Organic LETTERS

Letter

pubs.acs.org/OrgLett

Copper-Catalyzed Radical Cyclization To Access 3-Hydroxypyrroloindoline: Biomimetic Synthesis of Protubonine A

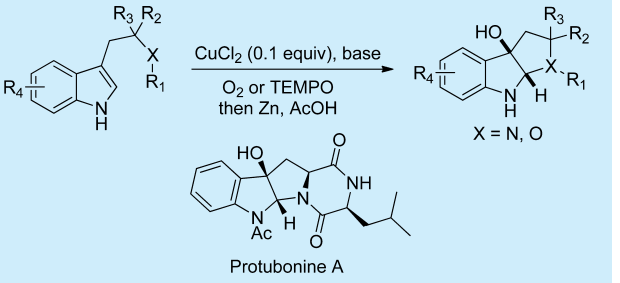
Xu Deng,[†,§] Kangjiang Liang,[†,‡,§] Xiaogang Tong,[†,‡] Ming Ding,[†,‡] Dashan Li,[†,‡] and Chengfeng Xia*[,†]

[†]State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, Yunnan, China

[‡]University of Chinese Academy of Sciences, Beijing 100049, China

Supporting Information

ABSTRACT: An unprecedented copper-catalyzed intramolecular radical cyclization was developed for the synthesis of 3-hydroxypyrroloindoline skeletons in excellent yields. The 3-hydroxyl group was introduced by trapping the radical intermediate with molecular oxygen or TEMPO. This process represents a unique radical oxidation pathway for tryptamine/tryptophan derivatives and allows a rapid biomimetic synthesis of natural product protubonine A.



Since first described in the late 1930s, the 3-hydroxypyrroloindoline alkaloids, as a large family of natural products, have received substantial attention among the scientific community for their diverse molecular architecture and wide range of biological profiles. Gypsetin (Figure 1), isolated from

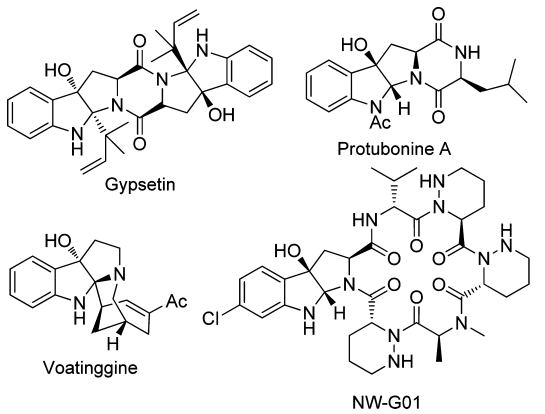


Figure 1. Representative 3-hydroxypyrroloindoline natural products.

fungal source *Nannizzia gypsea* var. incurvata IFO9228,[1] has evoked interest as the competitive inhibitor of acyl-CoA:cholesterol acyltransferase (ACAT) with a K_i value of 5.5 μM.[2] NW-G01 exhibited strong antibacterial activity against Gram-positive bacteria *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*, and methicillin-resistant *S. aureus*. Their MIC values were 3.90, 3.90, 7.81, and 7.81 μg/mL, respectively.[3] Recently, voatinggine, which is characterized by an unprecedented pentacyclic indole skeleton, was isolated from a Malayan *Tabernaemontana* species.[4] Moreover, unnatural 3-hydroxypyrroloindoline derivatives are important building blocks for the development of new drugs,[5] biological probes,[6] and chiral catalysts.[7]

