Preprint Title	Formal Total Synthesis of Macarpine via a Au(I)-Catalyzed 6-*endo*-dig Cycloisomerization Strategy
Authors	Jiayue Fu, Bingbing Li, Zefang Zhou, Maosheng Cheng, Lu Yang and Yongxiang Liu
Publication Date	14 Sep 2022
Article Type	Full Research Paper
Supporting Information File 1	Supporting Information File 1.pdf; 4.0 MB
ORCID® iDs	Lu Yang - https://orcid.org/0000-0001-9727-4849; Yongxiang Liu - https://orcid.org/0000-0003-0364-0137

Formal Total Synthesis of Macarpine via a Au(I)-Catalyzed 6-*endo*-dig Cycloisomerization Strategy

Jiayue Fu[1,2,3], Bingbing Li[1,2,3], Zefang Zhou[1,2,3], Maosheng Cheng[1,3], Lu Yang*[1,2,3], and Yongxiang Liu*[1,2,3]

Address:

[1]Key Laboratory of Structure-Based Drug Design and Discovery (Shenyang Pharmaceutical University), Ministry of Education, Shenyang 110016, P. R. China

[2]Wuya College of Innovation, Shenyang Pharmaceutical University, Shenyang 110016, P. R. China

[3]Institute of Drug Research in Medicine Capital of China, Benxi 117000, P. R. China

Email: yongxiang.liu@syphu.edu.cn; yanglusyphu@163.com

Abstract

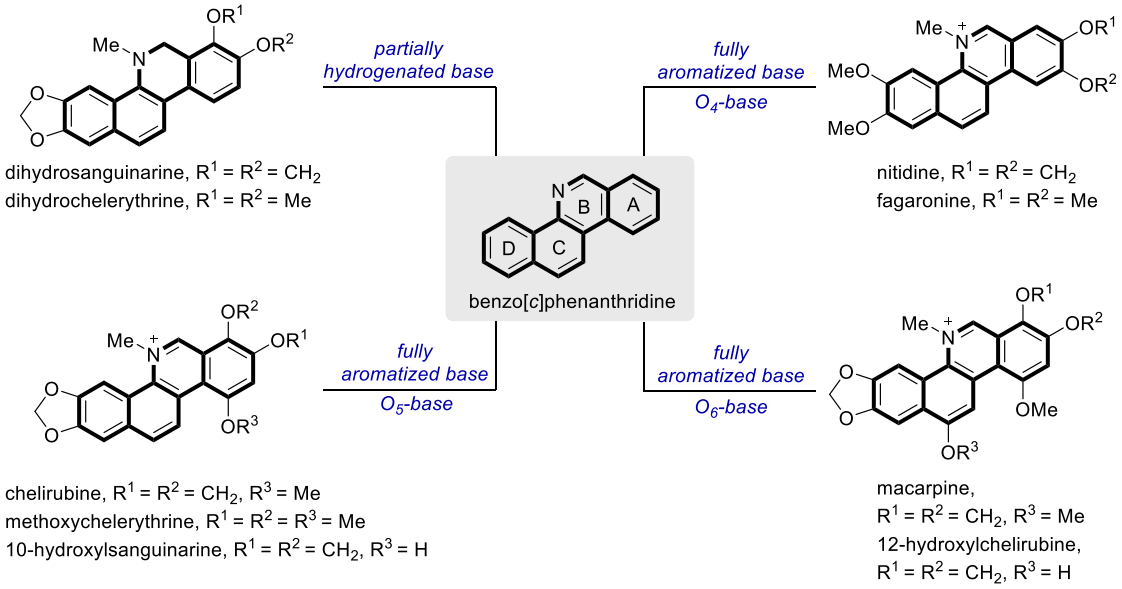
The formal total synthesis of macarpine was accomplished by the construction of a naphthol intermediate in Ishikawa's synthetic route in 8 steps with an overall yield of 42%. This convergent synthetic strategy features the utilization of a Au(I)-catalyzed cyclization of 1,5-enyne substrate, which was obtained by the Sonogashira coupling reaction.

