Organic LETTERS

Letter

pubs.acs.org/OrgLett

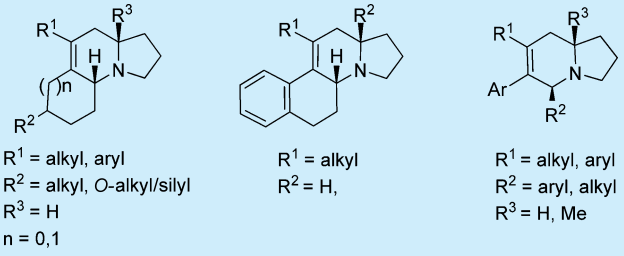
Iminium Ion–Enamine Cascade Cyclizations: Facile Access to Structurally Diverse Azacyclic Compounds and Natural Products

Stephen Hanessian* and Amit Kumar Chattopadhyay

Department of Chemistry, Université de Montréal, Station Centre Ville, C.P. 6128, Montreal, Quebec, H3C 3J7, Canada

Supporting Information

ABSTRACT: A one-pot, mild, two-component iminium ion–enamine cascade reaction to construct structurally diverse azacyclic frameworks from L-proline and L-pipecolic acid, and its application to indolizidine and quinolizidine alkaloids and azasteroids, is reported.



Azacyclic compounds in which the nitrogen atom is at the junction of two rings display a wide cross section of biological activities as exemplified by the quinolizidine and indolizidine alkaloids among others.[1,2] The ring conformations of such architecturally unique compounds also dictate the spatial orientation of the nitrogen lone pair with important consequences on their biological activities.[3] A unique family of such compounds are the phenanthroindolizidine and phenanthroquinolizidine alkaloids and their aryl and biaryl biogenetic precursors (Figure 1).

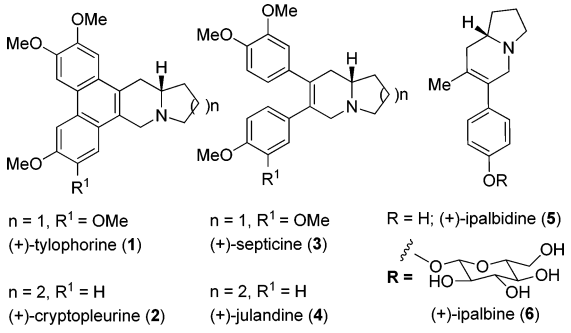


Figure 1. Quinolizidine and indolizidine alkaloids.

The total synthesis of these classes of alkaloids has been an active and fertile area of research for decades.[4] Despite their relatively simple structures, most methods have employed classical assembly approaches with varying degrees of step efficiencies.

Herein we report a mild, expedient, and stereoselective method for the synthesis of a variety of azacyclic compounds represented by the generic structures shown in Figure 2. The method was also applied toward the total synthesis of (+)-septicine **3**,[5] (+)-julandine **4**,[6] and (+)-ipalbidine **5**[7] (Figure 1).

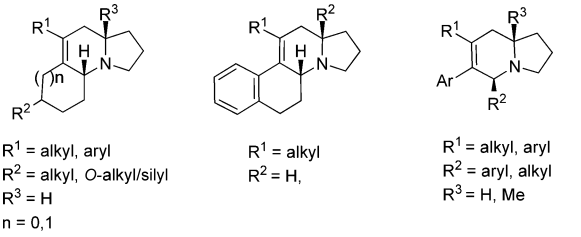


Figure 2. Azacyclic frameworks.

The basic sequence consists of a highly stereocontrolled one-pot cascade reaction involving a ketone derived form L-homoproline and a carbonyl compound exemplified by cyclohexanone, in the presence of trifluoroethyl triflate as a hitherto unexplored Lewis acid mediator. The cascade starts with the formation of the iminium intermediate **I**, which leads to the enamine **II**, followed by cyclization to **III**, dehydration to the azadienium ion **IV**, and finally stereoselective reduction with $NaBH_4$ to the intended prototypical tricycle **V**, without the need to isolate intermediates (Scheme 1).

