by 13–15 kcal mol⁻¹) in the *endo* TSs than the *exo* TSs, leading overall to the substantial *endo* preference. This is likely attributable to the stronger π – π interactions that occur between the cycloaddends in the *endo* TSs.

Of note, the two *endo* TSs are ambimodal.³¹ Each gives rise to two alternative cycloaddition pathways that branch out after the TS (i.e. [4 + 2] and [2 + 4] pathways) on a bifurcating energy surface. The forming bonds drawn in Fig. 4 depict one of the two possible pathways for each TS. In the case of **22d-TS**, the [4 + 2] and [2 + 4] pathways both give rise to the same cycloadduct by virtue of the C_2

symmetry of the TS. In the case of **21d-TS**, the two pathways give different products initially, as illustrated in Fig. 5. One pathway gives rise to **21d** whereas the other gives rise to the less stable cycloadduct **18d**. A facile Cope rearrangement of **18d** over a small barrier of (0.5 kcal mol⁻¹ relative to the starting cycloaddends) then leads to **21d**. The mechanism for the Cope rearrangement of **18** to afford **21** is shown in Fig. 5. A similar type of inter-conversion between isomeric Diels–Alder dimers of the parent cyclopentadienone has previously been described by Caramella and coworkers.³²

Conclusions

The cyclopentadienone dimers produced on hydrolysis of the natural pyrethrins pyrethrin I (**1a**), cinerin I (**1b**) and jasmolin I (**1c**) were isolated and the structures determined. In each case, isomeric products were isolated in ~1:1 ratio, a similar overall result to that obtained for the allethrolone esters.¹⁹ However, the products were shown, by 2-D NMR spectroscopy experiments, to be regioisomeric *endo* cyclopentadienone dimers **21** and **22**, rather than *exo* cyclopentadienone dimers as previously proposed for the allethrolone esters.¹⁹ Density functional theory calculations confirmed the experimental findings, and a study of the ambimodal *endo* TSs revealed that one of the TSs is associated with a bifurcating energy surface with two distinct initial products, with the less stable product converting to the more stable product by a facile Cope rearrangement. Given that in this work, the side chain of the cyclopentadienone does not seem to have a significant influence on the product distribution, the results of this study serve to raise doubt about the original assignments of the dimers derived from the allethrolone ester **10**.¹⁹ The present work also serves to clarify the structures of the altered (*verändert*) pyrethrolone first reported by Staudinger and Ruzicka in 1924.⁷

A study of the dimerisation of cyclopentadienones from allethrolone esters is warranted to confirm *endo* stereochemistry of the cycloadducts. For the natural pyrethrins, a study of this process with at least one of pyrethrin II, cinerin II or jasmolin II (**2a–c**) would be useful to check any influence the acryloyl moiety, embedded within the pyrethric acid side of these natural pyrethrins, may have on the outcome of the reactions. Furthermore, characterisation of the products from the reaction of pyrethrin I (**1a**) with AIBN may provide insight into the nature of this free radical process. With the exception of a recent study on autoxidation processes,³³ the present work appears to be the only example of free radical chemistry of pyrethrins. Finally, future work could explore the question as to whether the isolated dimers represent previously undiscovered natural products. The only known natural products that appear to form by cyclopentadienone Diels–Alder dimerisation processes are guaianes dimers, including vielanin A and

