Organic LETTERS

Letter

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A Route to the C,D,E Ring System of the *Aspidosperma* Alkaloids

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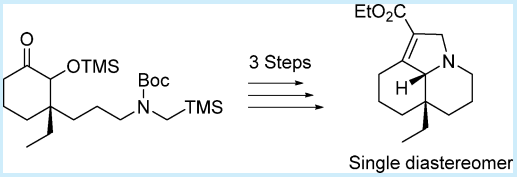
Supporting Information

ABSTRACT: A short synthetic sequence leading to the formation of the C,D,E-ring subunit of the *Aspidosperma* alkaloids is reported. This route is based on a ring fragmentation/intramolecular azomethine ylide 1,3-dipolar cycloaddition reaction sequence that gives the desired tricyclic product as a single diastereomer. A γ-amino-β-hydroxy-α-diazo carbonyl compound is shown to fragment in the presence of a Lewis acid to give an iminium product that can be directly reduced to the corresponding amine.



The *Aspidosperma* alkaloids are a group of structurally complex indole alkaloids comprised of over 250 members that contain the pentacyclic aspidospermidine skeleton (Figure 1).[1] The structural complexity and interesting biological activities

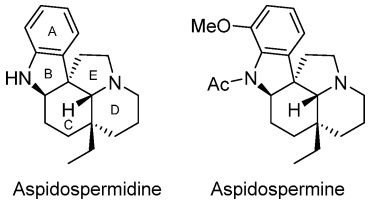
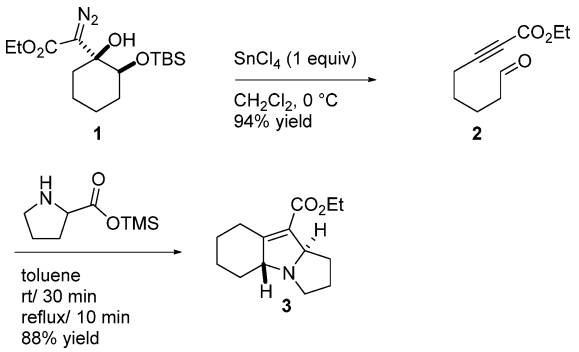


Figure 1. Structure of aspidospermidine and aspidospermine.

of this family of compounds have made them favored synthetic targets for evaluating new synthetic methods in the context of complex molecule synthesis. Over the years, a large number of elegant synthetic routes have been devised to prepare aspidospermidine.[2] Many of these routes, including Stork's landmark 1963 total synthesis of aspidospermine,[3] hinge on the synthesis of the nonindoline tricyclic core structure (i.e., the C,D,E ring system, Figure 1) of the *Aspidosperma* alkaloids as a key intermediate.

We have developed a convenient two-step reaction sequence to prepare polycyclic 2,5-dihydropyrroles by a Lewis acid mediated fragmentation of a γ-silyloxy-β-hydroxy-α-diazo carbonyl compound giving a tethered aldehyde ynoate[4] (e.g., **1** → **2**, Scheme 1) that can be used in a subsequent intramolecular azomethine ylide 1,3-dipolar cycloaddition. This sequence is fairly general, and it provides a variety of 2,5-dihydropyrroles in good to excellent yields.[5] We have recently used this methodology in the synthesis of the steroidal alkaloid demissidine[6] and the ergot alkaloid cycloclavine.[7] In order to further develop the scope and utility of this methodology we identified the C,D,E ring system of the *Aspidosperma* alkaloids as a target of interest, and in this letter we report a concise synthetic route to this key tricyclic structure. In addition, we show that a γ-amino-β-hydroxy-α-diazo carbonyl compound can also fragment leading to an iminium product.