Keywords

formal total synthesis; gold catalysis; 1,5-enyne; macarpine; benzo[*c*]phenanthridine alkaloids

Introduction

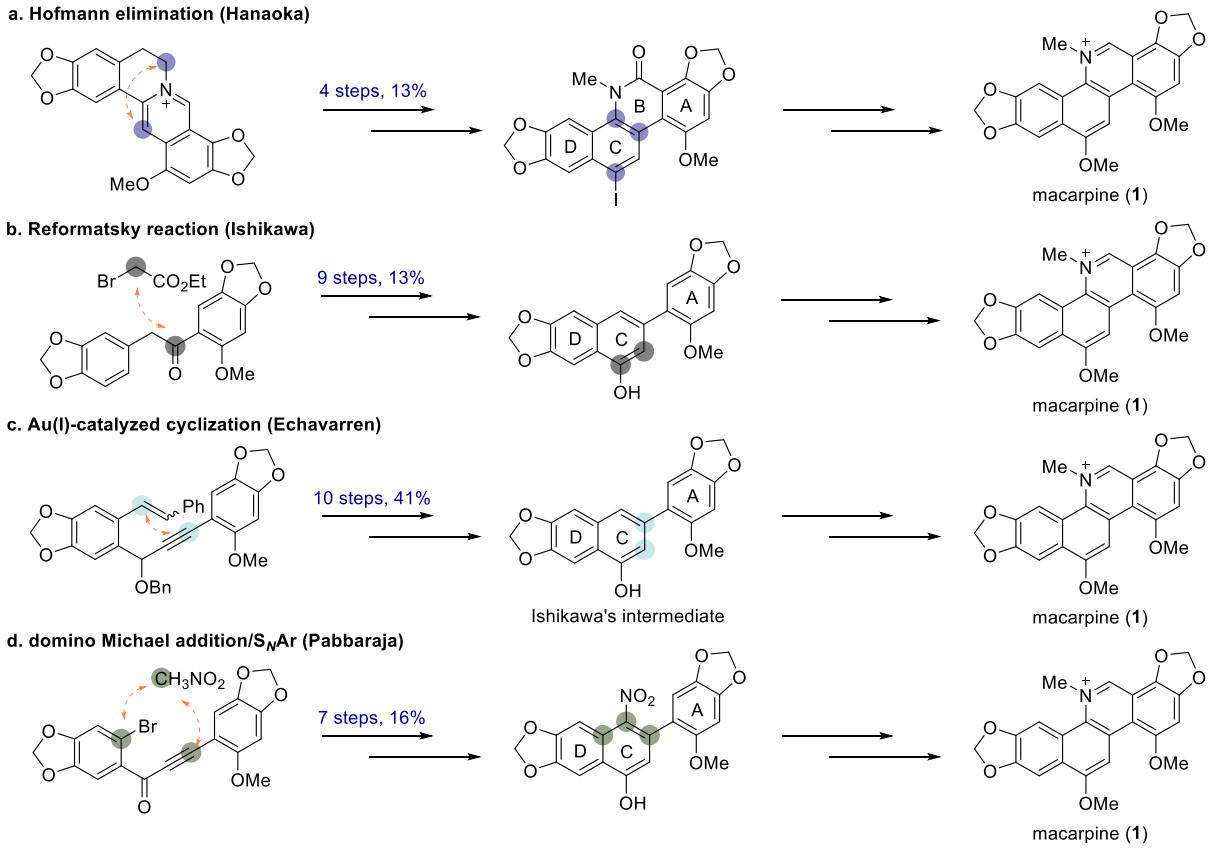
Benzo[*c*]phenanthridine alkaloids are an ancient and influential category of isoquinoline alkaloids, mainly found in Papaveraceous and Rucateae.[1,2] According to their oxidation states, benzo[*c*]phenanthridine alkaloids could be divided into two types: partially hydrogenated base and fully aromatized base, in which natural fully aromatic alkaloids could be further classified into three subclasses: O_4-base, O_5-base and O_6-base (Scheme 1).[3]



Scheme 1: Classification of benzo[*c*]phenanthridine alkaloids.

