Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of Illudinine from Dimedone

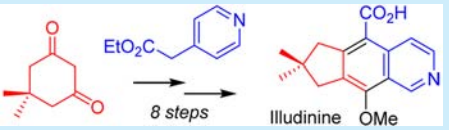
Alec E. Morrison,[†] Tung T. Hoang,[†] Mélodie Birepinte,[†] and Gregory B. Dudley*[,†,‡]

[†]Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306, United States

[‡]C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506, United States

Supporting Information

ABSTRACT: A total synthesis of the illudalane sesquiterpene illudinine was realized in eight steps and 14% overall yield from commercially available dimedone. The approach features tandem fragmentation/Knoevenagel-type condensation and microwave-assisted oxidative cycloisomerization to establish the isoquinoline core. Completion of the synthesis involves a recently reported cascade S_NAr/Lossen rearrangement on a densely functionalized aryl bromide and an optimized procedure for *O*-methylation of 8-hydroxyisoquinolines. The oxidative cycloisomerization proceeds by way of a novel inverse-demand intramolecular dehydro-Diels–Alder cycloaddition, which has a potentially broader appeal for preparing substituted isoquinolines.



The evolution of chemical synthesis can be tracked in terms of the ability to produce increasingly complex structures by increasingly efficient synthetic sequences.[1] Diverse molecular architectures inspire novel methods and strategies, and emerging methodologies enable new approaches to goal structures. We have been inspired by the illudalane family of 3,3-dimethylcyclopentane-fused aromatic sesquiterpenes, which present an attractive array of structural complexities and unresolved biological activities.

The illudalane sesquiterpenes share a carbon skeleton with illudalic acid and its alkaloid congener, illudinine (Figure 1).

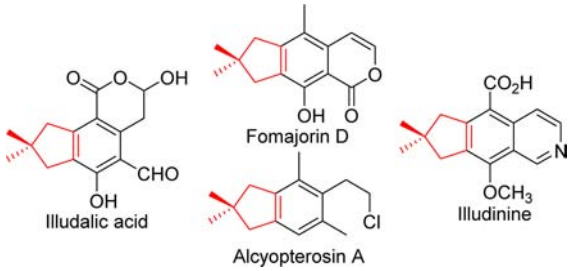


Figure 1. Illudalane sesquiterpenes.

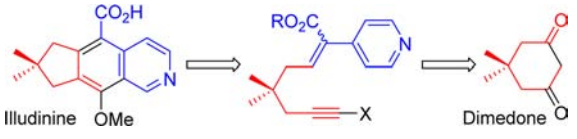
Illudinine is a metabolite of the jack o-lantern mushroom (*Clitocybe illudens*); it was isolated and characterized along with illudalic acid and illudacetalic acid in 1969.[2] The first total synthesis of these three natural products in 17–19 steps was described in a 1977 report by Woodward and Hoye,[3] who developed a unified approach based on aromatic substitution chemistry. Shen reported a 16-step synthesis of illudalic acid by a similar strategy in 2008 as a means of securing material for biological evaluation.[4] Meanwhile, Deiters developed an alkyne cyclotrimerization strategy that produced illudinine in 14 steps.[5] Various alcyopterosins, which have the same carbon skeleton, have also been prepared.[6]

These structures all feature a densely substituted benzene core fused to a 3,3-dimethylcyclopentane moiety. Substituted benzenes and 3,3-dimethylcyclopentanes each pose formidable synthetic challenges. The convergent synthesis of substituted benzene derivatives has attracted considerable attention,[7] and new methods continue to emerge.[8] On the other hand, direct synthesis of 3,3-dimethylcyclopentanes remains largely an unresolved problem, which typically has been circumvented by serial manipulation of tactically overoxidized intermediates.[9]

3,3-Dimethylcyclopentanes are ubiquitous in natural products, but they are virtually nonexistent in typical small-molecule libraries used for pharmacological screening. This is perhaps a consequence of limited synthetic accessibility. For example, after illudalic acid emerged from high-throughput screening as a promising and uniquely selective phosphatase inhibitor, most of the follow-up pharmacology focused on simplified analogues that lacked the 3,3-dimethylcyclopentane. These structural simplifications came at the cost of potency.[4,10] This is likewise true for alcyopterosin A pharmacology, which was largely examined with the 3,3-dimethyl substitution omitted for synthetic expediency at the cost of potency.[9e] Efficient access to 3,3-dimethylcyclopentanes is needed to explore this naturally validated but pharmaceutically underexplored chemical space.[11]

