Photoinduced Skeletal Rearrangements Reveal Radical-Mediated Synthesis of Terpenoids

Chem **2019**, *5*, 1671–1681

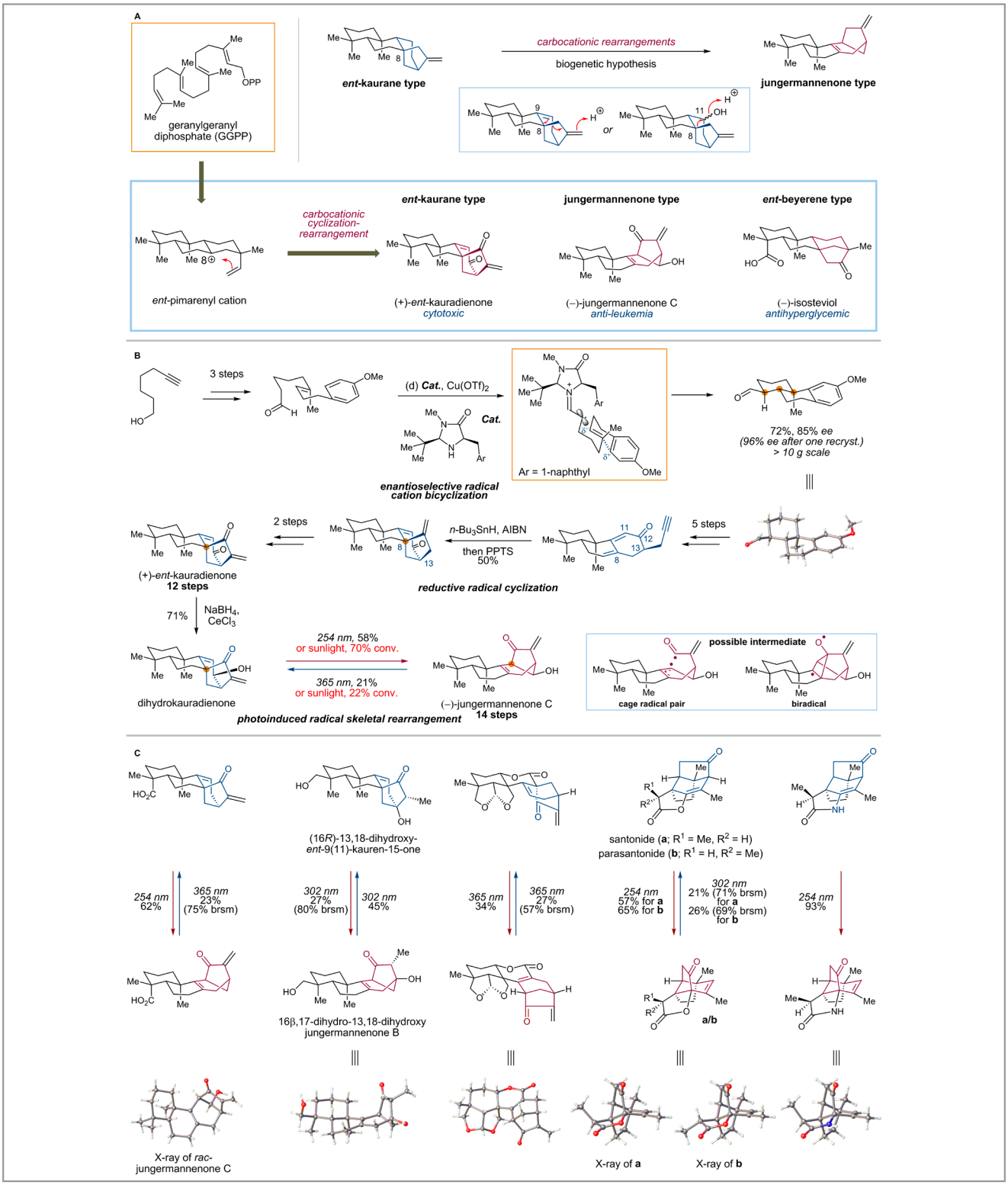
Isodon diterpenoids are a large family of bioactive polycyclic natural products isolated from plants of *Isodon* species. Biosynthetically, these diterpenoids are derived from geranylgeranyl-diphosphate (GGPP) by carbocationic cyclization rearrangements, which are catalyzed by a series of terpenoid cyclases. Several known bicyclo[3.2.1]octene containing isodon diterpenoid skeletons (*ent*-kaurane-type, jungermannenone-type, *ent*-beyerene-type, etc.) are generated via carbocationic rearrangements from a common intermediate *ent*-pimarenyl cation. An initial biosynthetic hypothesis speculated that jungermannenone-type diterpenoids could be generated from *ent*-kaurane diterpenoids via two intermediates through carbocationic rearrangements (Scheme 1A).[1] During a research program aimed at developing the synthesis of complex isodon diterpenoids, the research group led by Professor Xiaoguang Lei and Professor Houhua Li at Peking University (P. R. of China) discovered a late-stage photoinduced radical skeletal rearrangement of the bicylco[3.2.1]octene ring system, which suggested that these photoinduced radical rearrangements are possibly involved in the biosynthetic pathway of *ent*-kauranes and jungermannenones.

