JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

Asymmetric Total Synthesis of Arcutinidine, Arcutinine, and Arcutine

Shupeng Zhou, Kaifu Xia, Xuebing Leng, and Ang Li

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.9b05818 • Publication Date (Web): 05 Jul 2019

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Asymmetric Total Synthesis of Arcutinidine, Arcutinine, and Arcutine

Shupeng Zhou,† Kaifu Xia,† Xuebing Leng,‡ and Ang Li*,†

†State Key Laboratory of Bioorganic and Natural Products Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

‡State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences

Supporting Information Placeholder

ABSTRACT: We have accomplished the asymmetric total synthesis of arcutinidine, arcutinine, and arcutine, three arcutine type C20-diterpenoid alkaloids. A pentacyclic intermediate was rapidly assembled by using two Diels–Alder reactions. We developed a cascade sequence of Prins cyclization and Wagner–Meerwein rearrangement to construct the core of arcutinidine, which was then elaborated into an oxygenated pentacycle through a scalable route. Chemoselective reductive amination followed by spontaneous imine formation furnished the pyrroline motif at a final stage. We clarified the *S* configuration of the α-carbon of the acyl group within arcutine through chemical synthesis and crystallographic analysis.

The C_{20}-diterpenoid alkaloids[1] have long been attractive targets for chemical synthesis from the structural and biological perspectives.[2] Among them, members from the atisine,[3] hetisine,[4] denudatine,[5] veatchine,[6] napelline,[7] and hetidine[8,9] subclasses have been conquered by synthetic chemists. Nearly two decades ago, Bassonova and co-workers reported the discovery of two intricate C_{20}-diterpenoid alkaloids arcutine (the structure of which was originally described as **1**, Figure 1) and arcutinine (**2**) and their presumed biogenetic precursor arcutinidine (**3**).[10] Their scaffold contains two doubly fused bicyclo[2.2.2]octane moieties (Figure 1; highlighted in blue) and a congested pyrroline motif.[10] Of note, a non-alkaloidal natural product atropurpuran (**4**) relevant to **1**–**3** was later discovered by Wang and colleagues.[11] Compared to the alkaloids, diterpenoid **4** has drawn considerable attention from the synthesis community.[12–14] Suzuki et al. first disclosed an inspiring approach for construction of the core of **4**,[12a] and the Qin[13] and Xu[14] groups recently accomplished elegant syntheses of this molecule in a racemic form, respectively. Obviously, the pyrroline and tertiary alcohol within the alkaloids pose an additional challenge for chemical synthesis. Right before our submission of this paper, Qin and co-workers disclosed a beautiful enantioselective synthesis of arcutinidine and arcutinine.[15] During the course of our synthesis of hetidine type alkaloids,[9] we were intrigued by the relationship between the hetidine and arcutine skeletons. Wang and Liang recognized the arcutine skeleton as a rearrangement product of the hetidine or hetisine skeleton.[1a] More specifically, Sarpong and colleagues proposed a Wagner–Meerwein type 1,2-alkyl shift (Figure 1; key bonds highlighted in red) responsible for the biogenesis of the arcutine skeleton from the hetidine skeleton, and carried out DFT calculations to support this insightful hypothesis.[16] Indeed, tongolinine (**5**) bearing a tertiary alcohol may serve as a precursor of the carbocation species required for initiating the Wagner–Meerwein pathway. Our experience[17] with Prins reaction suggested an opportunity to generate a carbocation species at the end of this powerful C–C bond forming reaction.[18] Herein, we report the asymmetric total synthesis of arcutinidine, arcutinine, and arcutine.[19]

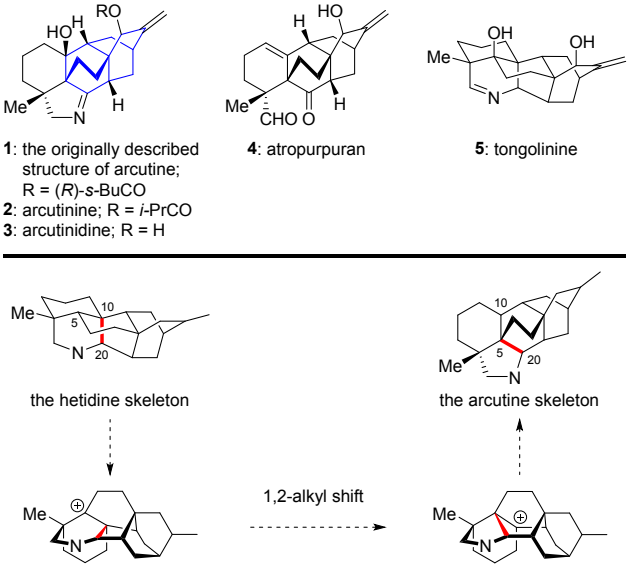


Figure 1. The structures of representative arcutine type alkaloids (**1**–**3**) and related natural products [atropurpuran (**4**) and tongolinine (**5**)] and the postulated biogenetic relationship between the hetidine and arcutine skeletons.