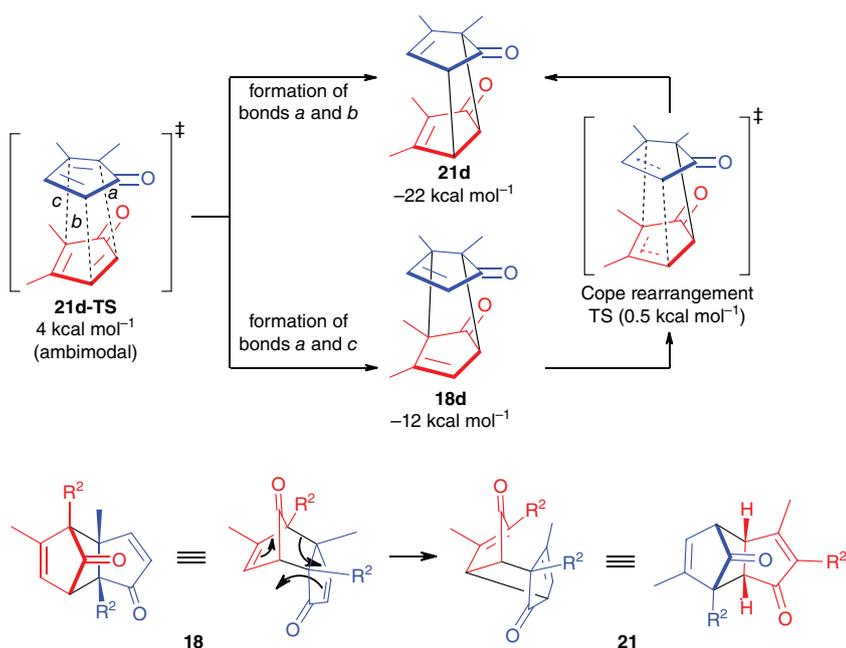


Fig. 5. Alternative reaction channels branching out from the ambimodal transition state **21d-TS** respectively leading to the cycloadducts **21d** and **18d**. A Cope rearrangement converts **18d** to the more stable cycloadduct **21d**. Mechanism for the Cope rearrangement of **18** to give **21**.

xylopidimers A–C and D, isolated from the roots of *Xylopiavielana*.^{23,34}

Experimental

General experimental

All reaction flasks were oven-dried, and all reactions were carried out under an atmosphere of N₂. All solvents used were HPLC grade. NMR spectra were recorded on a Bruker Av400 spectrometer. ¹H NMR and ¹³C NMR were recorded at 400 and 100 MHz respectively. ¹H NMR chemical shifts are reported in ppm with the internal chloroform signal at 7.26 ppm. The data are reported as s, singlet; d, doublet; t, triplet; m, multiplet or unresolved; brs, broad singlet; obs, obscured; coupling constant(s) in hertz, integration. ¹³C NMR chemical shifts are reported in ppm with the internal chloroform signal at 77.0 ppm. Infra-red spectra were recorded on a Thermo Scientific Nicolet 6700 Fourier transform (FT)-IR. High-resolution mass spectra (HRMS) were recorded on a Waters Q-TOF II, employing electrospray ionisation (ESI) with 35-eV cone voltage, lock spray and sodium iodide as a reference sample. Analyses were performed on a Waters Acquity UPLC with 50- × 2.1-mm BEH C18 column using 55% ACN/H₂O mobile phase at 0.4 mL min⁻¹ flow rate and detection by photo diode array detector scanning 190–400 nm. Data acquisition and processing used Waters Empower software and representative chromatograms were extracted at 223 nm. Prep-HPLC separations were performed on a Waters HPLC using a 300- × 40-mm Deltaprep C₁₈ column, a mobile phase of 50 or 55% acetonitrile/water, a flow rate of 80 mL min⁻¹, and

detection by a Waters 490E programmable multi wavelength detector set at 230 nm.

Isolation of pyrethrin I (1a)

A refined extract of natural pyrethrins (79% natural pyrethrins by HPLC, courtesy of Botanical Resources Australia Pty Ltd) was subjected to dry column vacuum chromatography (silica, gradient elution, pentane then ethyl acetate/petroleum spirits 1:23 v/v, then ethyl acetate/petroleum spirits 1:4 v/v). Fractions containing the faster-eluting natural pyrethrins **1a–c**, free from the slower-eluting natural pyrethrins **2a–c**, were concentrated under vacuum and subjected to column chromatography (silica gel, ethyl acetate/petroleum spirits 1:24, then 1:12 v/v). Fractions enriched in the slower-eluting pyrethrin I (**1a**) were combined and concentrated to afford pyrethrin I (**1a**) of 90% purity by UPLC analysis. The ¹³C NMR spectrum matched that reported in the literature.³⁵ Other mixed fractions were combined ready for treatment with AIBN (see below).

Isolation of cinerin I (1b) and jasmolin I (1c)

To a round-bottomed flask was added a ~90:9:1 mixture of pyrethrin I (**1a**), cinerin I (**1b**) and jasmolin I (**1c**, 11.5 g, ~35 mmol pyrethrin I) and toluene (50 mL). The flask was heated under nitrogen at 85°C for 15 min. A blast shield was installed, then AIBN (**caution**: special precautions should be taken when dealing with AIBN; please refer to safety data sheets) (2.8 g, 17.5 mmol) was dissolved in toluene (~25 mL) and added slowly dropwise, by a syringe fitted with a wide-bore needle, to the reaction flask. The reaction was stirred for 22 h at 85°C. TLC analysis (ethyl acetate/

petroleum spirits 1:4 v/v) showed a characteristic new spot on the baseline due to the products from pyrethrin I (**1a**). The reaction mixture was cooled and then filtered through a short column of silica, followed by elution with ethyl acetate/petroleum spirits (1:9 v/v, 200 mL) and ethyl acetate/petroleum spirits (1:4 v/v, 200 mL). The fractions containing the faster-eluting components were combined and concentrated to give a mixture of cinerin I (**1b**) and jasmolin I (**1c**) (1.3 g, **1b**:**1c** 94:6 v/v). This material was subjected to preparative HPLC, which yielded cinerin I (**1b**, 1.15 g) and jasmolin I (**1c**, 0.162 g) in 99.9 and 99.5% purity respectively as assessed by UPLC analysis. The ^{13}C NMR of **1b** and **1c** matched that reported in the literature.³⁵