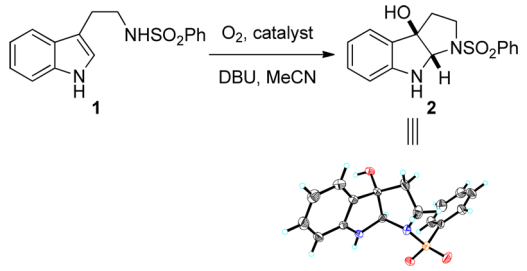
As an important precursor for these natural alkaloids, the development of C-3-functionalization/cyclization reaction of tryptamine or tryptophan derivatives has attracted extensive interest from synthetic chemists. Some remarkable efforts have been directed to the synthesis of 3-hydroxypyrroloindoline, including Nishiyama's and our group's previously reported iodine(III)-mediated intramolecular annulation,[8] selenocyclization/oxidative deselenation sequence,[9] Danishefsky's DMDO oxidation,[10] and photosensitized oxygenation.[11] All of these methods included a three-member onium salt as a key intermediate followed by intramolecular amide nucleophilic ring-opening reaction. However, most of these strategies are carried out in multistep procedures, with extensive use of protecting groups or with poor yield and unwanted side reactions. At the same time, enzymatic oxidation of indole is well-recognized as a key step in indole alkaloid biosynthesis,[12] rendering oxidative synthetic approaches inherently biomimetic.[2b,13] As part of our ongoing interest in developing new strategies for the synthesis of pyrroloindoline alkaloids, we herein report the first radical-mediated annulation/hydroxylation to access 3-hydoxypyrroloindoline.

Our initial investigation commenced with the copper-catalyzed aerobic reaction of readily available benzenesulfonyl-protected tryptamine **1**. By treating tryptamine **1** with a catalytic amount of cupric chloride in the presence of 3 equiv of DBU under 1 atm of oxygen in CH_3CN, the 3-hydroxypyrroloindoline **2** was delivered in moderate yield (Table 1, entry 1). Cupric bromide and cupric acetate also could catalyze this annulation/hydroxylation, albeit in lower yield. The relative

Received: May 6, 2014

   dx.doi.org/10.1021/ol501287x | *Org. Lett.* XXXX, XXX, XXX–XXX

Table 1. Screening of Conditions for the Metal-Catalyzed Aerobic Radical Cyclization/Hydroxylation of Tryptamine Derivatives



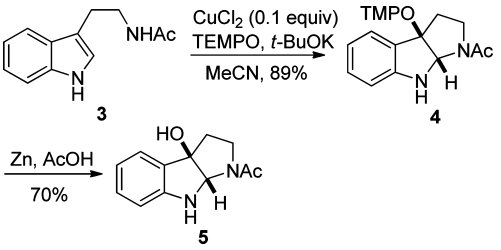
entry	catalyst	equiv	convn (%)	yield[a] (%)
1	$CuCl_2$	0.1	100	68
2	$CuBr_2$	0.1	100	40
3	$Cu(OAc)_2$	0.1	90[b]	26
4	$FeCl_3$	0.1	0	0
5	$K_3Fe(CN)_6$	0.1	0	0
6	$NiBr_2$	0.1	62[b]	50
7	$Mn(OAc)_2$	0.1	100[b]	82
8	$CoCl_2$	0.1	100	91
9	$Co(ClO_4)_2{\cdot}6H_2O$	0.1	85[b]	72
10	$Co(BF_4)_2{\cdot}6H_2O$	0.1	73[b]	61
11	$CoC_2O_4{\cdot}2H_2O$	0.1	80[b]	74

[a]Isolated yields by chromatography. [b]Incomplete conversion of starting materials.

stereochemistry of 3-hydroxypyrroloindoline **2** was confirmed by X-ray crystallography, indicating that the newly generated pyrrolo ring fuses with the indoline moiety in a *cis* manner. To improve the reaction yield, we then surveyed a series of one-electron oxidants as the catalyst with oxygen as the co-oxidant and DBU as the base. As indicated in Table 1, iron catalysts, such as ferric chloride and potassium hexacyanoferrate, failed to give any desired product, whereas manganese acetate catalyzed the annulation/hydroxylation in much better yield, and nickel bromide also promoted the reaction with only partial conversion. To our delight, we observed an excellent yield of annulation/hydroxylation product when cobalt chloride was utilized as a catalyst (Table 1, entry 8). Comparison of a series of cobalt salt, such as cobalt perchlorate and cobalt oxalate, revealed that cobalt chloride exerts significant effects on the conversion and the yield (Table 1, entries 9–11).