Our approach to illudinine hinged on two hypothetical key steps (Scheme 1). The first, tandem fragmentation/olefination (Scheme 2), required a logical but untested expansion of recent methodology from our laboratory.[12] We previously concluded that hydroxy triflate **1** can undergo anionic fragmentation to aldehyde **3**, which can be intercepted in situ by Horner–

Scheme 1. Synthetic Approach

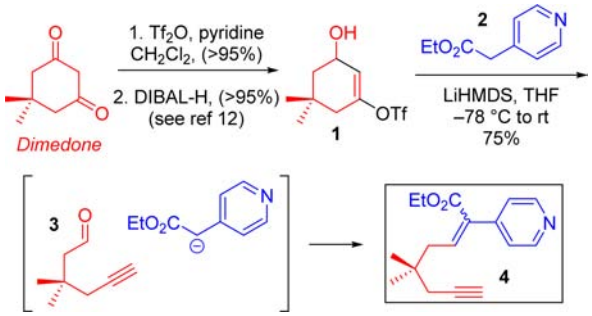


Received: December 29, 2016
Published: January 30, 2017

ACS Publications © 2017 American Chemical Society

DOI: 10.1021/acs.orglett.6b03887
Org. Lett. 2017, 19, 858–861

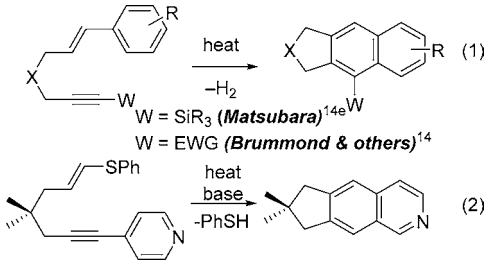
Scheme 2. Synthesis of Enyne 4 via Tandem Fragmentation/Knoevenagel-Type Condensation



Wadsworth–Emmons (HWE)-type phosphonate nucleophiles to give 1,6-enynes. Here, we report that phosphonate activation is not needed in the case of ethyl 4-pyridylacetate (**2**); reaction of **1** with **2** yields 1,6-enyne **4** in 75% yield as a mixture of alkene isomers (ca. 2:1). Considering the anion-stabilizing properties of the 4-pyridyl substituent, this new process is perhaps best classified as a tandem fragmentation/Knoevenagel-type condensation, and it suggests a broader potential of our prior methodology.

The second pivotal step in our synthetic approach to illudinine is a proposed oxidative cycloisomerization by way of an intramolecular inverse-demand dehydro-Diels–Alder reaction. Dehydro-Diels–Alder reactions[13] of tethered alkynylstyrenes[14] have received increasing attention recently (Scheme 3,

Scheme 3. Dehydro-Diels–Alder Reactions of Tethered Enynes

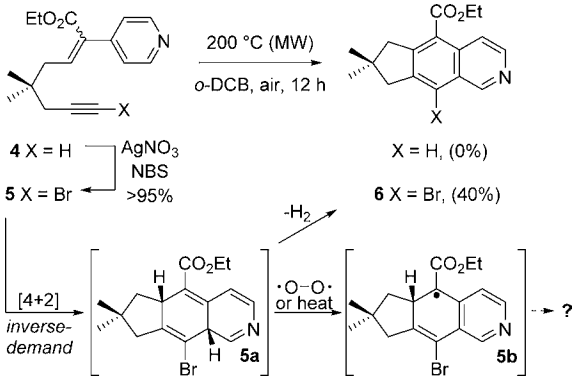


eq 1). Inverse-demand Diels–Alder reactions involving (unstrained) alkynes are rare, even in tethered systems,[15] and we could find no examples involving styrene-type dienes (vinylarenes). However, styrene-type dienes have not been as thoroughly examined as other diene classes. Because of their aromatic character, one must extrapolate with caution from other diene classes to vinylarenes. Our recent isoquinoline synthesis[16] established an alternative inverse-demand dehydro-Diels–Alder pathway (Scheme 3, eq 2), but it does not provide all of the requisite functionality for illudinine.