Representative procedure for hydrolysis of the natural pyrethrins: 3,6-dimethyl-2,7-di((Z)-penta-2,4-dien-1-yl)-3 α ,4,7,7 α -tetrahydro-1H-4,7-methanoindene-1,8-dione **21a**²⁹ and 3,5-dimethyl-2,4-di((Z)-penta-2,4-dien-1-yl)-3 α ,4,7,7 α -tetrahydro-1H-4,7-methanoindene-1,8-dione **22a**²⁹

To a round-bottomed flask was added pyrethrin 1 (**1a**, 0.232 g, 90% purity, 0.64 mmol of **1a**) and ethanol (2 mL). Freshly powdered sodium hydroxide (0.050 g, 1.2 mmol) was added, and the reaction mixture was stirred at room temperature for 30 min. At this time, TLC analysis (heptane/ethyl acetate 4:1 v/v) indicated that the starting material had been consumed. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was then dried with magnesium sulfate, filtered and the solvent removed under reduced pressure. The resulting oily yellow residue was subjected to chromatography on silica gel (gradient: dichloromethane, then 0.5% methanol in dichloromethane, then 1% acetone in dichloromethane, then 5% acetone in dichloromethane). The fractions containing the component (R_f 0.3, heptane/ethyl acetate 4:1 v/v) were evaporated under reduced pressure to give *title compound 21a* (0.031 g, 30%) as an oil. ν_{\max} (KBr) 1775, 1692, 1639 cm^{-1} . δ_{H} (400 MHz, CDCl_3) 6.92 (dtd, J 16.8, 10.2, 1.1, 1H, H12'), 6.72 (dtd, J 16.7, 10.2, 1.1, 1H, H12), 6.14 (t, J 11.0, 1H, H11'), 5.97 (t, J 10.9, 1H, H11), 5.68 (m, 1H, H5), 5.63 (m, 1H, H10'), 5.14–5.25 (m, 5H, H13, H13', H10), 3.22 (bt, J 5.2, 1H, H3a), 3.14 (t, J 4.2, 1H, H4), 3.06 (dd, J 15.1, 7.8, 1H, H9a), 2.99 (dd, J 14.8, 8.2, 1H, H9b), 2.90 (dd, J 15.2, 7.3, 1H, H9'a), 2.81 (dd, J 15.2, 7.3, 1H, H9'b), 2.64 (d, J 6.0, 1H, H7a), 1.95 (s, 3H, H14), 1.65 (d, J 1.6, 3H, H14'). δ_{C} (100 MHz, CDCl_3) 204.7 (C1/C8), 201.3 (C1/C8), 167.3 (C3), 145.7 (C6), 143.0 (C2), 132.2 (C12'), 131.9 (C11'), 131.7 (C12), 129.9 (C11), 127.4 (C10), 121.0 (C5), 118.0 (C13/C13'), 117.9 (C13/C13'), 59.2 (C7), 49.5 (C3a), 45.3 (C4), 45.1 (C7a), 24.0 (C9'), 21.8 (C9), 16.2 (H14), 15.8 (H14'). HRMS m/z (Q-TOF ES⁺) Calcd for $\text{C}_{22}\text{H}_{24}\text{O}_2\text{Na}$: 343.1674; found: 343.1657. Concentration of the fractions containing the component (R_f 0.2, heptane/ethyl acetate