Among these alkaloids macarpine is the most oxidized tetracyclic alkaloid with many bioactivities, including anesthesia, anti-cancer, anti-inflammatory,[4-9] insecticidal and fungicidal etc.[10] In addition to the above-mentioned activities, macarpine was also used as a DNA probe for flow cytometry and fluorescence microscopy for its fluorescent properties.[11] Despite some research on the activities of macarpine had been performed, more in-depth evaluation of the biological activity was still limited by the natural sources. Inspired by the requirement of further biological evaluation, the chemical syntheses of macarpine have been developed rapidly in the last three decades.

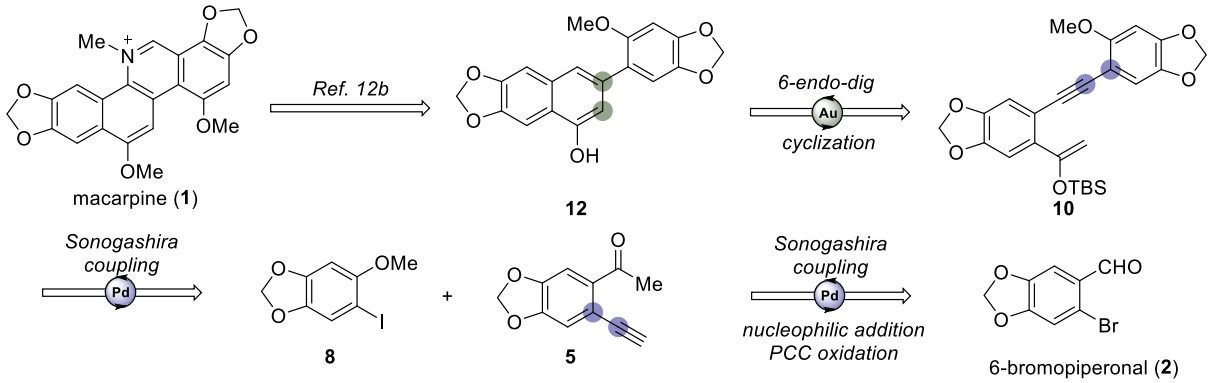
The benzo[*c*]phenanthridine skeleton consists of a phenanthridine (rings A, B, C) and a benzene (ring D), and most of the synthetic routes were completed in the last step by constructing ring B or ring C. Some representative examples and their key strategies were summarized in Scheme 2. In 1989, Hanaoka and coworkers realized the total synthesis of macarpine by Hofmann elimination from protoberberine by introducing rings B and C (Scheme 2a).[12a] In 1995, Ishikawa and coworkers accomplished the total synthesis via Reformatsky reaction and aromatic nitrosation through the building of rings B and C (Scheme 2b).[12b] In 2010, Echavarren and coworkers completed the formal total synthesis via the Au(I)-catalyzed cyclization (Scheme 2c).[12c] In 2018, Pabbaraja and coworkers disclosed the synthesis of macarpineby constructing ring C through the domino Michael addition/S_NAr reaction of nitromethane with ynone precursor (Scheme 2d).[12d]



Scheme 2: Representative synthetic strategies for macarpine.

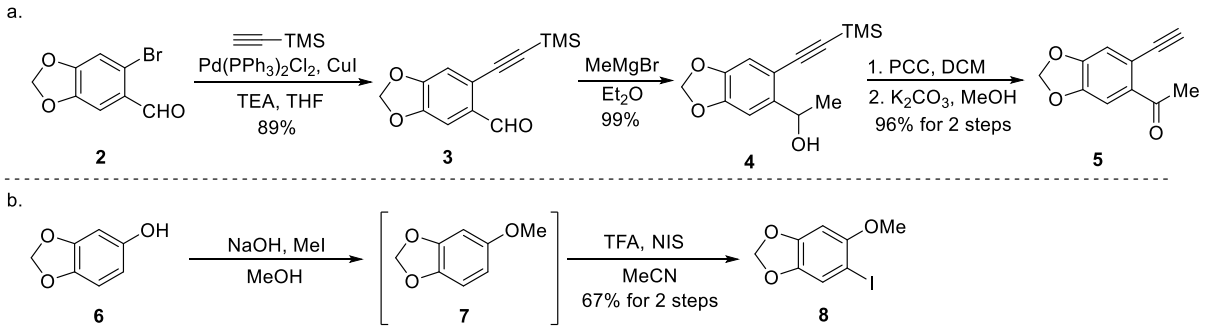
Results and Discussion

The efforts on developing efficient synthetic strategies to access macarpine never ceased during the last decades, and we have joined in this meaningful research. Herein, a strategy involving the synthesis of an intermediate reported by Ishikawa in 1995 in the total synthesis of macarpine[12b] was proposed via the Au(I)-catalyzed cyclization reaction.



