

Cite this: *Chem. Sci.*, 2025, 16, 11381

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 22nd April 2025

Accepted 4th June 2025

DOI: 10.1039/d5sc02952j

rsc.li/chemical-science

Concise total synthesis of the cage-like sesquiterpenoid (+)-daphnepapytone A†

Elijah C. Gonzalez, Isabel M. de la Torre Roehl and Brian M. Stoltz*

We report a non-biomimetic total synthesis of (+)-daphnepapytone A, an unprecedented member of the guaiane-derived sesquiterpenoids that displays moderate inhibitory activity against α -glycosidase ($IC_{50} = 159 \pm 2.1 \mu M$) and possesses a highly strained bridging cyclobutane motif. Our *de novo* approach provided expedient access to the tetracyclic core of (+)-daphnepapytone A through an intramolecular allenyl thermal [2 + 2] cycloaddition and a Pauson–Khand reaction with a labile cyclobutane. Finally, a late-stage oxidation/reduction sequence delivered (+)-daphnepapytone A with striking chemoselectivity and excellent diastereoselectivity.

Introduction

The guaiane-derived sesquiterpenoids (GDSs) are a diverse and expansive class of natural products with potent bioactivities such as anti-cancer activity,¹ neuroprotective effects,² and anti-microbial activity.³ Many GDSs possess a planar 5,7-fused ring system, while other congeners in this family exhibit more complex tricycyclic skeletons arising from the linkage of a single C–C bond from the guaiane core – such as the patchoulanes and aromadendranes (Fig. 1A). However, only a few GDSs have been isolated to date which contain cage-like polycyclic bridging ring systems resulting from the linkage of multiple C–C bonds in the guaiane core. These include molecules such as artatrovirens A and B,⁴ and daphnenoid A,⁵ which all possess identical carbon skeletons resulting from additional C–C bond linkages at C1/C11 and C4/12 of the guaiane core (Fig. 1A). Because of their unique cage-like architecture and topological complexity, these natural products have captured the attention of synthetic chemists, and elegant synthetic approaches to these members of the GDS family have recently been disclosed.⁶

Daphnepapytone A (1), recently isolated in 2022 by Zhao, Dai and coworkers,⁷ is an unprecedented member of the guaiane-derived sesquiterpenoids that possesses a novel tetracyclic skeleton formed through C–C bond linkage at C1/C12 and C10/C11 of the guaiane core. This gives rise to a highly congested and unusual cyclobutane motif that is structurally distinct from any GDS monomer isolated to date. From