4:1 v/v) afforded the *title compound 22a* (0.039 g, 38%) as an oil. ν_{\max} (KBr) 1775, 1695, 1653 cm^{-1} . δ_{H} (400 MHz, CDCl_3) 6.72 (m, 2H, H12, H12'), 6.16 (t, J 11.0, 1H, H11), 5.98 (t, J 10.7, 1H, H11'), 5.92 (m, 1H, H6), 5.60 (m, 1H, H10), 5.15–5.30 (m, 5H, H10', H13, H13'), 3.28 (dd, J 4.7, 3.7, 1H, H7), 3.09 (m, 1H, H3a), 3.04 (m, 2H, H9'), 2.83–2.87 (m, 3H, H7a, H9), 2.05 (s, 3H, H14), 1.62 (d, J 1.6, 3H, H14'). δ_{C} (100 MHz, CDCl_3) 205.2 (C1/C8), 201.1 (C1/C8), 167.5 (C3), 146.1 (C5), 140.9 (C2), 131.6 (C12), 131.4 (C12'), 131.3 (C11), 129.9 (C11'), 127.3 (C10'), 127.0 (C10), 123.2 (C6), 118.5 (C13), 118.1 (C13'), 58.9 (C4), 49.1 (C7), 45.6 (C3a), 45.2 (C7a), 24.3 (C9), 21.7 (C9'), 17.3 (C14), 15.8 (C14'). HRMS m/z (Q-TOF ES⁺) Calcd for $\text{C}_{22}\text{H}_{24}\text{O}_2\text{Na}$: 343.1674; found: 343.1657.

2,7-Di((Z)-but-2-en-1-yl)-3,6-dimethyl-3 α ,4,7,7 α -tetrahydro-1H-4,7-methanoindene-1,8-dione **21b** and 2,4-di((Z)-but-2-en-1-yl)-3,5-dimethyl-3 α ,4,7,7 α -tetrahydro-1H-4,7-methanoindene-1,8-dione **22b**

A sample of cinerin I (**1b**) (0.120 g, 0.37 mmol) was treated according to the representative procedure. After chromatography, concentration of the fractions containing the faster-eluting component (R_f 0.7, heptane/ethyl acetate 4:1 v/v) afforded the *title compound 21b* (0.014 g, 26%) as a colourless oil. ν_{\max} (KBr) 1776, 1692, 1638 cm^{-1} . δ_{H} (400 MHz, CDCl_3) 5.67 (brs, 1H, H5), 5.51–5.61 (m, 2H, H10', H11'), 5.39–5.47 (m, 1H, H11), 5.12–5.18 (m, 1H, H10), 3.20 (t, J 5.1, 1H, H3a), 3.13 (t, J 4.0, 1H, H4), 2.91 (dd, J 14.7, 7.2, 1H, H9a), 2.85 (dd, J 14.8, 7.5, 1H, H9b), 2.74 (dd, J 15.3, 7.0, 1H, H9a'), 2.68 (dd, J 15.5, 6.4, 1H, H9b'), 2.62 (d, J 6.0, 1H, H7a), 1.94 (s, 3H, H13), 1.74 (d, J 6.2, 3H, H12'), 1.68 (obscured d, 3H, H12), 1.66 (d, J 1.4, 3H, H13'). δ_{C} (100 MHz, CDCl_3) 205.0 (C1/C8), 201.7 (C1/C8), 166.8 (C3), 146.4 (C6/C2), 143.1 (C6/C2), 126.8 (C10'), 126.1 (C10), 125.4 (C11'), 124.8 (C11), 120.9 (C5), 59.3 (C7), 49.6 (C4), 45.2 (two signals coinciding: C3a, C7a), 23.1 (C9'), 21.0 (C9), 16.1 (C13), 15.7 (C13), 12.9 (C12'), 12.8 (C12). HRMS m/z (Q-TOF ES⁺) Calcd for $\text{C}_{20}\text{H}_{24}\text{O}_2\text{Na}$: 319.1674, found: 319.1664. Concentration of the fractions containing the slower-eluting component (R_f 0.6, heptane/ethyl acetate 4:1 v/v) afforded the *title compound 22b* (0.017 g, 31%) as a colourless oil. ν_{\max} (KBr) 1778, 1698, 1635 cm^{-1} . δ_{H} (400 MHz, CDCl_3) 5.91 (dd, J 3.2, 1.5, 1H, H6), 5.61 (m, 1H, H11'), 5.53 (m, 1H, H10'), 5.45 (m, 1H, H11), 5.14 (m, 1H, H10), 3.26 (t, J 4.2, 1H, H7), 3.07 (d, J 6.0, 1H, H3a), 2.94 (dd, J 14.9, 6.8, 1H, H9a), 2.87 (obscured dd, 1H, H9b), 2.84 (t, J 5.6, 1H, H7a), 2.68 (m, 2H, H9'), 2.05 (s, 3H, H13), 1.72 (d, J 6.4, 3H, H12'), 1.67 (d, J 6.9, 3H, H12), 1.63 (d, J 1.5, 3H, H13'). δ_{C} (100 MHz, CDCl_3) 205.6 (C1/C8), 201.5 (C1/C8), 167 (C3), 146.7 (C5), 141.1 (C2), 126.2 (C11'), 126.1 (C10), 125.5 (C10'), 124.9 (C11), 123.0 (C6), 59.1 (C4), 49.1 (C7), 45.6 (C3a), 45.2 (C7a), 23.4 (C9'), 20.9 (C9), 17.1 (C13), 15.7

(C13'), 13.1 (C12'), 12.8 (C12). HRMS m/z (Q-TOF ES⁺) Calcd for C₂₀H₂₄O₂Na: 319.1674; found: 319.1651.

