frontiers | Frontiers in Natural Products

TYPE Original Research
PUBLISHED 04 January 2024
DOI 10.3389/fntpr.2023.1332436

OPEN ACCESS

EDITED BY
Grzegorz Wegrzyn,
University of Gdansk, Poland

REVIEWED BY
Vaderament-A. Nchiozem-Ngnitedem,
University of Potsdam, Germany
Rachid Chahboun,
University of Granada, Spain

*CORRESPONDENCE
Christopher S. Jeffrey,
cjeffrey@unr.edu

RECEIVED 02 November 2023
ACCEPTED 11 December 2023
PUBLISHED 04 January 2024

CITATION
de Oliveira CR Jr, Ledvina ZD, Leonard MD, Odoh SO, Dodson CD and Jeffrey CS (2024), Isolation of new neolignans and an unusual meroterpenoid from *Piper cabagranum*. *Front. Nat. Produc.* 2:1332436. doi: 10.3389/fntpr.2023.1332436

Isolation of new neolignans and an unusual meroterpenoid from *Piper cabagranum*

Celso R. de Oliveira Jr[1], Zachary D. Ledvina[2], Michael D. Leonard[3], Samuel O. Odoh[2], Craig D. Dodson[2] and Christopher S. Jeffrey[2]*

[1]Department of Forestry and Wildlife Ecology, University of Wisconsin—Madison, Madison, WI, United States, [2]Hitchcock Center for Chemical-Ecology, Department of Chemistry, University of Nevada—Reno, Reno, NV, United States, [3]Truckee Meadows Community College, Reno, NV, United States

A novel meroterpenoid cabagranin D was isolated with related neolignans cabagranins A–C from the leaves of *Piper cabagranum* (Costa Rica). Cabagranins A–C represent the first examples of 3,3′-neolignans isolated from the plant genus *Piper*, and the meroterpenoid cabagranin D displays an unprecedented Diels–Alder conjugate of an unsubstituted phenylpropenone and α-phellandrene. Details of the full structural elucidation of these compounds and a discussion of their potential biosynthetic relationships are presented.

KEYWORDS

meroterpene, Diels–Alder, neolignan, *Piper cabagranum*, Piperaceae

1 Introduction

The *Piper* genus of plants (Piperaceae) is the source of a diversity of compounds isolated from over 2,600 accepted species distributed across the tropics (Parmar et al., 1997; Gutierrez et al., 2013; Mgbeahuruike et al., 2017; Gomez-Calvario and Rios, 2019; Salehi et al., 2019; Fan et al., 2023). Numerous studies have characterized the role of these compounds in various ecological interactions and uncovered novel compounds with a wide diversity of biological activities, including antimicrobial and anti-herbivore activities (Xu and Li, 2011).

In a phytochemical survey of *Piper* species within the Radula clade, we identified *Piper cabagranum* as having a unique chemistry based on GC-MS and ^{1}H NMR analysis of crude extracts (Uckele et al., 2021). We observed that general categories of natural products like lignans, sesquiterpenes, and flavonoids were shared among closely related species; however, ^{1}H NMR analysis of crude leaf extracts revealed that specific structural motifs varied widely (Richards et al., 2018; Uckele et al., 2021). This divergence in functional motifs likely stems from the distinct evolutionary paths of these plant species, creating fertile ground for the discovery of new natural products. The unique spectral features encountered in the crude methanolic extract of *P. cabagranum* (Costa Rica) distinguished it from the other 70 species in our study and motivated the phytochemical characterization of this species, with the goal of understanding the role of specialized metabolites in mediating ecological interactions. Our work led to the discovery of an unprecedented meroterpene Diels–Alder conjugate cabagranin D, **5** (Figure 1). Furthermore, this work identified a new series of dehydrodieugenol-derived 3,3′-neolignans (cabagranins A–C; **1**–**3**) which involve novel biosynthetic connections between cabagranin D (**5**) and the co-isolated neolignans (Figure 1). We here report the isolation, structural, and stereochemical characterization

of new meroterpenoid **5** and neolignans **1**–**3**—natural products from *P. cabagranum* (Costa Rica).

2 Materials and methods

2.1 Plant material

Leaf samples of *P. cabagranum* were collected from La Selva Biological Station and the Tirimbina Biological Reserve and verified (voucher # EJT3531) in March 2012. The leaves were oven-dried (35°C–40°C) and ground to a fine powder.

2.2 Extraction and isolation

The ground leaf material (1 g) was twice extracted with 400 mL of HPLC-grade hexanes for 2 h under mechanical agitation. The supernatants were pooled and evaporated under reduced pressure. The spent plant material was then twice extracted with HPLC-grade (Fisher Scientific, Hampton, NH) acetone under the same conditions, and the supernatants were combined and evaporated under reduced pressure, resulting in 200 mg of crude acetone extract and 100 mg of hexane extract. The crude acetone extract (180 mg) was dissolved in methanol (3 mL) and then purified via RP-HPLC (Poroshell C18, 21.2 mm × 150 mm, Agilent, Santa Clara, California, United States) using a 20 min gradient of 30%–100% acetonitrile: water (Optima grade: Fisher Scientific, Hampton, NH) and held for 7 min at 100% acetonitrile using an Agilent 1260/1290 Infinity II equipped with an Agilent 6140 Quadrupole LC/MS (Santa Clara, California, United States). This separation yielded compounds **1** (63 mg, elution time = 8.1 min), **2** (3 mg, elution time = 9.4 min), **3** (4 mg, elution time = 10.4 min), **4** (2 mg, elution time = 13.6 min), and **5** (2 mg, elution time = 18.9 min). The hexane extract (100 mg) was further purified through solid phase extraction (C-18 Sep-Pak) using a 10% step gradient of acetone:water from 50% to