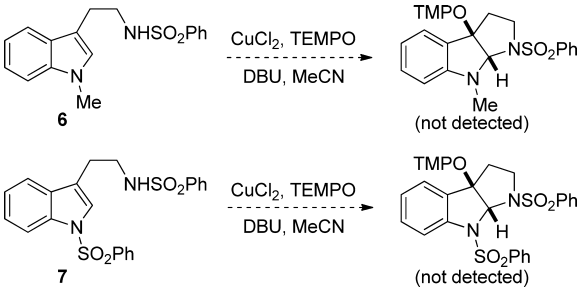
Encouraged by the cobalt chloride catalyzed annulation/hydroxylation, we extended the scope of the reaction to other substrates by changing the protecting groups of tryptamine. It is surprising that when acetyl tryptamine **3** was served as a reactant, very few products were detected after 48 h. Screening the solvents (THF, DMSO, and 1,4-dioxane) or varying the base (Et_3N, DABCO, NaH, and *t*-BuOK) did not make any improvements. Although other catalysts, such as cupric chloride, could catalyze acetyl tryptamine **3** to afford the desired 3-hydroxypyrroloindoline product **5**, only around 30% yield was achieved. We proposed that the lifetime of the radical intermediate was very short and the low concentration of oxygen in the solvent could not efficiently trap the radical intermediate. To circumvent this problem, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was used as the radical trapping reagent and the oxidant to recycle the catalyst.[14] However, few products were observed when cobalt chloride was used as catalyst and TEMPO as oxidant. To our delight, when the catalyst was switched to cupric chloride in the presence of TEMPO, the reaction went smoothly, giving the desired product **4** in excellent yield (Scheme 1). The tetramethylpiperidine (TMP) part was easily removed by reduction with zinc in acetic acid to afford the 3-hydroxypyrroloindoline **5**.

Scheme 1. Optimized Cyclization Conditions with TEMPO as a Radical Scavenger



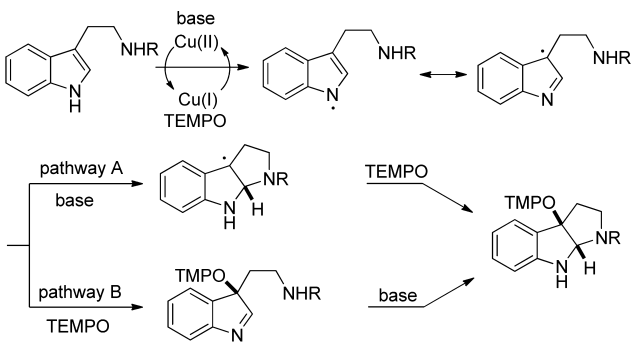
Given the reaction intermediate could be trapped by both molecular oxygen and TEMPO, a radical mechanism was proposed. To confirm whether the radical annulation originates from N1 of the indole moiety or Nb of the amide group, two analogues were prepared by masking the nitrogen of the indole moiety with a methyl or sulfonyl group (Scheme 2). When these two substrates were subjected to cupric chloride and TEMPO conditions, no reaction occurred, indicating that the radical originates on the N1 of the indole moiety.

Scheme 2. Masking N1 of the Indole Moiety with Methyl or Sulfonyl Group Inhibited the Cyclization



On the basis of the above results, a plausible mechanism was outlined as in Scheme 3. Cupric salt oxidizes the indole N1 to generate the radical in the presence of base, which transfers to C3 by forming an imine. Subsequently, the imine may be involved in two potential pathways. In pathway A, the imine undergoes a 5-*exo*-*trig* cyclization process first and the C3