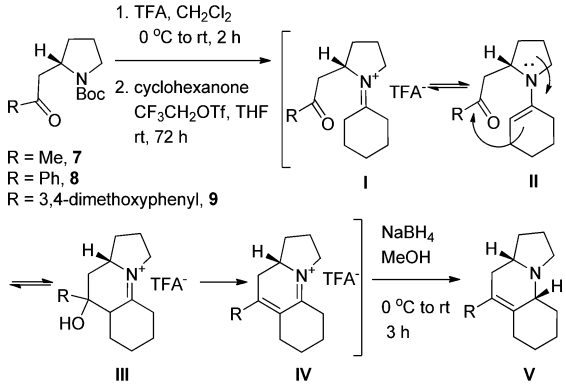
A systematic study of solvents revealed the following order of preferred reactivity: THF > benzene > toluene > DCM ≈ acetonitrile ≈ methanol.[8] We next investigated the effect of Lewis acids and secured complete conversion in decreasing order of reactivity: $CF_3CH_2OTf \geq TMSOTf \gg TfOH \approx$ metal triflates ≈ $BF_3{\cdot}OEt$.[8] Further optimization showed that use of 4 equiv of ketone was beneficial, since lesser equivalents resulted in lower yields.

Extension to a variety of ketones led to tricyclic and tetracyclic analogs in preparativly acceptable yields over three steps in most cases (Figure 3).[8] The absolute configurations of representative compounds shown in Figure 3 were determined

Received: November 8, 2013

   dx.doi.org/10.1021/ol403229q | Org. Lett. XXXX, XXX, XXX–XXX

Scheme 1. Proposed Mechanistic Pathway



based on single crystal X-ray structures of the corresponding methiodides (Scheme 2).

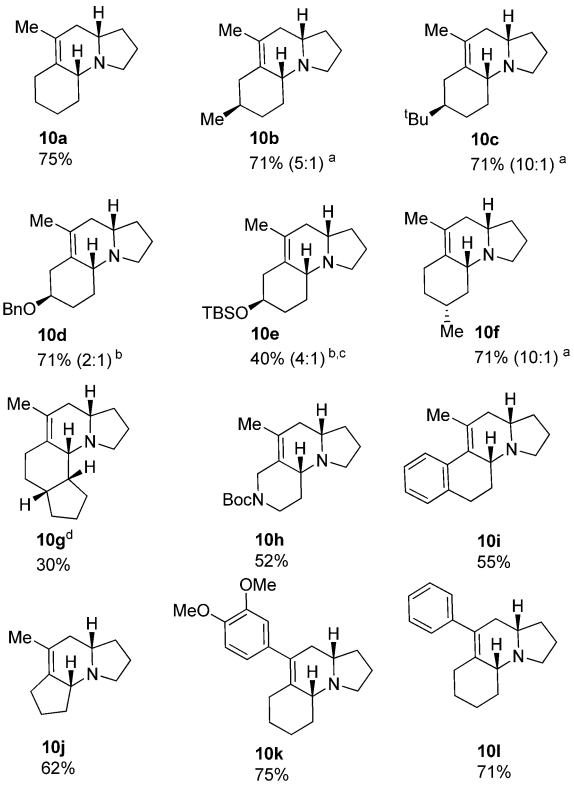
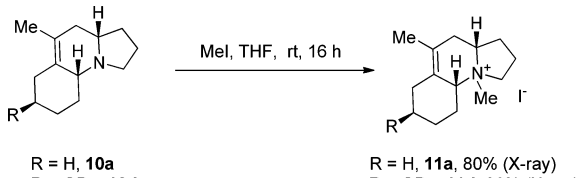


Figure 3. Scope of iminium−enamine reaction. [a] Nonseparable major isomer. [b] Separable major isomer. [c] TBS deprotected compound also observed. [d] Proposed stereochemistry.

