Organic LETTERS

Letter

pubs.acs.org/OrgLett

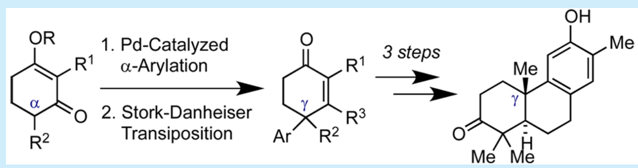
Palladium-Catalyzed α-Arylation of Cyclic Vinylogous Esters for the Synthesis of γ-Arylcyclohexenones and Total Synthesis of Aromatic Podocarpane Diterpenoids

Wen-Yi Hou and Yen-Ku Wu*

Department of Applied Chemistry, National Chiao Tung University, 1001 University Road, Hsinchu 30010, Taiwan

Supporting Information

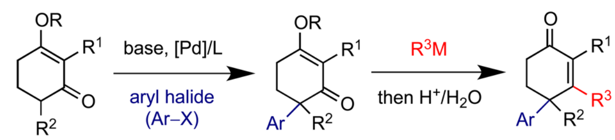
ABSTRACT: Described is a method for the formal γ-arylation of cyclohexenones allowing synthesis of a remote all-carbon quaternary center. The process involves the palladium-catalyzed α-arylation of a α-substituted cyclic vinylogous ester followed by the Stork–Danheiser transposition. The synthetic utility of this protocol is featured in the total syntheses of (±)-12-hydroxy-13-methylpodocarpa-8,11,13-trien-3-one, (±)-3β,12-dihydroxy-13-methylpodocarpane-8,11,13-triene, and (±)-O-methyl nimbinone.



An all-carbon quaternary stereocenter bearing an aryl unit is a prevailing structural motif in natural products and molecules of pharmaceutical significance.[1] A useful tactic for rapid access to this substitution pattern is the direct α-arylation of α-tertiary carbonyl compounds empowered by transition metal catalysis.[2] While the use of catalytic α-arylation of carbonyl derivatives to form a quaternary carbon center constitutes an extensively investigated field, analogous means for installing an aromatic grouping at the γ-position of γ-branched enone precursors have not yet reached the same level of refinement.[3] In particular, the construction of a γ-quaternary aryl stereocenter through distal arylation of cyclic dienolate species still represents a formidable challenge. Difficulties in developing the γ-arylation protocol are posed by a few factors including the liability of self-condensation through Michael addition and issues of controlling regioselectivity. Despite these obstacles, Hyde and Buchwald have demonstrated a few examples of palladium-catalyzed direct γ-arylation of unconjugated cyclohexenones to generate a remote all-carbon quaternary center.[4] Nevertheless, a general approach for the synthesis of γ-aryl-γ-alkyl cycloalkenones from readily accessible starting materials remains eminently desirable.[5]

In our quest for a united route to aromatic cyclic terpenoids, we sought to develop a sequence for the formal γ-arylation of 2-cyclohexenones that involves palladium-catalyzed α-arylation of α-substituted cyclic vinylogous esters in tandem with the Stork–Danheiser transposition[6,7] (Scheme 1). Central to our design plan is the exploitation of the regioselective enolate formation of 3-alkoxy-2-cyclohexenones[7] followed by parlaying it into the catalytic arylation step. It is noteworthy that Zhang and co-workers have reported a α-arylative, tertiary center-forming reaction of 3-ethoxy-2-cyclohexenone under catalysis of $Pd(OAc)_2$ and BINAP; however, yields of the coupling reaction fluctuated dramatically according to the electronic properties of the aryl donors.[8] At the outset of this project, intermolecular arylative substitution of α-methine hydrogen of

Scheme 1. Catalytic α-Arylation Approach for the Synthesis of γ-Arylcyclohexenones



generic structure **1** (R^2 = alkyl) had not been delineated for producing the strategic benzylic quaternary carbon.[9] Until very recently, such transformation was realized by Lautens and co-workers,[10] and it prompted us to disclose our effort in this field. Herein, we present our studies in the Pd-catalyzed cross-coupling reaction of **1** with various bromoarenes and synthetic studies toward podocarpane-type diterpenoids.

