Organic LETTERS

Letter

pubs.acs.org/OrgLett

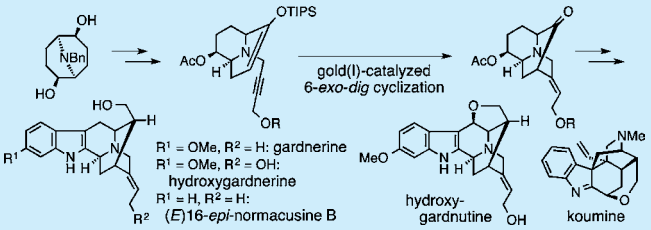
Asymmetric Total Synthesis of Sarpagine-Related Indole Alkaloids Hydroxygardnerine, Hydroxygardnutine, Gardnerine, (*E*)-16-*epi*-Normacusine B, and Koumine

Mariko Kitajima, Keisuke Watanabe, Hiroyuki Maeda, Noriyuki Kogure, and Hiromitsu Takayama*

Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8675, Japan

Supporting Information

ABSTRACT: Sarpagine-related indole alkaloids (−)-hydroxygardnerine, (+)-hydroxygardnutine, (−)-gardnerine, (+)-(*E*)-16-*epi*-normacusine B, and (−)-koumine were divergently synthesized via a common intermediate possessing a piperidine ring with an exocyclic (*E*)-ethylidene side chain, which was constructed by a gold(I)-catalyzed 6-*exo*-*dig* cyclization strategy.



We have recently developed a stereoselective gold(I)-catalyzed 6-*exo*-*dig* cyclization reaction of silyl enol ether having an internal alkyne, which affords a piperidine derivative with an exocyclic (*E*)-ethylidene side chain (Figure 1), and

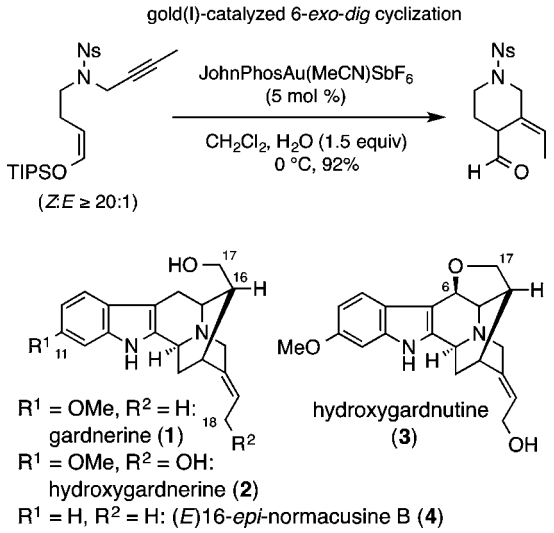


Figure 1. Gold(I)-catalyzed 6-*exo*-*dig* cyclization reaction and structures of gardnerine (**1**), hydroxygardnerine (**2**), hydroxygardnutine (**3**), and (*E*)-16-*epi*-normacusine B (**4**).

accomplished the total synthesis of conolidine and apparicine by using this product.[1] The piperidine ring with an exocyclic (*E*)-ethylidene side chain exists in many sarpagine-type monoterpenoid indole alkaloids[2] isolated from several genera, such as *Gardneria*, *Rauwolfia*, *Alstonia*, and *Gelsemium*.[3] Gardnerine (**1**),[4] one of the representative sarpagine-type indole alkaloids, was utilized for biomimetic chemical transformation into several *Gelsemium* alkaloids,[5] such as gelsenicine,[5a] des-N_a-methoxyhumantenirine,[5b] 11-methoxy-19(*R*)-hydroxygelselegine,[5c,d] and gelselegine.[5a] Further, the partial synthesis of koumine[6] and 11-methoxykoumine was achieved by the chemical conversion of natural hydoxygardnerine (**2**)[7] in our laboratory.[8] The total synthesis of several sarpagine-type alkaloids was accomplished by Cook's group, using mainly tryptophan derivatives as the starting material.[2b,9] Herein we report an asymmetric total synthesis of sarpagine-related alkaloids, which involves the first total synthesis of (−)-hydroxygardnerine (**2**), (+)-hydroxygardnutine (**3**),[4] and (−)-koumine (**34**) with natural absolute configuration[10] by applying the gold-catalyzed 6-*exo*-*dig* cyclization reaction.