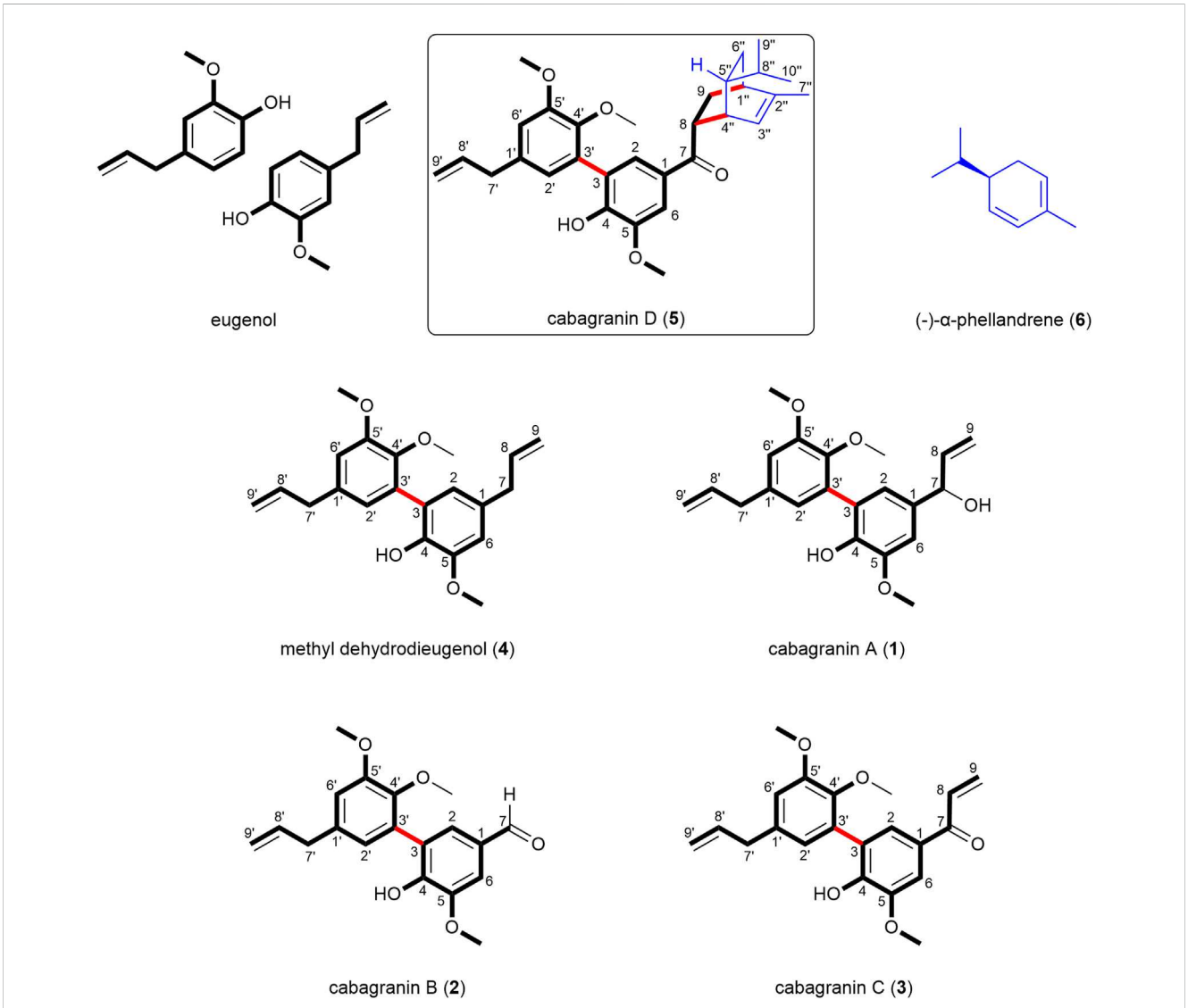


FIGURE 1
Structures of neolignans **1**–**4** and the meroterpenoid **5** isolated from *P. cabagranum*.

TABLE 1 ^{1}H and ^{13}C NMR assignments for the isolated compounds 1–3 in CD_3OD.