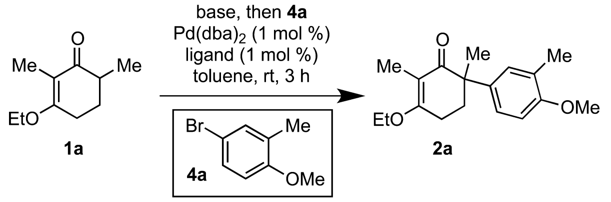
Our investigations commenced employing dimethyl-substituted cyclic vinylogous ester **1a**[11] and bromoarene **4a** as coupling partners, wherein the use of **1a** is pivotal to our research endeavor toward the diterpenoid synthesis (vide infra). Of numerous reaction parameters examined,[12] the conditions similar to those proven efficacious for the α-arylation of α-branched esters by Hartwig and co-workers afforded the cleanest reaction profile.[13] In our case, the optimal catalyst scheme called for the combination of $Pd(dba)_2$ (1 mol %) and $P(t\text{-}Bu)_3$ (1 mol %) with lithium dicyclohexylamide functioning as a base (Table 1, entry 4). On the other hand, the reactions employing either LDA or LiTMP gave a significant amount of intractable materials (entries 2 and 3). We showed that the arylation of **1a** by treating the air stable HBF_4 salt of $P(t\text{-}Bu)_3$[14] worked reasonably well to produce **2a** (entry 5).

The optimized conditions described above were utilized to carry out the α-arylation of **1a** with a range of aromatic

Received: January 25, 2017
Published: February 23, 2017

DOI: 10.1021/acs.orglett.7b00268
Org. Lett. 2017, 19, 1220–1223

Table 1. Effects of Base and Ligand on the α-Arylation of 1a[a]



entry	base	ligand	yield (%)[b]
1	LiHMDS	$P(t\text{-}Bu)_3$	75
2	LDA	$P(t\text{-}Bu)_3$	37
3	LiTMP	$P(t\text{-}Bu)_3$	58
4	$LiNCy_2$	$P(t\text{-}Bu)_3$	85
5	$LiNCy_2$	$P(t\text{-}Bu)_3\cdot HBF_4$	68

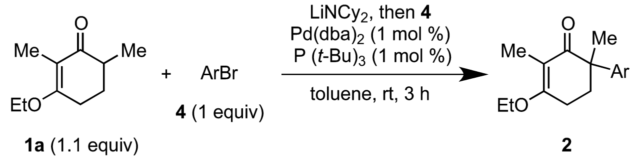
[a]Reactions were conducted with 1 equiv of **4a** (2.0 mmol) and 1.1 equiv of **1a**. For detailed procedures, see the Supporting Information. [b]Yield of isolated product based on **4a**. dba = *trans,trans*-dibenzylideneacetone. LiHMDS: lithium hexamethyldisilazide. LDA: lithium diisopropylamide. LiTMP: lithium 2,2,6,6-tetramethylpiperidide. $LiNCy_2$: lithium dicyclohexylamide.

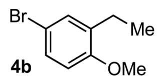
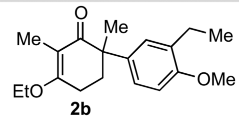
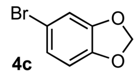
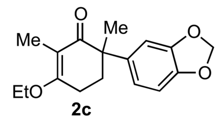
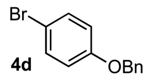
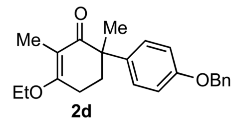
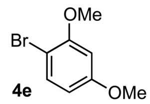
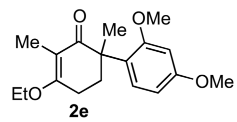
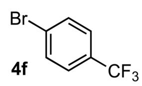
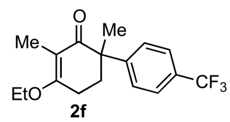
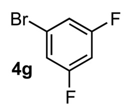
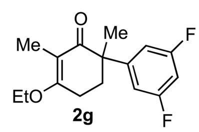
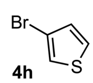
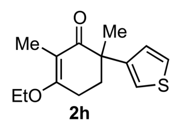
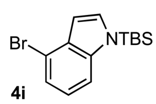
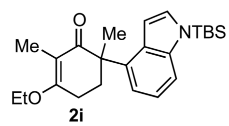
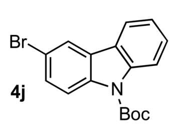
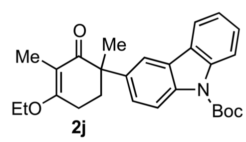
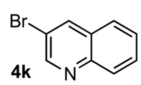
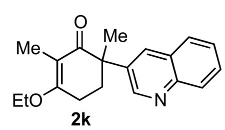
substrates **4b–k** (Table 2). The reactions of electron-rich aryl bromides produced desired aryl carbonyl products in good yields (entries 1–4). Notably, the arylation is compatible with a sterically demanding *ortho*-substituted substrate (**4e**), albeit at a slower rate. Even electron-deficient bromoarenes **4f** and **4g** were effectively cross-coupled with **1a** (entries 5 and 6). The scope of substituted bromobenzene appears broad in terms of electronic and steric considerations, so we next examined the compatibility of heterocyclic bromides in this transformation. The reaction of thiophene **4h** proceeded smoothly to install a 3-thienyl substituent at the α carbon of **1a** (entry 7). This method can accommodate *N*-silyl-indole **4i** and *N*-Boc-carbazole **4j** to deliver the corresponding α-heteroarylated compounds, but the reactions were relatively sluggish and required either a longer reaction time (entry 8) or a higher catalyst loading (entry 9). Although we found **4k** failed to react with **1a** under the standard conditions,[15] a modest yield of the coupling product **2k** could be obtained in the presence of $Pd(OAc)_2$ (entry 10). In this particular example, we observed a noticeable competing pathway to give 2,6-dimethyl-3-ethoxyphenol through oxidative aromatization of **1a**.