Our retrosynthetic analysis of sarpagine-type alkaloids gardnerine (**1**), (−)-hydroxygardnerine (**2**), and (+)-(*E*)-16-*epi*-normacusine B (**4**)[11] is shown in Scheme 1. Alkaloids **1**, **2**, and **4** and compound **5** are obtained from tricyclic ketone **6**, which could be a common intermediate for the divergent synthesis of various sarpagine-type alkaloids, by manipulation of the indole nucleus having various substituents on the benzene part and preservation/removal of the allylic hydroxyl group.

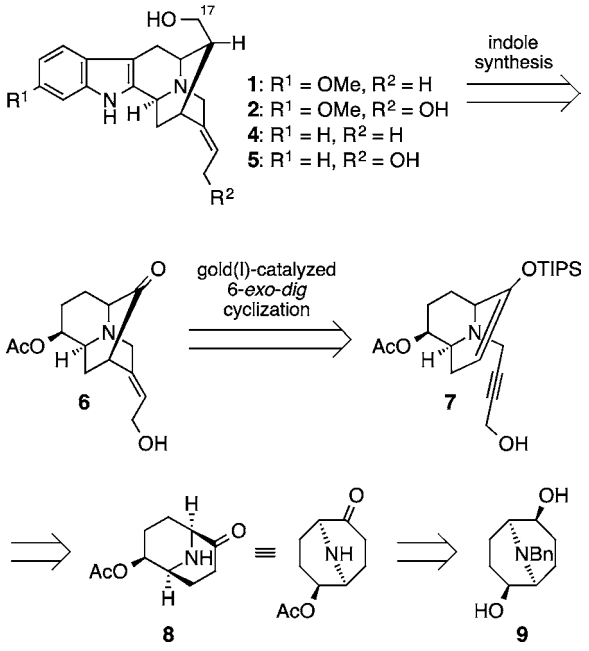
The piperidine ring with an (*E*)-ethylidene side chain in tricyclic ketone **6** could be constructed by the gold(I)-catalyzed 6-*exo*-*dig* cyclization of alkynyl silyl enol ether **7**. Silyl enol ether **7** would be derived by alkylation of keto amine **8**, which could be synthesized from known (+)-9-azabicyclo[3.3.1]nonane-2,6-diol derivative **9**.[12]

Employing azabicyclononane **9**, which was prepared from 1,5-cyclooctadiene in four steps, as the starting material, we initially prepared alkynyl silyl enol ether **10** for use as the substrate in the gold(I)-catalyzed cyclization (Scheme 2). Swern oxidation of **9** and subsequent partial reduction of the resultant diketone by treatment with BH_3·THF gave monoalcohol **11**. After acetylation of the hydroxyl group in **11** and deprotection of the benzyl group in acetate **12**, the resultant

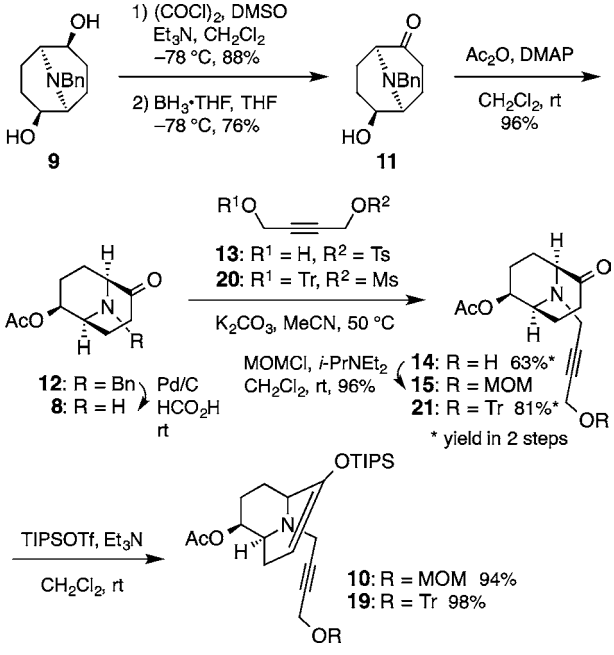
Received: March 15, 2016
Published: April 1, 2016