3,6-Dimethyl-2,7-di((Z)-pent-2-en-1-yl)-3 α ,4,7,7 α -tetrahydro-1H-4,7-methanoindene-1,8-dione **21c** and 3,5-dimethyl-2,4-di((Z)-pent-2-en-1-yl)-3 α ,4,7,7 α -tetrahydro-1H-4,7-methanoindene-1,8-dione **22c**

A sample of jasmolin I (**1c**) (0.120 g, 0.36 mmol) was treated according to the representative procedure. After chromatography, concentration of the fractions containing the faster-eluting component (R_F 0.9, 1% methanol in dichloromethane) afforded the *title compound 21c* (0.014 g, 24%) as a colourless oil. ν_{\max} (KBr) 1775, 1692, 1638 cm⁻¹. δ_H (400 MHz, CDCl₃) 5.67 (m, 1H, H5), 5.50 (m, 2H, H10', H11'), 5.35 (m, 1H, H11), 5.09 (m, 1H, H10), 3.20 (t, J 5.1, 1H, H3a), 3.13 (t, J 4.0, 1H, H4), 2.90 (dd, J 15.0, 7.4, 1H, H9a), 2.84 (1H, dd, J 14.9, 7.7, H9b), 2.74 (dd, J 15.5, 5.8, 1H, H9a'), 2.67 (dd, J 15.8, 5.1, 1H, H9b'), 2.62 (d, J 6, 1H, H7a), 2.22 (m, 2H, H12'), 2.11 (m, 2H, H12), 1.95 (s, H14), 1.65 (d, J 1.6, 3H, H14'), 0.98 (two coincidental t, J 7.8, 6H). δ_C (100 MHz, CDCl₃) 205.0 (C1/C8), 201.7 (C1/C8), 166.8 (C3), 146.4 (C6), 143.1 (C2), 134.5 (C10'), 132.5 (C10), 124.5 (C11'), 123.8 (C11), 120.9 (C5), 59.3 (C7), 49.6 (C4), 45.3 (C3a), 45.2 (C7a), 23.4 (C9'), 21.3 (C9), 20.6 (C12), 20.5 (C12'), 16.0 (C14), 15.8 (C14'), 14.1 (C13), 14.0 (C13'). HRMS m/z (Q-TOF ES⁺) Calcd for C₂₂H₂₈O₂Na requires 347.1987; found: 347.1989. Concentration of the fractions containing the slower-eluting component (R_F 0.5, 1% methanol in dichloromethane) afforded the *title compound 22c* (0.016 g, 27%) as a colourless oil. ν_{\max} (KBr) 1778, 1698, 1634 cm⁻¹. δ_H (400 MHz, CDCl₃) 5.91 (dd, J 3.3, 1.6, 1H, H6), 5.35 (m, 1H, H11), 5.49 (m, H10, 2H, H10'), 5.07 (m, 1H, H11'), 3.25 (dd, J 4.7, 3.7, 1H, H7), 3.08 (d, J 6.0, 1H, H3a), 2.93 (dd, J 15.1, 6.5, 1H, H9a), 2.87 (obscured dd, 1H, H9b), 2.83 (t, J 5.6, 1H, H7a), 2.68 (m, 2H, H9'), 2.14 (m, 4H, H12, H12'), 2.04 (s, 3H, H14), 1.60 (d, J 1.6 Hz, 3H, H14'), 1.02 (t, J 7.5, 3H, H13), 0.97 (t, J 7.5, 3H, H13'). δ_C (100 MHz, CDCl₃) 205.6 (C1/C8), 201.5 (C1/C8), 167.2 (C3), 146.7 (C5), 141.1 (C2), 133.9 (C11'), 132.6 (C10), 124.4 (C10'), 123.8 (C11), 123.0 (C6), 59.0 (C4), 49.1 (C7), 45.6 (C3a), 45.2 (C7a), 23.7 (C9'), 21.2 (C9), 20.8 (C12'), 20.5 (C12), 17.0 (C14), 15.8 (C14'), 14.1 (C13), 13.9 (C13'). HRMS m/z (Q-TOF ES⁺) Calcd for C₂₂H₂₈O₂Na requires 347.1987; found: 347.1981.