Scheme 2. Methiodide Formation



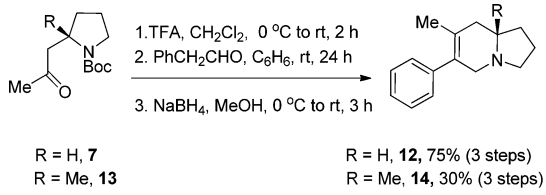
A fortuitous result in some of the cyclizations was the selective formation of one of the two possible diastereoisomers as the preponderant product in the reactions with 4-substituted cyclohexanones. Thus, with 4-benzyloxy and 4-*tert*-butyldimethylsilyloxy cyclohexanones, a 2:1 and 4:1 mixture of diastereomers respectively resulted that could be separated by column chromatography (Figure 3, entries **10d**, **10e**). The identity of the major diastereoisomer **10d** was ascertained from an X-ray structure of the corresponding methiodide salt (Scheme 2).[8] In the case of enantiomerically pure 3-(*R*)-methylcyclohexanone, the major product was enriched in one diastereomer, **10f**, the structure of which is based on steric arguments that would disfavor the reaction with the alternative regioisomeric enamine. Another example of diastereoselective cyclization was the case of *racemic* perhydro-1-indanone[9] which led to a single diastereomer in 30% yield, whose relative *cis*-stereochemistry at the Indane ring junction was provisionally assigned based on steric considerations (Figure 3, **10g**). Facile access to diazatricycles and 14-azasteroidal[10] core structures such as **10h** and **10i**, respectively, are noteworthy because of their potential diversification to other functionalized scaffolds (Figure 3).

Aiming at constrained analogs and congeners of indolizidine alkaloids of the septicine type, we subjected aryl ketones derived from L-homoproline to the same one-pot protocol shown in Scheme 1 (R = aryl, **8** and **9**). The corresponding aryl branched azatricylic compounds were easily formed (Figure 3, **10k** and **10l**). The stereochemistry of the cyclization products was deduced from the crystal structures of related methiodide salts.[8]

Although the reactivity of ketones such as cyclohexanone and cyclopentanone with cyclic imines to form iminium salts and enamines is a reversible process, the subsequent intramolecular cyclizations as depicted in Scheme 1 are less explored. An extensive literature survey shows that similar transformations require harsher conditions and are also low yielding.[11] In this regard, it is of interest that 2-substituted cyclohexanones, 1-decalone, and acyclic ketones such as 3-pentanone and 4-heptanone failed to react with amino ketone **7**. We attribute this to an inability of the initial iminium ion to form due to steric effects and to the reversibilty of the reaction. Adding cyclohexanone to any of the above inert reaction mixtures readily afforded the azatricyclic product **10a** after $NaBH_4$ reduction albeit in moderate yield, indicating the viability of the unreacted ketone. The piperidine analog corresponding to **7** also failed to react with cyclohexanone.

An interesting solvent effect was observed in moving from ketone to aldehyde substrates such as phenylacetaldehyde. Reactions performed in THF proceeded in low yield with partial racemization of the product. However, the expected cyclization took place with phenylacetaldehyde and **7** in benzene as solvent, without the need for the Lewis acid, to give the indolizidine analog **12** in good yield (Scheme 3).[5f] When an angular methyl group was present in the starting ketone (R = Me), a lower yield of product **14** was obtained, possibly due to steric effects (Scheme 3).

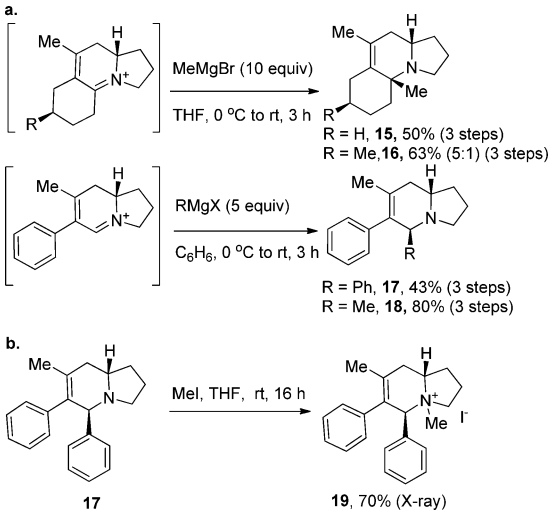
Scheme 3. 6-Aryl Indolizidine Frameworks



dx.doi.org/10.1021/ol403229q | Org. Lett. XXXX, XXX, XXX−XXX

The azadienium intermediates could be functionalized in situ in a 1,2-addition[12] mode by reaction with MeMgBr or PhMgBr to give angularly substituted novel azacyclic compounds. As expected from the results of **10b** (Figure 3), **16** was also obtained as the major isomer (5:1 ratio). Compounds **17** and **18** were obtained as single isomers, although the yield of **17** was modest (Scheme 4a). The absolute stereochemistry of the products was deduced by analogy with the X-ray crystal structure of the crystalline methiodide **19** (Scheme 4b).[8]

