JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

# Asymmetric Total Syntheses of Aspidodasycarpine, Lonicerine, and the Proposed Structure of Lanciferine

Yong Li,[†,‡,§] Shugao Zhu,[†,§] Jian Li,[†] and Ang Li*[,†]

[†]State Key Laboratory of Bioorganic and Natural Products Chemistry, Collaborative Innovation Center of Chemistry for Life Sciences, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

[‡]Zhejiang Key Laboratory of Alternative Technologies for Fine Chemicals Process, Shaoxing University, Shaoxing 312000, China

Supporting Information

**ABSTRACT:** Aspidodasycarpine and lonicerine are a pair of epimeric aspidophylline-type alkaloids bearing vicinal quaternary C7 and C16. The first and enantioselective total syntheses of these molecules are described here. A Ru-catalyzed asymmetric transfer hydrogenation established the first stereocenter. An Au-promoted Toste cyclization was exploited to assemble the bridged tetracyclic core and define the geometry of the exocyclic olefin; electron deficient $(p\text{-}CF_3C_6H_4)_3P$ was a suitable ligand for this transformation. An aldol condensation followed by an intramolecular indole C3 alkylation constructed the adjacent quaternary C7 and C16 diastereoselectively, leading to a pentacyclic lactol as an advanced common intermediate for synthesizing both alkaloids. The proposed structure of lanciferine, a highly oxidized congener of aspidodasycarpine, was synthesized from the lactol by tuning the oxidation states of various carbons.

The akuammiline (**1**, Figure 1) indole alkaloids have held the attention of synthetic chemists because of their molecular structures and biological properties.[1] In the past decade, a number of syntheses of vincorine[2] and scholarisine A[3] were accomplished with various elegant strategies. Aspidophylline A (**2**) represents a large subfamily of akuammiline alkaloids (including **1** itself), which share an indoline/indolenine fused azabicyclo[3.3.1]nonane system.[1] In 2011, Garg et al. made a breakthrough in the synthesis campaign toward the aspidophylline subfamily,[1] by accomplishing the first total synthesis of (±)-aspidophylline A.[4] They assembled the bridged ring system via a Heck annulation[5] connecting a geometry-defined alkenyl iodide with an $\alpha,\beta$-unsaturated ester, and then developed a creative strategy of interrupted Fisher indole synthesis[6] to build the quaternary C7. Recently, the same team disclosed the first synthesis of (±)-picrinine (**3**),[7] an aspidophylline congener with a higher oxidation state. In late 2013, the groups of Zhu[8] and Ma[9] simultaneously reported two independent syntheses of (±)-aspidophylline A. The former featured a beautiful desymmetrization strategy to establish the chiral C7, and the latter relied on a signature intramolecular oxidative coupling strategy of the team. These endeavors strategically simplified the problem of synthesizing aspidophylline-type alkaloids into two parts: *a*, the construction of a tetracyclic furoindoline, and *b*, the assembly of the bridged ring system at a late stage through a radical/metal mediated conjugate addition that was hinted by Garg's Heck cyclization.[4] During studies of indole terpenoid synthesis,[10] we realized that the reported synthetic strategies for aspidophylline-type alkaloids, despite being concise and elegant, were perhaps limited to the targets carrying tertiary C16 (e.g., **2** and **3**), considering the challenge of homologation at C16 on a congested bridged polycycle. Herein, we describe the first and asymmetric total syntheses of aspidodasycarpine (**4**) and lonicerine (**5**) and the proposed structure of lanciferine (**6**) bearing vicinal quaternary C7 and C16.[11] Notably, right before we submitted this manuscript, Garg et al. reported elegant asymmetric syntheses of (−)-**2**, (+)-strictamine, and (−)-2(*S*)-cathafoline;[12] during the review process, Zhu and Yang disclosed syntheses of (±)-strictamine and (−)-**2**,[13] respectively.