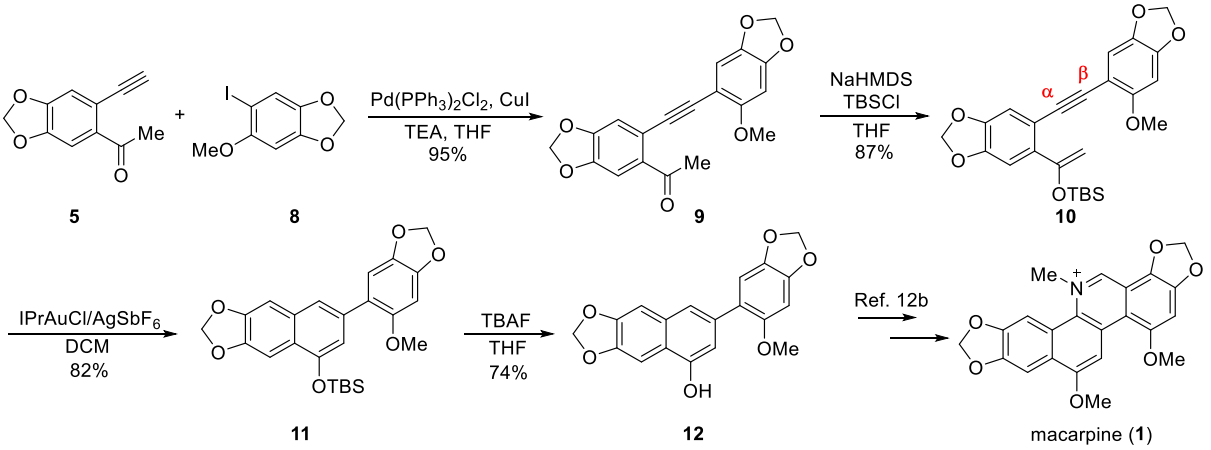
Scheme 3: Retrosynthetic analysis to macarpine.

Retrosynthetically, the target molecule macarpine **1** could be disconnected into naphthol **12**, a key intermediate reported by Ishikawa in the total synthesis of macarpine, which was synthesized from silyl enol ether compound **10** via the Au(I)-catalyzed cyclization reaction developed by our group.[13] The compound **10** could be constructed by the Sonogashira coupling reaction from readily prepared iodoarene **8**[12b,14] and ketone **5**, which could be synthesized by using cheap 6-bromopiperonal **2** as the starting material (Scheme 3).



Scheme 4: Syntheses of precursors **5** and **8**.

To finish the synthesis, the ketone **5** and iodoarene **8** were prepared by following the synthetic route in Scheme 4. The ketone **5** could be prepared in a four-step procedure. Firstly, a Sonogashira coupling between 6-bromopiprononal **2** and trimethylsilylacetylene was performed to furnish aldehyde **3**[15] in 89% yield. A following nucleophilic addition reaction of aldehyde **3** by methylmagnesium bromide (MeMgBr) gave alcohol **4** in 99% yield, which was oxidized by pyridinium chlorochromate (PCC) leading to the formation of ketone compound and the deprotection of silyl group was accomplished in the presence of potassium carbonate (K_2CO_3) and methanol to provide the terminal alkyne **5** in 96% yield in two steps. The iodoarene **8**[12b,14] was facilely synthesized from sesamol **6** via methylation and iodination in an overall yield of 67%.



Scheme 5: Formal total synthesis of macarpine.

