Acylphloroglucinols from *Callistemon lanceolatus* DC.

Rattanaburi S., Mahabusarakam W., Phongpaichit S., Carroll A.R. Tetrahedron 69 (30), 6070-6075

มีการอ้างอิงในช่วง 1 เม.ย.- 30 ก.ย. 68 จำนวน 1 บทความ

JOC The Journal of Organic Chemistry

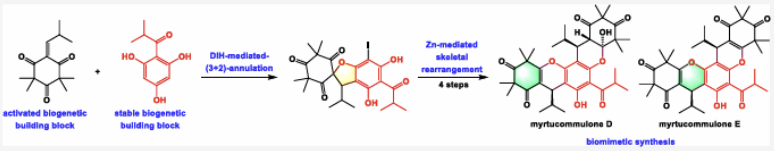
pubs.acs.org/joc Article

Biomimetic Synthesis of Myrtucommulones D−E

Hong Guo,[⊥] Ming-Fang Qi,[⊥] Si-Si Wang, Ya-Hang Zhu, Shi-Lin Lin, Mei-Qi Zheng, Yan-Yi Wu, Yan-Xia Hu, Chuang-Chuang Li, Lei Wang,* Min-Jing Cheng,* and Wen-Cai Ye*

Cite This: *J. Org. Chem.* 2025, 90, 8737−8744 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A concise and efficient biomimetic synthesis of myrtucommulones D−E has been achieved, proceeding in just 6−7 linear steps from readily available biogenetic building blocks. The key feature of the synthesis was the Zn-mediated skeletal rearrangement reaction, without the need for rare metal photocatalysts and visible light. Based on this biomimetic synthesis, four compounds demonstrated moderate to excellent cytotoxic activities against osteosarcoma cells (U2OS and 143B).

■ INTRODUCTION

Xanthenes, a prominent class of heterocyclic compounds, are widely distributed in natural products and exhibit diverse pharmacological activities.[1] Among them, myrtucommulones D−E (**1**−**2**; Figure 1) isolated from *Myrtus communis* L.[2] represent structurally unique angular 6/6/6/6/6-fused pentacyclic xanthenes, characterized by two to four stereocenters and a benzopyrano[2,3-*a*]xanthene core. These compounds display potent antibacterial and α-glucosidase inhibitory activities,[2,3] yet their therapeutic potential remains underexplored due to limited natural abundance. Notably, the angular pentacyclic motif is conserved in related natural products (e.g., **3**−**5**, highlighted in red, Figure 1),[4] underscoring the demand for versatile synthetic platforms to enable biological studies.

Over recent decades, xanthenes have attracted sustained interest from the synthetic chemistry community owing to their promising pharmacological properties and structural complexity, particularly as exemplified by the demanding 6/6/6/6/6-fused pentacyclic derivatives.[5] While linear skeletons, such as that of tomentosone C (**6**)[6] (Figure 1), can typically be constructed,[5a] the synthesis of the angular 6/6/6/6/6-fused pentacyclic natural xanthenes has presented persistent challenges, with only sporadic reports addressing their preparation.[7] This regioselectivity bias is hypothesized to arise from a critical hydrogen-bond interaction between the C7 ketone and C4 hydroxyl groups, which enhances the electron density on the phenolic oxygen, thereby favoring the formation of the linear product (Scheme 1A).[8]

Our group previously reported the asymmetric synthesis of myrtucommulones D−E using isomyrtucommulone B as a precursor.[9] However, racemization issues emerged during the *retro*-Friedel−Crafts reaction of myrtucommulone B, necessitating chiral resolution to obtain optically pure isomyrtucommulone B (Scheme 1B). To address this limitation, we recently developed a visible-light photocatalyzed skeletal rearrangement strategy employing a rare metal iridium photocatalyst and iron, which enabled the synthesis of *ent*-myrtucomvalones E-F (Scheme 1C).[10] Notably, the photocatalyst and Zn can also facilitate the rearrangement reaction; however, excessive reducing capacity of Zn led to predominant side-reactions and diminished yields.[10] This suggests that Zn may intrinsically drive skeletal rearrangement without photocatalyst mediation, enabling direct skeletal rearrangement. Based on this concept and our continued efforts, we herein report the concise biomimetic synthesis of (±)-myrtucommulones D−E, utilizing biogenetic building blocks[11] and a Zn-mediated skeletal rearrangement reaction as a key step. Subsequent bioactivity studies revealed that four compounds showed moderate to excellent efficacy against osteosarcoma growth in vitro.