Scheme 1. Ring Fragmentation/Intramolecular Azomethine Ylide 1,3-Dipolar Cycloaddition Approach to Polycyclic 2,5-Dihydropyrroles



Our initially conceived approach to aspidospermidine is shown in Scheme 2. The final target would be prepared by hydrolysis of ester **4** followed by acid catalyzed decarboxylation in the presence of sodium cyanoborohydride. The indoline ring in **4** would be formed by an intramolecular Heck reaction of hydroxyl amine **5** followed by N−O bond cleavage, and the requisite aryl hydroxyl amine fragment could be incorporated onto the key tricycle **6** by a N-nitroso Mukaiyama aldol reaction.[8] We envisioned the tricyclic target coming from the intramolecular cycloaddition of the azomethine ylide derived by fluoride mediated desilylation of iminium **7**.[9] This iminium ion could potentially come from the fragmentation of γ-amino-β-hydroxy-α-diazo carbonyl compound **8**. At the outset of this work we had no experimental evidence that a γ-amino derivative would fragment productively, but the similarity of these species to the γ-silyloxy derivatives made this seem like a reasonable proposition. The required diazo carbonyl could in turn be formed by the aldol-type addition of lithiated ethyl diazoacetate to octahydroquinolin-8-one derivative **9**.

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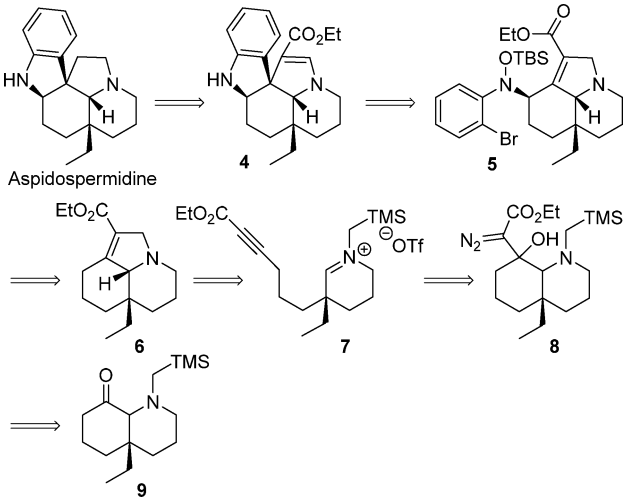
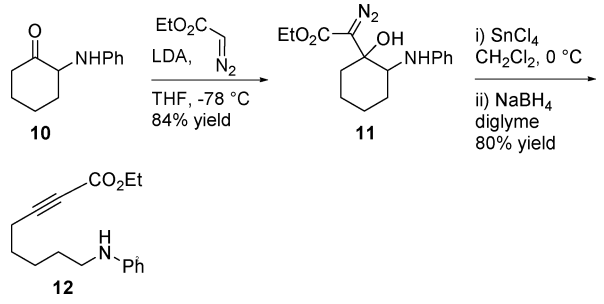
Scheme 2. Initial Retrosynthetic Disconnection of Aspidospermidine



Our initial studies focused on determining if γ-amino diazo carbonyl compounds would fragment similarly to their γ-silyloxy counterparts leading directly to an iminium product. With this in mind, we prepared the ethyl diazoacetate addition product of 2-(phenylamino)cyclohexanone (**11**) as a simple model system (Scheme 3). Treating this compound with $SnCl_4$ resulted in gas

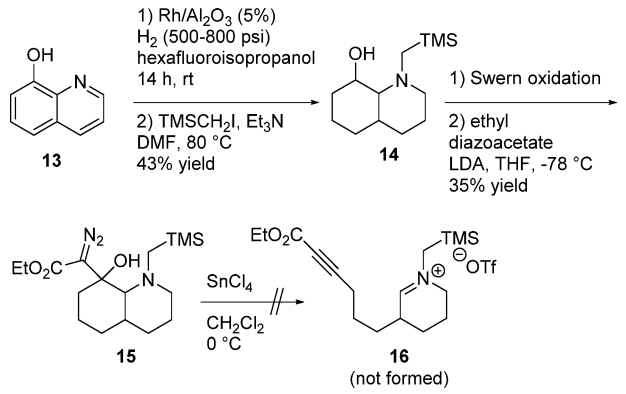
Scheme 3. Fragmentation of a γ-Amino-β-hydroxy-α-diazo Carbonyl Compound



evolution, and upon aqueous workup aldehyde tethered ynoate (**2**, Scheme 1) was isolated in low and variable yield. However, adding sodium borohydride in diglyme to the crude fragmentation mixture gave amine **12** in 80% yield.