DOI: 10.1021/acs.orglett.6b00661
Org. Lett. 2016, 18, 1912−1915

Scheme 1. Retrosynthetic Analysis of Alkaloids 1, 2, and 4



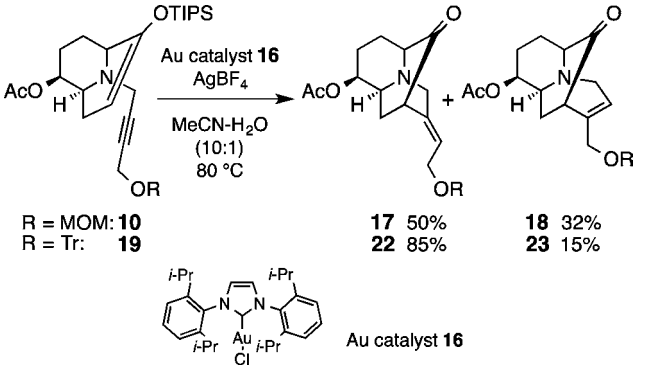
Scheme 2. Synthesis of Alkynyl Silyl Enol Ethers 10 and 19



keto amine **8** was alkylated with alkyne **13** in the presence of K_2CO_3 in MeCN to afford alkyne ketone **14**. The primary alcohol in **14** was protected by MOM ether, and treatment of ketone **15** with TIPSOTf in the presence of Et_3N in CH_2Cl_2 gave alkynyl silyl enol ether **10**.

Next, we carried out the gold(I)-catalyzed cyclization of alkynyl silyl enol ether **10** (Scheme 3). Treatment of **10** with Au catalyst **16**[13] (10 mol %) and $AgBF_4$ (10 mol %) in MeCN−H_2O (10:1) at 80 °C gave the desired 6-*exo-dig*-cyclized product **17** in 50% yield, together with undesired 7-*endo-dig* cyclized product **18** in 32% yield. To improve the selectivity of the cyclization mode, i.e., 6-*exo-dig* vs 7-*endo-dig*, the protecting group of alcohol in the alkyne part was changed from MOM to a bulky trityl group. Alkynyl silyl enol ether **19**

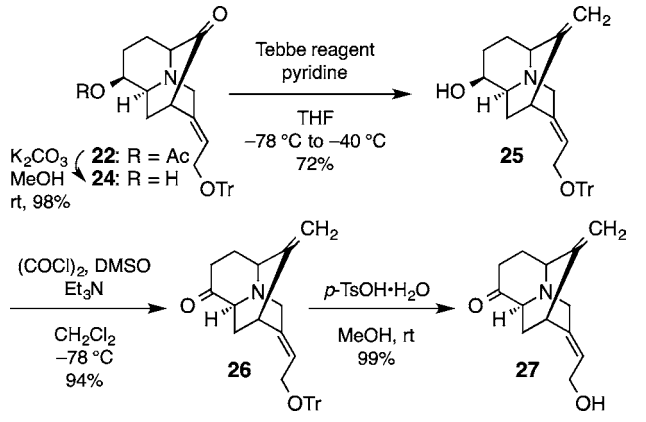
Scheme 3. Gold(I)-Catalyzed 6-*Exo-Dig* Cyclization of Alkynyl Silyl Enol Ethers 10 and 19



having a trityl ether was prepared from **12** via alkylation of **8** with alkyne **20** and silyl enol etherification of **21**. As expected, the gold(I)-catalyzed cyclization of **19** with Au catalyst **16** (3 mol %) and $AgBF_4$ (3 mol %) in MeCN−H_2O at 80 °C gave predominantly 6-*exo-dig*-cyclized product **22** in 85% yield along with 7-*endo-dig*-cyclized product **23** in 15% yield.

Thus, obtained cyclized product **22** was deacetylated, and the C1 unit corresponding to C-17 was introduced by treating ketone **24** with Tebbe reagent in the presence of pyridine in THF in 72% yield (Scheme 4). Swern oxidation of exo olefinic compound **25** followed by deprotection of the trityl group in **26** gave ketone **27**, the substrate for the indole synthesis.

