

Total Syntheses of Phlegghenrines A and C

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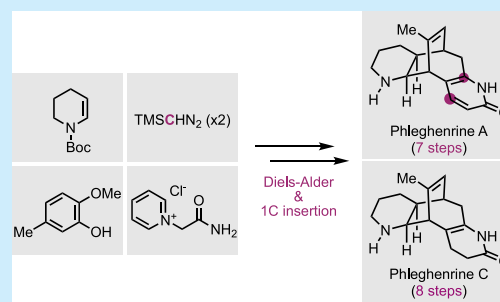
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ABSTRACT: Herein, we report the total syntheses of phlegghenrines A and C from commercially available starting materials in 7 and 8 steps, respectively. Notable steps include an inverse electron-demand Diels–Alder reaction between a masked *o*-benzoquinone and a *N*-protected enamine to prepare one key intermediate with a bicyclo[2.2.2]octenone core, a Büchner–Curtius–Schlotterbeck one-carbon insertion to expand the bicyclo[2.2.2]octenone to a bicyclo[3.2.2]nonenone, and Trauner’s modified 2-pyridone synthesis to install the 2-pyridone moiety.



Phlegghenrines A–D (1–4, Figure 1) and neophlegghenrine A (5) were isolated by Zhao and co-workers in 2016 from *Phlegghemarius henryi* Ching, part of the Huperziaceae.¹ In addition to the phlegghenrine molecules, *Phlegghemarius henryi* Ching was reported to produce huperzine A (6) and B (7), two famous *lycopodium* alkaloids with potent acetylcholinesterase inhibition activity. Huperzine A has been used as a new drug to treat Alzheimer’s disease in China and as a dietary supplement in the United States.² It was evaluated in human clinical trials to treat traumatic brain injury as well. The phlegghenrine molecules also demonstrated inhibitory activity against acetylcholinesterase with phlegghenrine A (1) and D (4) as the most potent family members ($IC_{50} = 4.91 \mu\text{M}$ for 1 and $4.32 \mu\text{M}$ for 4). Notably, the phlegghenrines showed low or no inhibition activity against butylcholinesterase; thus, they may

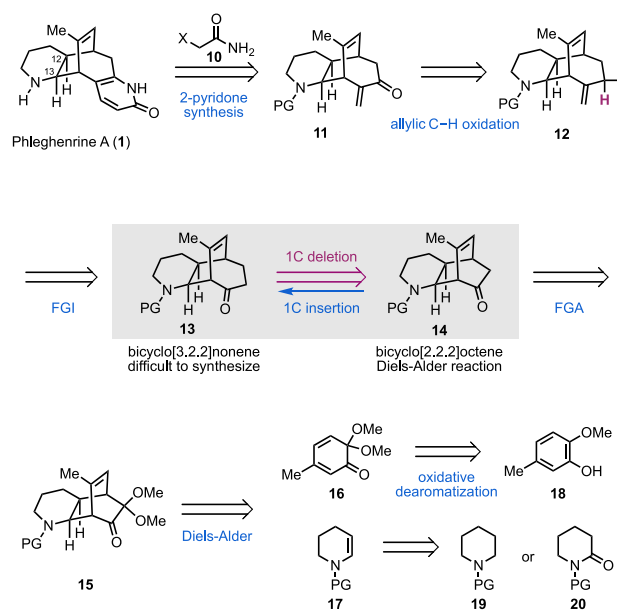


Figure 2. Retrosynthetic analysis.

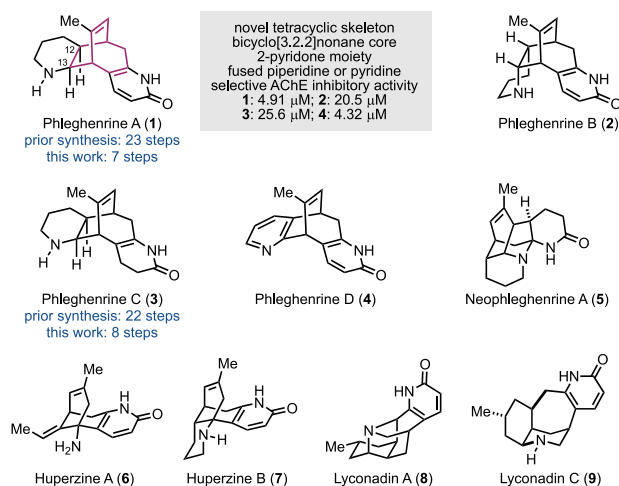


Figure 1. Phlegghenrines and related alkaloids.