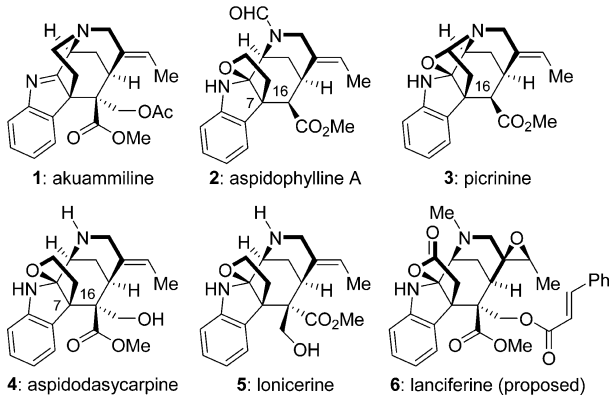



**Figure 1.** Selected akuammiline alkaloids from the aspidophylline subfamily.

Through the retrosynthetic analysis (Scheme 1), the synthetic challenge of aspidodasycarpine (**4**) is separated into the following problems: *a*, introducing the first stereocenter; *b*, assembling the 2-azabicyclo[3.3.1]nonane unit with an exocyclic C=C bond; *c*, constructing the adjacent quaternary C7 and C16. The natural product is first traced back to an advance intermediate **7**; lactol reductive opening may spontaneously furnish furoindoline motif. Disconnection at C6−C7 bond gives indole derivative **8**. A diastereoselective cyclization would secure the configuration of quaternary C7 based on the stereochemistry at C16. Compound **8** is simplified to aldehyde **9**, the benzylic

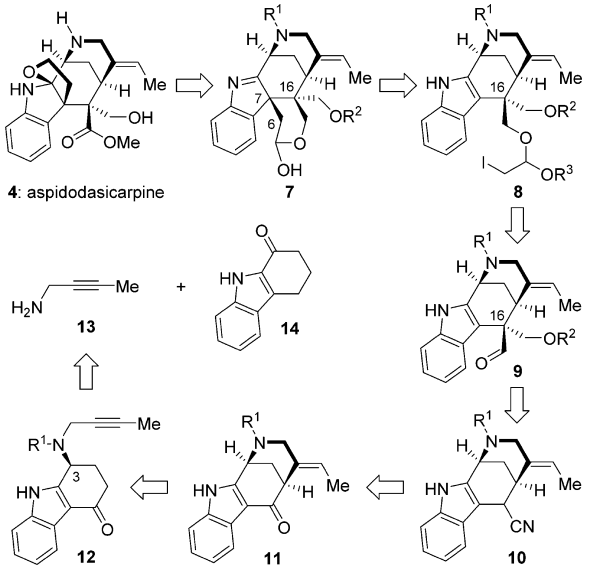
**Received:** January 21, 2016
**Published:** March 10, 2016





DOI: 10.1021/jacs.6b00764
J. Am. Chem. Soc. 2016, 138, 3982−3985

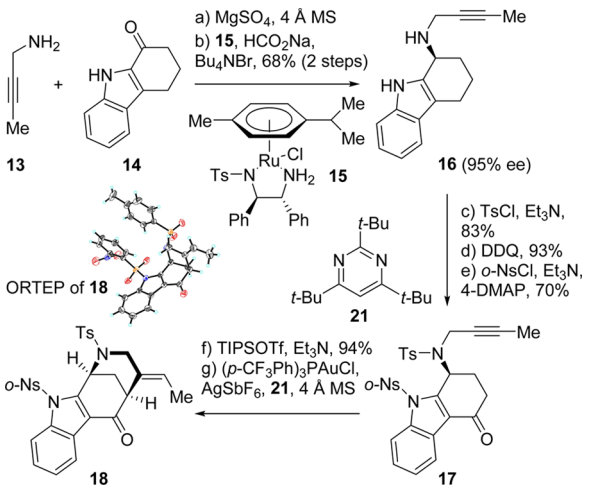
**Scheme 1. Retrosynthetic Analysis of 4**