We first undertook a retrosynthetic analysis of **1** (Figure 2). Disassembly of the pyrroline within **1** gave diketoaldehyde **6**; chemoselective reductive amination of the aldehyde

functionality of **6** could be a challenge at a late stage of the synthesis.[9] Compound **6** may arise from less oxygenated intermediate **7**. Position-selective C–H oxidation of the latter would furnish the corresponding lactone, and the quaternary C_4 could be constructed through α-methylation. A key retrosynthesis step from **7** to compound **8** bearing a simplified hetidine framework relied on the design of a cascade sequence of Prins cyclization and Wagner–Meerwein rearrangement.[20] The MOM group of **8** was expected to serve as a precursor of the oxonium ion species that would initiate the 6-*endo*-*trig* cyclization. Upon formation of the C–C bond highlighted in blue (Figure 2), the resultant tertiary carbocation at C_5 should induce the 1,2-alkyl shift to construct the C–C bond highlighted in red (Figure 2). On the basis of our experience of septedine synthesis,[9] the bicyclo[2.2.2]octane moiety of **8** could be assembled through an anionic Diels–Alder cycloaddition. Therefore, α,β-unsaturated enone **9** was considered a suitable precursor of **8**. Further simplification led to aldehyde **10**, which may result from an intermolecular Diels–Alder reaction[21] of known diene **11**[22] and dienophile **12**. The latter was traced back to known enantioenriched alcohol **13** that was readily available through lipase-mediated resolution.[23]

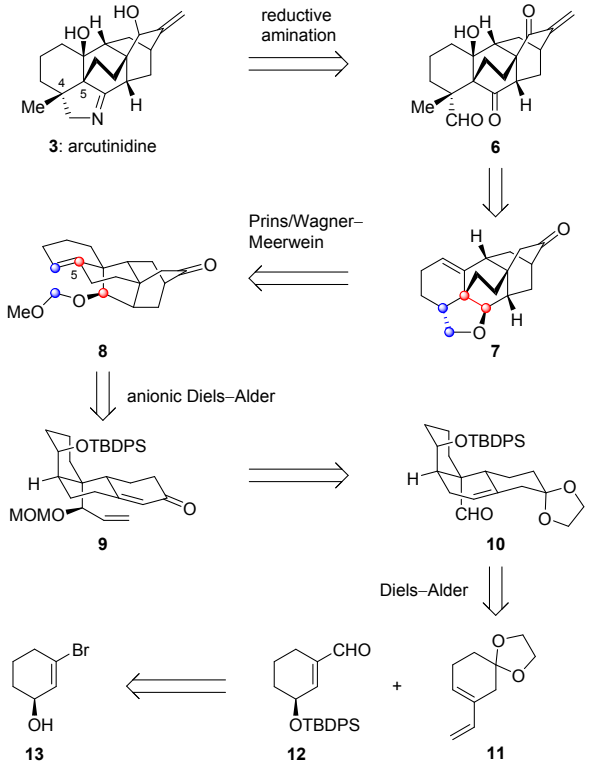


Figure 2. Retrosynthetic analysis of **3**.

The synthesis commenced with scalable preparation of pentacyclic intermediate **8** (Scheme 1). Silylation of enantioenriched alcohol **13** (>99% ee) provided compound **14** in 93% yield. Treatment of **14** with *t*-BuLi generated the alkenyl lithium species, which was quenched by DMF to give aldehyde **12** in 91% yield. We then examined a variety of conditions for the intermolecular Diels–Alder reaction of **11** and **12**; acid lability of the ketal group of the former turned out to be a problem. To our delight, BF_3•OEt_2 was found to be an effective promoter for the cycloaddition at −78 °C, and compound **10** was obtained in 68% isolated yield. One-pot vinyllithium addition and MOM protection afforded allylic ether **15** in 85% yield as a single detectable diastereomer. Exposure to aq. $HClO_4$ resulted in selective hydrolysis of the ketal followed by C=C bond migration, furnishing α,β-unsaturated enone **9** in 72% yield. Following from our experience with the anionic [4+2]-cycloaddition,[9] we subjected **9** to deprotonation with LiHMDS. The resultant 1,3-dienolate underwent an intramolecular Diels–Alder reaction at 22 °C, and subsequent desilylation of the cycloadduct with TBAF provided alcohol **16** in 84% overall yield. Of note, complete removal of O_2 in the reaction system by the freeze–pump–thaw cycling was crucial to the success of this anionic cycloaddition. X-ray crystallographic analysis of **16** (Scheme 1) confirmed the stereochemical outcomes of the two Diels–Alder reactions. Dehydration of **16** with $SOCl_2$/pyridine gave trisubstituted olefin **8** in 76% yield.[17a] Indeed, **8** could also serve as a versatile intermediate for the synthesis of hetidine type alkaloids.