Density functional theory calculations

Calculations were performed using Gaussian 16 (rev. C.01, see <https://gaussian.com/gaussian16/>).³⁶ Geometries were optimised^{37–41} with B3LYP-D3(BJ)/6-311+G(d,p) using the SMD⁴² of ethanol. Distortion–interaction analyses of each TS partner were performed at the same level of theory. Intrinsic reaction coordinate calculations^{43,44} were performed on all TSs, which allowed the reactant and product structures

connected to each TS along minimum-energy pathways to be identified. Gibbs free energies are reported at a standard state of 298.15 K and 1 mol L⁻¹.

Supplementary material

Numbering schemes, 1-D and 2-D NMR spectra and HPLC chromatograms of all new compounds; UPLC traces of representative samples of refined pyrethrum extract before and after heat treatment; computed geometries and energies of species calculated with density functional theory: supplementary material is available [online](#).

References

- 1 Fist AJ, Chung B. Pyrethrum and poppy: two Tasmanian industries of world significance. *Acta Hort* 2015; 1073: 85–90. doi:10.17660/ActaHort.2015.1073.11
- 2 Crombie L. Chemistry of Pyrethrins. In: Casida JE, Quistad GB, editors. *Pyrethrum Flowers: Production, Chemistry, Toxicology, and Uses*. New York, NY, USA: Oxford University Press; 1995. pp. 1232–1193.
- 3 Krief A. Pyrethroid insecticides. *Arkivoc* 2021; Part I: 48–54.
- 4 Fujitani J. Chemistry and pharmacology of insect powder. *Arch Exp Pathol Pharmacol* 1909; 61: 47–75. doi:10.1007/BF01841115
- 5 Yamamoto R. The insecticidal principle in *Chrysanthemum cinerariaefolium*. Part I. *J Chem Soc Jpn* 1919; 40: 126.
- 6 Yamamoto R. The insecticidal principle in *Chrysanthemum cinerariaefolium*. Parts II and III. On the constitution of the pyrethronic acid. *J Chem Soc Jpn* 1923; 44: 311.
- 7 Staudinger H, Ruzicka L. Insektentötende Stoffe. X. *Helv Chim Acta* 1924; 7: 448–458. [In German] doi:10.1002/hlca.19240070150
- 8 LaForge FB, Barthel WF. Constituents of pyrethrum flowers. XVI. Heterogeneous nature of pyrethrolone. *J Org Chem* 1944; 09: 242–249. doi:10.1021/jo01185a006
- 9 LaForge FB, Barthel WF. Constituents of pyrethrum flowers. XVII. The isolation of five pyrethrolone semicarbazones. *J Org Chem* 1945; 10: 106–113. doi:10.1021/jo01178a003
- 10 LaForge FB, Barthel WF. Constituents of pyrethrum flowers. XVII. The structure and isomerism of pyrethrolone and cinerolone. *J Org Chem* 1945; 10: 114–120. doi:10.1021/jo01178a004
- 11 Godin PJ, Sleeman RJ, Snarey M, Thain EM. The jasmolins, new insecticidally active constituents of *Chrysanthemum cinerariaefolium* VIS. *J Chem Soc C* 1966; 332–334. doi:10.1039/j39660000332
- 12 Crombie L, Harper SH. The chrysanthemumcarboxylic acids. Part VI. The configurations of the chrysanthemic acids. *J Chem Soc* 1954; 470. doi:10.1039/jr9540000470
- 13 Inouye Y, Takeshita Y, Ohno M. Studies on synthetic pyrethroids: part V. Synthesis of geometrical isomers of chrysanthemum dicarboxylic acid. *Bull Agric Chem Soc Jpn* 1955; 19: 193–199. doi:10.1271/bbb1924.19.193
- 14 Katsuda Y, Chikamoto T, Inouye Y. The absolute configuration of naturally derived pyrethrolone and cinerolone. *Bull Agric Chem Soc Jpn* 1958; 22: 427–428. doi:10.1080/03758397.1958.10857510
- 15 Staudinger H, Ruzicka L. Insektentötende Stoffe. I. Über Isolierung und Konstitution des wirksamen Teiles des dalmatinischen Insektenpulvers. *Helv Chim Acta* 1924; 7: 177–201. [In German] doi:10.1002/hlca.19240070124
- 16 Staudinger H, Ruzicka L. Insektentötende Stoffe. II. Zur Konstitution der Chrysanthemum-monocarbonsäure und -dicarbonsäure *Helv Chim Acta* 1924; 7: 201–211. [In German] doi:10.1002/hlca.19240070125
- 17 Staudinger H, Ruzicka L. Insektentötende Stoffe. III. Konstitution des Pyrethrolons. *Helv Chim Acta* 1924; 7: 212–235. [In German] doi:10.1002/hlca.19240070126
- 18 Ogliaruso MA, Romanelli MG, Becker EI. Chemistry of cyclopentadienones. *Chem Rev* 1965; 65: 261–367. doi:10.1021/cr60235a001