quaternary center of which could be built via an aldol condensation. Nitrile **10** and ketone **11** are then envisioned as intermediates in our synthetic route. Inspired by our synthesis of daphenylline,[14] we plan to use Toste cyclization[15] for constructing the bridged ring system from a simple precursor **12**. The geometry of the trisubstituted exocyclic olefin should be defined by a *trans* alkyne activation mode of Au(I) catalysis.[16] The initial stereocenter would be introduced by asymmetric reductive amination, which leads to a pair of known compounds **13** and **14**. Notably, lactol **7** can serve as a common intermediate for synthesizing lonicerine (**5**) and lanciferine (**6**). The flexibility of tuning the lactol oxidation state enables us to assemble the oxidized furoindoline moiety of **6**, although a late-stage diastereoselective epoxidation could be a challenge as well.

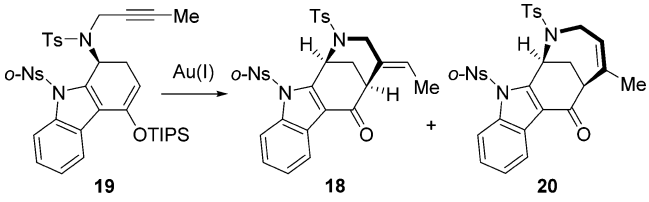
The synthesis commenced with assembling the bridged tetracyclic core of the natural products (Scheme 2). Condensation of ketone **14** with amine **13** ($MgSO_4$, 4 Å MS) afforded the corresponding imine, which was subjected to modified Deng conditions[17] (Noyori catalyst **15**, $HCO_2Na$, $Bu_4NBr$) to give amine **16** (68% yield for the two steps, 95% ee), along with a small amount of the benzylic alcohol. A sequence of amine

**Scheme 2. Assembly of a Bridged Tetracycle**




tosylation, DDQ oxidation, and indole *N*-protection with *o*-Ns gave compound **17** with good overall efficiency. The benzylic carbonyl facilitated the nosylation reaction under mild basic conditions. This indole *N*-protection was essential for the success of the next enol ether formation. To construct bridge tetracycle **18**, we had to activate ketone **17** as silyl enol ether **19** (94% yield) before the Toste cyclization. Table 1 briefly summarizes the

**Table 1. Studies of the Toste Cyclization**




| entry | conditions | **18** (%) | **20** (%) |
|---|---|---|---|
| 1 | $Ph_3PAuCl$, $AgSbF_6$[a] | 55 | 8 |
| 2 | IPrAuCl, $AgSbF_6$[a] | 61 | 27 |
| 3 | [JohnPhosAu(MeCN)]$SbF_6$[a] | 45 | 43 |
| 4 | $(p\text{-}CF_3C_6H_4)_3PAuCl$, $AgSbF_6$[a] | 62 | 6 |
| 5 | $(p\text{-}CF_3C_6H_4)_3PAuCl$, $AgSbF_6$, **21**, 4 Å MS[b] | 86 | 9 |

[a] 5 mol % of [Au], MeOH/toluene (1:10), 3 h. [b] 3 mol % of [Au], 10 mol % of **21**, 4 Å MS, *i*-PrOH/$CH_2Cl_2$ (7:100), 3 d.