■ RESULTS AND DISCUSSION

Given the concurrent isolation of flavesone (**7a**),[12] myrtucommulone B′ (**9**),[13] myrtuspirone A (**11**),[14] isomyrtucommulone B (**12**),[15] 6-methylisomyrtucommulone B (**13**),[16] myrtucommulone B (**14**),[17] and syncarpic acid (**16**)[18] from Myrtaceae plants, the potential biosynthetic pathways of myrtucommulones D−E (**1**−**2**) are outlined in Scheme 2. The stable biogenetic building block **7a** may be activated through

Received: April 8, 2025
Revised: May 27, 2025
Accepted: May 30, 2025
Published: June 13, 2025

https://doi.org/10.1021/acs.joc.5c00859
J. Org. Chem. 2025, 90, 8737−8744

510632, P. R. China; orcid.org/0000-0002-2810-1001; Email: chywc@aliyun.com

Authors

Hong Guo − *State Key Laboratory of Bioactive Molecules and Druggability Assessment, Guangdong Basic Research Center of Excellence for Natural Bioactive Molecules and Discovery of Innovative Drugs, Jinan University, Guangzhou 510632, P. R. China; Center for Bioactive Natural Molecules and Innovative Drugs, and Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, College of Pharmacy, Jinan University, Guangzhou 510632, P. R. China*

Ming-Fang Qi − *State Key Laboratory of Bioactive Molecules and Druggability Assessment, Guangdong Basic Research Center of Excellence for Natural Bioactive Molecules and Discovery of Innovative Drugs, Jinan University, Guangzhou 510632, P. R. China; Center for Bioactive Natural Molecules and Innovative Drugs, and Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, College of Pharmacy, Jinan University, Guangzhou 510632, P. R. China*

Si-Si Wang − *State Key Laboratory of Bioactive Molecules and Druggability Assessment, Guangdong Basic Research Center of Excellence for Natural Bioactive Molecules and Discovery of Innovative Drugs, Jinan University, Guangzhou 510632, P. R. China; Center for Bioactive Natural Molecules and Innovative Drugs, and Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, College of Pharmacy, Jinan University, Guangzhou 510632, P. R. China*

Ya-Hang Zhu − *State Key Laboratory of Bioactive Molecules and Druggability Assessment, Guangdong Basic Research Center of Excellence for Natural Bioactive Molecules and Discovery of Innovative Drugs, Jinan University, Guangzhou 510632, P. R. China; Center for Bioactive Natural Molecules and Innovative Drugs, and Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, College of Pharmacy, Jinan University, Guangzhou 510632, P. R. China*

Shi-Lin Lin − *State Key Laboratory of Bioactive Molecules and Druggability Assessment, Guangdong Basic Research Center of Excellence for Natural Bioactive Molecules and Discovery of Innovative Drugs, Jinan University, Guangzhou 510632, P. R. China; Center for Bioactive Natural Molecules and Innovative Drugs, and Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, College of Pharmacy, Jinan University, Guangzhou 510632, P. R. China*

Mei-Qi Zheng − *Center for Bioactive Natural Molecules and Innovative Drugs, and Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, College of Pharmacy, Jinan University, Guangzhou 510632, P. R. China*

Yan-Yi Wu − *State Key Laboratory of Bioactive Molecules and Druggability Assessment, Guangdong Basic Research Center of Excellence for Natural Bioactive Molecules and Discovery of Innovative Drugs, Jinan University, Guangzhou 510632, P. R. China; Center for Bioactive Natural Molecules and Innovative Drugs, and Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, College of Pharmacy, Jinan University, Guangzhou 510632, P. R. China*