One of the major challenges posed by electron-deficient dienes is their tendency to dimerize,[17] oligomerize, or otherwise decompose[18] faster than they react with unstrained alkyne dienophiles. The dimerization pathway[19] is suppressed in vinylarenes, and it is not unreasonable to anticipate a differential impact of aromaticity on other competing reaction pathways. Therefore, despite a lack of encouraging precedent, we proceeded with focused investigations into the pivotal dehydro-Diels–Alder reaction (Scheme 4).

Our investigations into the proposed dehydro-Diels–Alder reaction began with 4-pyridylenyne **4**. Enyne **4** was heated at

Scheme 4. Microwave-Assisted Oxidative Cycloisomerizations



increasing temperatures in various solvents without success. In general, the starting enyne either decomposed or was recovered unchanged. A brief screening of metal catalysts was likewise unproductive. No reaction products consistent with dehydro-Diels–Alder reaction were ever identified in our (nonexhaustive) survey of conditions, although we cannot rule out the feasibility of this pathway.

Meanwhile, we were mindful that terminal functionality on the alkyne would not be inconsistent with our end goals, so we also investigated bromoalkyne **5** as well as silyl- and iodoalkynes (X = Me_3Si or I, not shown). Bromination of terminal alkyne **4** under standard conditions provided **5** in essentially quantitative yield. Bromoalkynes can be competent dienophiles,[20] and computational data suggest that alkyne π bonds are weaker in bromoalkynes than in terminal alkynes.[21] Indeed, productive thermal reactivity was observed by heating a 0.06 M solution of **5** in *o*-dichlorobenzene (*o*-DCB) at 200 °C in the microwave[22] (300 W) in a sealed vial under air for 12 h to produce a 40% isolated yield of isoquinoline **6**. The aforementioned silyl- and iodoalkynes were not viable substrates. Presumably, thermal inverse-demand dehydro-Diels–Alder cycloaddition of **5** yields intermediate **5a** (Scheme 4), which oxidizes to **6** under the reaction conditions. Oxidation may occur by concerted extrusion of hydrogen[14b] or possibly by serial hydrogen atom abstraction via stabilized radical intermediate **5b**.[23] In the end, the operationally simple thermal cyclization of **5** provides convenient access to isoquinoline **6** en route to illudinine.

With bromoisoquinoline **6** in hand, the final hurdle to be cleared before reaching the target illudinine system was a bromo → methoxy substitution event. Perhaps the best way to underscore the challenge of this particular transformation is to recognize that the bromobenzene core is fully substituted and fused to a potential catalyst inhibitor. Traditional S_NAr protocols and metal-catalyzed aryl ether formation were not satisfactory in our hands.[24] However, treatment of **6** with acetohydroxamic acid and base (Maloney–Fier conditions[25]) produced hydroxyisoquinoline **7** in 89% yield (Scheme 5), presumably via tandem S_NAr/Lossen rearrangement.[25]

O-Methylation of **7** would generate illudinine ethyl ester (**9**), but *N*- vs *O*-selectivity is a challenge.[26] Most methylation conditions overwhelmingly favored *N*-methylation to zwitterion **8** (Table 1, entries 1–4).[24] Trimethylsilyldiazomethane ($TMSCHN_2$) has been shown to be good for *O*-methylation of phenols and enols in the presence of nucleophilic heterocycles.[26] Here, Aoyama and Shioiri's conditions[26a]

DOI: 10.1021/acs.orglett.6b03887
Org. Lett. 2017, 19, 858–861

Scheme 5. Tandem S_NAr/Lossen Rearrangement

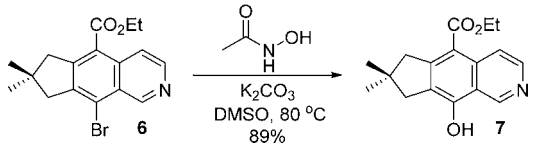
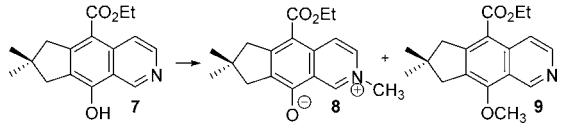