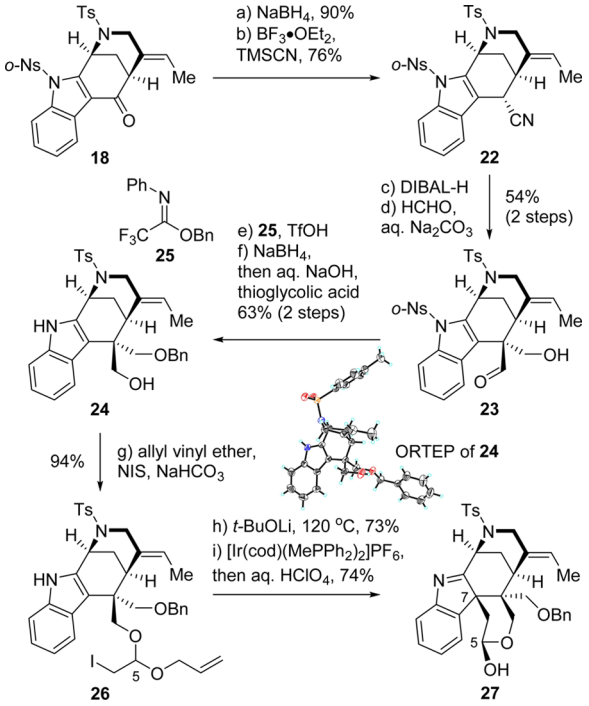
results of the cyclization studies. The standard conditions (entry 1) gave a reasonable yield of the desired 6-*exo*-*dig* cyclization product **18**, together with a small portion of 7-*endo*-*trig* cyclization product **20**.[12] Alkyne hydration was a severe side reaction under these conditions. Bulky, electron-rich ligands[18,19] enhanced the overall yields of cyclization products but resulted in poor exo/endo ratio (entries 2 and 3). In contrast, $(p\text{-}CF_3C_6H_4)_3P$ improved this ratio to ca. 10:1 (entry 4). Furthermore, pyrimidine[20] **21** suppressed acid-promoted desilylation of **19**, and 4 Å MS inhibited the alkyne hydration process; thus, **18** was obtained in 86% yield on decagram scale, albeit with prolonged reaction times (entry 5). Its structure was verified by X-ray crystallographic analysis (Scheme 2).

We then direct our attention to constructing the vicinal quaternary C7 and C16 (Scheme 3). Ketone **18** was converted to nitrile **22** with good overall efficiency, through a two-step sequence of homologation[10d] ($NaBH_4$ reduction and $BF_3{\cdot}OEt_2$ promoted cyanation). DIBAL-H reduction of **22** followed by aldol condensation with HCHO gave $\beta$-hydroxyaldehyde **23** (54% for the two steps) as a single diastereomer, which indicated a steric bias arising from the *N*-containing ridge. Compound **23** underwent benzylation, reduction, and Ns deprotection to reach alcohol **24** in 63% overall yield, the structure of which was confirmed by X-ray crystallographic analysis (Scheme 3). Notably, basic benzylation conditions resulted in retro-aldol type decomposition of **23**, and $Cl_3C(C{=}NH)OBn$ suffered self-instability issues against acid promoters. Yamada–Yu reagent **25** in the presence of TfOH was optimal for the benzyl protection in this case.[21] Building the quaternary C7 proved to be challenging, even when powerful intramolecular metal–carbenoid and allylic substitution reactions were used. Inspired by our syntheses of anominine and epoxyeujindole A, we prepared iodides such as **26** (ca. 1:1 dr at C5) from readily available vinyl ethers and **24**. Although Ueno–Stork radical cyclization was fruitless in this case, Magnus' elegant synthesis of codeine[22] reminded us of the dearomatizing alkylation[3a,b] of such substrates. Under optimized conditions [*t*-BuOLi, DMSO, 120 °C (microwave)], cyclization



DOI: 10.1021/jacs.6b00764
J. Am. Chem. Soc. 2016, 138, 3982–3985

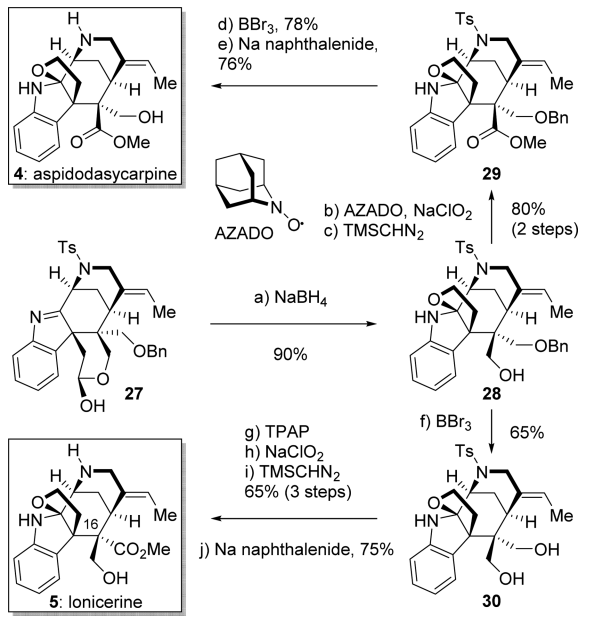
**Scheme 3. Construction of a Common Intermediate**