- 19 LaForge FB, Green N, Schechter MS. Dimerized cyclopentadienones from esters of allethrolone. *J Am Chem Soc* 1952; 74: 5392–5394. doi:10.1021/ja01141a050
- 20 Allen CFH, VanAllen JA. A carbonyl bridged compound in which the bridge ring is saturated. *J Org Chem* 1955; 20: 323–327. doi:10.1021/jo01121a009
- 21 Crombie L, Elliot M, Harper SH. Experiments on the synthesis of the pyrethrins. Part III. Synthesis of dihydrocinerin I and tetrahydro-pyrethrin I; a study of the action of *N*-bromosuccinimide on 3-methyl-2-*n*-alkyl (and alkenyl) cyclopent-2-en-1-ones. *J Chem Soc* 1950; 971–978. doi:10.1039/jr9500000971
- 22 Elliott M, Harper SH, Kazi MA. Experiments on the synthesis of the pyrethrins. XIV. Rethrins and the cyclopentadienone related to 3-methylcyclopent-2-enone. *J Sci Food Agric* 1967; 18: 167–171. doi:10.1002/jsfa.2740180409
- 23 Guo Y, Xie Y, Wu G, Cheng T, Zhu S, Yan S, Jin H, Zhang W. Xylopidimers A–E, five new guaianes dimers with various carbon skeletons from the roots of *Xylopia vielana*. *ACS Omega* 2019; 4: 2047–2052. doi:10.1021/acsomega.8b00828
- 24 Kong X, Yang S, Yu F, Vasamsetty L, Liu J, Liu S, Liu X, Fang X. Cyclopentadienone formation from β,γ -unsaturated cyclopentenones and its application in Diels–Alder reactions. *J Org Chem* 2018; 83: 8953–8961. doi:10.1021/acs.joc.8b01150
- 25 Harmata M, Barnes CL, Brackley J, Bohnert G, Kirchoefer P, Kürtli L, Rashatasakhon P. Generation of cyclopentadienones from 2-bromocyclopentenones. *J Org Chem* 2001; 66: 5232–5236. doi:10.1021/jo015671+
- 26 Fuchs B, Pasternak M, Scharf G. The dimer of 2,3-dimethyl-3,4-(*o,o'*-biphenylene)cyclopentadienone: thermal and photochemical transformations. *J Chem Soc, Chem Commun* 1976; 53–54. doi:10.1039/C39760000053
- 27 DePuy CH, Isaks M, Eilers KL, Morris GF. The formation of cyclopentadienones. *J. Org. Chem* 1964; 29: 3503–3507. doi:10.1021/jo01035a013
- 28 Eaton PE, Cole TW. The cubane system. *J Am Chem Soc* 1964; 86: 962–964. doi:10.1021/ja01059a072
- 29 Hutt OE, Freemont JA, Littler S, Duggan PJ, Tsanaktsidis J, Cole H, Kerr M, Ryan JH. Staudinger and Ruzicka's altered pyrethrolone: the cyclopentadienone dimers derived from pyrethrin I. *Acta Hort* 2015; 1073: 181–190. doi:10.17660/ActaHortic.2015.1073.25
- 30 Bickelhaupt FM, Houk KN. Analysing reaction rates with the distortion/interaction–activation strain model. *Angew Chem Int Ed* 2017; 56: 10070–10086. doi:10.1002/anie.201701486
- 31 McLeod D, Thøgersen MK, Jessen NI, Jørgensen KA, Jamieson CS, Xue X-S, Houk KN, Liu F, Hoffmann R. Expanding the frontiers of higher-order cycloadditions. *Acc Chem Res* 2019; 52: 3488–3501. doi:10.1021/acs.accounts.9b00498
- 32 Quadrelli P, Romano S, Toma L, Caramella P. A bispericyclic transition structure allows for efficient relief of antiaromaticity enhancing reactivity and endo selectivity in the dimerization of the fleeting cyclopentadienone. *J Org Chem* 2003; 68: 6035–6038. doi:10.1021/jo034401j
- 33 Freemont JA, Littler SW, Hutt OE, Mauger S, Meyer AG, Winkler DA, Kerr MG, Ryan JH, Cole HF, Duggan PJ. Molecular makers for pyrethrin autoxidation in stored pyrethrum crop: analysis and structure determination. *J Agric Food Chem* 2016; 64: 7134–7141. doi:10.1021/acs.jafc.6b02959
- 34 Kamperdick C, Phuong NM, Sung TV, Adam G. Guaianes dimers from *Xylopia vielana*. *Phytochem* 2001; 56: 335–340. doi:10.1016/s0031-9422(00)00344-7
- 35 Crombie L, Pattenden G, Simmonds DJ. Carbon-13 magnetic resonance spectra of natural pyrethrins and related compounds. *J Chem Soc Perkin Trans 1* 1975; 1500–1502.