Position	Cabagranin A (1)		Cabagranin B (2)		Cabagranin C (3)	
	^{1}H (*J* in Hz)	^{13}C	^{1}H (*J* in Hz)	^{13}C	^{1}H (*J* in Hz)	^{13}C
1		135.2		129.5		129.4
2	6.74 (1H, dd, 2.1, 0.6)	122.6	7.36 (1H, d, 1.9)	129.9	7.52 (1H, d, 2.1)	127.4
3		133.9		132.5		132.9
4		144.3		152.2		151.1
5		149.1		149.5		149.3
5-OMe	3.90 (3H, s)	56.5	3.98 (3H, s)	56.7	3.98 (3H, s)	56.6
6	6.96 (1H, d, 2.0)	109.9	7.46 (1H, d, 1.9)	109.5	7.59 (1H, d, 2.1)	110.9
7	5.07 (1H, d, 5.6)	76.0	9.76 (1H, s)	193.0		191.1
8	6.05 (1H, ddd, 17.1, 10.3, 5.9)	142.3			7.33 (1H, dd, 17.0, 10.6)	133.4
9-*cis*	5.16–5.09 (1H, m)	114.5			5.87 (1H, dd, 10.6, 2.0)	129.6
9-*trans*	5.28 (1H, dt, 17.1, 1.6)				6.37 (1H, dd, 17.0, 2.0)	
1′		136.9		137.0		137.2
2′	6.65 (1H, d, 2.2)	124.4	6.68 (1H, dd, 2.1, 0.6)	124.0	6.68 (1H, dt, 2.0, 0.6)	124.2
3′		126.7		127.1		126.7
4′		146.2		146.2		146.4
4′-OMe	3.58 (3H, s)	61.1	3.60 (3H, s)	60.9	3.60 (3H, s)	61.1
5′		153.9		153.8		154.0
5′-OMe	3.86 (3H, s)	56.3	3.88 (3H, s)	56.3	3.88 (3H, s)	56.4
6′	6.83 (1H, d, 2.1)	113.1	6.87 (1H, d, 2.1)	113.6	6.87 (1H, d, 2.0)	113.7
7′	3.35 (2H, br d, 6.7)	40.8	3.38 (2H, br d, 6.7)	41.0	3.38 (2H, dt, 6.7, 0.8)	41.0
8′	5.98 (1H, ddt, 16.8, 10.0, 6.7)	138.9	5.99 (1H, ddt, 16.9, 9.9, 6.7)	138.8	5.99 (1H, ddt, 16.9, 10.0, 6.7)	138.9
9′-*cis*	5.04 (1H, ddt, 10.0, 2.2, 1.3)	116.0	5.05 (1H, ddt, 10.0, 2.0, 1.3)	115.9	5.05 (1H, ddt, 10.1, 2.0, 1.3)	116.1
9′-*trans*	5.16–5.04 (1H, m)		5.18–5.07 (1H, m)		5.11 (1H, ddt, 17.0, 2.0, 1.6)	

100% acetone, yielding a 70% acetone:water fraction that was enriched in compound **5**. Further purification using the preparatory HPLC methods described above yielded an additional 3 mg of compound **5**.

2.3 Spectroscopic acquisition methods

High-resolution mass spectrometry data were collected using an Agilent TOF LC/MS (model G6230B, Santa Clara, California, United States). NMR spectra were gathered using a two-channel 400 MHz Varian VNMRS spectrometer (399.78 MHz ^{1}H and 100.53 MHz ^{13}C) equipped with an ATB automation probe (400 ATB PFG) (Agilent, Santa Clara, California, United States). Circular dichroism experiments were performed on a Jasco J-1500 CD-spectrometer (model J-1500-150, Jasco Corporation, Tokyo, Japan). Polarimetry experiments were conducted on a Jasco P-2000 polarimeter (Jasco Corporation, Tokyo, Japan).

2.3.1 High-resolution mass spectrometry measurements

High-resolution mass spectrometry (HRMS) analysis was performed using an Agilent TOF LC/MS (Santa Clara, California, United States) fitted with an electrospray ionization source (ESI). The isolated compound was taken up into methanol (1 μg/mL) and injected directly into the ionization source. Instrument parameters were: gas temperature, 325°C; gas flow, 5 L/min; nebulizer, 20 psig; and ion polarity, positive.

2.3.2 Nuclear magnetic resonance measurements

Reported chemical shifts were recorded in parts per million (δ) using CD_3OD as a standard for ^{1}H and ^{13}C (δ_H 3.31; δ_C 49.0). Coupling constants (*J*) are reported in Hz. Nuclear magnetic resonance (NMR) assignments were made based on ^{1}H and ^{13}C spectra, as well as various 2D experimental spectra (COSY, HMBC, HSQC, and NOESY). For individual compounds, ^{1}H spectra were acquired using the parameters set automatically by the instrument with the number of transients (nt = 128), ^{13}C spectra with the

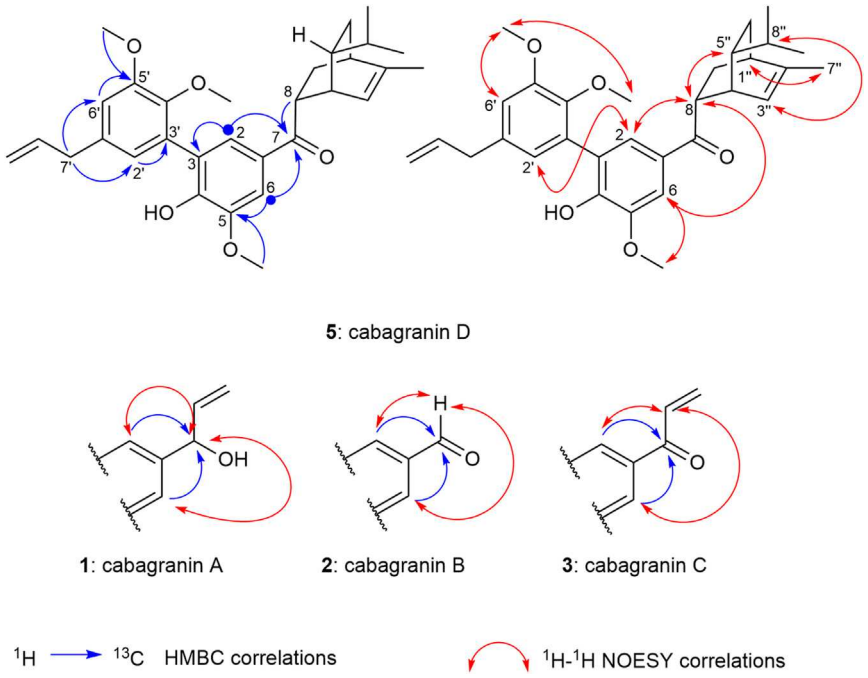


FIGURE 2
2D NMR correlations establishing the proposed structures and relative configurations of cabagranins A–D.