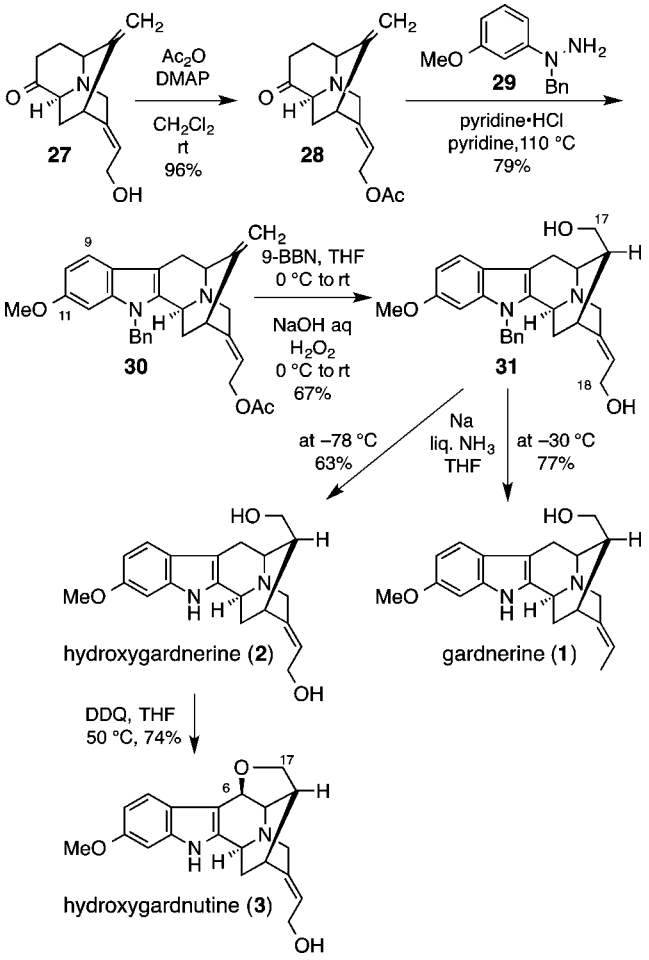
Scheme 4. Synthesis of Ketone 27



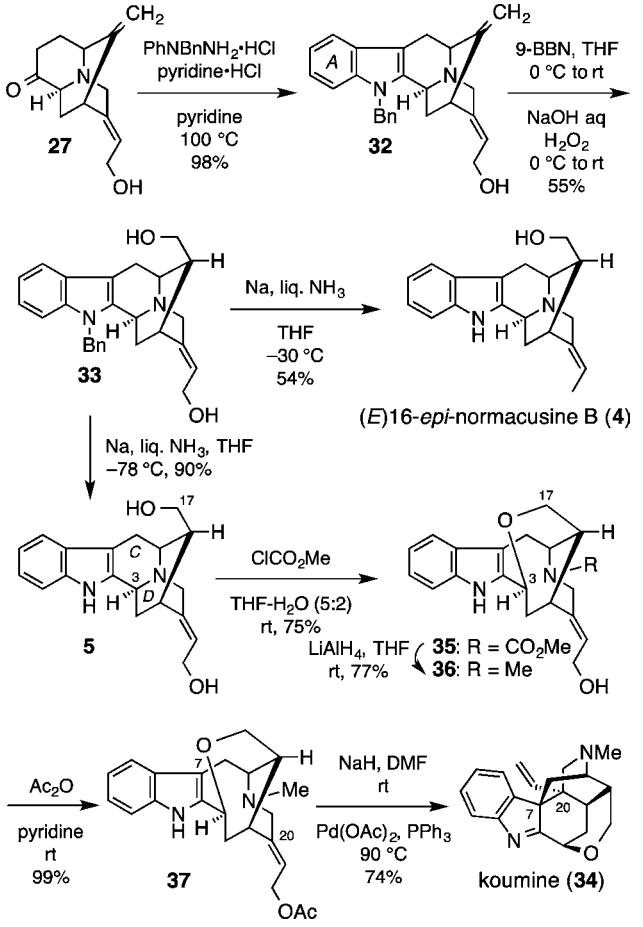
Next, we turned our attention to the synthesis of gardnerine (**1**)[14] and hydroxygardnerine (**2**) (Scheme 5). After protection of allyl alcohol in ketone **27** with an acetyl group, Fischer indole synthesis of ketone **28** with phenylhydrazine **29** in the presence of pyridine·HCl in pyridine[15] was conducted to give desired 11-methoxyindole **30** in 79% yield together with 9-methoxy isomer in 15% yield. The regio- and diastereoselective introduction of a hydroxyl group at the C-17 position was achieved by hydroboration of **30** by 9-BBN followed by oxidation[14] in 67% yield. Finally, deprotection of the benzyl group on N_a in **31** by the Birch reduction at −78 °C gave hydroxygardnerine (**2**) in 63% yield. When the Birch reduction was carried out at −30 °C, gardnerine (**1**) was selectively obtained in 77% yield via deoxygenation at C-18 position and debenzylation.[10] Hydroxygardnerine (**2**) was oxidized with DDQ in THF[16] to afford hydroxygardnutine (**3**).