With the building blocks **5** and **8** in hand, the ketone **9** was prepared via a palladium-catalyzed Sonogashira coupling reaction in a yield of 95%. The precursor **10** for the gold(I)-catalyzed cycloisomerization was then synthesized by treating ketone **9** with sodium bis(trimethylsilyl)amide (NaHMDS) and *tert*-butyldimethylsilyl chloride (TBSCl). The Au(I)-catalyzed cyclization reaction of substrate **10** occurred under the catalysis of 5 mol% [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold (I) chloride (IPrAuCl)

and 5 mol% silver hexafluoroantimonate ($AgSbF_6$) to yield a benzene ring smoothly, leading to the exclusive formation of biaryl intermediate **11** in a yield of 82%. It's worth noting that the methoxy substitution in the substrate played a crucial role in controlling the selectivity of the cycloisomerization according to our previous study.[13] Next, the compound **11** was subjected to a solution of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF), resulting in the formation of naphthol **12**,[12b,12c] a key intermediate in the previous total synthesis of macarpine **1** reported by Ishikawa (Scheme 5).

Conclusion

In summary, the formal total synthesis of the natural product macarpine was achieved in a convergent strategy by synthesizing a naphthol intermediate reported by Ishikawa via the Au(I)-catalyzed cyclization reaction. This synthetic route provides a new approach to macarpine and related benzo[*c*]phenanthridine alkaloids and the application of this strategy to access benzo[*c*]phenanthridine derivatives and further assessments of their bioactivities are in progress in our laboratory.

Supporting Information

Supporting Information File 1:

Synthetic procedures and characterization data for compounds **3**-**5**, **8**-**12**, and their ^{1}H NMR and ^{13}C NMR spectra.

Acknowledgements

Y.L. acknowledge the financial support from the National Natural Science Foundation of China (No. 21977073), Natural Science Foundation of Liaoning, China (No. 2022-

MS-245) and the Liaoning Provincial Foundation of Educational Department (No, LJKZ0908). The authors would like to thank the Program for the Innovative Research Team of the Ministry of Education and the Program for the Liaoning Innovative Research Team in University.

References

1. Slaninová, I.; Slunská, Z.; Šinkora, J.; Vlková, M.; Táborská, E. *Pharm. Biol.*, **2007**, *45*, 131–139.
2. Al-Snafi, A. E. *Indo Am. J. Pharm. Sci.*, **2017**, *4*, 257–263.
3. Cheng, P.; Zeng, J. *Chin. J. Org. Chem.*, **2012**, *32*, 1605–1619.
4. Orhan, I.; Özçelik, B.; Karaoglu, T.; Sener, B. *Naturforsch.*, **2007**, *62c*, 19–26.
5. Wang, Q.; Dai, P.; Bao, H.; Liang, P.; Wang, W.; Xing, A.; Sun, J. *Exp. Ther. Med.*, **2017**, *13*, 263–268.
6. a) Slunská, Z.; Gelnarová, E.; Hammerová, J.; Táborská, E.; Slaninová, I. *Toxicol. Vitr.*, **2010**, *24*, 697–706; b) Balažová, A.; Urdová, J.; Forman, V.; Mucaji, P. *Molecules*, **2020**, *25*, 1261.
7. Gaziano, R.; Moroni, G.; Buè, C.; Miele, M.T.; Sinibaldi-Vallebona, P.; Pica, F. *World J. Gastrointest. Oncol.*, **2016**, *8*, 30–39.
8. Slaninová, I.; Slunská, Z.; Šinkora, J.; Vlková, M.; Táborská, E. *Pharm. Biol.*, **2007**, *45*, 131–139.
9. Pica, F.; Balestrieri, E.; Serafino, A.; Sorrentino, R.; Gaziano, R.; Moroni, G.; Moroni, N.; Palmieri, G.; Mattei, M.; Garaci, E.; Sinibaldi-Vallebona, P. *Anticancer Drugs*, **2012**, *23*, 32–42.
10. Schmeller, T.; Latz-Bruning, B.; Wink, M. *Phytochemistry*, **1997**, *44*, 257–266.