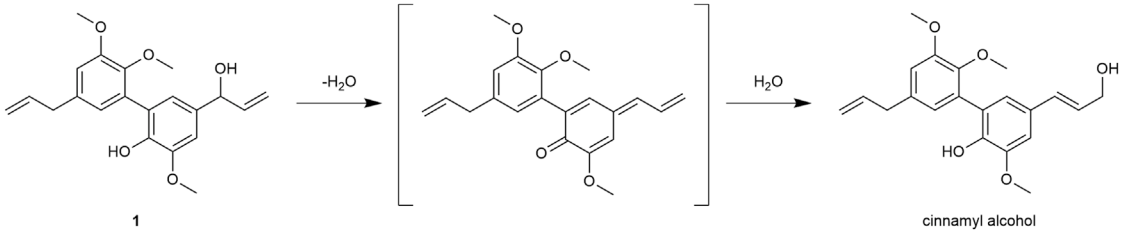


FIGURE 3
Proposed rearrangement of alcohol **1** to the cinnamyl alcohol derivative through a *p*-quinone methide intermediate.

number of transients (nt = 15,000), ^{1}H–^{1}H gCOSY (nt = 4 × 128), ^{1}H–^{13}C gHMBCAD (nt = 8 × 512), ^{1}H–^{13}C gHSQCAD (nt = 4 × 256), and ^{1}H–^{1}H NOESY (nt = 32 × 256).

2.3.3 Polarimetry measurements

Polarimetry measurements were taken on a Jasco P-2000 polarimeter. Each compound was dissolved in 10 mL of dichloromethane and placed into a 10-cm polarimeter cell along with a dichloromethane blank. The samples were placed in the polarimeter to obtain the optical rotation in degrees.

2.3.4 Electronic circular dichroism measurements

Electronic circular dichroism (ECD) measurements were obtained on a Jasco J-1500 CD spectrometer. The isolated compound was dissolved in methanol (0.5 mM) and placed into the CD spectrometer along with a methanol blank. The acquisition parameters were as follows: photometric mode, CD, HT; measure range, 400–200 nm; data pitch, 0.5 nm; CD scale, 200 mdeg/0.1 dOD; FL scale, 200 mdeg/0.1 dOD; D.I.T., 1 s; bandwidth, 1.00 nm; accumulations, 1; and scanning speed, 10 nm/min.

3 Results and discussion

Cabagranin A (**1**) was purified from the 50% acetone:water eluent as a colorless oil, which was found to have the formula $C_{21}H_{24}O_5$ from HRESIMS m/z = 379.1551 $[M + Na]^+$, corresponding to an oxygenated dehydrodieugenol derivative. ^{1}H NMR analysis revealed the clear presence of a bis-phenylpropanoid with differing propenyl units (Table 1). One of these units was hydroxylated at C-7, indicated by the resonance δ_H 5.07 (d, J = 5.6 Hz)/δ_C 76.0, which was coupled to the C-8 vinylic methine δ_H

10.3389/fntpr.2023.1332436

TABLE 2 ^{1}H and ^{13}C NMR data for cabagranin D (**5**) in CD_3OD.

Position	Cabagranin D (5)	
	^{1}H (*J* in Hz)	^{13}C
1		128.8
2	7.44 (1H, d, 2.0)	126.5
3		133.1
4		150.2
5		149.1
5-OMe	3.95 (3H, s)	56.6
6	7.48 (1H, d, 2.0)	110.8
7		202.4
8	3.50 (1H, ddd, 9.4, 5.8, 1.9)	48.4
9	1.77–1.70 (2H, m)	29.5
1′		137.2
2′	6.67 (1H, d, 2.0)	124.2
3′		126.5
4′		146.4
4′-OMe	3.60 (3H, s)	61.0
5′		113.6
5′-OMe	3.88 (3H, s)	56.3
6′	6.87 (1H, d, 2.0)	154.0
7′	3.37 (2H, br d, 6.8)	41.0
8′	5.99 (1H, ddt, 16.9, 10.0, 6.7)	138.9
9′-*cis*	5.05 (1H, dq, 10.0, 2.0)	116.0
9′-trans	5.11 (1H, dq, 17.0, 2.0)	
1″	2.40 (1H, m)	37.5
2″		144.6
3″	5.49 (1H, dt, 6.2, 1.7)	121.9
4″	2.93 dt (1H, 6.5, 2.0)	38.7
5″	1.48 (1H, m)	48.5
6″-α	1.80 (1H, m)	32.7
6″-β	0.97 (1H, m)	
7″	1.76 (3H, d, 1.7)	20.0
8″	1.08 (1H, m)	34.5
9″	0.88 (3H, d, 6.5)	21.7
10″	0.82 (3H, d, 6.6)	20.9

6.05 (ddd, J = 17.1, 10.3, 5.9 Hz)/δ_C 142.3 based on COSY and HMBC analyses. HMBC correlations to quaternary oxygenated aromatic carbons led to the assignment of the three different methoxy singlets as aryl methyl ethers (Figure 2).

Proton resonances in the aromatic region indicate the presence of two pairs of *meta*-coupled protons (δ_H 6.96/6.74 and δ_H 6.83/6.65, J ~ 2 Hz), each pair displaying HMBC correlations with each set of the two aromatic *O*-substituted carbons (δ_C 144–154) and one of the benzylic carbons (δ_C 76.0 and 40.8, respectively). NOESY correlations between the most shielded protons in each ring supported the proximity of the two rings through direct linkage. Lastly, NOESY correlations were used to assign the location of three methoxy groups across the aromatic rings, which supported the lone phenol being *para* to the modified propenyl moiety.