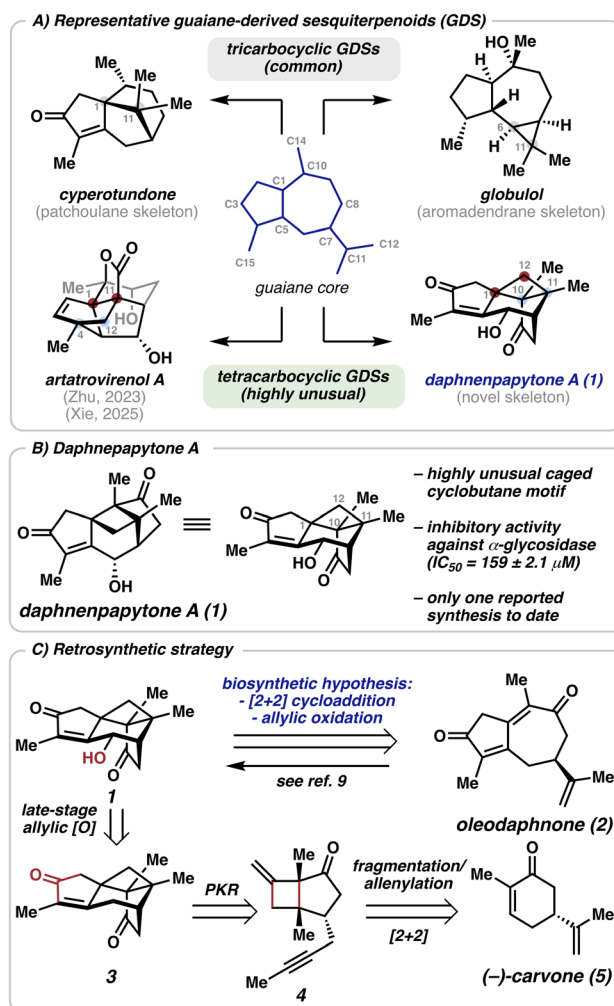


Fig. 1 (A) Representative guaiane-derived sesquiterpenoids with varying carbon skeletons. (B) Key information regarding (+)-daphnepapytone A. (C) Retrosynthetic strategy.

Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA, 91125, USA. E-mail: stoltz@caltech.edu

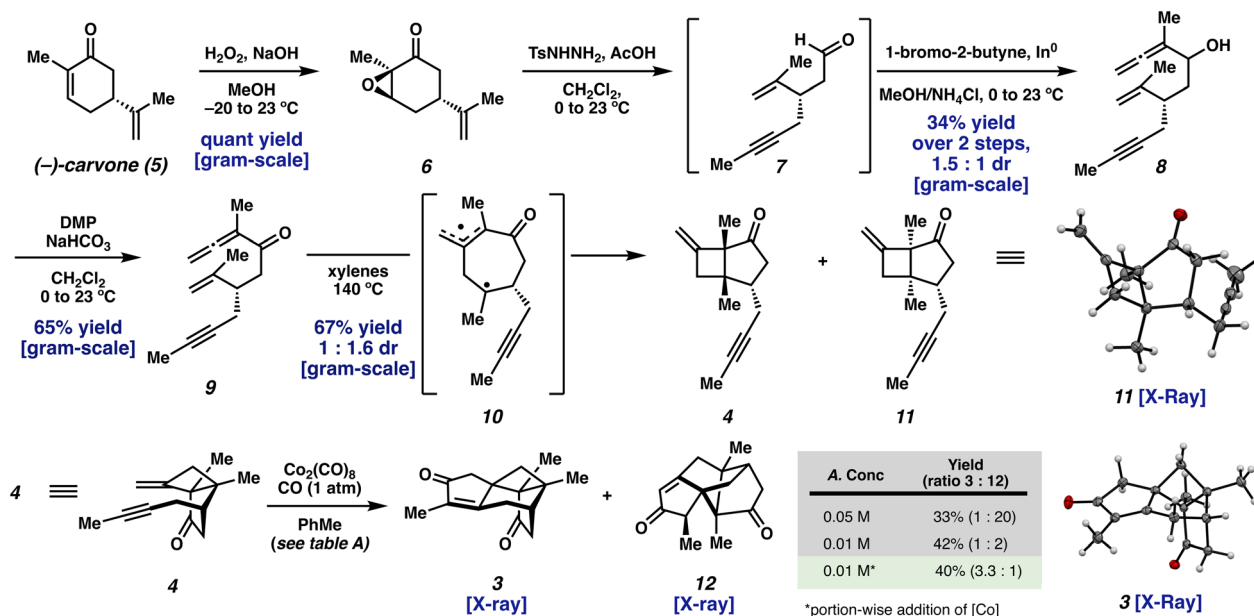
† Electronic supplementary information (ESI) available: Experimental procedures, ¹H NMR, ¹³C NMR, and IR spectra, supplementary crystallographic data. CCDC 2432244–2432246. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d5sc02952j>

a synthetic perspective, the strained cage-like topology, dense stereochemical complexity, and potentially labile cyclobutane moiety all pose challenges. In addition, daphnepapytone A (**1**) displays moderate inhibitory activity against α -glycosidase ($IC_{50} = 159 \pm 2.1 \mu M$), suggesting its potential as a lead compound for the treatment of diabetes. Because of its promising bioactivity and unprecedented skeleton among the guaiane-derived sesquiterpenoids, we were motivated to pursue a total synthesis of daphnepapytone A (**1**).