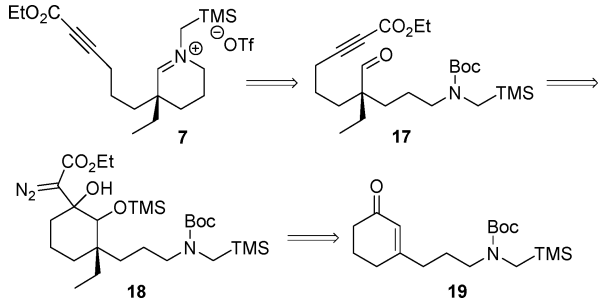
In an attempt to apply this fragmentation to a model system that was more similar to the aspidospermine core, we prepared diazo ester **15**, which lacks the angular ethyl group, by the route shown in Scheme 4. Exhaustive reduction of 8-hydroxyquinoline and alkylation of the resulting amine with (iodomethyl)-trimethylsilane gave decahydroquinoline derivative **14** as a mixture of diastereomers in 43% yield. Oxidation under Swern conditions gave the corresponding ketone, and aldol addition of lithiated ethyl diazoacetate gave the desired fragmentation precursor **15** in 35% yield. Unfortunately, all attempts to fragment this compound were unsuccessful and starting material was returned. The inability of **15** to fragment may be a ramification of the bicyclic structure causing poor stereo-electronic alignment of the reacting groups,[10] or the presence of a more basic tertiary amine which could coordinate to the Lewis acid.

Scheme 4. Unsuccessful Attempt To Fragment Bicyclic Diazo 15



With the failure of diazo **15** to fragment, we developed the alternative approach to iminium ion **7** shown in Scheme 5. This

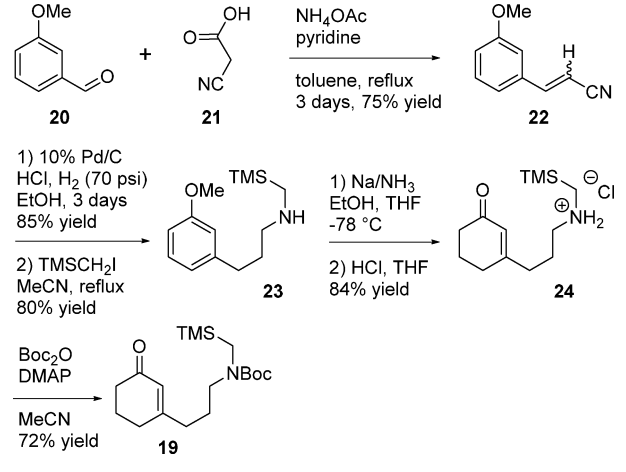
Scheme 5. Alternative Approach to Iminium 7



route involves fragmentation of γ-silyloxy-β-hydroxy-α-diazo carbonyl **18** to give aldehyde **17** that could condense with a pendent amine to give **7**. Fragmentation precursor **18** could in turn be prepared from enone **19** by conjugate addition of an ethyl group followed by oxidation α to the carbonyl and aldol type addition of lithiated ethyl diazoacetate.

Our initial route to enone **19** is shown in Scheme 6. A Doebner modified Knoevenagel condensation[11] of *m*-anisaldehyde and 2-cyanoacetic acid provided acrylonitrile **22** in 75% yield. Reduction of the acrylonitrile moiety gave *m*-(3-aminopropyl)-anisol, which was alkylated with (iodomethyl)trimethylsilane to