Attempts to evaluate the enantiopurity of cabagranin A (**1**) and assign the absolute configuration of the alcohol were unsuccessful due to decomposition of the material under a variety of derivatization conditions. ECD analysis demonstrated no Cotton effects and a low optical rotation value $\{[\alpha]_D^{20} = +4.1$ (*c* 0.38, $CH_2Cl_2)\}$, leaving the optical purity of this compound in question. We found that the labile hydroxyl group of cabagranin A (**1**) rearranged into a cinnamyl alcohol derivative when it remained dissolved for months at room temperature or when treated with aqueous acid (Figure 3).

Further purification of the 50% acetone:water fractions resulted in four minor components that retained most of the structural features in **1**, including **4,** which is presumed to be the biosynthetic precursor to **1**, and a coumarin (Scheme 1, see SI). Two new compounds were isolated from this fraction which bore the identical bis-aryl phenol moiety of **1** but differed in their modified propenyl moieties. These compounds were assigned as cabagranin B (**2**), which contains an aldehyde substituent, and cabagranin C (**3**), which contains a 1-propenone substituent (Figure 1). It is important to note that neolignans containing the vinyl ketone substituent of **3** have only been isolated in a few cases and that most reports suggest that this product is the result of lignin pyrolysis.

Cabagranin D (**5**) was isolated as the predominant component of the 70% acetone:water fractions and found to have the formula $C_{31}H_{38}O_5$ from HRESIMS m/z = 513.2653 $[M + Na]^+$. NMR spectral analysis indicated the presence of the 3,3′-biaryl structure analogous to **1**–**4** in addition to an *iso*-propyl group (δ_H 0.85), an allylic methyl (δ_H 1.76 and δ_C 20.0), and a vinylic proton [δ_H 5.49 (dt, J = 6.5 and 2.0 Hz), δ_C 121.9] (Table 2). ^{1}H–^{1}H COSY correlations were consistent with a [2.2.2] bicyclic structure, which was supported by key HMBC correlations between H-2 and H-6 aryl methines and the H-8 methine with the carbonyl carbon at δ_C 202. Relative configuration of C-8 and C-5″ were assigned from NOESY correlations between H-8 to H-5″ and H-8″ to H-3”. Further 2-D NMR correlations were consistent with the structural assignment of **5**, which is postulated to be the *endo* product of a Diels–Alder cycloaddition between the enone of **3** and the monoterpene α-phellandrene (**6**, Figure 1). This new molecule seems to represent a novel late-stage merger between a terpene and a neolignan, presumably through a Diels–Alder reaction.

Compound 5 was found to be optically active and have an optical rotation of $[\alpha]_D^{20} = -56.3$ (*c* 0.03, CH_2Cl_2). The ECD spectrum of **5** showed strong Cotton effects at 250, 290, and 330 nm (Figure 4). Simulation of the ECD spectra using time-dependent density functional theory (TDDFT) calculations (M06/6- 31G+*) of energy-minimized structures of both