- 36 Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Petersson GA, Nakatsuji H, Li X, Caricato M, Marenich AV, Bloino J, Janesko BG, Gomperts R, Mennucci B, Hratchian HP, Ortiz JV, Izmaylov AF, Sonnenberg JL, Williams-Young D, Ding F, Lipparini F, Egidi F, Goings J, Peng B, Petrone A, Henderson T, Ranasinghe D, Zakrzewski VG, Gao J, Rega N, Zheng G, Liang W, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Throssell K, Montgomery JA Jr, Peralta JE, Ogliaro F, Bearpark MJ, Heyd JJ, Brothers EN, Kudin KN, Staroverov VN, Keith TA, Kobayashi R, Normand J, Raghavachari K, Rendell AP, Burant JC, Iyengar SS, Tomasi J, Cossi M, Millam JM, Klene M, Adamo C, Cammi R, Ochterski JW, Martin RL, Morokuma K, Farkas O, Foresman JB, Fox DJ. *Gaussian 16, revision C.01*. Wallingford, CT, USA: Gaussian, Inc.; 2019.
- 37 Lee C, Yang W, Parr RG. Development of the Colle–Salvetti correlation-energy formula into a functional of the electron density. *Phys Rev B* 1988; 37: 785–789. doi:10.1103/physrevb.37.785
- 38 Becke AD. Density-functional thermochemistry. III. The role of exact exchange. *J Chem Phys* 1993; 98: 5648–5652. doi:10.1063/1.464913
- 39 Becke AD. A mixture of Hartree–Fock and local density-functional theories. *J Chem Phys* 1993; 98: 1372–1377. doi:10.1063/1.464304
- 40 Stephens PJ, Devlin FJ, Chabalowski CF, Frisch MJ. *Ab initio* calculation of vibrational absorption and circular dichroism spectra using density functional force fields. *J Phys Chem* 1994; 98: 11623–11627. doi:10.1021/j100096a001
- 41 Grimme S, Antony J, Ehrlich S, Krieg H. A consistent and accurate *ab initio* parametrization of density functional dispersion correction (DFT-D) for the 94 elements H–Pu. *J Chem Phys* 2010; 132: 154104. doi:10.1063/1.3382344
- 42 Marenich AV, Cramer CJ, Truhlar DG. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J Phys Chem B* 2009; 113: 6378–6396. doi:10.1021/jp810292n
- 43 Gonzalez C, Schlegel HB. An improved algorithm for reaction path following. *J Chem Phys* 1989; 90: 2154–2161. doi:10.1063/1.456010
- 44 Gonzalez C, Schlegel HB. Reaction path following mass-weighted internal coordinates. *J Phys Chem* 1990; 94: 5523–5527. doi:10.1021/j100377a021

Data availability. The data that support this study are available in the article and accompanying online supplementary material. Further details can be shared on reasonable request to the corresponding author.

Conflicts of interest. The authors declare that they have no conflicts of interest.

Declaration of funding. The CSIRO research was partly funded by Horticulture Australia Ltd (Project Number PY09004), the Commonwealth of Australia DIISR Enterprise Connect 'Researchers in Business' Program and Botanical Resources Australia Pty Ltd. We thank the Australian Research Council for funding (DP180103047 to E. H. Krenske).

Acknowledgements. The authors thank Dr Roger Mulder, Dr Jo Cosgriff and Carl Braybrook for their assistance with collection of NMR and MS data. Computational resources were provided by the Australian National Computational Infrastructure through the National Computational Merit Allocation Scheme.

Author affiliations

^ACSIRO Manufacturing, Ian Wark Laboratory, Bayview Avenue, Clayton, Vic. 3168, Australia.

^BSchool of Chemistry and Molecular Biosciences, The University of Queensland, St Lucia, Qld 4072, Australia.

^CCollege of Science and Engineering, Flinders University, Adelaide, SA 5042, Australia.

^DBotanical Resources Australia Pty Ltd, 44-46 Industrial Drive, Ulverstone, Tas. 7315, Australia.