Previously, the Lei group had accomplished the scalable total synthesis of isodon diterpenoids *rac*-jungermannenones B and C via a regioselective 1,6-dienyne reductive cyclization reaction.[2] Professor Lei said: "We are interested in studying the biosynthetic pathways of natural products. Based on our previous work and inspired by the aforementioned biosynthetic hypotheses, we undertook the investigation of the biomimetic rearrangement of *ent*-kaurane diterpenoids to jungermannenone diterpenoids." As a result, in this work the authors developed an enantioselective and protecting-group-free synthesis of the *ent*-kaurane-type diterpenoid (+)-*ent*-kauradienone using several radical-based reactions (Scheme 1B). Professor Lei said: "The development of an enantioselective synthetic route to these compounds is very challenging. Gratifyingly, after extensive experimentation of enantioselective polyene cyclization methods, the enantioselective synthesis was achieved by using MacMillan's organocatalytic radical cation bicyclization.[3]" Another challenge faced by the authors was to construct the *ent*-kaurane bicyclo[3.2.1]octene framework. After extensive conditions screening, the desired *ent*-kaurane-type skeleton was obtained as a sole product via regioselective 1,6-dienyne reductive radical cyclization. "In our previous work, the reductive radical cyclization occurred exclusively at the C11 position to form the jungermannenone-type scaffold in the presence of a C12 hydroxy group," said Professor Lei, who continued: "Interestingly, when the C12-OH was converted into the oxidized ketone, the radical cyclization occurred at the C8 position exclusively, instead of occurring at the C11 position. Further mechanistic studies using density functional theory (DFT) calculations showed that the regioselectivity is mainly controlled by geometric factors."

Then the biomimetic transformation of *ent*-kaurane to jungermannenone skeleton was investigated. Unfortunately, initial extensive attempts to convert biosynthetically *ent*-kaurane-type into jungermannenone-type scaffolds on model substrates via a carbocationic rearrangement were unsuccessful. Professor Lei said: "To our delight, we finally achieved the interconversion between *ent*-kauranes and jungermannenones via a photoinduced rearrangement of bicyclo[3.2.1]octene." A detailed previous mechanistic study had suggested that this photoinduced skeletal rearrangement possibly occurred via 1,3-acyl migration involving a cage radical pair or a bi-radical intermediate.[4] Professor Lei remarked: "The interconversion between dihydrokauradienone and (–)-jungermannenone C also occurred smoothly promoted by sunlight, which indicated that *ent*-kaurane-type and jungermannenone-type diterpenoids are biosynthetically interrelated via this photoinduced radical rearrangement, which was previously thought to be a carbocation rearrangement. We therefore speculate that dihydrokauradienone is most likely a natural product."

Furthermore, a series of structurally diverse *ent*-kaurane-type and jungermannenone-type diterpenoids or analogues and sesquiterpenoids also underwent this late-stage photoinduced skeleton rearrangement smoothly (Scheme 1C). "These transformations show that the photochemical rearrangements are highly functional-group-tolerant, so allylic alcohols, acids, primary and tertiary alcohols, lactones and enamide can all be present," explained Professor Lei, who continued: "Careful examinations were conducted case by case to improve the yields. We discovered the optimal wavelengths didn't correlate with the UV absorption data of the substrates. The computed study indicated that the

  • Published online: January 21, 2020 • DOI: 10.1055/s-0039-1691148



Scheme 1 (A) Proposed carbocationic biosynthetic pathway of isodon diterpenoids. (B) Protecting-group-free synthesis of isodon diterpenoids (+)-*ent*-kauradienone and (–)-jungermannenone C. (C) Late-stage photoinduced skeletal rearrangements of terpenoids.

photochemical rearrangement is not a thermodynamic equilibrium."

Professor Lei concluded: "The enantioselective and protecting-group-free synthesis of (+)-*ent*-kauradienone and (–)-jungermannenone C were achieved in 12 and 14 steps, respectively, relying on three radical-based reactions, including a late-stage photoinduced radical rearrangement. Further applications of the late-stage rearrangements to various diterpenoids show good functional-group compatibility and suggest they are possibly involved in the biosynthetic pathways. We hope the photochemical 1,3-acyl migration will find more applications in natural products synthesis. Our work, together with previous examples contributed by other groups,[5] is expected to spur more interest in radical chemistry for natural products synthesis."