Scheme 1. Construction of Pentacyclic Intermediate 8

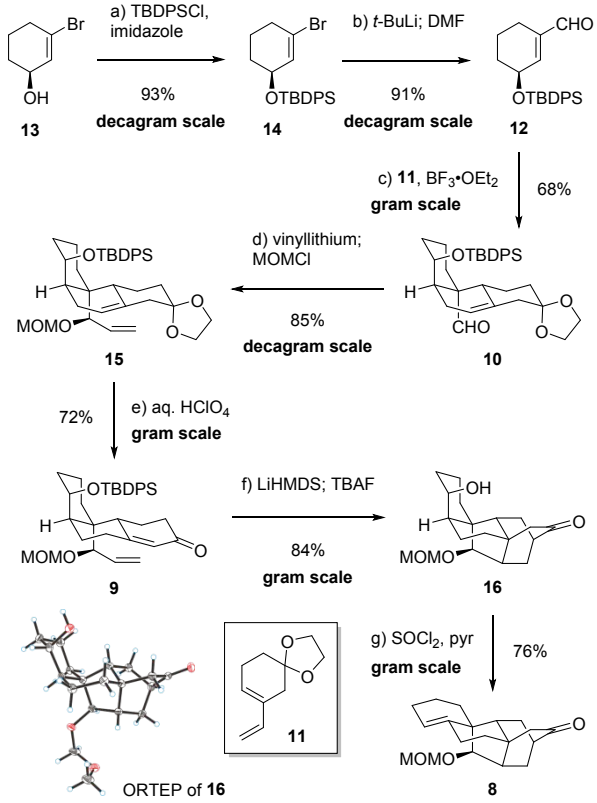
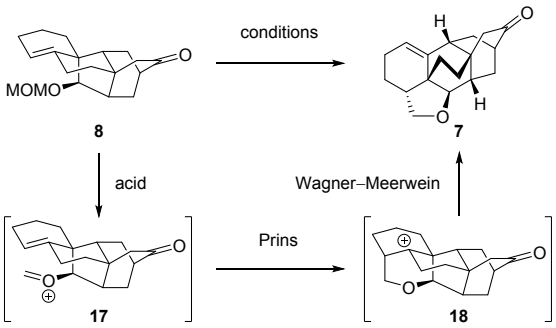


Table 1. Conditions for the Cationic Cascade Reaction

With a large quantity of **8** in hand, we investigated the conditions for its conversion into **7**; the results are summarized in Table 1. In the presence of a suitable, stoichiometric acid promoter, **8** should undergo a Prins/Wagner–Meerwein cascade to give **7** bearing an arcutine scaffold, presumably via the intermediacy of two cationic species **17** and **18**. To our delight, exposure of **8** to TFA gave **7** in 22% yield (entry 1), despite a significant amount of the alcohol resulting from MOM deprotection. TESOTf caused severe substrate decomposition (entry 2). BF_3•OEt_2 slightly increased the yield of **7** (entry 3), while $TiCl_4$ preferentially led to MOM removal (entry 4). $SnCl_4$ was then found to be an optimal promoter for the cascade

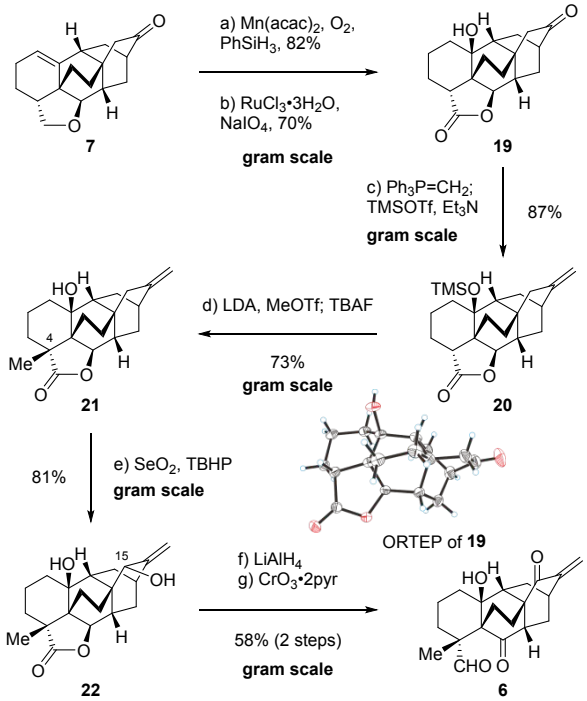
reaction, and **7** was obtained in 63% yield on a gram scale (entry 5). We briefly explored the possibility of trapping the post-rearrangement carbocation species with an oxygen nucleophile (TMSOAc); however, proton elimination (leading to olefin **7**) remained the predominant reaction pathway (entry 6).



entry	conditions[a]	yield (%)
1	TFA, 0 °C, 24 h	22
2	TESOTf, 0 °C, 1 h	16
3	BF_3•OEt_2, –15 °C, 6 h	37
4	$TiCl_4$, –15 °C, 1 h	24
5	$SnCl_4$, –15 °C, 1 h	63
6	$SnCl_4$, TMSOAc, –15 °C, 1 h	55

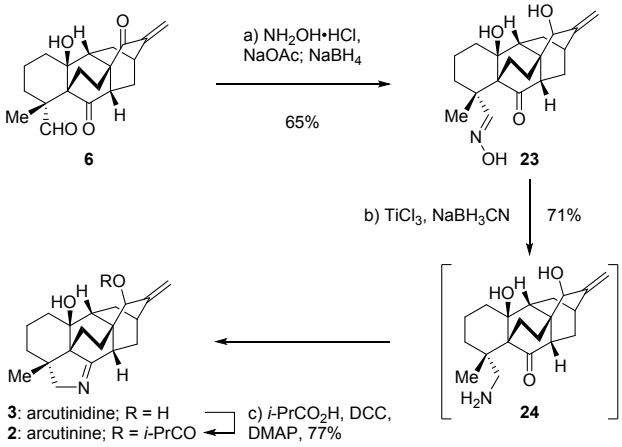
[a] 1.0 equiv. acid. Reactions performed in CH_2Cl_2.