Scheme 3. Proposed Copper-Catalyzed Radical Cyclization Mechanism

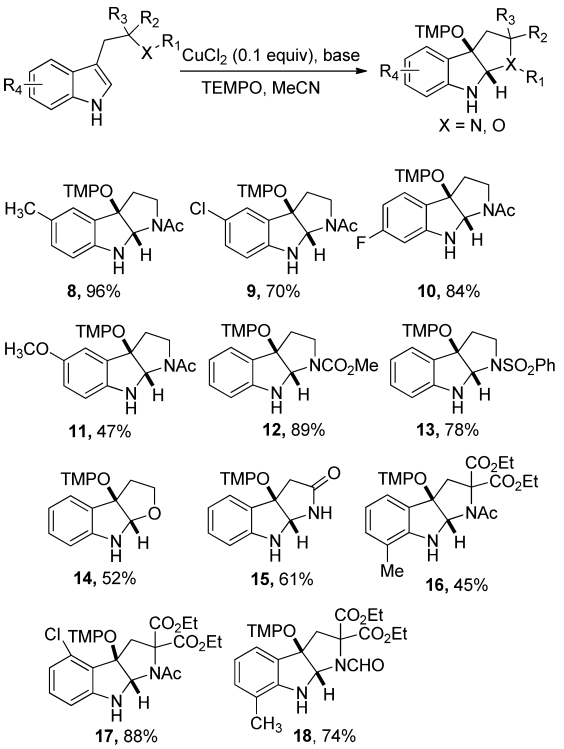


dx.doi.org/10.1021/ol501287x | Org. Lett. XXXX, XXX, XXX–XXX

radical is quenched by TEMPO to give the annulation product. Alternatively, the imine radical may be trapped by TEMPO first and the cyclization occurs afterward as shown in pathway B. We speculate that pathway A is favored for sulfonamide **1**, while pathway B is favored for acetyl protected tryptamine **3**, as the former is more nucleophilic than the latter.

We then examined a number of different tryptamine derivatives for the oxidative annulation reaction under the optimized reaction conditions (Scheme 4). It was found that

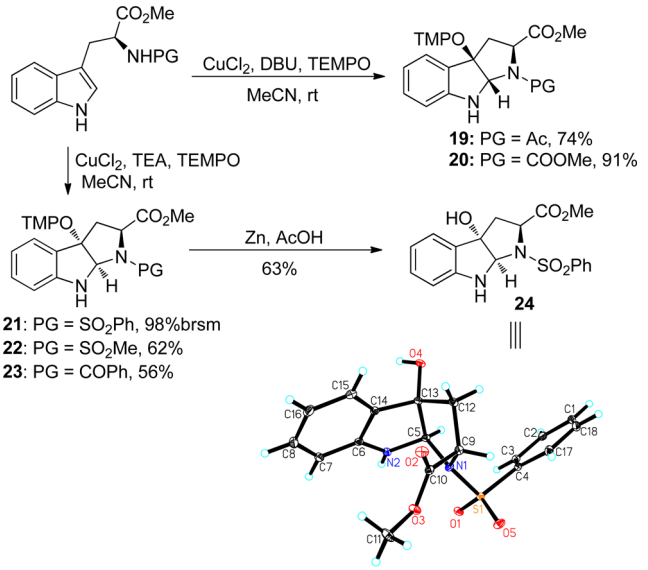
Scheme 4. Scope of Copper-Catalyzed Oxidative Cyclization



the aryl substitution pattern exerted a significant effect on the yield. Electron-withdrawing substituents could be tolerated, providing the 3-hydroxypyrroloindoline in good to excellent yield (**8**–**10**). Electron-donating substituents (**11**) gave us moderate yield. This may be due to the low electrophilicity of the imine intermediate. Variation at the amide part could be tolerated (**12**, **13**, and **15**). In addition to the amide and sulfonamide nucleophiles, it is also noteworthy that alcohol could also serve as the nucleophile for cyclization by using DBU instead of *t*-BuOK as a base (**14**), which further validated the proposal that the radical originates from N1 of the indole moiety. Moreover, tryptophan derivatives were also suitable substrates, providing 3-functionized products in moderate to good yield (**16**–**18**). Thus, a wide range of substrates are tolerated in this copper-catalyzed oxidative annulation reaction.

In an effort to investigate the diastereoselectivity of the annulation/hydroxylation reaction, a series of trptophan derivatives with different protecting groups were subjected to the standard reaction condition. All of these substrates underwent highly diastereoselective cyclization. Interestingly, when Nb was protected by an acetyl group or methyl formate group, the reaction provided *syn-cis* products **19** and **20**, whose stereochemistry were assigned by diagnostic chemical shift of the ester methyl group because of the absence of shielding by the aromatic ring current (Scheme 5).[15] In this setting, we

Scheme 5. Controlling the Cyclization Stereochemistry by Changing the Nb-Protecting Groups