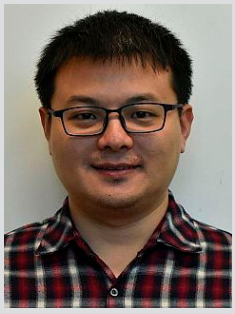
REFERENCES

(1) (a) F. Nagashima, M. Kondoh, M. Fujii, S. Takaoka, Y. Watanabe, Y. Asakawa *Tetrahedron* **2005**, *61*, 4531–4544. (b) L.-M. Li, G.-Y. Li, W.-L. Xiao, Y. Zhou, S.-H. Li, S.-X. Huang, Q.-B. Han, L.-S. Ding, L.-G. Lou, H.-D. Sun *Tetrahedron Lett.* **2006**, *47*, 5187–5190.
(2) W. Liu, H. Li, P.-J. Cai, Z. Wang, Z.-X. Yu, X. Lei *Angew. Chem. Int. Ed.* **2016**, *55*, 3112–3116.
(3) S. Rendler, D. W. C. MacMillan *J. Am. Chem. Soc.* **2010**, *132*, 5027–5029.
(4) (a) R. S. Givens, W. K. Chae *J. Am. Chem. Soc.* **1978**, *100*, 6278–6280. (b) R. S. Givens, W. K. Chae, B. Matuszewski *J. Am. Chem. Soc.* **1982**, *104*, 2456–2466. (c) B. Reimann, D. E. Sadler, K. Schaffner *J. Am. Chem. Soc.* **1986**, *108*, 5527–5530. (d) S. Wilsey, M. J. Bearpark, F. Bernardi, M. Olivucci, M. A. Robb *J. Am. Chem. Soc.* **1996**, *118*, 176–184. (e) G. Xu, M. Elkin, D. J. Tantillo, T. R. Newhouse, T. J. Maimone *Angew. Chem. Int. Ed.* **2017**, *56*, 12498–12502.
(5) K. J. Romero, M. S. Galliher, D. A. Pratt, C. R. J. Stephenson *Chem. Soc. Rev.* **2018**, *47*, 7851–7866.

About the authors

Dr. B. Hong

Benke Hong received his B.Sc. degree in pharmaceutical engineering from Liaoning University (P. R. of China). In 2011, he joined Professor Xiaoguang Lei's group to start his Ph.D. studies on natural product synthesis. After receiving his Ph.D. in 2016, he is currently staying in the same group as a research assistant. His research project focuses on isodon diterpenoids total synthesis.

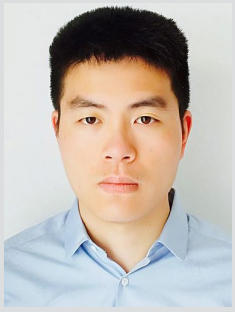


Dr. W. Liu

Weilong Liu received his B.Sc. degree in chemistry at Beijing Normal University (P. R. of China) in 2010. He then began his Ph.D. research under the supervision of Professor Xiaoguang Lei at Peking University (P. R. of China). He received his Ph.D. in 2015 and then joined BeiGene (P. R. of China) as a research investigator. In 2017, he moved to Geneva University (Switzerland) to conduct postdoctoral research with Professor Nicolas Winssinger.

J. Wang

Jin Wang was born in Jiangsu (P. R. of China) in 1995. He received his B.Sc. degree in chemistry from Nanjing University (P. R. of China). He commenced his Ph.D. studies under the supervision of Professor Xiaoguang Lei at Peking University (P. R. of China) in 2017, focusing on total synthesis of natural products.



Prof. H. Li

Houhua Li was born in Jiangxi (P. R. of China) in 1985. He studied carbohydrate chemistry under the supervision of Professor Xinshan Ye during his B.Sc. and M.Sc. at Peking University (P. R. of China). In 2009, he moved to National Institute of Biological Sciences (NIBS) in Beijing (P. R. of China) and worked with Professor Xiaoguang Lei on the synthesis of lycopodium alkaloids. He received his Ph.D. under the supervision of Professor Clément Mazet at the University of Geneva (Switzerland) in 2016 and then conducted postdoctoral work with Professor Herbert Waldmann at the Max Planck Institute of Molecular Physiology (Germany). Since 2019, he has been an assistant professor at the School of Pharmaceutical Sciences in Peking University. His research interests lie mainly in the chemistry and biology of bioactive natural products.

Prof. X. Lei

Xiaoguang Lei was born and raised in Beijing, P. R. of China. He obtained B.Sc. degree in chemistry at Peking University (P. R. of China) in 2001. He then moved to Boston (USA) and conducted his Ph.D. research studies on natural product synthesis and chemical biology under the supervision of Professor John. A. Porco at Boston University. He received his Ph.D. in 2006, and then moved to New York City (USA) and joined Professor Samuel J. Danishefsky's group at Columbia University (USA) as a postdoctoral fellow in bioorganic chemistry. In early 2009, he returned to China, and started his independent research career as a Principal Investigator and Director of Chemistry Center at the National Institute of Biological Sciences (NIBS) in Beijing (P. R. of China). In early 2014, he received a tenured professorship from Peking University (P. R. of China), and moved his research group to the College of Chemistry there. He also joined the Peking-Tsinghua Center for Life Science as a senior PI. The major research areas of Professor Lei's laboratory are chemical biology, natural product total synthesis and medicinal chemistry.

© Georg Thieme Verlag Stuttgart • New York – Synform **2020/02**, A19–A22 • Published online: January 21, 2020 • DOI: 10.1055/s-0039-1691148