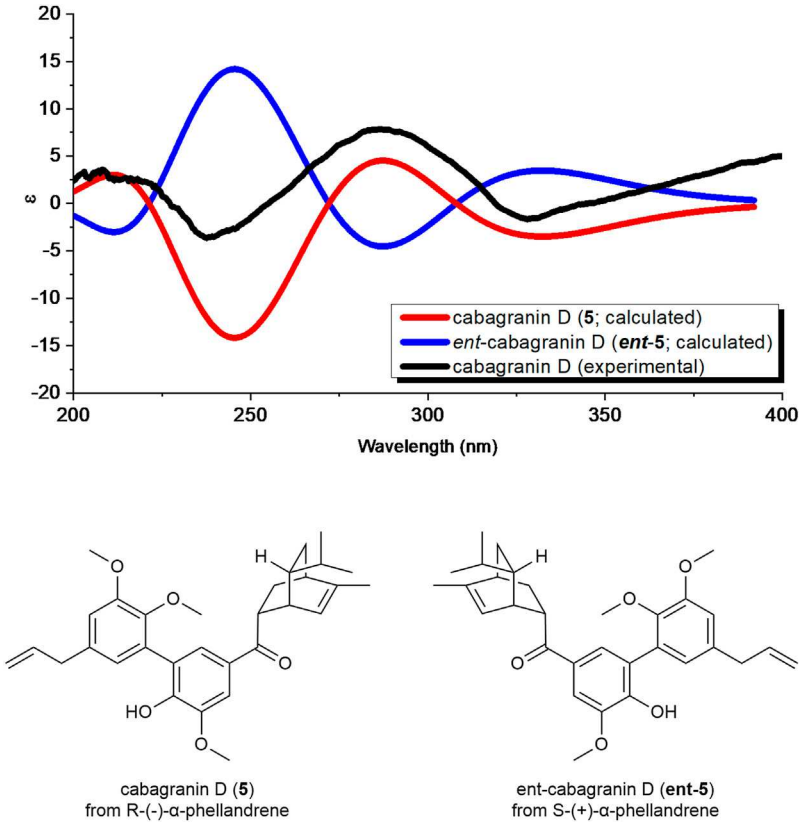


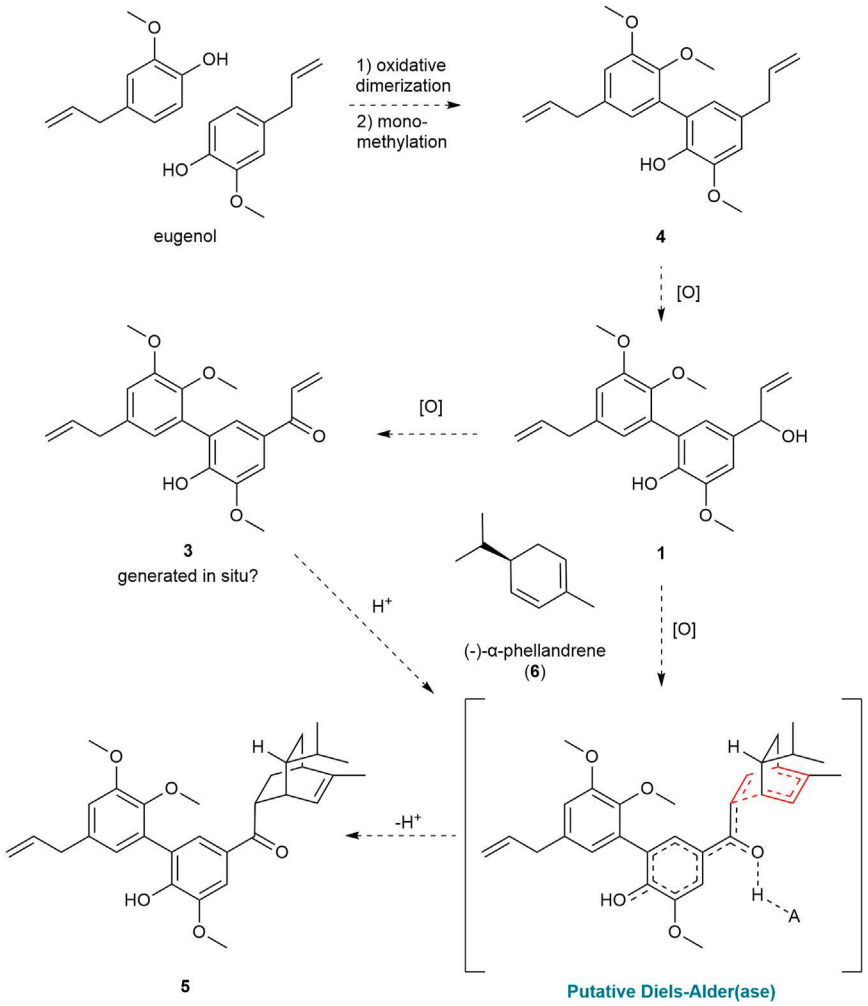
FIGURE 4
Comparison of the calculated ECD spectra of both enantiomers of cabagranin D using time-dependent density functional theory (TDDFT) calculations and experimental ECD spectra.

enantiomers of cabagranin D in an implicit solvent model (PCM) for methanol strongly aligned with the UV absorbances and sign corresponding to an *endo* cycloaddition of R-(-)-α-phellandrene (**6**) with cabagranin C from the face opposite the *iso*-propyl substituent, thus confirming the assignment of the absolute configuration of **5**.

4 Conclusion

The co-isolation of the series of neolignans **1**–**4** supports the proposed biosynthetic pathway shown in Scheme 1. This hypothesis suggests that eugenol undergoes oxidative dimerization followed by monomethylation to yield compound **4**. The major constituent of the crude extract is formed through the selective oxidation of the allyl group of the phenolic ring. A variety of neolignans have been isolated from other *Piper* species, but this represents the first example that contains a hydroxylated propenyl side chain (Macedo et al., 2017). While the conversion of the alcohol to ketone **3** is anticipated to be facile, compound **3** was not always present in detectable concentrations in the crude extracts of the leaves. The high electrophilic reactivity of **3**, its rare occurrence (Chen et al., 2012; de Sousa et al., 2017; de Sousa et al., 2020), and the presumed toxicity of the vinyl ketone suggest that this compound could be an artifact of isolation and is not present in high concentrations *in vivo* (Chen et al., 2012; de Sousa et al., 2017; de Sousa et al., 2020).

The discovery of meroterpenoid **5** effectively represents a Diels–Alder cycloaddition reaction between ketone **3** and α-phellandrene (**6**). Although some similar examples exist, the isolation of **5** provides the first example of a Diels–Alder product between an unsubstituted phenylpropenone and a terpene (Pasfield et al., 2013; Alves et al., 2017; Qiu et al., 2018; Tortora et al., 2022; Zhou et al., 2023). Given the instability of **3**, we hypothesize that the ketone precursor could be formed *in situ* and simultaneously trapped by α-phellandrene in a single enzymatic step. In this scenario, the Diels–Alder product could emerge from the activity of an oxidase enzyme acting on the hydroxyl group of compound **1**. This oxidation of **1** would lead to the formation of a vinyl *p*-quinone methide intermediate, representing the protonated enone, which would produce **5** (Scheme 1) from the reaction with α-phellandrene. Recent research highlights the role of redox-active enzymes that have likely diverged from their ancestral functions to act as Diels–Alderases in the biosynthesis of prenylated phenol and alkaloid natural products (Oikawa and Tokiwano, 2004; Gao et al., 2020; Gao et al., 2022; Liu et al., 2023). Other investigations have shown that phenols and their ethers can act as redox tags in electrocatalytic Diels–Alder reactions and that silver



SCHEME 1
Hypothetical biosynthetic pathway from eugenol to cabagranin D **(5)**.

nanoparticles can catalyze related Diels–Alder reactions involving phenolic chalcones and terpenoid dienes (Cong et al., 2008; Cong et al., 2010). When comparing biomimetic Diels–Alder reactions involving a chalcone and a 2,4-disubstituted diene, it was found that the desired reactions with moderate yield require high pressures or temperatures, or strong Lewis acids (ONeill et al., 2006; Tee et al., 2016; Chai et al., 2020; Tangdenpaisal et al., 2022). However, when using enzymatic (Gao et al., 2020) or redox-active catalysts (Cong et al., 2010; Ohmura et al., 2023), nearly identical reactants can undergo the Diels–Alder reaction at room temperature or even below, demonstrating a more efficient and milder process. While these reports support our hypothesis, we cannot distinguish the role of Lewis-acid or single-electron processes in catalyzing the proposed Diels–Alder reaction. Ongoing experimental and computational investigations are evaluating our biosynthetic hypothesis surrounding the formation of **5**.