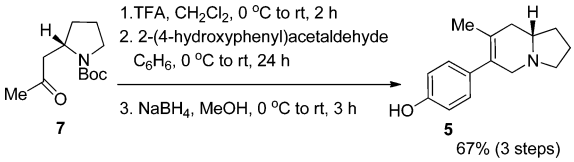
Scheme 4. Stereoselective 1,2 Grignard Addition



With a versatile method toward diverse azacyclic compounds in hand, we turned our attention to the total synthesis of enantiopure aryl indolizidine alkaloids such as ipalbidine, septicine, and julandine. A variety of synthetic approaches have been reported toward these alkaloids. Notable among these is the four-step total synthesis of (±)-ipalbidine by Herbert and co-workers,[7l] also exploiting an enamine ring closing step. The same group also reported expeditious routes toward racemic tylophorine[5e,f] and julandine,[6f−h] albeit in modest yields.

Herein we report a total synthesis of (+)-ipalbidine in three steps from ketone **7** (eight steps and 38% overall yield starting from *N*-Boc L-proline) (Scheme 5). Applying the same general

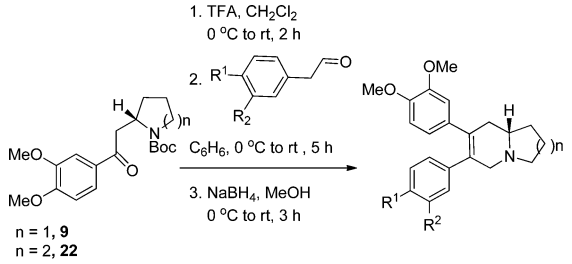
Scheme 5. Total Synthesis of (+)-Ipalbidine



protocol, we completed the total synthesis of (+)-septicine **3** and *seco*-antofine **20** (eight steps, 35% overall yields) and (+)-julandine **4** (eight steps, 10% overall yields) (Scheme 6). The intermediate compounds **7**, **9**, and **22** were synthesized from *N*-Boc L-proline and *N*-Boc L-pipecolic acid in five consecutive steps with an overall yield of 57%, 59%, and 26% respectively.

seco-Alkaloids such as **3**[5b] and **4**[6a] are considered to be biogenetic precursors to the corresponding phenanthroindolizidines and phenanthroquinolizidine alkaloids respectively (Figure 1). Facile oxidation of **3** with VOF_3 and **4** with $Tl(TFA)_3$ leads to tylophorine **1**[5b] and cryptopleurine **2**[6a] respectively.

Scheme 6. Total Syntheses of (+)-Septicine, (+)-*seco*-Antofine, (+)-Julandine, and Related Aryl Indolizidines



n = 1, R^1, R^2 = OMe, **3** (+)-septicine, 60%, (3 steps)
n = 1, R^1 = OMe, R^2 = H, **20** (+)-seco-antofine, 60%, (3 steps)
n = 1, R^1 = OH, R^2 = H, **21**, 53%, (3 steps)
n = 2, R^1 = OMe, R^2 = H, **4** (+)-julandine, 40%, (3 steps)

In conclusion, we have reported a one-pot, mild, and efficient three-step iminium−ion enamine cascade cyclization to construct structurally diverse, novel bi-, tri-, and tetra-azacyclic compounds. These could be potentially useful scaffolds toward the elaboration of biologically interesting compounds in the CNS field.[13] We have also reported the most recent syntheses to date of known 6-aryl and 5,6-diaryl indolizidine alkaloids using the iminium ion−enamine cascade cyclization. In the process, we also introduced trifluoroethyl triflate as a versatile and hitherto seldom exploited organic Lewis acid for iminium ion−enamine cascade cyclizations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, ^1H and ^{13}C NMR spectra, spectroscopic data for new compounds. This material is available free of charge *via* the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: stephen.hanessian@umontreal.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSERC and FQRNT for financial asistance. We thank Robert Giacometti, Université de Montréal for X-ray analysis.

■ REFERENCES

(1) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139−165. (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603−626. (c) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458−475.