DOI: 10.1021/acs.orglett.6b00661
Org. Lett. 2016, 18, 1912−1915

Scheme 5. Synthesis of Gardnerine (1), Hydroxygardnerine (2), and Hydroxygardnutine (3)



Scheme 6. Synthesis of (*E*)-16-*epi*-Normacusine B (4) and Koumine (34)



According to the above-mentioned procedure, ketone **27** was converted into (*E*)-16-*epi*-normacusine B (**4**)[17] having a nonsubstituted indole A ring in three steps: indole synthesis by using 1-benzyl-1-phenylhydrazine; hydroboration/oxidation of indole **32**; and the Birch reduction of **33** at −30 °C to yield **4** (Scheme 6). On the other hand, the Birch reduction of **33** at −78 °C selectively afforded **5** in 90% yield. Then, using compound **5**, the synthesis of (−)-koumine (**34**) was achieved in four steps according to a previously reported method[8] that featured the C/D ring opening of **5** to give **35** and the intramolecular coupling reaction between C-7 and C-20 positions in **37** using palladium catalysis.

In conclusion, we have succeeded in the asymmetric total synthesis of sarpagine-related indole alkaloids, including the first total synthesis of (−)-hydroxygardnerine (**2**), (+)-hydroxygardnutine (**3**), and (−)-koumine (**34**) with natural absolute configuration. The divergent synthesis of sarpagine-type compounds features the gold(I)-catalyzed 6-*exo*-*dig* cyclization to furnish a piperidine ring having an exocyclic (*E*)-ethylidene side chain, the construction of an indole nucleus having various substituents on the benzene ring, and the preservation/removal of the allylic hydroxyl group by temperature control in the Birch reduction. Further synthetic study of other sarpagine-related alkaloids is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00661.

Experimental procedures for the preparation of compounds **1**−**5**, **8**, **10**−**12**, **14**, **15**, **17**−**28**, and **30**−**37** and ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: takayamah@faculty.chiba-u.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant Nos. 25293023 and 26293023.

■ REFERENCES

(1) Takanashi, N.; Suzuki, K.; Kitajima, M.; Takayama, H. *Tetrahedron Lett.* **2016**, *57*, 375−378.

(2) (a) Lounasma, M.; Hanhinen, P.; Westersund (Née Halonen), M. The Sarpagine Group of Indole Alkaloids. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, 1999; Vol. *52*, pp 103−195 and references cited therein. (b) Namjoshi,