The compounds isolated in this study establish *P. cabagranum* as a chemically distinct species within its genus, primarily due to the presence of oxidized 3,3′-neolignans and a distinctive neolignan meroterpenoid, cabagranin D, marking the first occurrence of a Diels–Alder between a vinyl ketone dienophile and a terpene diene. It inspires future studies on the biosynthetic origins of this unique compound.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

Author contributions

CO: conceptualization, investigation, methodology, writing–original draft, writing–review and editing, data curation, formal analysis, and validation. ZL: data curation, formal analysis, investigation, validation, and writing–review and editing. ML: data curation, investigation, writing–review and editing, and methodology. SO: formal analysis, investigation, writing–review and editing, and methodology.

CD: formal analysis, investigation, writing–review and editing, conceptualization, funding acquisition, and validation. CJ: investigation, methodology, writing–review and editing, conceptualization, funding acquisition, project administration, resources, supervision, and writing–original draft.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by grants from the NSF (EF-2133818) and by the Hitchcock Center for Chemical-Ecology fund. CO was supported by a Hitchcock Center for Chemical-Ecology graduate fellowship. Collection and export permits were granted by Sistema Nacional De Areas De Conservación (SINAC), Costa Rica (113-DGVS-2016).

Acknowledgments

The authors thank Christopher Harris for assistance with collecting the ECD spectra and Eric J. Tepe and Humberto Garcia for their help in identification and collection of the plant tissue.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fntpr.2023.1332436/full#supplementary-material

References

Alves, H. D. S., Rocha, W., Braz-Filho, R., and Chaves, M. C. O. (2017). Isolation of monoterpene dihydrochalcones from piper montealegreanum yuncker (piperaceae). *Molecules* 22 (6), 874. doi:10.3390/molecules22060874

Chai, G. L., Qiao, Y., Zhang, P., Guo, R., Wang, J., and Chang, J. (2020). Chiral hydroxytetraphenylene-boron complex catalyzed asymmetric diels-alder cycloaddition of 2'-hydroxychalcones. *Org. Lett.* 22, 8023–8027. doi:10.1021/acs.orglett.0c02978

Chen, Q. F., Chen, X. Z., Li, G. Y., Wang, C., and Zhang, G. L. (2012). Two new 2-phenylbenzofurans from the bark of Styrax perkinsiae. *Chin. J. Nat. Med.* 10 (2), 92–97. doi:10.3724/sp.j.1009.2012.00092

Cong, H., Becker, C. F., Elliott, S. J., Grinstaff, M. W., and Porco, J. A., Jr (2010). Silver nanoparticle-catalyzed Diels– alder cycloadditions of 2′-hydroxychalcones. *J. Am. Chem. Soc.* 132 (21), 7514–7518. doi:10.1021/ja102482b

Cong, H., Ledbetter, D., Rowe, G. T., Caradonna, J. P., and Porco, J. A., Jr (2008). Electron transfer-initiated diels– alder cycloadditions of 2′-hydroxychalcones. *J. Am. Chem. Soc.* 130 (29), 9214–9215. doi:10.1021/ja803094u

de Sousa, F. S., Baldim, J. L., Azevedo, R. A., Figueiredo, C. R., Pieper, P., Sear, C. E., et al. (2020). Structure-activity relationship study of cytotoxic neolignan derivatives using multivariate analysis and computation-aided drug design. *Bioorg Med. Chem. Lett.* 30 (16), 127349. doi:10.1016/j.bmcl.2020.127349

de Sousa, F. S., Grecco, S. S., Girola, N., Azevedo, R. A., Figueiredo, C. R., and Lago, J. H. G. (2017). Neolignans isolated from Nectandra leucantha induce apoptosis in melanoma cells by disturbance in mitochondrial integrity and redox homeostasis. *Phytochemistry* 140, 108–117. doi:10.1016/j.phytochem.2017.04.024

Fan, D., Zhou, C., Chen, C., Li, X., Ma, J., Hu, Y., et al. (2023). Lignans from the genus Piper L. and their pharmacological activities: an updated review. *Fitoterapia* 165, 105403. doi:10.1016/j.fitote.2022.105403

Gao, L., Su, C., Du, X., Wang, R., Chen, S., Zhou, Y., et al. (2020). FAD-dependent enzyme-catalysed intermolecular [4+2] cycloaddition in natural product biosynthesis. *Nat. Chem.* 12 (7), 620–628. doi:10.1038/s41557-020-0467-7

Gao, L., Yang, J., and Lei, X. (2022). Enzymatic intermolecular Diels-Alder reactions in synthesis: from nature to design. *Tetrahedron Chem.* 2, 100013. doi:10.1016/j.tchem.2022.100013

Gomez-Calvario, V., and Rios, M. Y. (2019). ^{1}H and ^{13}C NMR data, occurrence, biosynthesis, and biological activity of Piper amides. *Magn. Reson Chem.* 57 (12), 993–1070. doi:10.1002/mrc.4941