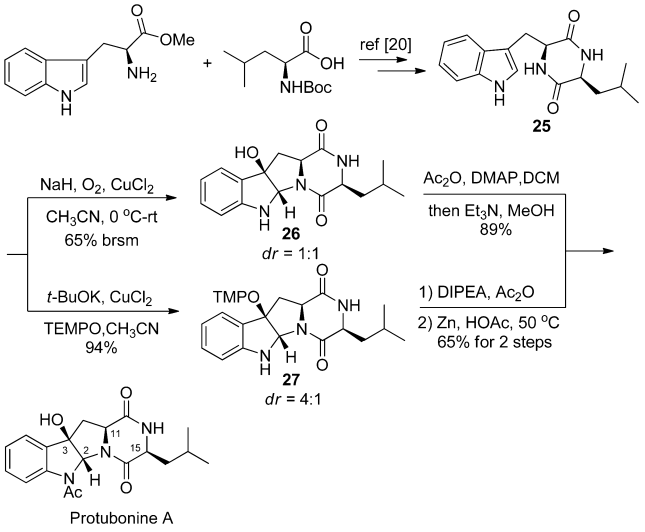
proposed that the reactions involve in pathway A as depicted in Scheme 3, during which the steric hindrance and the stability of the radical intermediate are the dominate controlling factors for the *exo* selectivity.[15] However, when Nb was protected by a benzenesulfonyl, methylsulfonyl, or benzoyl group, the reaction furnished the *anti-cis* products **20**, **22** and **23**, whose absolute stereochemistry was unambiguously assigned by NMR with the upfield shift of the ester methyl group[15] and also by the X-ray crystallography of the reductive derivative **24**. We reasoned that the lower pK_a value and higher nucleophilicity of these amide are the main driving forces behind the *endo* selectivity.[15,16] Unlike most of the previously reported methods that provide only the *anti-cis* products,[15,17] both *anti-cis* and *syn-cis* products could be simply assembled by changing the Nb protecting groups.

To highlight the utility and efficiency of this direct 3-hydroxylation method for the synthesis of pyrroloindoline natural products, we sought to complete the total synthesis of protubonine A. Protubonine A was isolated from the cultured marine-derived fungus *Aspergillus* sp. SF-5044.[18] Its C-11 absolute configuration was originally assigned as (*R*) configuration. Very recently, de Lera revised this configuration by total synthesis of two C-11 epimers. They found that the synthetic (11*S*) epimer's spectroscopic data were in full agreement with those reported for the natural product.[19]

Tryptophan-derived diketopiperazines **25** was prepared on a gram-scale from L-tryptophan methyl ester hydrochloride and *N*-(*tert*-butoxycarbonyl)-L-leucine according to literature methods (Scheme 6).[20] When diketopiperazines **25** was subjected to the copper-catalyzed annulation under aerobic conditions, product **26** was obtained in excellent regioselectivity with the five-membered pyrroloindoline but not the six-membered pyridoindole structure. However, no diastereoselectivity of this annulation was observed. When TEMPO was employed as the radical scavenger instead, the desired product **27** was generated in excellent yield and with acceptable diastereoselectivity (dr value 4:1). These two epimers could be easily separated by chromatography. Clearly, the steric hindrance of the radical trapping reagents was important for the observed diastereoselectivity. After acetylation of the N1 position and

dx.doi.org/10.1021/ol501287x | *Org. Lett.* XXXX, XXX, XXX–XXX

Scheme 6. Total Synthesis of Protubonine A with Copper-Catalyzed Cyclization



reductive removal of the TMP, protubonine A was obtained in good yield. The spectroscopic data of the synthetic one was in full agreement with those reported for the natural product.[18,19]

In summary, we have developed a novel and efficient synthetic method for the synthesis of 3-hydroxy pyrroloindoline through a copper-catalyzed radical annulation process from readily available tryptamine derivatives. Importantly, the reported conditions were suitable for a wide range of tryptamine/tryptophan derivatives and will be applicable for the preparation of 3-hydroxypyrroloindoline natural products and drugs. Both the *syn-cis* and *anti-cis* 3-hydroxypyrroloindoline skeletons exist in nature. The previously reported methods could not furnish both of these two skeletons. This method can furnish both of the isomers simply by changing the Nb protecting groups. The efficiency and utility of the method was further demonstrated by the total synthesis of indole alkaloid protubonine A.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xiachengfeng@mail.kib.ac.cn.