DOI: 10.1021/acs.orglett.6b00661
Org. Lett. 2016, 18, 1912−1915

O. A.; Cook, J. M. Sarpagine and Related Alkaloids. In *The Alkaloids: Chemistry and Biology*; Knölker, H.-J., Ed.; Academic Press: San Diego, 2016; Vol. *76*, pp 63−169 and references cited therein.
(3) (a) Jin, G.-L.; Su, Y.-P.; Liu, M.; Xu, Y.; Yang, J.; Liao, K.-J.; Yu, C.-X. *J. Ethnopharmacol.* **2014**, *152*, 33−52. (b) Takayama, H.; Sakai, S. *Gelsemium* Alkaloids. In *The Alkaloids: Chemistry and Pharmacology*; Cordell, G. A., Ed.; Academic Press: San Diego, 1997; Vol. *49*, Chapter 1, and references cited therein. (c) Kitajima, M. *J. Nat. Med.* **2006**, *61*, 14−23.
(4) (a) Sakai, S.; Kubo, A.; Hamamoto, T.; Wakabayashi, M.; Takahashi, K.; Ohtani, Y.; Haginiwa, J. *Tetrahedron Lett.* **1969**, *10*, 1489−1492. (b) Sakai, S.; Kubo, A.; Haginiwa, J. *Tetrahedron Lett.* **1969**, *10*, 1485−1488.
(5) (a) Takayama, H.; Tominaga, T.; Kitajima, M.; Aimi, N.; Sakai, S. *J. Org. Chem.* **1994**, *59*, 4381−4385. (b) Takayama, H.; Masubuchi, K.; Kitajima, M.; Sakai, S. *Tetrahedron* **1989**, *45*, 1327−1336. (c) Takayama, H.; Kitajima, M.; Ogata, K.; Sakai, S. *J. Org. Chem.* **1992**, *57*, 4583−4584. (d) Takayama, H.; Kitajima, M.; Sakai, S. *Tetrahedron* **1994**, *50*, 11813−11820.
(6) Liu, C.-T.; Wang, Q.-W.; Wang, C.-H. *J. Am. Chem. Soc.* **1981**, *103*, 4634−4635.
(7) Aimi, N.; Yamaguchi, K.; Sakai, S.; Haginiwa, J.; Kubo, A. *Chem. Pharm. Bull.* **1978**, *26*, 3444−3449.
(8) (a) Takayama, H.; Kitajima, M.; Sakai, S. *Heterocycles* **1990**, *30*, 325−327. (b) Sakai, S.; Yamanaka, E.; Kitajima, M.; Yokota, M.; Aimi, N.; Wongseripipatana, S.; Ponglux, D. *Tetrahedron Lett.* **1986**, *27*, 4585−4588.
(9) (a) Fonseca, G. O.; Wang, Z.-J.; Namjoshi, O. A.; Deschamps, J. R.; Cook, J. M. *Tetrahedron Lett.* **2015**, *56*, 3052−3056. (b) Edwankar, R. V.; Edwankar, C. R.; Deschamps, J. R.; Cook, J. M. *J. Org. Chem.* **2014**, *79*, 10030−10048. (c) Rallapalli, S. K.; Namjoshi, O. A.; Tiruveedhula, V. V. N. P. B.; Deschamps, J. R.; Cook, J. M. *J. Org. Chem.* **2014**, *79*, 3776−3780. (d) Edwankar, C. R.; Edwankar, R. V.; Namjoshi, O. A.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2013**, *78*, 6471−6487. (e) Edwankar, C. R.; Edwankar, R. V.; Deschamps, J. R.; Cook, J. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11762−11765. (f) Edwankar, R. V.; Edwankar, C. R.; Deschamps, J.; Cook, J. M. *Org. Lett.* **2011**, *13*, 5216−5219. (g) Yin, W.; Kabir, M. S.; Wang, Z.; Rallapalli, S. K.; Ma, J.; Cook, J. M. *J. Org. Chem.* **2010**, *75*, 3339−3349.
(10) (a) The total synthesis of (+)-koumine was reported. Magnus, P.; Mugrage, B.; DeLuca, M. R.; Cain, G. A. *J. Am. Chem. Soc.* **1990**, *112*, 5220−5230. (b) Formal synthesis of (−)-koumine was reported. Bailey, P. K.; McLay, N. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 441−449. (c) Formal synthesis of (−)-koumine was reported. Bailey, P. K.; McLay, N. R. *Tetrahedron Lett.* **1991**, *32*, 3895−3898.
(11) Clivio, P.; Richard, B.; Deverre, J.-R.; Sevenet, T.; Zeches, M.; Le Men-Oliver, L. *Phytochemistry* **1991**, *30*, 3785−3792.
(12) (a) Michel, P.; Rassat, A. *J. Org. Chem.* **2000**, *65*, 2572−2573. (b) Gennet, D.; Michel, P.; Rassat, A. *Synthesis* **2000**, *2000*, 447−451. (c) Bieliūnas, V.; Račkauskaitė, D.; Orentas, E.; Stončius, S. *J. Org. Chem.* **2013**, *78*, 5339−5348.
(13) de Frémont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411−2418.
(14) Zhou, H.; Han, D.; Liao, X.; Cook, J. M. *Tetrahedron Lett.* **2005**, *46*, 4219−4224.
(15) Adams, G. L.; Carroll, P. J.; Smith, A. B., III *J. Am. Chem. Soc.* **2013**, *135*, 519−528.
(16) (a) Endreß, S.; Suda, S.; Takayama, H.; Aimi, N.; Sakai, S.; Stöckigt, J. *Planta Med.* **1992**, *58*, 410−412. (b) Yu, J.; Liao, X.; Cook, J. M. *Org. Lett.* **2002**, *4*, 4681−4684.
(17) Yu, J.; Wang, T.; Wearing, X. Z.; Ma, J.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 5852−5859.

DOI: 10.1021/acs.orglett.6b00661
Org. Lett. 2016, 18, 1912−1915