11. Slaninová, I.; López-Sánchez, N.; Šebrlová, K.; Vymazal, O.; Frade, J. M.; Táborská, E. *Biol. Cell*, **2016**, *108*, 1–18.
12. a) Hanaoka, M.; Cho, W. J.; Yoshida, S.; Fueki, T.; Mukai, C. *Heterocycles*, **1989**, *29*, 857–860; b) Ishikawa, T.; Saito, T.; Ishii, H. *Tetrahedron*, **1995**, *51*, 8447–8458; c) Solorio-Alvarado, C. R.; Echavarren, A. M. *J. Am. Chem. Soc.*, **2010**, *132*, 11881–11883; d) Singh, S.; Samineni, R.; Pabbaraja, S.; Mehta, G. *Angew. Chem., Int. Ed.*, **2018**, *57*, 16847–16851.
13. Fu, J.; Li, B.; Wang, X.; Liang, Q.; Peng, X.; Yang, L.; Wan, T.; Wang, X., Lin, B.; Cheng, M.; Liu, Y. *Chin. J. Chem.*, **2022**, *40*, 46–52.
14. Huang, Q.; Wang, P.; Tian, Y.; Song, N.; Ren, S.; Tao, J.; Hang, K.; Li, M. *Synlett*, **2015**, *26*, 1385–1390.
15. a) Shimizu, K.; Takimoto, M.; Mori, M. *Org. Lett.*, **2003**, *5*, 2323–2325; b) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.*, **2008**, *130*, 15720–15725; b) Takahashi, H.; Yoshida, K.; Yanagisawa, A. *J. Org. Chem.*, **2009**, *74*, 3632–3640; c) Cikotiene, I.; Buksnaitiene, R.; Sazinas, R. *Tetrahedron*, **2011**, *67*, 706–717; d) Yoshida, K.; Shida, H.; Takahashi, H.; Yanagisawa, A. *Chem. Eur. J.*, **2011**, *17*, 344–349; e) Hashmi, A. S. K.; Hofmann, J.; Shi, S.; Schütz, A.; Rudolph, M.; Lothschütz, C.; Wieteck, M.; Buehrle, M.; Woelfle, M.; Rominger, F., *Chem. Eur. J.*, **2013**, *19*, 382–389; f) García-Rubín, S.; González-Rodríguez, C.; García-Yebra, C.; Varela, J. A.; Esteruelas, M. A.; Saá, C. *Angew. Chem., Int. Ed.*, **2014**, *53*, 1841–1844; g) Shen, H.; Fu, J.; Gong, J.; Yang, Z. *Org. Lett.*, **2014**, *16*, 5588–5591; h) Wu, X.; Li, M. L.; Chen, D. F.; Chen, S. S. *J. Org. Chem.*, **2014**, *79*, 4743–4750; i) Du, Y. L.; Zhu, Y. F.; Han, Z. Y., *J. Org. Chem.*, **2015**, *80*, 7732–7738; j) Cao, Z.; Zhang, H.; Zhang, X.; Zhang, L.; Meng, X.; Chen, G.; Zhao, X. E.; Sun, X.; You, J. *RSC Adv.*, **2015**, *5*, 103155–103158; k) Hack, D.; Dürr, A. B.; Deckers, K.; Chauhan, P.; Seling, N.; Rübenach,

L.; Mertens, L.; Raabe, G.; Schoenebeck, F.; Enders, D. *Angew. Chem., Int. Ed.*, **2016**, *55*, 1797–1800; l) Zhou, N.; Liu, J.; Yan, Z.; Wu, Z.; Zhang, H.; Li, W.; Zhu, C. *Chem. Commun.*, **2017**, *53*, 2036–2039; m) Rong, M. G.; Qin, T. Z.; Liu, X. R.; Wang, H. F.; Zi, W. *Org. Lett.*, **2018**, *20*, 6289–6293; n) Pramanik, S.; Jash, M.; Mondal, D.; Chowdhury, C. *Adv. Synth. Catal.*, **2019**, *361*, 5223–5238; o) Yu, B.; Yu, H.; Huang, H. *Org. Lett.*, **2020**, 22, 8962–8966; p) Shang, H.; Li, L. Y.; Tian, Y.; Jia, H. M.; Zou, Z. M. *RSC Adv.*, **2020**, *10*, 39067–39071; q) Xie, F.; Zhang, B.; Chen, Y.; Jia, H.; Sun, L.; Zhuang, K.; Yin, L.; Cheng, M.; Lin, B.; Liu, Y. *Adv. Synth. Catal.*, **2020**, *362*, 3886–3897; r) Liu, X. J.; Zhou, S. Y.; Xiao, Y.; Sun, Q.; Lu, X.; Li, Y.; Li, J. H. *Org. Lett.*, **2021**, *23*, 7839–7844.