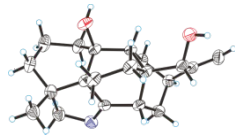
Scheme 2. Preparation of Oxygenated Pentacycle 6

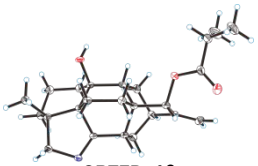


We then developed a robust route from **7** to oxygenated pentacycle **6** (Scheme 2). Face-selective Mukaiyama hydration of the trisubstituted olefin followed by position-selective C–H oxidation using the Sharpless protocol[24] ($RuCl_3$•$3H_2O$, $NaIO_4$) afforded alcohol **19**, the structure of which was confirmed by X-ray crystallographic analysis (Scheme 2). Of note, $Mn(acac)_2$[25] was superior to $Co(acac)_2$ as a precatalyst for this particular olefin hydration. The alcohol underwent one-pot Wittig methylenation and silylation to give compound **20** in 87% yield. α-Methylation of this lactone turned out to be a challenge; MeI was ineffective under various conditions. To our delight, MeOTf proved to be a more powerful reagent in this case.[26] The lithium enolate of **20** was methylated smoothly in the presence of HMPA, and desilylation with TBAF furnished alcohol **21** in one pot with good overall efficiency. The stereochemistry at C_4 was secured by the rigid polycyclic system. Oxidation of **21** with SeO_2/TBHP gave allylic alcohol **22** in 81% yield as an undesired diastereomer, which was then subjected to a sequence of $LiAlH_4$ reduction and CrO_3•2pyr oxidation.[27] Thus, diketoaldehyde **6** was obtained in 58% overall yield. We expected to address the stereochemical issue at C15 by face-selective ketone reduction at a final stage of the synthesis.

Scheme 3. Completion of the Synthesis of 3 and 2




ORTEP of **3**

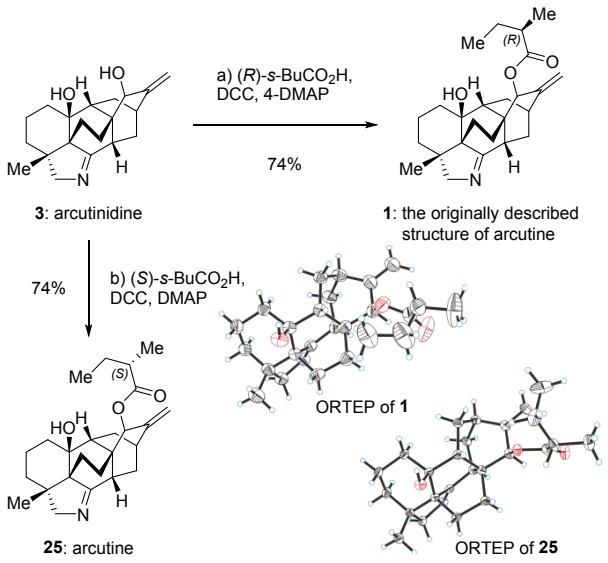

ORTEP of **2**

Completion of the synthesis of **3** and **2** relied on differentiating the reactivity of the three carbonyls of **6** (Scheme 3). Chemoselective condensation of the aldehyde with NH_2OH followed by face-selective 1,2-reduction of the α,β-unsaturated enone with $NaBH_4$ afforded compound **23** as a single diastereomer in 65% yield. The most hindered carbonyl group remained untouched through this reaction sequence. Exposure of **23** to $TiCl_3$ led to reductive cleavage of the N–O bond.[28] The resultant aldimine intermediate was further reduced in situ by $NaBH_3CN$ to form primary amine **24**,[28] which underwent spontaneous cyclization upon aqueous workup to give **3** in 71% yield. More than 200 mg of **3** have been prepared in total. Acylation of the allylic alcohol (*i*-$PrCO_2H$, DCC, DAMP) provided **2** in 77% yield. The structures of **2** and **3** were verified by X-ray crystallographic analysis (Scheme 3).

Finally, we directed our attention to the synthesis of arcutine (Scheme 4). Under the esterification conditions used for preparing **2**, arcutinidine (**3**) reacted with commercially available (*R*)-*s*-$BuCO_2H$ to form the originally described structure of arcutine (**1**). However, the crystal

structure of synthetic **1** (Scheme 4) differed from that of authentic arcutine presented in the isolation paper,[10a] with regard to the acyl groups. We then checked the X-ray crystallographic data of authentic arcutine (CCDC 1150924) and realized that the configuration of the α-carbon of the acyl group was *S*. The description of this crucial configuration in the literature[10a] was incorrect. To our delight, acylation of arcutinidine (**3**) with commercially available (*S*)-*s*-$BuCO_2H$ afforded arcutine (**25**) in 74% yield; the crystal structures of synthetic **25** (Scheme 4) and authentic arcutine were identical.