of **26** proceeded with high facial selectivity to give the desired product (73% yield, a single diastereomer at C7 with a ca. 1.6:1 dr at C5), indicating that one epimer of **26** performed better than the other in this reaction. Notably, the Li base was superior to the K counterpart. Treatment with $[Ir(cod)(MePPh_2)_2]PF_6$ caused the terminal C=C bond migration to afford acid-labile enol ether,[23] hydrolysis of which gave lactol **27** in 74% overall yield as a single epimer at C5 (stereochemistry determined by NOE studies), which was presumably the thermodynamically more favored one.

We further converted the common intermediate **27** into aspidodasycarpine and lonicerine (**4** and **5**, Scheme 4),

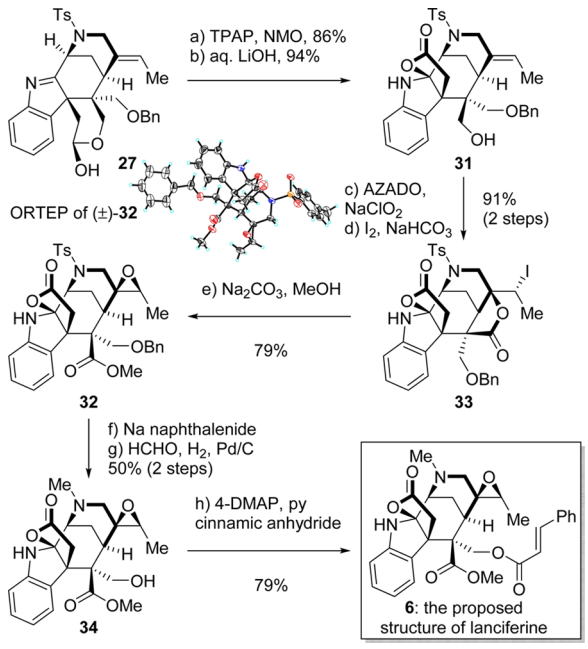
**Scheme 4. Completion of the Syntheses of 4 and 5**




respectively. Reductive opening of the lactol followed by spontaneous aminal formation provided furoindoline **28** in 90% yield. AZADO oxidation[24] and $TMSCHN_2$ methylation gave ester **29** smoothly. Removal of Bn with $BBr_3$ and reductive desulfonation with Na naphthalenide[2a,9] afforded **4** with good overall efficiency. We then swapped the reaction sequence to synthesize **5**. Debenzylation of **28** furnished diol **30** (65% yield). This compound was exposed to TPAP to form the $\beta$-hydroxyaldehyde (ca. 3:1 dr at C16, chromatographically inseparable), which underwent Lindgren–Krauss–Pinnick oxidation followed by esterification to give *N*4-Ts-**5** in 65% isolation yield for the three steps, along with 11% of *N*4-Ts-**4**. Final detosylation rendered **5**. The $^1H$ and $^{13}C$ NMR spectra and optical rotation direction and values of the synthetic **4** and **5** were consist with those of the authentic samples isolated by Kam et al.[11e]

The proposed structure of lanciferine (**6**) was synthesized from the common intermediate **27** as well (Scheme 5).