Results and discussion

Biosynthetically, daphnepapytone A (**1**) is proposed to arise from the guaiane-type sesquiterpenoid oleodaphnone (**2**)⁸ via an allylic oxidation and [2 + 2] cycloaddition sequence (Fig. 1C), where the exact order of these events remains unknown. In our initial synthetic efforts toward daphnepapytone A (**1**) we had limited success with this strategy, deeming the late-stage [2 + 2] cycloaddition to be a difficult disconnection. During the preparation of our manuscript, an elegant synthesis of **1** was preliminarily disclosed by Nay and coworkers wherein they successfully achieved this biomimetic approach.⁹ Because this strategy had proved challenging in our hands, we had devised a *de novo* approach to daphnepapytone A (**1**), wherein we proposed that daphnepapytone A (**1**) could be traced back to 6-*des*-hydroxy daphnepapytone A (**3**) through a late-stage C–H oxidation. We hypothesized that the cage-like tetracyclic core of **1** could be assembled using a Pauson–Khand reaction (PKR)¹⁰ on cyclobutane-containing enyne **4**, which could be accessed through a fragmentation and allenylation/[2 + 2] cycloaddition sequence from (–)-carvone (**5**), allowing us to repurpose intermediates from our initial biomimetic synthetic approach to daphnepapytone A (**1**) (Scheme 1).

Thus, our synthetic investigations began with the epoxidation and subsequent Eschenmoser–Tanabe fragmentation of (–)-carvone (**5**).¹¹ The resultant ynal **7** proved challenging to purify in our hands, so we chose to advance the crude reaction mixture through subsequent allenylation by subjecting the incipient ynal **7** to a Barbier-type reaction using 1-bromo-2-butyne and indium metal.¹² This delivered alcohol **8** as a separable mixture of diastereomers in a modest yield over two steps. Oxidation of alcohol **8** with Dess–Martin periodinane (DMP) smoothly delivered allenylic ketone **9** in 65% yield. At this point, the stage was set to construct cyclobutane **4** through a [2 + 2] cycloaddition. Disappointingly, allenylic ketone **9** was unreactive under various photocycloaddition conditions, however turning to the literature, we were delighted to find precedent for the intramolecular thermal [2 + 2] cycloaddition of activated allenes with olefins.¹³ Gratifyingly, heating allenylic ketone **9** to 140 °C in xylenes afforded the desired PKR precursor **4** and its diastereomer **13** in a combined 66% yield (1 : 1.6 dr), and we were able to confirm the absolute stereochemistry of the major diastereomer **11** through X-ray crystallography.¹⁴ To our surprise, we observed exclusive cycloaddition across the proximal allene double bond, despite the possibility of thermal [2 + 2] cycloaddition across the distal allene double bond.^{13a–c} Based on previous studies of intramolecular thermal allenyl [2 + 2] cycloadditions, we hypothesize that this transformation proceeds stepwise beginning with homolysis of the allene double bond to generate a vinyl radical and resonance-stabilized allyl radical. The more nucleophilic vinyl radical then undergoes 7-*endo-trig* cyclization with the olefin cycloaddition partner to generate intermediate **10** possessing a tertiary radical that furnishes bicycle **4/11** upon radical recombination. Given that the alternative 6-*exo-trig* cyclization would forge an unstable primary radical, we hypothesize that the substitution



Scheme 1 Synthesis of the tetracyclic core of (+)-daphnepapytone A (**1**).