Scheme 6. Initial Route to Intermediate 19



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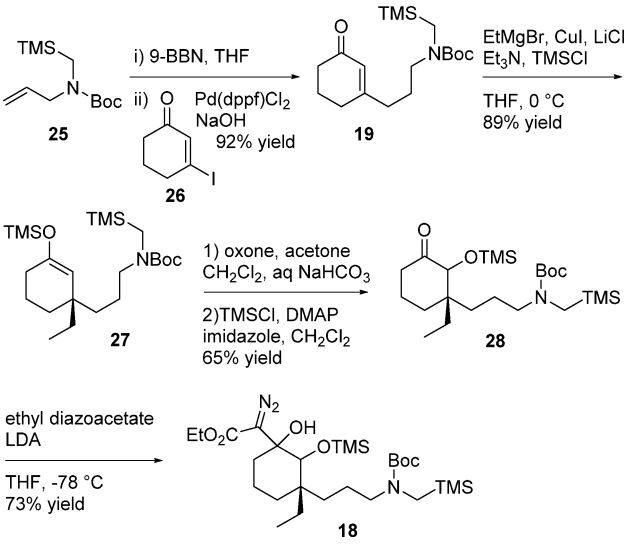
give anisole **23** in 68% yield over the two steps. Birch reduction and acid catalyzed isomerization gave enone **24** in 84% yield. This compound was unstable as a free base but could be stored as the amine hydrochloride salt. Boc protection of the amine gave the desired enone (**19**) in 72% yield. While this route provided access to **19**, it was lengthy and we encountered difficulties when attempting to scale up; the acrylonitrile reduction step proved to be irreproducible, and the Birch reduction step became inconvenient on a larger scale.

To circumvent these scalability issues, we developed the significantly more concise route to **19** shown in Scheme 7. *N*-

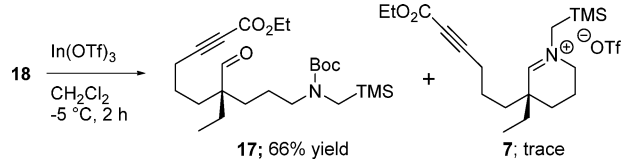
Scheme 7. Preparation of Fragmentation Precursor 18 via Optimized Route to 19



Boc-*N*-(trimethylsilyl)methylallylamine (**25**), prepared by alkylation of N-Boc-allylamine, was subjected to a one-pot hydroboration/Suzuki coupling sequence,[12] which gave enone **19** in 92% yield on gram scale. With convenient access to **19** now in hand, copper catalyzed 1,4-conjugate addition of ethyl magnesium bromide in the presence of TMSCl provided enoxysilane **27** in 89% yield. Subjecting this material to a biphasic Rubottom oxidation using in situ generated DMDO as oxidant gave the α-hydroxy ketone, and subsequent TMS protection of the alcohol provided silyl ether **28** as a mixture of two diastereomers in 65% yield. Aldol addition of lithiated ethyl diazoacetate to this mixture provided the desired ring fragmentation precursor (**18**) in 73% yield as a mixture of diastereomers. The lack of diastereoselectivity in these steps is inconsequential since both stereocenters adjacent to the oxygen atoms are cleared during the fragmentation step.

With diazo ester **18** in hand, we attempted the key fragmentation reaction. We were disappointed to discover that subjecting **18** to the standard fragmentation conditions ($SnCl_4$, 0 °C) led to a complex mixture of products; no aldehyde was present in the crude mixture, and it was clear that the Boc group had been cleaved. In prior studies[4] we had determined that indium(III) triflate was also effective in promoting the fragmentation of γ-silyloxy-β-hydroxy-α-diazo carbonyl compounds and we were pleased to observe that treating **18** with a suspension of indium(III) triflate in CH_2Cl_2 at −5 °C for 2 h (Scheme 8) gave the expected tethered aldehyde ynoate **17** in 66% yield. Importantly, we also isolated trace quantities of a highly polar material that we identified as being iminium salt **7**.

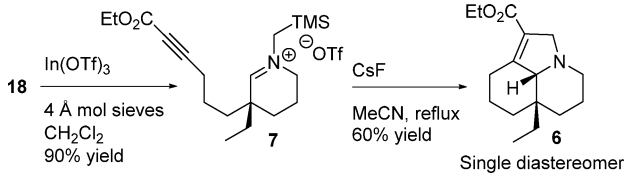
Scheme 8. Results of Initial Fragmentation Studies of Diazo 18



This material, which would be the direct precursor of the requisite azomethine ylide, was apparently formed by a serendipitous sequence of reactions involving Lewis acid mediated fragmentation, Boc cleavage, and subsequent intramolecular condensation.