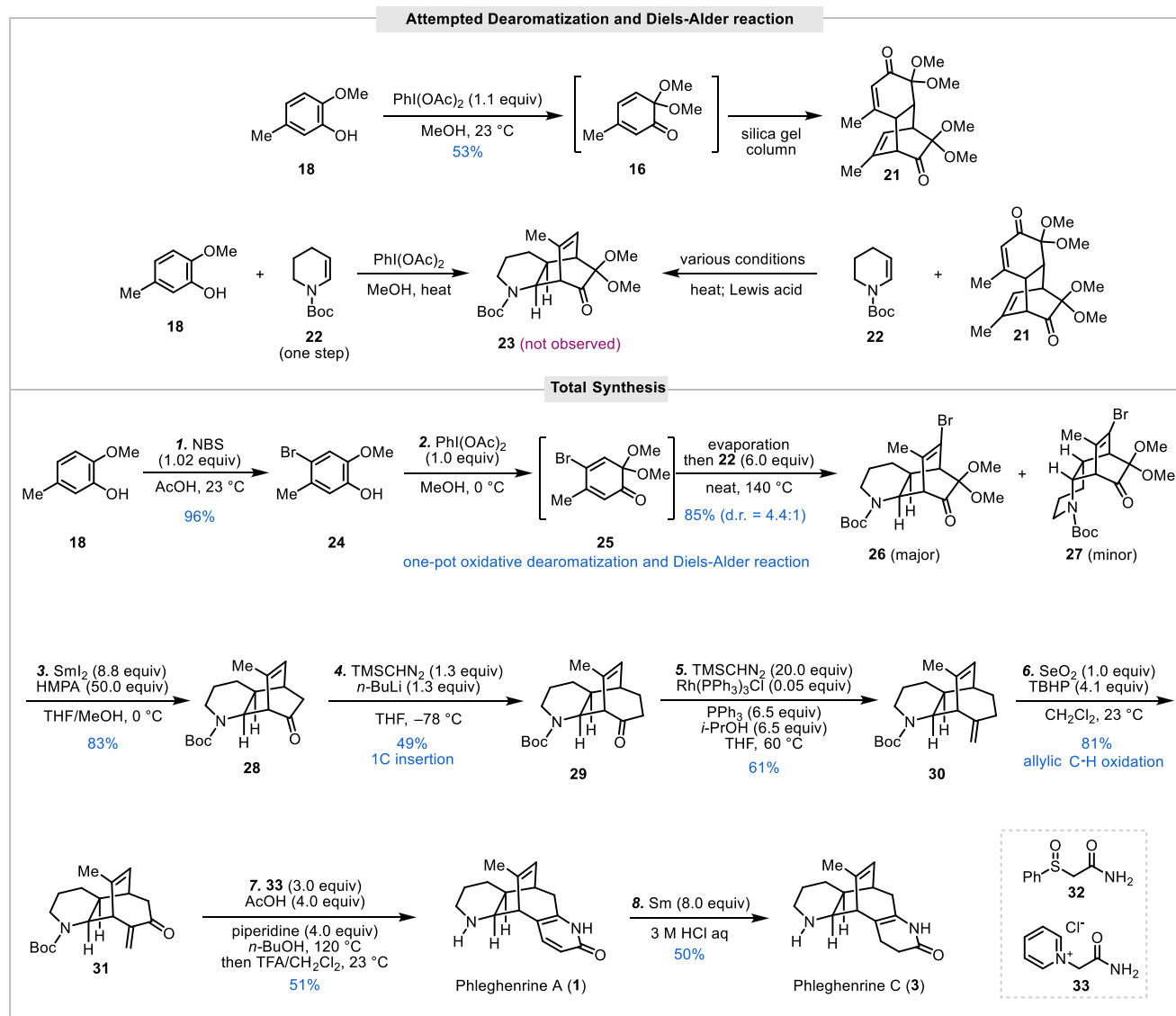
exhibit less side effects such as hepatotoxicity. While phlegghenrines A, B, and D share a similar 2-pyridone moiety as huperzines A and B as well as lyconadins A and C,³ another two *lycopodium* alkaloids with neurotrophic activity, the

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Scheme 1. Total Syntheses of Phlegghenrines A and C



phlegghenrines have a distinct and complex tetracyclic skeleton featuring a bicyclo[3.2.2]nonene core. Their novel chemical structures and potent acetylcholinesterase inhibition activity render them promising lead compounds for the drug discovery efforts in searching for effective treatment of Alzheimer's disease and other related neurodegenerative disorders. However, the low isolation yield (<0.0003%) is a major hurdle for their further biomedical development. In 2019, Sarpong and co-workers reported their synthetic studies to construct the [3.2.2] bicycles of the phlegghenrines.⁴ While this manuscript was in preparation, She and co-workers reported their total syntheses of phlegghenrines A and C in 19 and 18 steps, respectively, from a known diene, which requires 4 steps to prepare.⁵ Herein, we reported our total syntheses of phlegghenrines A and C in 7 and 8 steps, respectively.⁶