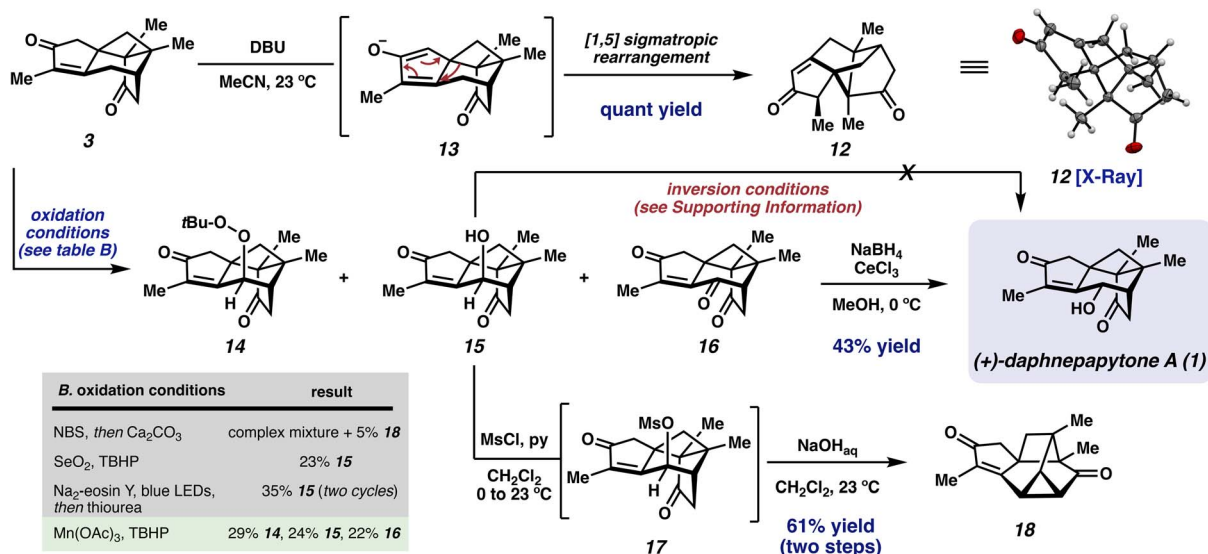
pattern of the olefin cycloaddition partner is responsible for the periselectivity of this transformation.

With the requisite cyclobutane now installed at an early stage in our synthetic sequence, we focused our attention on the key Pauson–Khand reaction of bicycle **4**. Initial treatment of **4** with stoichiometric $\text{Co}_2(\text{CO})_8$ at 70 °C resulted in isolation of the cobalt-complexed alkyne species and no conversion to the desired carbonylated PKR product. To our surprise, heating cobalt-complexed **4** in toluene (0.05 M) at reflux delivered an unexpected rearranged product **12** and only trace amounts of the desired PKR product **3**. This rearranged product likely results from the desired PKR product through enolization and subsequent [1,5] sigmatropic rearrangement. This hypothesis was later supported by subjecting **3** to DBU, which resulted in quantitative rearrangement to **12** (Scheme 2). After extensive optimization (Table SI-1†), we identified that the concentration of the PKR was crucial in suppressing the formation of rearranged product **12**.¹⁵ We hypothesize that any unreacted, cobalt-complexed starting material can act as a Lewis acid to promote the rearrangement of the desired PKR product **3**. This hypothesis was supported by the fact that despite the similar overall yields of the PKR across various reaction concentrations, the best product distribution arises when $\text{Co}_2(\text{CO})_8$ is added portion-wise to the reaction mixture. That is, this portion-wise addition ensures that the concentration of Lewis acidic cobalt-complexed **4** is kept exceedingly low throughout the course of the reaction, and a carbon monoxide atmosphere likely inhibits the formation of excess coordinatively unsaturated cobalt species. Thus, conducting the Pauson–Khand reaction at 0.01 M with portion-wise addition of $\text{Co}_2(\text{CO})_8$ at 110 °C in toluene under a CO atmosphere afforded a 1 : 3.3 ratio of rearranged product **12** and desired product **3** in a combined yield of 40%.