Author Contributions

§These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the National Natural Science Foundation of China (21272242 and 21302193), Yunnan High-End Technology Professionals Introduction Program (2010CI117), and National Basic Research Program of China (2011CB915500).

■ REFERENCES

(1) Shinohara, C.; Hasumi, K.; Takei, Y.; Endo, A. *J. Antibiot.* **1994**, *47*, 163−167.

(2) (a) Schkeryantz, J. M.; Woo, J. C. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 7025−7026. (b) Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964−11975. (c) Shibata, N.; Tarui, T.; Doi, Y.; Kirk, K. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 4461−4463.

(3) (a) Guo, Z.; Shen, L.; Ji, Z.; Zhang, J.; Huang, L.; Wu, W. *J. Antibiot.* **2009**, *62*, 201−205. (b) Guo, Z.; Ji, Z.; Zhang, J.; Deng, J.; Shen, L.; Liu, W.; Wu, W. *J. Antibiot.* **2010**, *63*, 231−235.

(4) Nge, C.-E.; Gan, C.-Y.; Low, Y.-Y.; Thomas, N. F.; Kam, T.-S. *Org. Lett.* **2013**, *15*, 4774−4777.

(5) Daugan, A.; Grondin, P.; Ruault, C.; Le Monnier de Gouville, A.-C.; Coste, H.; Linget, J. M.; Kirilovsky, J.; Hyafil, F.; Labaudinière, R. *J. Med. Chem.* **2003**, *46*, 4533−4542.

(6) (a) Lepthien, S.; Hoesl, M. G.; Merkel, L.; Budisa, N. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 16095−16100. (b) Zhong, W.; Gallivan, J. P.; Zhang, Y.; Li, L.; Lester, H. A.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 12088−12093.

(7) Ishihara, K.; Fushimi, M.; Akakura, M. *Acc. Chem. Res.* **2007**, *40*, 1049−1055.

(8) (a) Tu, D.; Ma, L.; Tong, X.; Deng, X.; Xia, C. *Org. Lett.* **2012**, *14*, 4830−4833. (b) Kajiyama, D.; Saitoh, T.; Yamaguchi, S.; Nishiyama, S. *Synthesis* **2012**, *44*, 1667−1671.

(9) (a) Ley, S. V.; Cleator, E.; Hewitt, P. R. *Org. Biomol. Chem.* **2003**, *1*, 3492−3494. (b) Crich, D.; Huang, X. *J. Org. Chem.* **1999**, *64*, 7218−7223. (c) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953−11963.

(10) Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964−11975.

(11) (a) Anthoni, U.; Christophersen, C.; Nielsen, P. H.; Christoffersen, M. W.; Sorensen, D. *Acta Chem. Scand.* **1998**, *52*, 958−960. (b) Sakai, A.; Tani, H.; Aoyama, T.; Shioiri, T. *Synlett* **1998**, 257−258. (c) Fukui, Y.; Somei, M. *Heterocycles* **2001**, *55*, 2055−2057.

(12) Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. In *Biosynthesis: aromatic Polyketides, Isoprenoids, Alkaloids*; Topics in Current Chemistry; Leeper, F. J., Vederas, J. C., Eds.; Springer: Berlin, 2000.

(13) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2002**, *36*, 127−139.

(14) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638−17639.

(15) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151−161.

(16) Crich, D.; Chan, C. O.; Davies, J. W.; Natarjan, S.; Vinter, J. G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2233−2240.

(17) (a) Depew, K. W.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Daneshefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953−11963. (b) Crich, D.; Huang, X. *J. Org. Chem.* **1999**, *64*, 7218−7223. (c) Kamenecka, T. M.; Danishefsky, S. J. *Chem.−Eur. J.* **2001**, *7*, 41−63.

(18) Lee, S. U.; Asami, Y.; Lee, D.; Jang, J.-H.; Ahn, J. S.; Oh, H. *J. Nat. Prod.* **2011**, *74*, 1284−1287.

(19) Lorenzo, P.; Alvarez, R.; de Lera, A. R. *Eur. J. Org. Chem.* **2014**, *12*, 2557−2564.

(20) Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 5557−5560.

dx.doi.org/10.1021/ol501287x | *Org. Lett.* XXXX, XXX, XXX−XXX