In their comprehensive study,[10] Lautens and colleagues showed that the coupling of **1b** with 4-bromoveratrole (**4l**) catalyzed by commercially available palladacycle (Pd-P(*t*-Bu)$_3$-G2) was accompanied by alkene isomerization, thus generating compound **5** in moderate yield (Scheme 2a). With our catalytic system, the reaction of **1b** and **4l** furnished **2l** as the sole product, and a quaternary allyl aryl stereocenter was conveniently synthesized (Scheme 2b). From a synthetic standpoint, these examples are complementary tools for assembling highly functionalized building blocks.

To further demonstrate the significance of our arylative methodology, we embarked on total syntheses of (±)-12-hydroxy-13-methylpodocarpa-8,11,13-trien-3-one (**9**),[16] (±)-3β,12-dihydroxy-13-methylpodocarpane-8,11,13-triene (**10**),[17] and (±)-*O*-methyl nimbinone (**11**).[18] Compounds **9** and **10** belong to a family of podocarpane diterpenoids that have been isolated from several terrestrial plant sources,[19] and compound **11** is known as a synthetic derivative of naturally occurring nimbinone.[20] These structurally unique bisnorditerpenoids possess a γ-quaternary-γ-aryl cyclohexanone scaffold,

Table 2. Catalytic Cross-Coupling of 1a with Different Aromatic Bromides[a]



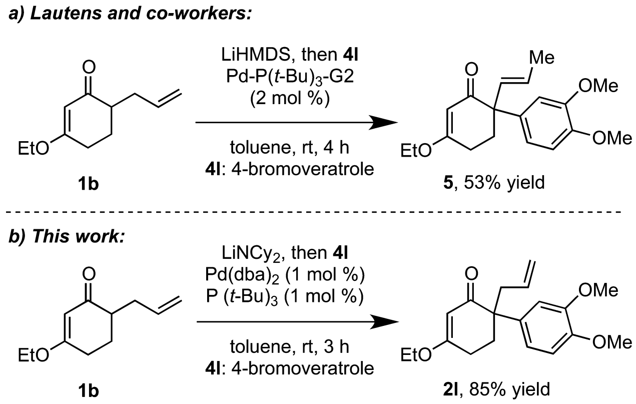
entry	ArBr	product	yield (%)[b]
1	 **4b**	 **2b**	74
2	 **4c**	 **2c**	76
3	 **4d**	 **2d**	84
4[c]	 **4e**	 **2e**	68
5	 **4f**	 **2f**	79
6	 **4g**	 **2g**	80
7	 **4h**	 **2h**	77
8[d]	 **4i**	 **2i**	58
9[e]	 **4j**	 **2j**	55
10[f]	 **4k**	 **2k**	20

[a]Scope was evaluated using 2.0 mmol of bromoarenes. [b]Yield of isolated product based on **4**. [c]Reaction time = 18 h. [d]Reaction time = 4.5 h. [e]With 7.5 mol % $Pd(dba)_2$ and 8 mol % $P(t\text{-}Bu)_3\cdot HBF_4$. [f]With 5 mol % $Pd(OAc)_2$ and 10 mol % $P(t\text{-}Bu)_3$; Reaction time = 18 h.