**Scheme 5. Completion of the Synthesis of the Proposed Structure of Lanciferine**




Oxidation with TPAP/NMO followed by saponification of the resultant lactone with aq. LiOH afforded oxofuroindoline **31** with good overall efficiency. The presumed carboxylate intermediate generated during the hydrolysis should be instantaneously trapped by the imine. The epoxidation of the trisubstituted olefin from the sterically more hindered face took advantage of an internal directing effect. AZADO oxidation of **31** gave the corresponding carboxylic acid, which underwent a sequence of iodolactonization, transesterification, and $S_N2$-type epoxide formation to reach compound **32**, with the intermediacy of iodide **33**.[25] The structure of **32** was secured by X-ray crystallographic analysis of a racemic sample (Scheme 5). Ts was swapped with Me via desulfonation and hydrogenative reductive amination, during which Bn was removed as well; alcohol **34** was furnished in 50% overall yield. Treatment of **34** with cinnamic anhydride and 4-DMAP delivered **6** in 79% yield. However, the $^1H$ NMR chemical shift of C18 methyl of synthetic **6** ($\delta$ = 1.4) drastically differed from that reported for natural lanciferine ($\delta$ =



DOI: 10.1021/jacs.6b00764
J. Am. Chem. Soc. 2016, 138, 3982–3985

1.2).[11c] Thus, we ended up with a synthesis of the proposed structure of lanciferine. The structural reassignment attempts were hampered by the ambiguous and incomplete $^{1}$H NMR data ($^{13}$C NMR data not even available) reported in the isolation paper.[11c] Uncovering the structural mystery of lanciferine has to rely on reisolation of the sample from nature.

In summary, we accomplished enantioselective syntheses of aspidodasycarpine, lonicerine, and the proposed structure of lanciferine (**4**–**6**). A versatile common intermediate was constructed by using an asymmetric imine hydrogenation, a Toste cyclization, a diastereoselective aldol condensation, and an indole dearomatizing cyclization as key steps. An iodolactonization furnished the epoxide moiety of **6** at a late stage. These endeavors toward synthesis of akuammiline alkaloids with the vicinal quaternary C7 and C16 may facilitate their biological studies.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00764.

Experimental procedures (PDF)
Compound characterization (CIF)
Compound characterization (CIF)
Compound characterization (CIF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*ali@sioc.ac.cn

### Author Contributions

§Y.L. and S.Z. contributed equally to this work.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This article is dedicated to the memory of Chaochao Gao. We thank Prof. Toh-Seok Kam for providing the authentic $^{1}$H and $^{13}$C NMR spectra and data and optical rotation direction and values of **4** and **5**, and Dr. Zhanchao Meng for processing some NMR data. Financial support was provided by Ministry of Science & Technology (2013CB836900), National Natural Science Foundation of China (21525209, 21290180, 21172235, 21222202), and Shanghai Science and Technology Commission (15JC1400400).

## ■ REFERENCES


(1) (a) Echermann, R.; Gaich, T. *Synthesis* **2013**, *45*, 2813. (b) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 400. (c) Adams, G.; Smith, A. B. III. The Chemistry of the Akuammiline Alkaloids. In *The Alkaloids*; Knolker, H.-J., Ed.; Elsevier: New York, 2016; Vol. *76*, pp 171–257.

(2) (a) Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6013. (b) Zi, W.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2012**, *134*, 9126. (c) Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442.

(3) (a) Adams, G. L.; Carroll, P. J.; Smith, A. B., III *J. Am. Chem. Soc.* **2012**, *134*, 4037. (b) Adams, G. L.; Carroll, P. J.; Smith, A. B., III *J. Am. Chem. Soc.* **2013**, *135*, 519. (c) Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964.

(4) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877.

(5) Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695.

(6) (a) Boal, B. W.; Schammel, A. W.; Garg, N. K. *Org. Lett.* **2009**, *11*, 3458. (b) Çelebi-Ölçüm, N.; Boal, B. W.; Hunters, A. D.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 5752. (c) Li, S.; Han, J.; Li, A. *Huaxue Xuebao* **2013**, *71*, 295.

(7) (a) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2014**, *136*, 4504. (b) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. *J. Org. Chem.* **2015**, *80*, 8954.

(8) Ren, W.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1818.

(9) Teng, M.; Zi, W.; Ma, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 1814.