Scheme 4. Completion of the Synthesis of Arcutine and the Originally Described Structure of Arcutine



In summary, we have accomplished the asymmetric total synthesis of arcutinidine (**3**), arcutinine (**2**), and arcutine (**25**). An expeditious and scalable route to a pentacyclic intermediate with hetidine features was established. A bioinspired Prins/Wagner–Meerwein cascade was then developed for conversion of the hetidine core structure into an arcutine core structure. These endeavors may facilitate studies of the biology of arcutine and hetidine type alkaloids.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectroscopic data of compounds, NMR spectra of compounds, CIF files

AUTHOR INFORMATION

Corresponding Author

*ali@sioc.ac.cn

ACKNOWLEDGMENT

This paper is dedicated to Prof. Qing-Yun Chen on the occasion of his 90th birthday. We thank Prof. Richmond Sarpong, Shelby McCowen, and Xiang Zhang for discussions. This work was supported by National Natural Science Foundation of China (21525209, 21621002, 21772225, and 21761142003), Chinese Academy of Sciences (Strategic Priority Research Program XDB20000000 and Key Research Program of Frontier Sciences QYZDB-SSW-SLH040), Shanghai Science and Technology Commission (17XD1404600), and the K. C. Wong Education Foundation.

REFERENCES

(1) (a) Wang, F.-P.; Liang, X.-T. C_{20}-Diterpenoid Alkaloids. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier Science: New York, 2002; Vol. 59, pp 1–280. (b) Wang, F.-P.; Chen, Q.-H.; Liang, X.-T. Diterpenoid alkaloids. *Nat. Prod. Rep.* **2010**, *27*, 529.

(2) (a) Cherney, E. C.; Baran, P. S. Terpenoid-alkaloids: their biosynthetic twist of fate and total synthesis. *Isr. J. Chem.* **2011**, *51*, 391. (b) Hamlin, A. M.; Kisunzu, J. K.; Sarpong, R. Synthetic strategies toward hetidine and hetisine-type diterpenoid alkaloids. *Org. Biomol. Chem.* **2014**, *12*, 1846. (c) Liu, X.-Y.; Qin, Y. Ongoing pursuit of diterpenoid alkaloids: a synthetic view. *Asian J. Org. Chem.* **2015**, *4*, 1010. (d) Zhu, G.-L.; Liu, R.; Liu, B. Total synthesis of atisane-type diterpenoids and related diterpenoid alkaloids. *Synthesis* **2015**, *47*, 2691. (e) Liu, X.-Y.; Qin, Y. Enabling syntheses of diterpenoid alkaloids and related diterpenes by an oxidative dearomatization/Diels–Alder cycloaddition strategy. *Nat. Prod. Rep.* **2017**, *34*, 1044.

(3) (a) Pelletier, S. W.; Jacobs, W. A. The aconite alkaloids. XXXI. A partial synthesis of atisine, isoatisine and dihydroatisine. *J. Am. Chem. Soc.* **1956**, *78*, 4144. (b) Pelletier, S. W.; Parthasarathy, P. C. The diterpene alkaloids: a partial synthesis of atisine. *Tetrahedron Lett.* **1963**, *4*, 205. (c) Nagata, W.; Sugasawa, T.; Narisada, M.; Wakabayashi, T.; Hayase, Y. Stereospecific total synthesis of *dl*-atisine. *J. Am. Chem. Soc.* **1963**, *85*, 2342. (d) Masamune, S. Total syntheses of diterpenes and diterpene alkaloids. V. atisine. *J. Am. Chem. Soc.* **1964**, *86*, 291. (e) Guthrie, R. W.; Valenta, Z.; Wiesner, K. Synthesis in the series of diterpene alkaloids VI. A simple synthesis of atisine. *Tetrahedron Lett.* **1966**, *7*, 4645. (f) Nagata, W.; Sugasawa, T.; Narisada, M.; Wakabayashi, T.; Hayase, Y. Total synthesis of *dl*-atisine. *J. Am. Chem. Soc.* **1967**, *89*, 1483. (g) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kametani, T.; Kabuto, C. Stereoselective total synthesis of (±)-atisine via intramolecular double Michael reaction. *J. Am. Chem. Soc.* **1988**, *110*, 1963. (h) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kametani, T.; Kabuto, C. Asymmetric total synthesis of atisine via intramolecular double Michael reaction. *J. Am. Chem. Soc.* **1990**, *112*, 1164. (i) Liu, X.-Y.; Cheng, H.; Li, X.-H.; Chen, Q.-H.; Xu, L.; Wang, F.-P. Oxidative dearomatization/intramolecular Diels–Alder cycloaddition cascade for the syntheses of (±)-atisine and (±)-isoazitine. *Org. Biomol. Chem.* **2012**, *10*, 1411. (j) Cherney, E. C.; Lopchuk, J. M.; Green, J. C.; Baran, P. S. A unified approach to *ent*-atisane diterpenes and related alkaloids: synthesis of (–)-methyl atisenoate, (–)-isoatisine, and the hetidine skeleton. *J. Am. Chem. Soc.* **2014**, *136*, 12592. (k) Cheng, H.; Zeng, F.-H.; Yang, X.; Meng, Y.-J.; Xu, L.; Wang, F.-P. Collective total syntheses of atisane-type diterpenes and atisine-type diterpenoid alkaloids: (±)-spiramilactone B, (±)-spiraminol, (±)-dihydroajaconine, and (±)-spiramines C and D. *Angew. Chem., Int. Ed.* **2016**, *55*, 392. (l) Li, X.-H.; Zhu, M.; Wang, Z.-X.; Liu, X.-Y.; Song, H.; Zhang, D.; Wang, F.-P.; Qin, Y. Synthesis of atisine, ajaconine, denudatine, and hetidine diterpenoid alkaloids by a bioinspired approach. *Angew. Chem., Int. Ed.* **2016**, *55*, 15667. (m) Liu, J.; Ma, D. Total syntheses of azitine and the proposed structure of navirine C. *Angew. Chem., Int. Ed.* **2018**, *57*, 6676.