Table 1. Methylation Optimization



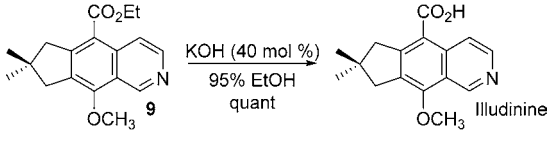
entry[a]	conditions	8/9
1	K_2CO_3, MeI, acetone, 50 °C	100:0
2	NaH, MeI, DMF, 0 °C→rt	100:0
3	Me_2CO_3, DBU, 90 °C	100:0
4	MeOH, DEAD, PPh_3, THF, 0 °C→rt	>95:<5
5[b]	$TMSCHN_2$, DIPEA, MeCN/MeOH (9:1)	65:35
6[c]	$TMSCHN_2$, toluene/MeOH (9:1)	55:45
7[d]	$TMSCHN_2$, toluene/*i*-BuOH (9:1)	40:60
8	$TMSCHN_2$, benzene/MeOH (9:1)	55:45
9[e]	$TMSCHN_2$, benzene/*i*-BuOH (9:1)	30:70
10[f]	$TMSCHN_2$, benzene/*i*-BuOH (19:1)	

[a]Experiments involved <5 mg of **7** except entry 9 (19 mg of **7**); product ratios estimated by ^{1}H NMR analysis of concentrated mixture after consumption of **7**. Entries 5−10: rt, 12−18 h, 0.1 M **7**. [b]No change in the absence of DIPEA. [c]Negligible conversion to products in the absence of MeOH. [d]Trace amounts of **7** observed in crude product mixture. [e]Methoxyisoquinoline **9** isolated in 63% yield. [f]Incomplete conversion.

(Table 1, entry 5) produced a mixture of **8** and **9** that, although favoring **8**, was sufficiently encouraging to warrant further optimization for the synthesis of **9**.

Mechanistic studies[27] support a reaction pathway involving desilylation and protonation of $TMSCHN_2$ to produce an intermediate methyldiazonium ($CH_3N_2^+$) phenoxide salt, which decomposes to either **8** or **9** with loss of N_2. We reasoned that a tight contact ion pair would favor *O*-methylation, so we explored the use of less polar reaction media (Table 1, entries 6−10). Switching solvents from acetonitrile to toluene provided a slightly improved ratio with respect to **9** (Table 1, entries 5 and 6; note that DIPEA did not alter product ratios), whereas switching the alcohol cosolvent from methanol to isobutyl alcohol had an important impact (Table 1, entry 7). Larger aliphatic alcohols (not shown) and/or less of the alcoholic cosolvent created problems with solubility and resulted in poor conversion. A similar trend was observed in benzene (Table 1, entries 8−10), with the optimal conditions (Table 1, entry 9) producing illudinine ethyl ester (**9**) in 63% yield after purification by silica gel chromatography. Finally, known saponification conditions[3,5] for **9** gave rise to illudinine in quantitative yield (Scheme 6).

Scheme 6. Saponification of Illudinine Ethyl Ester



In conclusion, the synthesis of illudinine has been accomplished in eight steps (14% overall yield) from dimedone. Key steps include the tandem fragmentation/Knoevenagel-type condensation of triflate **1** to give enyne **4** and the oxidative cycloisomerization of enyne **5** to deliver isoquinoline **6**, each of which represents a substantial extension of previous knowledge. Tactical hurdles en route from **6** to illudinine were overcome in ways that are broadly instructive. In terms of synthetic strategy, serial execution of ring-opening fragmentation and ring-closing cycloisomerization reactions provides an attractive and general approach to diverse value-added synthetic targets, especially 3,3-dimethylcyclopentane derivatives that are otherwise difficult to prepare. Efforts to develop strategically related approaches to other terpenoid natural products and to novel polycyclic aromatic systems are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03887.

Experimental procedures, spectroscopic characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gregory.dudley@mail.wvu.edu.

ORCID

Gregory B. Dudley: 0000-0001-6133-3747

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Foundation (NSF CHE 1300722) for support of this work.