and are therefore well suited for our methodology.[21] Compound **9** exhibited notable biological profiles including antifungal activity[22] and in vitro cytotoxic activity against selected human tumor cell lines with IC_{50} values ranging from

DOI: 10.1021/acs.orglett.7b00268
Org. Lett. 2017, 19, 1220–1223

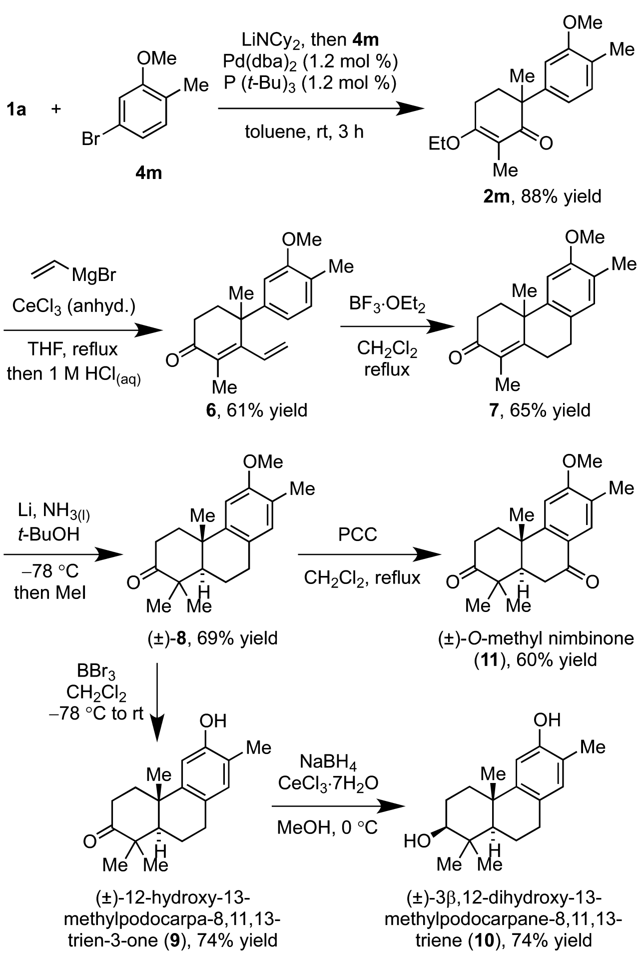
Scheme 2. Reaction Courses of an Allyl Substrate



3.0 to 6.3 μM.[23] Compound **10** displays anti-HCV activity[24] as well as inhibitory effects on lipopolysaccharide-induced NO production.[25] Despite promising biomedicinal potentials of these targets, there has been only one total synthesis of **9**, described by Zhang and co-workers,[26] and total synthesis of **10** is hitherto unknown.

Integrating our own protocol with a cyclialkylation-based strategy developed by Majetich and co-workers allowed us to streamline the synthesis of functionalized hydrophenanthrene skeletons (Scheme 3).[27] The coupling reaction of **1a** with **4m**[28]

Scheme 3. Total Synthesis of Aromatic Podocarpane Diterpenoids



took place uneventfully to give the desired arylated product **2m**. Conjugated dienone **6** was prepared via a Stork–Danheiser transposition comprising 1,2-addition of vinylmagnesium bromide followed by acidic hydrolysis. In this case, it was necessary to apply cerium(III) chloride to facilitate the organometallic addition to the sterically congested carbonyl carbon.[29] Intramolecular Friedel–Crafts reaction of **6** mediated by a Lewis acid led to the formation of tricyclic compound **7**. Reductive alkylation of **7** under dissolving-metal conditions gave **8** by establishment of the *trans*-decalin system and introduction of the gem-dimethyl moiety.[30] The facile removal of the *O*-methyl group with boron tribromide delivered **9** in 74% yield. Accordingly, the total synthesis of racemic 12-hydroxy-13-methylpodocarpa-8,11,13-trien-3-one (**9**) was achieved in five steps and 18% overall yield from known vinylogous ester **1a**.[11] When subjected to Luche conditions,[31] ketone **9** was reduced in excellent diastereoselectivity, thus accomplishing the first total synthesis of racemic 3β,12-dihydroxy-13-methylpodocarpane-8,11,13-triene (**10**). Additionally, we showed that ($\pm$)-*O*-methyl nimbinone (**11**) could be prepared through regioselective benzylic oxidation of a common intermediate **8**.[32]