Our continued interest⁷ in the total synthesis and biological studies of *lycopodium* alkaloids with the therapeutic potential to treat various neurodegenerative disorders prompted us to pursue the total synthesis of the phlegghenrine alkaloids. Retrosynthetically (Figure 2), similar to our total synthesis of lycnadins A and C,^{7a} we decided to install the 2-pyridone

moiety in the end by using the Fukuyama-Yokoshima 2-pyridone synthesis.⁸ Thus, tricyclic α -methylene ketone 11 with a bicyclo[3.2.2]nonene core was needed and could be synthesized from ketone 13 via a sequence of methylenation and allylic oxidation. In comparison to the bicyclo[3.2.2]nonene ring systems, the bicyclo[2.2.2]octene ring systems are much more accessible via reactions, including the Diels-Alder cycloaddition. With this in mind, we practiced a one-carbon deletion retrosynthetically and proposed intermediate 14 with a bicyclo[2.2.2]octene core as the precursor of 11. In the forward sense, a one-carbon insertion protocol is needed. Accordingly, we envisioned an approach involving a Büchner-Curtius-Schlotterbeck one-carbon homologation with (trimethylsilyl)diazomethane to convert the cyclohexenone to a cycloheptenone (14 \rightarrow 13).⁹ Retrosynthetically, an acetal functional group addition strategy at this stage would lead to compound 15 as a precursor of 14. We planned to assemble 15 via an inverse electron-demand Diels-Alder reaction between masked *o*-benzoquinone (MOB) 16 and *N*-protected enamine 17.¹⁰ MOB 16 could be synthesized via an oxidative dearomatization of commercially available 2-methoxy-5-meth-

ylphenol (**18**), and **17** could be prepared via a formal dehydrogenation of piperidine derivative **19**¹¹ or reduction of the corresponding δ -valerolactam **20**.¹²

Our synthesis started from commercially available 2-methoxy-5-methylphenol (**18**) and known Boc-protected enamine **22** (Scheme 1). The latter can be synthesized in one step from commercially available *N*-Boc-protected δ -valerolactam¹² or *N*-Boc-protected piperidine.¹¹ We first tried to generate MOB **16** via an oxidative dearomatization of **18** with phenyliodonium diacetate in MeOH. While **16** could be formed smoothly, it underwent spontaneous Diels–Alder dimerization and cannot be isolated. Instead, dimeric product **21** was obtained. Efforts were then directed to trap MOB **16** in situ with dienophile **22** to form **23** but were unsuccessful. Since the Diels–Alder dimerization of **16** is reversible, we also explored the possibility of generating **16** via a retro-Diels–Alder reaction from **21** and trapping it in situ with **22**. Unfortunately, no desired product **23** was observed, as well. To avoid the problematic MOB dimerization, we decided to install a bromide at the C-4 position of **16** (see **25**). The bromide has been shown to block the dimerization and can be removed later.¹³ Thus, known compound **24** was prepared in 96% yield by bromination of **18** with a reported procedure using *N*-bromosuccinimide (NBS) in AcOH.¹⁴ As expected, oxidative dearomatization of **24** with phenyliodonium diacetate in MeOH gave known Br-MOB **25**, which can be purified and characterized. After evaporation of MeOH, **22** was added, and the resulting neat mixture was heated at 140 °C to deliver the Diels–Alder adducts via a one-pot procedure in 85% yield as a separable 4.4:1 *endo/exo* (**26/27**) mixture. The bromide, after serving its purpose of blocking the MOB dimerization, was then removed with SmI₂, which also removed the extra dimethyl acetal at the α -position of the ketone. Tricyclic compound **28** with a bicyclo[2.2.2]octenone core was obtained in 83% yield.