■ REFERENCES

(1) Wender, P. A. *Nat. Prod. Rep.* **2014**, *31*, 433.
(2) Nair, M. S. R.; Takeshita, H.; McMorris, T. C.; Anchel, M. *J. Org. Chem.* **1969**, *34*, 240.
(3) Woodward, R. B.; Hoye, T. R. *J. Am. Chem. Soc.* **1977**, *99*, 8007.
(4) Ling, Q.; Huang, Y.; Zhou, Y.; Cai, Z.; Xiong, B.; Zhang, Y.; Ma, L.; Wang, X.; Li, X.; Li, J.; Shen, J. *Bioorg. Med. Chem.* **2008**, *16*, 7399.
(5) Teske, J. A.; Deiters, A. *J. Org. Chem.* **2008**, *73*, 342.
(6) (a) Witulski, B.; Zimmermann, A.; Gowans, N. D. *Chem. Commun.* **2002**, 2984. (b) Jones, A. L.; Snyder, J. K. *J. Org. Chem.* **2009**, *74*, 2907. (c) Welsch, T.; Tran, H.-A.; Witulski, B. *Org. Lett.* **2010**, *12*, 5644. (d) Hoang, T. T.; Birepinte, M.; Kramer, N. J.; Dudley, G. B. *Org. Lett.* **2016**, *18*, 3470.
(7) (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901.
(8) (a) Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208. (b) Raji Reddy, C.; Dilipkumar, U.; Damoder Reddy, M. *Org. Lett.* **2014**, *16*, 3792. (c) Marell, D. J.; Furan, L. R.; Woods, B. P.; Lei, X.; Bendelsmith, A. J.; Cramer, C. J.; Hoye, T. R.; Kuwata, K. T. *J. Org. Chem.* **2015**, *80*, 11744. (d) Jia, F.-C.; Xu, C.; Zhou, Z.-W.; Cai, Q.; Wu, Y.-D.; Wu, A.-X. *Org. Lett.* **2016**, *18*, 5232.
(9) (a) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (b) Johnson, E. P.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 381. (c) Paquette, L. A.; Geng, F. *Org. Lett.* **2002**, *4*, 4547. (d) Ashfeld, B. L.; Martin, S. F. *Org. Lett.* **2005**, *7*, 4535. (e) Finkielsztein, L. M.; Bruno, A. M.; Renou, S. G.; Moltrasio Iglesias, G. Y. *Bioorg. Med. Chem.* **2006**, *14*, 1863.