In summary, we have developed a method for the Pd-catalyzed α-arylation of cyclic vinylogous esters. This process enables the synthesis of an all-carbon quaternary aryl stereocenter and is effective with a range of aryl or heteroaryl bromides. We have demonstrated the utility of the α-arylated products in a Stork–Danheiser transposition that provides ready access to densely substituted γ-arylcyclohexenones. The combined arylation/Stork–Danheiser transposition sequence is highlighted in a united route to aromatic podocarpane-type diterpenoids. Further applications of this protocol in natural product synthesis are underway and will be described in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00268.

Experimental procedures and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yenkuwu@nctu.edu.tw.

ORCID

Yen-Ku Wu: 0000-0002-9269-7444

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Ministry of Science and Technology, Taiwan (104-2113-M-009-022-MY2) for financial support of this work. We also thank the Center of Interdisciplinary Science at National Chiao Tung University for additional support. This work is dedicated to Prof. Hsing-Jang Liu on the occasion of his 75th birthday.

REFERENCES

(1) (a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2005. (b) Ling, T.; Rivas, F. *Tetrahedron* **2016**, *72*, 6729−6777. (c) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740−751. (d) Quasdorf, K. L.; Overman, L. E. *Nature* **2014**, *516*, 181−191.
(2) For reviews, see: (a) Sivanandan, S. T.; Shaji, A.; Ibnusaud, I.; Seechurn, C. C. C. J.; Colacot, T. J. *Eur. J. Org. Chem.* **2015**, *2015*, 38−49. (b) Novák, P.; Martin, R. *Curr. Org. Chem.* **2011**, *15*, 3233−3262. (c) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082−1146. (d) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234−245. (e) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211−241.
(3) For selected key advances, see: (a) Franzoni, I.; Guénée, L.; Mazet, C. *Chem. Sci.* **2013**, *4*, 2619−2624. (b) Huang, D. S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 5757−5761. (c) Hyde, A. M.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 2663−2666.
(4) Hyde, A. M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 177−180.
(5) Lightly substituted targets were conventionally prepared by Robinson-type annulation. For selected examples, see: (a) Martinez, L. P.; Umemiya, S.; Wengryniuk, S. E.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 7536−7539. (b) Yang, H.; Carter, R. G. *Org. Lett.* **2010**, *12*, 3108−3111. (c) Inokoishi, Y.; Sasakura, N.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Org. Lett.* **2010**, *12*, 1616−1619. (d) Otani, G.; Yamada, S.-I. *Chem. Pharm. Bull.* **1973**, *21*, 2112−2118. For a dearomatization approach, see: (e) Guérard, K. C.; Sabot, C.; Racicot, L.; Canesi, S. *J. Org. Chem.* **2009**, *74*, 2039−2045. For an alkene isomerization approach, see: (f) Kress, S.; Johnson, T.; Weisshar, F.; Lautens, M. *ACS Catal.* **2016**, *6*, 747−750.
(6) For recent applications of the Stork−Danheiser transposition, see: (a) Yu, G.; Clive, D. L. J. *J. Org. Chem.* **2016**, *81*, 8470−8484. (b) Das, M. K.; De, S.; Shubhashish; Bisai, A. *Synthesis* **2016**, *48*, 2093−2104. (c) Bennett, N. B.; Hong, A. Y.; Harned, A. M.; Stoltz, B. M. *Org. Biomol. Chem.* **2012**, *10*, 56−59.
(7) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775−1776.
(8) Zhao, Y.; Zhou, Y.; Liang, L.; Yang, X.; Du, F.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 555−558.