Gutierrez, R. M., Gonzalez, A. M., and Hoyo-Vadillo, C. (2013). Alkaloids from piper: a review of its phytochemistry and pharmacology. *Mini Rev. Med. Chem.* 13 (2), 163–193. doi:10.2174/138955713804805148

Liu, Z., Rivera, S., Newmister, S. A., Sanders, J. N., Nie, Q., Liu, S., et al. (2023). An NmrA-like enzyme-catalysed redox-mediated Diels-Alder cycloaddition with anti-selectivity. *Nat. Chem.* 15 (4), 526–534. doi:10.1038/s41557-022-01117-6

Macedo, A. L., Dos Santos, T. C. C., Valverde, A. L., Moreira, D. L., and Vasconcelos, T. R. A. (2017). An overview of neolignans of the genus piper L.: isolation methods and biological activities. *Mini Rev. Med. Chem.* 17 (8), 693–720. doi:10.2174/1389557516666161130094826

Mgbeahuruike, E. E., Yrjönen, T., Vuorela, H., and Holm, Y. (2017). Bioactive compounds from medicinal plants: focus on Piper species. *South Afr. J. Bot.* 112, 54–69. doi:10.1016/j.sajb.2017.05.007

Ohmura, S., Katagiri, K., Kato, H., Horibe, T., Miyakawa, S., Hasegawa, J. Y., et al. (2023). Highly enantioselective radical cation [2 + 2] and [4 + 2] cycloadditions by chiral iron(III) photoredox catalysis. *J. Am. Chem. Soc.* 145, 15054–15060. doi:10.1021/jacs.3c04010

Oikawa, H., and Tokiwano, T. (2004). Enzymatic catalysis of the Diels-Alder reaction in the biosynthesis of natural products. *Nat. Prod. Rep.* 21 (3), 321–352. doi:10.1039/b305068h

O'Neill, P. M., Verissimo, E., Ward, S. A., Davies, J., Korshin, E. E., Araujo, N., et al. (2006). Diels–Alder/thiol–olefin co-oxygenation approach to antimalarials incorporating the 2,3-dioxabicyclo[3.3.1]nonane pharmacophore. *Bioorg. Med. Chem. Lett.* 16 (11), 2991–2995. doi:10.1016/j.bmcl.2006.02.059

Parmar, V. S., Jain, S. C., Bisht, K. S., Jain, R., Taneja, P., Jha, A., et al. (1997). Phytochemistry of the genus piper. *Phytochemistry* 46 (4), 597–673. doi:10.1016/s0031-9422(97)00328-2

Pasfield, L. A., de la Cruz, L., Ho, J., Coote, M. L., Otting, G., and McLeod, M. D. (2013). Synthesis of (±)-Panduratin A and related natural products using the high pressure diels–alder reaction. *Asian J. Org. Chem.* 2 (1), 60–63. doi:10.1002/ajoc.201200171

Qiu, Y. W., Hai, P., Xiao, H., Gao, Y., Tao, Y. H., Miao, D. R., et al. (2018). Glabralides A-C, three novel meroterpenoids from Sarcandra glabra. *Tetrahedron* 74 (2), 341–347. doi:10.1016/j.tet.2017.12.001

Richards, L. A., Oliveira, C., Dyer, L. A., Rumbaugh, A., Urbano-Muñoz, F., Wallace, I. S., et al. (2018). Shedding light on chemically mediated tri-trophic interactions: a 1H-NMR network approach to identify compound structural features and associated biological activity. *Front. Plant Sci.* 9, 1155. doi:10.3389/fpls.2018.01155

Salehi, B., Zakaria, Z. A., Gyawali, R., Ibrahim, S. A., Rajkovic, J., Shinwari, Z. K., et al. (2019). Piper species: a comprehensive review on their phytochemistry, biological activities and applications. *Molecules* 24 (7), 1364. doi:10.3390/molecules24071364

Tangdenpaisal, K., Songthammawat, P., Ruchirawat, S., and Ploypradith, P. (2022). Total synthesis of palodesangrens A and C. *J. Org. Chem.* 87, 386–398. doi:10.1021/acs.joc.1c02417

Tee, J. T., Keane, T., Meijer, AJHM, Khaledi, H., Abd Rahman, N., and Chee, C. F. (2016). A strategy toward the biomimetic synthesis of (±)-Morusalbanol A pentamethyl ether. *Synthesis* 48, 2263–2270. doi:10.1055/s-0035-1560434

Tortora, C., Pisano, L., Vergine, V., Ghirga, F., Iazzetti, A., Calcaterra, A., et al. (2022). Synthesis, biosynthesis, and biological activity of diels-alder adducts from morus genus: an update. *Molecules* 27 (21), 7580. doi:10.3390/molecules27217580

Uckele, K. A., Jahner, J. P., Tepe, E. J., Richards, L. A., Dyer, L. A., Ochsenrider, K. M., et al. (2021). Phytochemistry reflects different evolutionary history in traditional classes versus specialized structural motifs. *Sci. Rep.* 11 (1), 17247. doi:10.1038/s41598-021-96431-3

Xu, W. H., and Li, X. C. (2011). Antifungal compounds from piper species. *Curr. Bioact. Compd.* 7 (4), 262–267. doi:10.2174/157340711798375822

Zhou, B., Gong, Q., Fu, Y., Zhou, J. S., Zhang, H. Y., and Yue, J. M. (2023). Sarglamides A–E, indolidinoid–monoterpenoid hybrids with anti-neuroinflammatory activity from a *sarcandra* species. *Org. Lett.* 25 (9), 1464–1469. doi:10.1021/acs.orglett.3c00196