To optimize the formation of iminium **7** the reaction time was extended to 24 h with little effect. Changing the work up procedure from quenching with a saturated aqueous $NaHCO_3$ solution to quenching with water resulted in a noticeable increase in the yield of the iminium that was isolated. Adding molecular sieves to the fragmentation reaction and running the reaction at room temperature for 12 h further promoted the formation of the desired iminium salt. Under these reaction conditions the desired product was isolated in 90% yield after trituration with hexanes in a form that was sufficiently pure to carry on without further purification (Scheme 9). Treating this material with

Scheme 9. Ring Fragmentation/Intramolecular Azomethine Ylide 1,3-Dipolar Cycloaddition To Give the *Aspidosperma* Tricyclic Core



cesium fluoride in acetonitrile generated the requisite azomethine ylide, which underwent intramolecular 1,3-dipolar cycloaddition with the pendent alkyne to give the target 2,5-dihydropyrrole **6**, the tricyclic core of the *Aspidosperma* alkaloids, in 60% yield as a single diastereomer.

In summary, we have devised a short sequence leading to the formation of the C,D,E-ring subunit of the *Aspidosperma* alkaloids. Fragmentation of a γ-silyloxy-β-hydroxy-α-diazo carbonyl containing a side chain bearing a Boc-protected amine led directly to an iminium ion by in situ cleavage of the Boc protecting group and subsequent condensation of the amine with the newly formed aldehyde. Incorporation of a (trimethylsilyl)methyl group onto the amine prior to fragmentation led directly to an azomethine ylide precursor, which upon treatment with CsF provided the desired tricyclic product as a single diastereomer. Although an octahydroquinolin-8-one derived substrate (**15**) failed to fragment productively, we have shown that a γ-amino-β-hydroxy-α-diazo carbonyl compound (**11**) does fragment in the presence of a Lewis acid to give an iminium product that can be directly reduced to the corresponding amine.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Saxton, J. E. In *The Alkaloids: Chemistry and Biology*; Geoffrey, A. C., Ed.; Academic Press: 1998; Vol. *51*, p 1.
(2) (a) Camerman, A.; Camerman, N.; Kutney, J. P.; Piers, E.; Trotter, J. *Tetrahedron Lett.* **1965**, *6*, 637. (b) Kuehne, M. E.; Bayha, C. *Tetrahedron Lett.* **1966**, *7*, 1311. (c) Kutney, J. P.; Abdurahman, N.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1966**, *88*, 3656. (d) Harley-Mason, J.; Kaplan, M. *Chem. Commun. (London)* **1967**, *0*, 915. (e) Kutney, J. P.; Piers, E.; Brown, R. T. *J. Am. Chem. Soc.* **1970**, *92*, 1700. (f) J.-Y. Laronze, p.; Laronze-Fontaine, J.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1974**, *15*, 491. (g) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990. (h) Gallagher, T.; Magnus, P.; Huffman, J. *J. Am. Chem. Soc.* **1982**, *104*, 1140. (i) Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901. (j) Mandal, S. B.; Giri, V. S.; Sabeena, M. S.; Pakrashi, S. C. *J. Org. Chem.* **1988**, *53*, 4236. (k) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673. (l) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517. (m) Le Menez, P.; Kunesch, N.; Liu, S.; Wenkert, E. *J. Org. Chem.* **1991**, *56*, 2915. (n) Desmaeele, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292. (o) Wenkert, E.; Liu, S. *J. Org. Chem.* **1994**, *59*, 7677. (p) Forns, P.; Diez, A.; Rubiralta, M. *J. Org. Chem.* **1996**, *61*, 7882. (q) Schultz, A. G.; Pettus, L. *J. Org. Chem.* **1997**, *62*, 6855. (r) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995. (s) Iyengar, R.; Schildknegt, K.; Aube, J. *Org. Lett.