(2) (a) Chemler, S. R. *Curr. Bioact. Compd.* **2009**, *5*, 2−19. (b) Wang, K.; Su, B.; Wang, Z.; Wu, M.; Li, Z.; Hu, Y.; Fan, Z.; Mi, N.; Wang, Q. *J. Agric. Food Chem.* **2010**, *58*, 2703−2709. (c) Wei, L.; Shi, Q.; Bastow, K. F.; Brossi, A.; Morris-Natschke, S. L.; Nakagawa-Goto, K.; Wu, T. S.; Pan, S. L.; Teng, C. M.; Lee, K. H. *J. Med. Chem.* **2007**, *50*, 3674−3680. (d) Shiah, H. S.; Gao, W. L.; Baker, D. C.; Cheng, Y. C. *Mol. Cancer Ther.* **2006**, *5*, 2484−2493. (e) Yang, C. W.; Chen, W. L.; Wu, P. L.; Tseng, H. Y.; Lee, S. *J. Mol. Pharmacol.* **2006**, *69*, 749−758. (f) Wu, P. L.; Rao, K. V.; Su, C. H.; Kuoh, C. S.; Wu, T. S. *Heterocycles* **2002**, *57*, 2401−2408. (g) Ganguly, T.; Khar, A. *Phytomedicine* **2002**, *9*, 288−295.

(3) See for example: (a) Casy, A. F.; Parfitt, R. T. *Opioid Alkaloids*; Springer: Heidelberg, 1986; p 465. (b) Hanessian, S.; Parthasarathy, S.; Mauduit, M.; Payza, K. *J. Med. Chem.* **2003**, *46*, 34−48. (c) Shiotani, S.; Kometani, T.; Iitaka, Y.; Itai, A. *J. Med. Chem.* **1978**, *21*, 153−154. (d) Belleau, B.; Conway, T.; Ahmed, F. R.; Hardy, A. D. *J. Med. Chem.* **1974**, *17*, 907−908. (e) Portoghese, P. S. *J. Med. Chem.* **1965**, *8*, 609−616.

(4) (a) Li, Z.; Jin, Z.; Huang, R. *Synthesis* **2001**, *16*, 2365−2378. (b) Gellert, E. *J. Nat. Prod.* **1982**, *45*, 50−73. (c) Bick, I. R. C.; Sinchai, W. *The Alkaloids* **1981**, *XIX*, 193. (d) Govindachari, T. R.; Viswanathan, N. *Heterocycles* **1978**, *11*, 588−613.

(5) Synthesis of (+)-*septicine*: (a) Reddy, K. U.; Reddy, A. P. *Synth. Commun.* **2013**, *43*, 2678−2684. Synthesis of (-)-*septicine* (and cyclization to *tylophorine*): (b) Comins, D. L.; Chen, X.; Morgan, L. A. *J. Org. Chem.* **1997**, *62*, 7435−7438. Synthesis of (±)-*septicine*: (c) Xu, X.; Liu, Y.; Park, C.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9372−9376. (d) Ciufolini, M. A.; Roschangar, F. *J. Am. Chem. Soc.* **1996**, *118*, 12082−12089. (e) Cragg, J. E.; Herbert, R. B.; Jackson, F. B.; Moody, C. J.; Nicolson, I. T. *J. Chem. Soc., Perkin Trans.1* **1982**, 2477−2485. (f) Herbert, R. B.; Jackson, F. B.; Nicolson, I. T. *J. Chem. Soc., Chem. Commun.* **1976**, 450−451.

(6) Synthesis of (+)-*julandine* (and cyclization to *cryptopleurine*): (a) Pansare, S. V.; Dyapa, R. *Org. Biomol. Chem.* **2012**, *10*, 6776−6784. Synthesis of (−)-*julandine*: (b) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1995**, *60*, 6114−6122. Synthesis of (±)-julandine: (c) Ciufolini, M. A.; Roschangar, F. *J. Am. Chem. Soc.* **1996**, *118*, 12082−12089. (d) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3325−3330. (e) Iida, H.; Watanabe, Y.; Tanaka, M.; Kibayashi, C. *J. Org. Chem.* **1984**, *49*, 2412−2418. (f) Cragg, J. E.; Herbert, R. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2487−2490. (g) Cragg, J. E.; Hedges, S. H.; Herbert, R. B. *Tetrahedron Lett.* **1981**, *22*, 2127−2130. (h) Herbert, R. B. *J. Chem. Soc., Chem. Commun.* **1978**, 794−795.