(10) (a) Bian, M.; Wang, Z.; Xiong, X.; Sun, Y.; Matera, C.; Nicolaou, K. C.; Li, A. *J. Am. Chem. Soc.* **2012**, *134*, 8078. (b) Sun, Y.; Li, R.; Zhang, W.; Li, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 9201. (c) Sun, Y.; Chen, P.; Zhang, D.; Baunach, M.; Hertweck, C.; Li, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 9012. (d) Lu, Z.; Yang, M.; Chen, P.; Xiong, X.; Li, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 13840. (e) Meng, Z.; Yu, H.; Li, L.; Tao, W.; Chen, H.; Wan, M.; Yang, P.; Edmonds, D. J.; Zhong, J.; Li, A. *Nat. Commun.* **2015**, *6*, 6096. (f) Zhou, S.; Zhang, D.; Sun, Y.; Li, R.; Zhang, W.; Li, A. *Adv. Synth. Catal.* **2014**, *356*, 2867. (g) Zhou, S.; Chen, H.; Luo, Y.; Zhang, W.; Li, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 6878. (h) Xiong, X.; Zhang, D.; Li, J.; Sun, Y.; Zhou, S.; Yang, M.; Shao, H.; Li, A. *Chem. - Asian J.* **2015**, *10*, 869. (i) Lu, Z.; Li, H.; Bian, M.; Li, A. *J. Am. Chem. Soc.* **2015**, *137*, 13764.

(11) (a) Ohashi, M.; Joule, J. A.; Djerassi, C. *Tetrahedron Lett.* **1964**, *5*, 3899. (b) Naranjo, J.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1970**, *53*, 749. (c) Lewin, G.; Kunesch, N.; Posson, J. *J. Indian Chem. Soc.* **1978**, *55*, 1096. (d) Lewin, G.; Poisson, J. *Bull. Soc. Chim. Fr.* **1980**, II-400. (e) Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1783.

(12) Moreno, J.; Picazo, E.; Morrill, L. A.; Smith, J. M.; Garg, N. K. *J. Am. Chem. Soc.* **2016**, *138*, 1162.

(13) (a) Ren, W.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 3500. (b) Jiang, S.-Z.; Zeng, X.-Y.; Liang, X.; Lei, T.; Wei, K.; Yang, Y.-R. *Angew. Chem., Int. Ed.* **2016**, *55*, 4044.

(14) (a) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679. (b) Xiong, X.; Li, Y.; Lu, Z.; Wan, M.; Deng, J.; Wu, S.; Shao, H.; Li, A. *Chem. Commun.* **2014**, *50*, 5294.

(15) (a) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991. (b) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671. (c) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J.; Kar, M. *J. Am. Chem. Soc.* **2009**, *131*, 15909.

(16) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276.

(17) (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (b) Wu, J.; Wang, F.; Ma, Y.; Cui, X.; Cun, L.; Zhu, J.; Deng, J.; Yu, B. *Chem. Commun.* **2006**, 1766.

(18) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.

(19) Wang, W.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2012**, *134*, 5697.

(20) Zhang, X.; Zhou, Y.; Zuo, J.; Yu, B. *Nat. Commun.* **2015**, *6*, 5879.

(21) (a) Okada, Y.; Ohtsu, M.; Bando, M.; Yamada, H. *Chem. Lett.* **2007**, *26*, 992. (b) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405.

(22) Magnus, P.; Sane, N.; Fauber, B. P.; Lynch, V. *J. Am. Chem. Soc.* **2009**, *131*, 16045.

(23) Oltyoort, J. J.; Van Boeckel, C. A. A.; De Koning, J. H.; Van Boom, J. H. *Synthesis* **1981**, *1981*, 305.

(24) (a) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412. (b) Shibuya, M.; Sato, T.; Tomizawa, M.; Iwabuchi, Y. *Chem. Commun.* **2009**, 1739. (c) Deng, J.; Zhou, S.; Zhang, W.; Li, J.; Li, R.; Li, A. *J. Am. Chem. Soc.* **2014**, *136*, 8185.

(25) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K. *J. Am. Chem. Soc.* **1969**, *91*, 5675.




DOI: 10.1021/jacs.6b00764
*J. Am. Chem. Soc.* 2016, 138, 3982–3985