(4) (a) Muratake, H.; Natsume, M. Total synthesis of (±)-nominine, a heptacyclic hetisine-type aconite alkaloid. *Angew. Chem., Int. Ed.* **2004**, *43*, 4646. (b) Muratake, H.; Natsume, M. Synthetic study of hetisine-type aconite alkaloids. Part 1: preparation of tetracyclic intermediate containing the C14–C20 bond. *Tetrahedron* **2006**, *62*, 7056. (c) Muratake, H.; Natsume, M. Synthetic study of hetisine-type aconite alkaloids. Part 2: preparation of hexacyclic compound lacking the C-ring of the hetisan skeleton. *Tetrahedron* **2006**, *62*, 7071. (d) Muratake, H.; Natsume, M.; Nakai, H. Synthetic study of hetisine-type aconite alkaloids. Part 3: total synthesis of (±)-nominine. *Tetrahedron* **2006**, *62*, 7093. (e) Peese, K. M.; Gin, D. Y. Efficient synthetic access to the hetisine C20-diterpenoid alkaloids. A concise synthesis of nominine via oxidoisoquinolinium-1,3-dipolar and dienamine-Diels–Alder cycloadditions. *J. Am. Chem. Soc.* **2006**, *128*, 8734. (f) Peese, K. M.; Gin, D. Y. Total synthesis of (+)-nominine.

Chem. Eur. J. **2008**, *14*, 1654. (g) Zhang, Q.-Z.; Zhang, Z.-S.; Huang, Z.; Zhang, C.-H.; Xi, S.; Zhang, M. Stereoselective total synthesis of hetisine-type C20-diterpenoid alkaloids: spirasine IV and XI. *Angew. Chem., Int. Ed.* **2018**, *57*, 937. (h) Kou, K. G. M.; Pflueger, J. J.; Kiho, T.; Morrill, L. C.; Fisher, E. L.; Clagg, K.; Lebold, T. P.; Kisunzu, J. K.; Sarpong, R. A benzyne insertion approach to hetisine-type diterpenoid alkaloids: synthesis of cossonidine (davisine). *J. Am. Chem. Soc.* **2018**, *140*, 8105.

(5) (a) Nishiyama, Y.; Han-ya, Y.; Yokoshima, S.; Fukuyama, T. Total synthesis of (–)-lepenine. *J. Am. Chem. Soc.* **2014**, *136*, 6598. (b) Kou, K. G. M.; Li, B. X.; Lee, J. C.; Gallego, G. M.; Lebold, T. P.; DiPasquale, A. G.; Sarpong, R. Syntheses of denudatine diterpenoid alkaloids: cochlearenine, *N*-ethyl-1α-hydroxy-17-veratroyldictyzine, and paniculamine. *J. Am. Chem. Soc.* **2016**, *138*, 10830. (c) Kou, K. G. M.; Kulyk, S.; Marth, C. J.; Lee, J. C.; Doering, N. A.; Li, B. X.; Gallego, G. M.; Lebold, T. P.; Sarpong, R. A unifying synthesis approach to the C18-, C19-, and C20-diterpenoid alkaloids. *J. Am. Chem. Soc.* **2017**, *139*, 13882. Also see ref. 3l.

(6) (a) Masamune, S. Total syntheses of diterpenes and diterpene alkaloids. IV. Garryine. *J. Am. Chem. Soc.* **1964**, *86*, 290. (b) Nagata, W.; Narisada, M.; Wakabayashi, T.; Sugasawa, T. Total synthesis of *dl*-garryine and *dl*-veatchine. *J. Am. Chem. Soc.* **1964**, *86*, 929. (c) Valenta, Z.; Wiesner, K.; Wong, C. M. Synthesis in the diterpene alkaloid series - II. A total synthesis of the garrya alkaloids. *Tetrahedron Lett.* **1964**, *5*, 2437. (d) Nagata, W.; Narisada, M.; Wakabayashi, T.; Sugasawa, T. Total synthesis of *dl*-veatchine and *dl*-garryine. *J. Am. Chem. Soc.* **1967**, *89*, 1499. (e) Wiesner, K.; Uyeo, S.; Philipp, A.; Valenta, Z. Synthesis in the series of diterpene alkaloids. IX. A new simple synthesis of veatchine. *Tetrahedron Lett.* **1968**, *9*, 6279.

(7) (a) Wiesner, K.; Ho, P.; Tsai, C. S. J.; Lam, Y. The Total synthesis of racemic napelline. *Can. J. Chem.* **1974**, *52*, 2355. (b) Sethi, S. P.; Atwal, K. S.; Marini-Bettolo, R. M.; Tsai, T. Y. R.; Wiesner, K. A stereospecific synthesis of napelline. *Can. J. Chem.* **1980**, *58*, 1889.