At this stage, construction of the carbon skeleton of daphnepapytone A (**1**) was complete, and the last synthetic transformation necessary was C6 hydroxylation. We initially

anticipated that the stereochemical bias of substrate **3** might lead to a mixture of hydroxylated diastereomers at C6 resulting from a steric mismatch between the convex (β -) face of the bridging ring system and the nearby cyclobutane methylene. Our preliminary investigations into hydroxylation conditions using anionic aerobic oxidation conditions¹⁶ quickly revealed the propensity of 6-*des*-hydroxy daphnepapytone A (**3**) to rearrange in the presence of base to enone **12**. Disappointingly, this rearrangement pathway ruled out many canonical conditions for the γ -hydroxylation of enones – including vinylogous Rubottom/Davis oxidations – as we were unable to generate extended enolate products without concomitant rearrangement under basic conditions. Attempting to access other vinylogous oxidation precursors such as an alkoxy diene using Lewis acidic conditions simply resulted in recovered starting material. With these observations in hand, we looked towards Riley oxidation conditions, and we found that treatment of **3** with selenium dioxide and TBHP led to successful C6 hydroxylation, however we observed exclusive formation of the undesired diastereomer 6-*epi*-daphnepapytone A (**15**) with no detected formation of daphnepapytone A (**1**). Similarly, employing recently developed enone-directed hydroxylation conditions¹⁷ resulted in an identical stereochemical outcome albeit in higher yield (35% over two cycles).

Ultimately, we recognized that the neighboring cyclobutane had little effect on overturning the stereochemical bias for the convex (β -) face of the system. Correspondingly, we turned our attention toward identifying reaction conditions that could invert the C6 stereochemistry of alcohol **15**. In our initial attempts to invert **15**, we were surprised to find that the mesylation and subsequent attempted hydrolysis¹⁸ of **15** resulted in 3-*exo-tet* cyclization to form a highly strained cyclopropane **18** in good yield (61%, two steps).¹⁹ We reasoned that this cyclization may arise from the unusually large overlap between the C6 σ -anti-bonding orbital of mesylate **17** with the nearby C8 enolate π -bond as a consequence of the constrained geometry of this



Scheme 2 Unexpected late-stage rearrangements and completion of the total synthesis of (+)-daphnepapytone A (**1**).

system. Additionally, in our initial attempts toward allylic oxidation of **3**, we found that an allylic bromination/hydrolysis sequence afforded a complex reaction profile which included the formation of **18** in 5% yield, likely proceeding through an analogous pathway (Scheme 2). Later attempts to subject 6-*epi*-daphnepapytone A (**15**) to Mitsunobu inversion conditions yielded an unexpected benzoic ester with retention of configuration at C6, which we hypothesize results from either direct esterification or from the transient formation of cyclopropane **18** followed by benzoate addition in an SN2'-type fashion, which is supported by the presence of trace **18** in the reaction profile. In addition, our attempts to employ recently developed conditions for radical-mediated inversion of axially disposed hydroxyl groups²⁰ also proved unsuccessful in our hands.

With the challenge of undesired substrate stereochemical bias and the unsuccessful attempts at inversion of 6-*epi*-daphnepapytone A (**15**), we wondered whether we might be able to leverage the inherent bias of the system in an over-oxidation/reduction sequence. To this end, we subjected **3** to allylic oxidation conditions using Mn(OAc)₃ and TBHP,²¹ which delivered a distribution of products which included the C6 peroxide **14**,²² 6-*epi*-daphnepapytone A (**15**),²³ and 6-*oxo*-daphnepapytone A (**16**). With 6-*oxo*-daphnepapytone A (**16**) in hand, we attempted a final late-stage Luche reduction. Despite the presence of three unprotected ketones in our system, we were delighted to successfully isolate (+)-daphnepapytone A (**1**) in a satisfactory yield (43%).²⁴ Putatively, we reason this selectivity may arise from a cerium-activated hydrogen bonding network between the C6 and C9 ketones within the *endo* (α -) face of this system.