DOI: 10.1021/acs.orglett.6b03887
Org. Lett. 2017, 19, 858−861

(10) (a) Yang, X.; Li, J.; Zhou, Y.; Shen, Q.; Chen, J.; Li, J. *Biochim. Biophys. Acta, Gen. Subj.* **2005**, *1726*, 34. (b) Nam, H.-J.; Poy, F.; Krueger, N. X.; Saito, H.; Frederick, C. A. *Cell* **1999**, *97*, 449. (c) Ajay, D.; Sobhia, M. E. *J. Mol. Model.* **2012**, *18*, 187.
(11) Ramsubhag, R. R.; Massaro, C. L.; Dadich, C. M.; Janeczek, A. J.; Hoang, T. T.; Mazzio, E. A.; Eyunni, S.; Soliman, K. F. A.; Dudley, G. B. *Org. Biomol. Chem.* **2016**, *14*, 7855.
(12) Hoang, T. T.; Dudley, G. B. *Org. Lett.* **2013**, *15*, 4026.
(13) (a) Wessig, P.; Müller, G. *Chem. Rev.* **2008**, *108*, 2051. (b) Li, W.; Zhou, L.; Zhang, J. *Chem. - Eur. J.* **2016**, *22*, 1558. (c) Burrell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1996**, *118*, 4218. (d) Yu, P.; Yang, Z.; Liang, Y.; Hong, X.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **2016**, *138*, 8247.
(14) (a) Li, W.; Zhou, L.; Zhang, J. *Chem. - Eur. J.* **2016**, *22*, 1558. (b) Kocsis, L. S.; Kagalwala, H. N.; Mutto, S.; Godugu, B.; Bernhard, S.; Tantillo, D. J.; Brummond, K. M. *J. Org. Chem.* **2015**, *80*, 11686. (c) Benedetti, E.; Kocsis, L. S.; Brummond, K. M. *J. Am. Chem. Soc.* **2012**, *134*, 12418. (d) Kocsis, L. S.; Benedetti, E.; Brummond, K. M. *Org. Lett.* **2012**, *14*, 4430. (e) Ozawa, T.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2011**, *13*, 5390.
(15) Select examples: (a) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717. (b) Yan, X.; Ling, F.; Zhang, Y.; Ma, C. *Org. Lett.* **2015**, *17*, 3536. (c) Muthukrishnan, I.; Vinoth, P.; Vivekanand, T.; Nagarajan, S.; Maheswari, C. U.; Menéndez, J. C.; Sridharan, V. *J. Org. Chem.* **2016**, *81*, 1116.
(16) Morrison, A. E.; Hrudka, J. J.; Dudley, G. B. *Org. Lett.* **2016**, *18*, 4104.
(17) Spino, C.; Pesant, M.; Dory, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 3262.
(18) Bodwell, G. J.; Pi, Z.; Pottie, I. R. *Synlett* **1999**, *1999*, 477.
(19) Domingo, L. R. *Eur. J. Org. Chem.* **2004**, *2004*, 4788.
(20) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2014**, *47*, 2483.
(21) (a) Prall, M.; Wittkopp, A.; Fokin, A. A.; Schreiner, P. R. *J. Comput. Chem.* **2001**, *22*, 1605. (b) Bent, H. A. *Chem. Rev.* **1961**, *61*, 275.
(22) Conventional heating experiments in an oil bath at 200 °C were slower (2 days vs 12 h), likely due to better bulk heating in the microwave, although microwave-specific thermal effects cannot be ruled out. For discussions of microwave-specific rate acceleration by selective heating, see: (a) Rosana, M. R.; Tao, Y.; Stiegman, A. E.; Dudley, G. B. *Chem. Sci.* **2012**, *3*, 1240. (b) Chen, P.-K.; Rosana, M. R.; Dudley, G. B.; Stiegman, A. E. *J. Org. Chem.* **2014**, *79*, 7425. (c) Rosana, M. R.; Hunt, J.; Ferrari, A.; Southworth, T. A.; Tao, Y.; Stiegman, A. E.; Dudley, G. B. *J. Org. Chem.* **2014**, *79*, 7437. (d) Dudley, G. B.; Richert, R.; Stiegman, A. E. *Chem. Sci.* **2015**, *6*, 2144. (e) Wu, Y.; Gagnier, J.; Dudley, G. B.; Stiegman, A. E. *Chem. Commun.* **2016**, *52*, 11281.
(23) Brummond and Tantillo examined similarly diverging dehydrogenation pathways experimentally and computationally in their related system (Scheme 3, eq 1, and ref 14b). They report that concerted release of molecular hydrogen is the productive pathway for Scheme 3, eq 1, and that the competing hydrogen atom abstraction event triggers a radical chain reaction process that leads to dihydronaphthalenes. We do not observe the analogous dihydroisoquinolines, and we are mindful of important electronic differences between their "normal" and our "inverse-demand" system. Ongoing efforts to understand and improve this key step in our illudinine synthesis, coupled with preliminary explorations into illudinine pharmacology, will be reported in due course.
(24) See the Supporting Information for details.
(25) Fier, P. S.; Maloney, K. M. *Org. Lett.* **2016**, *18*, 2244.
(26) (a) Aoyama, T.; Terasawa, S.; Sudo, K.; Shioiri, T. *Chem. Pharm. Bull.* **1984**, *32*, 3759. (b) Boger, D. L.; Takahashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12452. (c) Xu, W.; Huang, L. F.; Bauer, L.; Bhargava, H. N.; Dunn, W. J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3375.
(27) (a) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475. (b) Kühnel, E.; Laffan, D. D. P.; Lloyd-Jones, G. C.; Martínez del Campo, T.; Shepperson, I. R.; Slaughter, J. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7075.

DOI: 10.1021/acs.orglett.6b03887
Org. Lett. 2017, 19, 858−861