(8) For recent synthetic studies, see: (a) Hamlin, A. M.; Cortez, F. J.; Lapointe, D.; Sarpong, R. Gallium(III)-catalyzed cycloisomerization approach to the diterpenoid alkaloids: construction of the core structure for the hetidines and hetisines. *Angew. Chem., Int. Ed.* **2013**, *52*, 4854. (b) Hamlin, A. M.; Lapointe, D.; Owens, K.; Sarpong, R. Studies on C_{20}-diterpenoid alkaloids: synthesis of the hetidine framework and its application to the synthesis of dihydronavirine and the atisine skeleton. *J. Org. Chem.* **2014**, *79*, 6783. (c) Zhu, M.; Li, X.-H.; Song, X.; Wang, Z.-X.; Liu, X.-Y.; Song, H.; Zhang, D.; Wang, F.-P.; Qin, Y. Studies towards bioinspired synthesis of hetidine-type C_{20}-diterpenoid alkaloids. *Chin. J. Chem.* **2017**, *35*, 991. Also see ref. 3j, l, m.

(9) Zhou, S.; Guo, R.; Yang, P.; Li, A. Total synthesis of septedine and 7-deoxyseptedine. *J. Am. Chem. Soc.* **2018**, *140*, 9025.

(10) (a) Tashkhodzhaev, B.; Saidkhodzhaeva, S. A.; Bessonova, I. A.; Antipin, M. Y. Arcutine-a new type of diterpene alkaloids. *Chem. Nat. Compd.* **2000**, *36*, 79. (b) Saidkhodzhaeva, S. A.; Bessonova, I. A.; Abdullaev, N. D. Arcutinine, a new alkaloid from *Aconitum arcuatum*. *Chem. Nat. Compd.* **2001**, *37*, 466.

(11) Tang, P.; Chen, Q.-H.; Wang, F.-P. Atropurpuran, a novel diterpene with an unprecedented pentacyclic cage skeleton, from *Aconitum hemsleyanum var. atropurpureum*. *Tetrahedron Lett.* **2009**, *50*, 460.

(12) (a) Suzuki, T.; Sasaki, A.; Egashira, N; Kobayashi, S. A synthetic study of atropurpuran: construction of a pentacyclic framework by an intramolecular reverse-electron-demand Diels–Alder reaction. *Angew. Chem. Int. Ed.* **2011**, *50*, 9177. (b) Hayashi, R.; Ma, Z. X.; Hsung, R. P. A tandem 1,3-H-shift–6pelectrocyclization–cyclic 2-amido-diene intramolecular Diels–Alder cycloaddition approach to BCD-ring of atropurpuran. *Org. Lett.* **2012**, *14*, 252. (c) Chen, H.; Zhang, D.; Xue, F.; Qin, Y. Synthesis of the atropurpuran A-ring via an organocatalytic asymmetric intramolecular Michael addition. *Tetrahedron* **2013**, *69*, 3141. (d) Chen, H.; Li, X.-H.; Gong, J.; Song, H.; Liu, X.-Y.; Qin, Y. Synthetic approach to the functionalized tricyclic core of atropurpuran. *Tetrahedron* **2016**, *72*, 347. (e) Jarhad, D. B.; Singh, V. π^4s + π^2s Cycloaddition of spiroepoxycyclohexa-2,4-dienone, radical cyclization, and oxidation–aldol–oxidation cascade: synthesis of BCDE ring of atropurpuran. *J. Org. Chem.* **2016**, *81*, 4304.

(13) Gong, J.; Chen, H.; Liu, X.-Y.; Wang, Z.-X.; Nie, W.; Qin, Y. Total synthesis of atropurpuran. *Nat. Comm.* **2016**, *7*, 12183.

(14) Xie, S.; Chen, G.; Yan, H.; Hou, J.; He, Y.; Zhao, T.; Xu, J. 13-Step total synthesis of atropurpuran. *J. Am. Chem. Soc.* **2019**, *141*, 3435.

(15) Nie, W.; Gong, J.; Chen, Z.; Liu, J.; Tian, D.; Song, H.; Liu, X.-Y.; Qin, Y. Enantioselective total synthesis of (–)-arcutinine. *J. Am. Chem. Soc.* **2019**, *141*, 9712.

(16) Weber, M.; Owens, K.; Sarpong, R. Atropurpuran–missing biosynthetic link leading to the hetidine and arcutine C_{20}-diterpenoid alkaloids or an oxidative degradation product? *Tetrahedron Lett.* **2015**, *56*, 3600.