(7) Synthsis of (+)-*ipalbidine*: (a) Pansare, S. V.; Lingampally, R.; Dyapa, R. *Eur. J. Org. Chem.* **2011**, 2235−2238. (b) Niphakis, M. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6019−6022. (c) Honda, T.; Namiki, H.; Nagase, H.; Mizutani, H. *ARKIVOC* **2003**, *Viii*, 188−198. (d) Honda, T.; Namiki, H.; Nagase, H.; Mizutani, H. *Tetrahedron Lett.* **2003**, *44*, 3035−3038. (e) Liu, Z.-J.; Lu, R.-R.; Chen, Q.; Hong, H. *Acta Chimica Since* **1985**, *43*, 262−265. (f) Wick, A. E.; Bartlett, P. A.; Dolphin, D. *Helv. Chim. Acta* **1971**, *54*, 513−522. Synthesis of (±)-*ipalbidine*: (g) Ikeda, M.; Shikaura, J.; Maekawa, N.; Daibuzono, K.; Teranishi, H.; Teraoka, Y.; Oda, N.; Ishibashi, H. *Heterocycles* **1999**, *50*, 31−34. (h) Sheehan, S. M.; Padwa, A. *J. Org. Chem.* **1997**, *62*, 438−439. (i) Jefford, C. W.; Kubota, T.; Zaslona, A. *Helv. Chim. Acta* **1986**, *69*, 2048−2061. (j) Danishefsky, S. J.; Vogel, C. *J. Org. Chem.* **1986**, *51*, 3916−3918. (k) Iida, H.; Watanabe, Y.; Kibayashi, C. *Chem. Lett.* **1983**, *12*, 1195−11967. (l) Cragg, J. E.; Hedges, S. H.; Herbert, R. B. *Tetrahedron Lett.* **1981**, *22*, 2127−2130. (m) Stevens, R. V.; Luh, Y. *Tetrahedron Lett.* **1977**, *18*, 979−982. (n) Govindachari, T. R.; Sidhaye, A. R.; Viswanathan, N. *Tetrahedron* **1970**, *26*, 3829−3831.

(8) See Supporting Information for Experimental details.

(9) (a) Ghosh, A. K.; Chapsal, B. D.; Baldridge, A.; Steffey, M. P.; Walters, D. E.; Koh, Y.; Amano, M.; Mitsuya, H. *J. Med. Chem.* **2011**, *54*, 622−634. (b) Tsantali, G. G.; Takakis, I. M. *J. Org. Chem.* **2003**, *68*, 6455−6458.

(10) Loven, R. P.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 1023−1025.

(11) (a) Meyers, A. I.; Elworthy, T. R. *J. Org. Chem.* **1992**, *57*, 4732−4740. (b) lyle, R. E.; Heavner, G. A. *J. Org. Chem.* **1975**, *40*, 50−54. (c) Meyers, A. I.; Beverung, W. N. *Chem Commun.* **1968**, *15*, 877−877. (d) Meyers, A. I.; Sircar, J. C. *Tetrahedron* **1967**, *23*, 785−791. (e) Horii, Z-i.; Morikawa, K.; Tamura, Y.; Ninomiya, I. *Chem. Pharm. Bull.* **1966**, *14*, 1399−1404. (f) Clarkson, R. *J. Chem. Soc.* **1965**, 4900−4906. (g) Nelson, N. A.; Tamura, Y. *Can. J. Org. Chem.* **1965**, *43*, 1323−1328. (h) Sobotka, W.; Beverung, W. N.; Munoz, G. G.; Sircar, J. C.; Meyers, A. I. *J. Org. Chem.* **1965**, *30*, 3667−3671. (i) Meyers, A. I.; Munoz, G. G.; Sobotka, W.; Baburao, K. *Tetrahedron Lett.* **1965**, *6*, 255−260.

(12) (a) Muramatsu, W.; Nakano, K.; Li, C.-J. *Org. Lett.* **2013**, *15*, 3650−3653. (b) King, S. M.; Calandra, N. A.; Herzon, S. B. *Angew. Chem., Int. Ed.* **2013**, *52*, 3642−3645.

(13) (a) Rogers, M. E.; Sam, J. *J. Med. Chem.* **1974**, *17*, 657−659. (b) Sam, J.; England, J. D.; Temple, D. *J. Med. Chem.* **1969**, *12*, 144−146.

dx.doi.org/10.1021/ol403229q | *Org. Lett.* XXXX, XXX, XXX−XXX