Conclusions

We have completed a non-biomimetic total synthesis of (+)-daphnepapytone A (**1**), an unprecedented member of the guaiane-derived sesquiterpenoids, in eight steps starting from commercially available (–)-carvone. In constructing this strained, cage-like natural product we encountered unusual rearrangements, such as the [1,5] sigmatropic rearrangement of 6-*des*-hydroxy daphnepapytone A (**3**), which afforded enone **12**. We also encountered the unexpected ring closure of 6-*epi*-daphnepapytone A (**15**) to the cyclopropane containing compound **18** during attempts at inversion through hydrolysis. These unusual and facile transformations may hint at the existence of related, undiscovered natural products which arise from analogous downstream biological transformations.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

E. C. G. and I. M. T. R. conceived of and performed experiments. B. M. S. supported and supervised the research. E. C. G. wrote

the original draft of the manuscript, which was edited by all authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors gratefully acknowledge Caltech, the NIH-NIGMS (R35GM145239), and the Heritage Medical Research Investigators Program for financial support of our research program. We thank Dr David VanderVelde (Caltech) for NMR expertise and maintenance; Dr Mona Shagholi (Caltech) for mass spectrometry assistance; Dr Michael Takase (Caltech) for assistance with X-ray crystallography; and Dr Scott C. Virgil (Caltech) for instrumentation and HPLC assistance. Additional thanks to Ben Gross, Hao Yu, Elliot Hicks, and Samir Rezgui, Veronica Hubble, and Melissa Ramirez for many helpful discussions.

Notes and references

- W. Shao, X. Wang, Z. Liu, X. Song, F. Wang, X. Liu and Z. Yu, *Sci. Rep.*, 2023, **13**, 1384.
- Q. Ren, W. Y. Zhao, S. C. Shi, F. Y. Han, Y. Y. Zhang, Q. B. Liu, G. D. Yao, B. Lin, X. X. Huang and S. J. Song, *J. Nat. Prod.*, 2019, **82**, 1510–1517.
- M. Tan, L. Zhou, Y. Huang, Y. Wang, X. Hao and J. Wang, *Nat. Prod. Res.*, 2008, **22**, 569–575.
- L. H. Su, C. A. Geng, T. Z. Li, Y. B. Ma, X. Y. Huang, X. M. Zhang and J. J. Chen, *J. Org. Chem.*, 2020, **85**, 13466–13471.
- P. Zhao, Z. Y. Li, S. Y. Qin, B. S. Xin, Y. Y. Liu, B. Lin, G. D. Yao, X. X. Huang and S. J. Song, *J. Org. Chem.*, 2021, **86**, 15298–15306.
- For recent approaches to the synthesis of related cage-like guaiane-derived sesquiterpenoids, see: (a) R. Lavernhe, P. Domke, Q. Wang and J. Zhu, *J. Am. Chem. Soc.*, 2023, **145**, 24408–24415; (b) Y. Yang, D. Xie, L. Huo, Y. Liu, J. Duan, H. Li, P. P. Zhou, X. Xie and X. She, *Nat. Commun.*, 2025, **16**, 322; (c) J. Zong, K. E. Christensen and J. Robertson, *Org. Lett.*, 2024, **26**, 1556–1560.
- S. Z. Huang, Q. Wang, J. Z. Yuan, C. H. Cai, H. Wang, A. Mándi, T. Kurtán, H. F. Dai and Y. X. Zhao, *J. Nat. Prod.*, 2022, **85**, 3–14.
- H. Taninaka, Y. Takaishi, G. Honda, Y. Imakura, E. Sezik and E. Yesilada, *Phytochemistry*, 1999, **52**, 1525–1529.
- J. Pereira, N. Casaretto, G. Frison and B. Nay, *ChemRxiv*, 2025, preprint, DOI: [10.26434/chemrxiv-2025-0gds5](https://doi.org/10.26434/chemrxiv-2025-0gds5).
- Select examples of the Pauson–Khand reaction in the syntheses of cage-like or angular synthetic targets: (a) E. C. Y. Lee, L. I. Nevels and J. D. Winkler, *Org. Lett.*, 2005, **7**, 1489–1491; (b) Y. Qu, Z. Wang, Z. Zhang, W. Zhang, J. Huang and Z. Yang, *J. Am. Chem. Soc.*, 2020, **142**, 6511–6515; (c) K. V. Chaung, C. Xu and S. E. Reisman, *Science*, 2016, **353**, 912–915.