* **2000**, *2*, 1625. (t) Patro, B.; Murphy, J. A. *Org. Lett.* **2000**, *2*, 3599. (u) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642. (v) Banwell, M. G.; Smith, J. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2613. (w) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628. (x) Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398. (y) Fukuda, Y.-i.; Shindo, M.; Shishido, K. *Org. Lett.* **2003**, *5*, 749. (z) Gnecco, D.; Vazquez, E.; Galindo, A.; Teran, J. L.; Orea, L.; Bernes, S.; Enriquez, R. G. *ARKIVOC* **2003**, 185. (aa) Tanino, H.; Fukuishi, K.; Ushiyama, M.; Okada, K. *Tetrahedron* **2004**, *60*, 3273. (ab) Banwell, M. G.; Lupton, D. W.; Willis, A. C. *Aust. J. Chem.* **2005**, *58*, 722. (ac) Iyengar, R.; Schildknegt, K.; Morton, M.; Aube, J. *J. Org. Chem.* **2005**, *70*, 10645. (ad) Pearson, W. H.; Aponick, A. *Org. Lett.* **2006**, *8*, 1661. (ae) Sharp, L. A.; Zard, S. Z. *Org. Lett.* **2006**, *8*, 831. (af) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 6159. (ag) Callier-Dublanchet, A.-C.; Cassayre, J.; Gagosz, F.; Quiclet-Sire, B.; Sharp, L. A.; Zard, S. Z. *Tetrahedron* **2008**, *64*, 4803. (ah) Ishikawa, T.; Kudo, K.; Kuroyabu, K.; Uchida, S.; Kudoh, T.; Saito, S. *J. Org. Chem.* **2008**, *73*, 7498. (ai) Burrell, A. J. M.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. *J. Org. Chem.* **2009**, *74*, 2290. (aj) Sabot, C.; Guerard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941. (ak) Suzuki, M.; Kawamoto, Y.; Sakai, T.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2009**, *11*, 653. (al) Cho, H.-K. T.; Tam, N. T.; Cho, C.-G. *Bull. Korean Chem. Soc.* **2010**, *31*, 3382. (am) De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5767. (an) Guérard, K. C.; Sabot, C.; Beaulieu, M.-A.; Giroux, M.-A.; Canesi, S. *Tetrahedron* **2010**, *66*, 5893. (ao) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (ap) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563. (aq) Lajiness, J. P.; Jiang, W.; Boger, D. L. *Org. Lett.* **2012**, *14*, 2078. (ar) McMurray, L.; Beck, E. M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9288. (as) Huang, J.-Z.; Jie, X.-K.; Wei, K.; Zhang, H.; Wang, M.-C.; Yang, Y.-R. *Synlett* **2013**, *24*, 1303. (at) Kawano, M.; Kiuchi, T.; Negishi, S.; Tanaka, H.; Hoshikawa, T.; Matsuo, J.-i.; Ishibashi, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 906. (au) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 4117. (av) Nidhiry, J. E.; Prasad, K. R. *Tetrahedron* **2013**, *69*, 5525. (aw) Zhao, S.; Andrade, R. B. *J. Am. Chem. Soc.* **2013**, *135*, 13334. (ax) Wagnières, O.; Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 15102. (ay) Pandey, G.; Burugu, S. K.; Singh, P. *Org. Lett.* **2016**, *18*, 1558.
(3) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872.
(4) Draghici, C.; Brewer, M. *J. Am. Chem. Soc.* **2008**, *130*, 3766.
(5) Draghici, C.; Huang, Q.; Brewer, M. *J. Org. Chem.* **2009**, *74*, 8410.
(6) Zhang, Z.; Giampa, G. M.; Draghici, C.; Huang, Q. F.; Brewer, M. *Org. Lett.* **2013**, *15*, 2100.
(7) Jabre, N. D.; Watanabe, T.; Brewer, M. *Tetrahedron Lett.* **2014**, *55*, 197.
(8) Tian, G.-Q.; Yang, J.; Rosa-Perez, K. *Org. Lett.* **2010**, *12* (21), 5072.
(9) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452.
(10) Jabre, N. D.; Brewer, M. *J. Org. Chem.* **2012**, *77*, 9910.
(11) Doebner, O. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 2140.
(12) (a) Kamatani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743. (b) Brosius, A. D.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 440.

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