We then moved on to explore the Büchner–Curtius–Schlotterbeck one-carbon insertion and were happy to learn that desired product **29** with a bicyclo[3.2.2]nonenone core could be obtained in 41% yield by exposing **28** to (diazo(trimethylsilyl)methyl)lithium generated from treating (trimethylsilyl)diazomethane with *n*-BuLi in THF at low temperature. Compound **29** was further advanced to α -methylene ketone **31** in two steps for the next 2-pyridone synthesis. The Wittig one-carbon homologation was realized by using the Lebel modification, which releases methylene-triphenylphosphorane catalytically from the Wilkinson's catalyst, PPh₃ and trimethylsilyldiazomethane.¹⁵ Product **30** was obtained in 61% yield. Notably, the yield from conventional Wittig methylenation is much lower (36%). Allylic C–H oxidation with a combination of SeO₂ and *tert*-butyl hydroperoxide (TBHP) occurred smoothly and delivered **31** in 81% yield. The last step is to install the 2-pyridone moiety, which turned out to be nontrivial. We first explored the Fukuyama–Yokoshima 2-pyridone synthesis protocol using 2-(phenylsulfinyl)acetamide **32**. After comprehensive explorations, we were able to get the desired product phlegghenrine A (**1**) via one-pot Boc removal, but the yield never went above 10%. Acetamide derivative **33** was used by Trauner and co-workers in their lycoposerramine T total synthesis to build the corresponding 2-pyridone.¹⁶ Thus, we explored Trauner's protocol and were able to achieve a one-pot 2-pyridone synthesis and Boc-deprotection to synthesize phlegghenrine A (**1**) in 51% yield. We further demonstrated that phlegghenrine

A (**1**) could be partially reduced to phlegghenrine C (**3**) with Sm in HCl in modest yield.¹⁷ Overall, from commercially available starting materials, phlegghenrine A (**1**) and phlegghenrine C (**3**) were prepared in 7 and 8 steps, respectively, which are significantly shorter than the syntheses (23 and 22 steps) reported recently by She and co-workers.⁵

In summary, concise total syntheses of the structurally novel and scarce *lycopodium* alkaloids phlegghenrine A (**1**) and phlegghenrine C (**3**) with potent and selective acetylcholinesterase inhibition activities were achieved. The combination of an inverse electron-demand Diels–Alder reaction and a Büchner–Curtius–Schlotterbeck one-carbon insertion enabled an efficient construction of the bicyclo[3.2.2]nonene core of the phlegghenrine alkaloids. Other key steps include a Lebel-modified Wittig olefination, allylic C–H oxidation, and Trauner's modified 2-pyridone synthesis. This current synthetic route could potentially be adapted for phlegghenrine analogue synthesis, thus facilitating further biological evaluations of the phlegghenrine alkaloids.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.3c01784>.

Experimental procedures and spectra data (PDF)