- 11 Z. Meng and A. Fürstner, *J. Am. Chem. Soc.*, 2019, **141**, 805–809.
- 12 (a) M. B. Isaac and T. H. Chan, *J. Chem. Soc., Chem. Commun.*, 1995, 1003–1004; (b) B. Alcaide, P. Almendros and R. Rodríguez-Acebes, *J. Org. Chem.*, 2005, **70**, 3198–3204.
- 13 (a) M. Meske, S. S. Murphree, S. H. Watterson, Z. Ni and A. Padwa, *J. Am. Chem. Soc.*, 1995, **117**, 7071–7080; (b) M. Filipkowski, M. Meske, S. H. Watterson, Z. Ni and A. Padwa, *J. Am. Chem. Soc.*, 1993, **115**, 3776–3777; (c) M. Yoshida, Y. Hidaka, Y. Nawata, J. M. Rudziński, E. Ōsawa and K. Kanematsu, *J. Am. Chem. Soc.*, 1988, **110**, 1232–1238; (d) T. V. Hansen, L. Skattebøl and Y. Stenstrøm, *Tetrahedron*, 2003, **59**, 3461–3466.
- 14 Deposition numbers 2432246 (for **3**), 2432244 (for **11**), and 2432245 (for **12**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre.
- 15 Similar observations on the influence of concentration and $\text{Co}_2(\text{CO})_8$ equivalents toward Pauson–Khand-type reactivity have been reported; see: (a) S. J. McKerrall, L. Jørgensen, C. A. Kuttruff, F. Ungeheuer and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 5799–5810; (b) T. W. Sun, D. D. Liu, K. Y. Wang, B. Q. Tong, J. X. Xie, Y. L. Jiang, Y. Li, B. Zhang, Y. F. Liu, Y. X. Wang, J. J. Zhang, J. H. Chen and Z. Yang, *J. Org. Chem.*, 2018, **83**, 6893–6906; (c) W. Zhang, Z. Zhang, J. C. Tang, J. T. Che, H. Y. Zhang, J. H. Chen and Z. Yang, *J. Am. Chem. Soc.*, 2020, **142**, 19487–19492.
- 16 B. M. Gross, S. J. Han, S. C. Virgil and B. M. Stoltz, *J. Am. Chem. Soc.*, 2023, **145**, 7763–7767.
- 17 C. Y. Zheng and J. M. Yue, *Nat. Commun.*, 2023, **14**, 2399.
- 18 K. Hung, M. L. Condakes, T. Moriwaka and T. J. Maimone, *J. Am. Chem. Soc.*, 2016, **138**, 16616–16619.
- 19 Similar strained cyclopropane-containing molecules have been synthesized, see: C. Ravikrishna, K. Ravikumar and G. Mehta, *J. Chem. Soc., Chem. Commun.*, 1994, 2321–2322.
- 20 H. M. Carder, Y. Wang and A. E. Wendlandt, *J. Am. Chem. Soc.*, 2022, **144**, 11870–11877.
- 21 T. K. M. Shing, Y. Y. Yeung and P. L. Su, *Org. Lett.*, 2006, **8**, 3149–3151.
- 22 Under canonical Kornblum–DeLaMare conditions, we could not convert the dialkyl peroxide **14** to ketone **16**.
- 23 When trying to oxidize alcohol **15** to ketone **16**, we encountered challenges with isolating ketone **16** in any appreciable yields.
- 24 Under similar conditions, Nay and coworkers report 19% yield of the natural product and 16% yield of bis-reduced product. In our protocol, a stock solution of NaBH_4 in MeOH is prepared separately. This likely generates $\text{NaBH}_n(\text{OMe})_{4-n}$ prior to addition which acts as a milder active reducing agent. We have separately replicated the result reported by Nay and coworkers upon direct addition of solid NaBH_4 to the reaction mixture.