(9) Synthesis of a α-aryl quaternary center-containing vinylogoues ester was accomplished via a three-step sequence with tricarbonyl(4-methoxycyclohexadienyl)iron complex acting as the formal aryl donor; see: Pearson, A. J.; Richards, I. C.; Gardner, D. V. *J. Org. Chem.* **1984**, *49*, 3887−3891.
(10) Johnson, T.; Pultar, F.; Menke, F.; Lautens, M. *Org. Lett.* **2016**, *18*, 6488−6491.
(11) Compound **1a** can be prepared from 1,3-cyclohexanedione in three steps on multigram scale; see: Pirrung, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 82−87.
(12) Selected reaction conditions are summarized in Table 1. So far, we observed that only sterically demanding phosphines are effective in this transformation. Employing toluene, instead of ether-type solvents, enables the reaction to occur more cleanly at room temperature.
(13) Jørgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557−12565.
(14) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.
(15) This obscure reactivity is presumably due to the catalyst poisoning by the quinolone nitrogen.
(16) Itokawa, H.; Ichihara, Y.; Takeya, K.; Morita, H.; Motidome, M. *Phytochemistry* **1991**, *30*, 4071−4073.
(17) Ravindranath, N.; Ravinder Reddy, M.; Ramesh, C.; Ramu, R.; Prabhakar, A.; Jagadeesh, B.; Das, B. *Chem. Pharm. Bull.* **2004**, *52*, 608−611.
(18) Burnell, R. H.; Dumont, N.; Théberge, N.; Desfossés, S. *Synth. Commun.* **1992**, *22*, 2571−2578.
(19) Hanson, J. R. *Nat. Prod. Rep.* **2016**, *33*, 1227−1238 and references cited therein.
(20) (a) Ara, I.; Siddiqui, B. S.; Faizi, S.; Siddiqui, S. *Phytochemistry* **1988**, *27*, 1801−1804. (b) Burnell, R. H.; Dumont, N.; Théberge, N. *J. Nat. Prod.* **1993**, *56*, 1930−1936.
(21) Over the years, there have been numerous synthetic studies toward aromatic polycyclic terpenoids; see: (a) Ho, T.-L. *Carbocycle Construction in Terpene Synthesis*; Wiley-VCH: Weinheim, 1988. (b) Banerjee, A. K.; Laya, M. S.; Mora, H. R.; Cabrera, E. V. *Curr. Org. Chem.* **2008**, *12*, 1050−1070. (c) Dhambri, S.; Mohammad, S.; Van Buu, O. N.; Galvani, G.; Meyer, Y.; Lannou, M.-I.; Sorin, G.; Ardisson, J. *Nat. Prod. Rep.* **2015**, *32*, 841−864. (d) González, M. A. *Tetrahedron* **2015**, *71*, 1883−1908.
(22) Baraza, L. D.; Joseph, C. C.; Munissi, J. J. E.; Nkunya, M. H. H.; Arnold, N.; Porzel, A.; Wessjohann, L. *Phytochemistry* **2008**, *69*, 200−205.
(23) In a recent paper, cytotoxic activity of compound **9** was evaluated against human myeloid leukemia (HL-60), hepatocellular carcinoma (SMMC-7721), lung cancer (A-549), breast cancer (MCF-7), and colon cancer (SW480) cell lines; see: Cheng, L.; Ji, K.; Liao, S.-g.; Gan, L.-S.; Yang, L.; Cao, D.-h.; Liu, Y.-q.; Guo, J.; Zhang, P.; Lu, C.-l.; Hu, H.-b.; Xu, Y.-k. *Tetrahedron Lett.* **2016**, *57*, 2262−2265.
(24) Chao, C.-H.; Cheng, J.-C.; Shen, D.-Y.; Wu, T.-S. *J. Nat. Prod.* **2014**, *77*, 22−28.
(25) Xu, J.; Peng, M.; Sun, X.; Liu, X.; Tong, L.; Su, G.; Ohizumi, Y.; Lee, D.; Guo, Y. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4785−4789.
(26) Zhang, C. L.; Zhu, X. L.; Ma, Y. G.; Zou, L. W. *Chin. Chem. Lett.* **2006**, *17*, 163−164.
(27) Majetich, G.; Liu, S.; Fang, J.; Siesel, D.; Zhang, Y. *J. Org. Chem.* **1997**, *62*, 6928−6951.
(28) Du, Z.-T.; Zheng, S.; Chen, G.; Lv, D. *Molecules* **2011**, *16*, 8053−8061.
(29) Liu, H.-J; Shia, K.-S.; Shang, X.; Zhu, B.-Y. *Tetrahedron* **1999**, *55*, 3803−3830.
(30) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275−286.
(31) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.
(32) Parish, E. J.; Chitrakorn, S.; Wei, T.-Y. *Synth. Commun.* **1986**, *16*, 1371−1375.

DOI: 10.1021/acs.orglett.7b00268
Org. Lett. 2017, 19, 1220−1223