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Author Contributions

X.C. and L.L. contributed equally

Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Dong, L.-B.; Wu, X.-D.; Shi, X.; Zhang, Z.-J.; Yang, J.; Zhao, Q.-S. Phlegghenrines A–D and Neophlegghenrine A, Bioactive and Structurally Rigid *Lycopodium* Alkaloids from *Phlegmariurus henryi*. *Org. Lett.* **2016**, *18*, 4498–4501.
- (2) Zhang, H.-Y. New insights into huperzine A for the treatment of Alzheimer's disease. *Acta Pharmacol. Sin.* **2012**, *33*, 1170–1175.
- (3) Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. Lyconadin A, a Novel Alkaloid from *Lycopodium complanatum*. *J. Org. Chem.* **2001**, *66*, 5901–5904.
- (4) Gritsch, P. J.; Gimenez-Nueno, I.; Wonilowicz, L.; Sarpong, R. Copper-Catalyzed [4 + 2] Cycloaddition of 9*H*-Cyclohepta[*b*]pyridine-9-one and Electron-Rich Alkenes. *J. Org. Chem.* **2019**, *84*, 8717–8723.
- (5) Shi, H.; Hou, H.; Duan, J.; Huang, J.; Duan, X.; Xie, X.; Li, H.; She, X. Total Syntheses of Phlegghenrines A and C: A [4 + 2] Cycloaddition and Ring-Expansion Approach. *Org. Lett.* **2023**, *25*, 3358–3363.
- (6) (a) Cai, X. *Palladium-Catalyzed Hydroxycyclopropanol Ring-Opening Carbonylative Lactonization to Fused Bicyclic Lactones and Total Synthesis of Phlegghenrine Alkaloids*, Ph.D. Thesis, Purdue University, 2021. DOI: 10.25394/PGS.15078792.v1. (b) Cai, X.; Li, L.; Wang, Y.-C.; Zhou, J.; Dai, M. Concise Total Syntheses of Phlegghenrines A and C. *ChemRxiv* 2023. DOI: 10.26434/chemrxiv-2023-8f4rz.
- (7) (a) Yang, Y.; Haskins, C. W.; Zhang, W.; Low, P. L.; Dai, M. Divergent Total Syntheses of Lyconadins A and C. *Angew. Chem., Int. Ed.* **2014**, *53*, 3922–3925. (b) Ma, D.; Martin, B. S.; Gallagher, K. S.; Saito, T.; Dai, M. One-Carbon Insertion and Polarity Inversion Enabled a Pyrrole Strategy to the Total Syntheses of Pyridine-Containing *Lycopodium* Alkaloids: Complanadine A and Lycodine. *J. Am. Chem. Soc.* **2021**, *143*, 16383–16387. (c) Martin, B. S.; Ma, D.; Saito, T.; Gallagher, K. S.; Dai, M. Concise Total Synthesis of Complanadine A Enabled by Pyrrole-to-Pyridine Molecular Editing. *Synthesis* **2023**, DOI: 10.1055/a-2107-5159.
- (8) (a) Fujii, M.; Nishimura, T.; Koshihara, T.; Yokoshima, S.; Fukuyama, T. 2-Pyridone Synthesis Using 2-(Phenylsulfinyl)acetamide. *Org. Lett.* **2013**, *15*, 232–234. (b) Nishimura, T.; Unni, A. K.; Yokoshima, S.; Fukuyama, T. Total Syntheses of Lyconadins A–C. *J. Am. Chem. Soc.* **2013**, *135*, 3243–3247.
- (9) Candeias, N. R.; Paterna, R.; Gois, P. M. P. Homologation Reaction of Ketones with Diazo Compounds. *Chem. Rev.* **2016**, *116*, 2937–2981.
- (10) Liao, C.-C.; Peddinti, R. K. Masked *o*-Benzoquinones in Organic Synthesis. *Acc. Chem. Res.* **2002**, *35*, 856–866.
- (11) Holmberg-Douglas, N.; Choi, Y.; Aquila, B.; Huynh, H.; Nicewicz, D. A. β -Functionalization of Saturated Aza-Heterocycles Enabled by Organic Photoredox Catalysis. *ACS Catal.* **2021**, *11*, 3153–3158.
- (12) Yu, J.; Truc, V.; Riebel, P.; Hierl, E.; Mudryk, B. One-pot synthesis of cyclic enecarbamates from lactam carbamates. *Tetrahedron Lett.* **2005**, *46*, 4011–4013.
- (13) (a) Lai, C.-H.; Shen, Y.-L.; Liao, C.-C. Synthesis of Stable Bromo-substituted Masked *o*-Benzoquinones and their Application to the Synthesis of Bicyclo[2.2.2]octenones. *Synlett* **1997**, *12*, 1351–1352. (b) Lai, C.-H.; Shen, Y.-L.; Wang, M.-N.; Kameswara Rao, N. S.; Liao, C.-C. Intermolecular Diels-Alder Reactions of Brominated Masked *o*-Benzoquinones with Electron-Deficient Dienophiles. A Detour Method to Synthesize Bicyclo[2.2.2]octenones from 2-Methoxyphenols. *J. Org. Chem.* **2002**, *67*, 6493–6502. (c) Surasani, S. R.; Parumala, S. K. R.; Peddinti, R. K. Diels-Alder reactions of 4-halo masked *o*-benzoquinones. Experimental and theoretical investigations. *Org. Biomol. Chem.* **2014**, *12*, 5656–5668.
- (14) Magnus, P.; Seipp, C. Concise Synthesis of the Hasubanan Alkaloid (\pm)-Cepharatine A Using a Suzuki Coupling Reaction To Effect *o,p*-Phenolic Coupling. *Org. Lett.* **2013**, *15*, 4870–4871.
- (15) (a) Lebel, H.; Guay, D.; Paquet, V.; Huard, K. Highly efficient synthesis of terminal alkenes from ketones. *Org. Lett.* **2004**, *6*, 3047–3050. (b) Xu, B.; Liu, C.; Dai, M. Catalysis-Enabled 13-Step Total Synthesis of (–)-Peyssonoside A. *J. Am. Chem. Soc.* **2022**, *144*, 19700–19703.
- (16) Hartrampf, F. W. W.; Furukawa, T.; Trauner, D. A Conia-Ene-Type Cyclization under Basic Conditions Enables an Efficient Synthesis of (–)-Lycoposerramine R. *Angew. Chem., Int. Ed.* **2017**, *56*, 893–896.
- (17) Ding, R.; Fu, J.-G.; Xu, G.-Q.; Sun, B.-F.; Lin, G.-Q. Divergent Total Synthesis of the *Lycopodium* Alkaloids Huperzine A, Huperzine B, and Huperzine U. *J. Org. Chem.* **2014**, *79*, 240–250.