(17) (a) Sun, Y.; Li, R.; Zhang, W.; Li, A. Total synthesis of indotertine A and drimentines A, F, and G. *Angew. Chem., Int. Ed.* **2013**, *52*, 9201. (b) Sun, Y.; Chen, P.; Zhang, D.; Baunach, M.; Hertweck, C.; Li, A. Bioinspired total synthesis of sespenine. *Angew. Chem., Int. Ed.* **2014**, *53*, 9012. (c) Lu, Z.; Yang, M.; Chen, P.; Xiong, X.; Li, A. Total synthesis of hapalindole-type natural products. *Angew. Chem., Int. Ed.* **2014**, *53*, 13840. (d) Deng, J.; Zhou, S.; Zhang, W.; Li, J.; Li, R.; Li, A. Total synthesis of taiwaniadducts B, C, and D, *J. Am. Chem. Soc.* **2014**, *136*, 8185. (e) Lu, Z.; Li, H.; Bian, M.; Li, A. Total synthesis of epoxyeujindole A. *J. Am. Chem. Soc.* **2015**, *137*, 13764. (f) Li, H.; Chen, Q.; Lu, Z.; Li, A. Total syntheses of aflavazole and 14-hydroxyaflavinine, *J. Am. Chem. Soc.* **2016**, *138*, 15555. (g) Sun, Y.; Meng, Z.; Chen, P.; Zhang, D.; Baunach, M.; Hertweck, C.; Li, A. A concise total synthesis of sespenine, a structurally unusual indole terpenoid from *Streptomyces*. *Org. Chem. Front.* **2016**, *3*, 368.

(18) (a) Gahman, T. C.; Overman, L. E. Stereoselective synthesis of carbocyclic ring systems by pinacol-terminated Prins cyclizations. *Tetrahedron* **2002**, *58*, 6473. (b) Pennington, L. D.; Overman, L. E. Strategic use of pinacol-terminated Prins cyclizations in target-oriented total synthesis. *J. Org. Chem.* **2003**, *68*, 7143. (c) Velthuisen, E.; J.; Overman, L. E. Scope and facial selectivity of the Prins–pinacol synthesis of attached rings. *J. Org. Chem.* **2006**, *71*, 1581.

(19) For the original version of this paper, see ChemRxiv Preprint 2019, doi: 10.26434/chemrxiv.8202242. Sarpong and co-workers disclosed an elegant synthesis of (±)-arcutinidine, as we disclosed this study.

(20) For recent examples, see: (a) Andrez, J.-C.; Giroux, M.-A.; Lucien, J.; Canesi, S. Rapid formation of hindered cores using an oxidative Prins process. *Org. Lett.* **2010**, *12*, 4368. (b) Reddy, B. V. S.; Muralikrishna, K.; Yadav, J. S.; Babu, N. J.; Sirisha, K.; Sarma, A. V. S. Tandem Prins/Wagner/Ritter process for the stereoselective synthesis of (3-oxabicyclo[4.2.0]octanyl)amide and (1-(5-aryltetrahydrofuran-3-yl)cyclobutyl)amide derivatives. *Org. Biomol. Chem.* **2015**, *13*, 5532. For a conceptually relevant example from our group, see ref. 17b, g.

(21) Carreño, M. C., Urbano, A.; Di Vitta, C. Enantioselective Diels–Alder approach to C3-oxygenated angucyclinones from (*SS*)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone. *Chem. Eur. J.* **2000**, *6*, 906.

(22) For strategically inspiring examples: see: (a) Bergmann, E. D.; Becker, A. Diels–Alder reactions with 1-formylcyclohexene and 1-formylcyclopentene. *J. Am. Chem. Soc.* **1959**, *81*, 221. (b) Stoltz, B. M.; Kano, T.; Corey, E. J. Enantioselective total synthesis of nicandrenones. *J. Am. Chem. Soc.* **2000**, *122*, 9044. (c) Jung, M. E.; Lui, R. M. Studies toward the total syntheses of cucurbitacins B and D. *J. Org. Chem.* **2010**, *75*, 7146. (d) Tartakoff, S. S.; Vanderwal, C. D. A synthesis of the ABC tricyclic core of the clionastatins serves to corroborate their proposed structures. *Org. Lett.* **2014**, *16*, 1458.

(23) We developed an improved resolution protocol using the *Candida antarctica* lipase (see the SI). For a relevant example, see: Li, J.; Zhang, W.; Zhang, F.; Chen, Y.; Li, A. Total synthesis of daphniyunnine C (longeracinphyllin A). *J. Am. Chem. Soc.* **2017**, *139*, 14893.

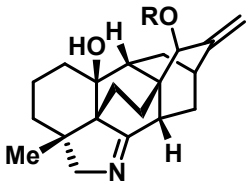
(24) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. A greatly improved procedure for ruthenium tetroxide catalyzed oxidations of organic compounds. *J. Org. Chem.* **1981**, 46, 3936. For a recent application by our group, see ref. 17d.

(25) See, Y. Y.; Herrmann, A. T.; Aihara, Y.; Baran, P. S. Scalable C–H oxidation with copper: synthesis of polyoxypregnanes. *J. Am. Chem. Soc.* **2015**, *137*, 13776.

(26) Uenishi, J.; Tatsumi, Y.; Kobayashi, N.; Yonemitsu, O. Highly

stereoselective alkylation at neopentyl position on β,β-dialkyl substituted γ-butyrolactone ring. *Tetrahedron Lett.* **1995**, *36*, 5909.
(27) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. Selective oxidation of a primary hydroxyl in the presence of secondary one. *Tetrahedron Lett.* **1981**, *22*, 1605.
(28) Leeds, J. P.; Kirst, H. A. A mild single-step reduction of oximes to amines. *Synth. Commun.* **1988**, *18*, 777.

The graphic entry for the TOC



arcutinidine; R = H
arcutinine; R = *i*-PrCO
arcutine; R = (*S*)-*s*-BuCO