Yan-Xia Hu − *Center for Bioactive Natural Molecules and Innovative Drugs, and Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, College of Pharmacy, Jinan University, Guangzhou 510632, P. R. China*

Chuang-Chuang Li − *Department of Chemistry, Shenzhen Grubbs Institute, Southern University of Science and Technology, Shenzhen 518055, P. R. China;* orcid.org/0000-0003-4344-0498

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.5c00859

Author Contributions

[⊥]H.G. and M.-F.Q. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Nos. 82473801, 82373750, 82104019, 82293681 (82293680), 82430108), National Key R&D Program of China (No. 2022YFE0205500), the Science & Technology Projects in Guangzhou (Nos. 202102070001, 2024B03J1286, 2025A04J3399), and the Guangdong Basic and Applied Basic Research Foundation (Nos. 2024B1515040014, 2025A1515011064), and National/Guangdong Province/Jinan University College Student Innovation and Entrepreneurship Training Program (Nos. 202510559072, CX25274, CX25283). We are grateful to Prof. Ren-Wang Jiang and Dr. Wei Xu from the public research platform of the College of Pharmacy, Jinan University, for testing and partially analyzing all single crystals in this article.

■ REFERENCES

(1) For some representative reviews, see: (b) Winter, D. K.; Sloman, D. L.; Porco Jr, J. A. Polycyclic xanthone natural products: structure, biological activity and chemical synthesis. *Nat. Prod. Rep.* **2013**, *30*, 382−391. (c) Nicoletti, R.; Salvatore, M. M.; Ferranti, P.; Andolfi, A. Structures and bioactive properties of myrtucommulones and related acylphloroglucinols from myrtaceae. *Molecules* **2018**, *23*, 3370. (d) Kong, L.; Deng, Z.; You, D. Chemistry and biosynthesis of bacterial polycyclic xanthone natural products. *Nat. Prod. Rep.* **2022**, *39*, 2057−2095. (e) Gogoi, U.; Pathak, K.; Saikia, R.; Pathak, M. P.; Paul, T.; Khan, S. A.; Das, A. Recent advances on natural and non-natural xanthones as potential anticancer agents: A review. *Med. Chem.* **2023**, *19*, 757−784.

(2) Shaheen, F.; Ahmad, M.; Khan, S. N.; Hussain, S. S.; Anjum, S.; Tashkhodjaev, B.; Turguniv, K.; Sultankhodzhaev, M. N.; Choudhary, M. I.; Rahman, A.-U. New α-glucosidase inhibitors and antibacterial compounds from *Myrtus communis L. Eur. J. Org Chem.* **2006**, *2371*, 2371.

(3) Wu, Y.; Chen, M.; Wang, W. J.; Li, N. P.; Ye, W. C.; Wang, L. Phloroglucinol derivatives from *Myrtus communis* 'Variegata' and their antibacterial activities. *Chem. Biodivers.* **2020**, *17*, No. e2000292.

(4) For some representative examples, see: (b) Carroll, A. R.; Lamb, J.; Moni, R.; Guymer, G. P.; Forster, P. I.; Quinn, R. J. Myrtucommulones F−I, phloroglucinols with thyrotropin-releasing hormone receptor-2 binding affinity from the seeds of *Corymbia scabrida*. *J. Nat. Prod.* **2008**, *71*, 1564. (c) Hiranrat, A.; Mahabusarakam, W. New acylphloroglucinols from the leaves of *Rhodomyrtus tomentosa*. *Tetrahedron* **2008**, *64*, 11193. (d) Rattanaburi, S.; Mahabusarakam, W.; Phongpaichit, S.; Carroll, A. R. Acylphloroglucinols from *Callistemon lanceolatus* DC. *Tetrahedron* **2013**, *69*, 6070−6075. (e) Choudhary, M. I.; Khan, N.; Ahmad, M.; Yousuf, S.; Fun, H. K.; Soomro, S.; Asif, M.; Mesaik, M. A.; Shaheen, F. New inhibitors of ROS generation and T-cell proliferation