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# Total Synthesis of Aplykurodinone-1

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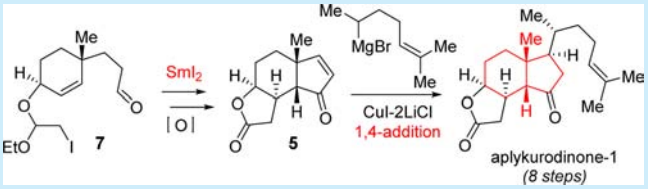
Supporting Information

**ABSTRACT:** The concise total synthesis of aplykurodinone-1 with an unusual *cis*-fused hydrindane moiety has been accomplished without the need for any protecting group chemistry using a unique $SmI_2$ mediated reductive cascade cyclization reaction and a direct cuprate mediated 1,4-addition. This work represents the first example of the use of a $SmI_2$-mediated intramolecular cascade cyclization reaction between "halide, alkene and aldehyde" groups.




The aplykurodines are a family of highly degraded marine steroids that show cytotoxic activities toward a variety of human cancer cell lines.[1] Aplykurodinone-1[2] (**1**) and aplykurodinone-B[2] (**2**) (Figure 1) are both members of this particular

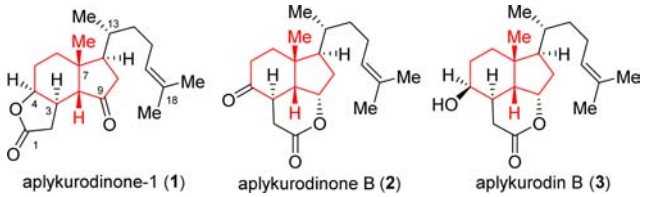



**Figure 1.** Structures of aplykurodinone-1, aplykurodinone B, and aplykurodin B.

family and were first isolated in 2005 from the sea hare *Syphonota geographica*. Although very little is currently known about the biological profile of aplykurodinone-1 (**1**), aplykurodinone B[1b] (**2**) has been reported to be very toxic toward the mosquito fish at 10 ppm, and the 4-acetyl derivative of aplykurodin B[1a] (**3**) has also been reported to be toxic at the same concentration.[1b] Structurally, **1** and **2** contain six contiguous stereocenters, whereas **3** contains seven, all of which contain an all-carbon quaternary center. **1**−**3** also possess an unusual *cis*-fused hydrindane moiety (red in Figure 1), with a $\gamma$- or $\delta$-lactone, as well as an unsaturated side chain with the stereocenter at C13 linked to the tricyclic core.

Based on these interesting structural features, the aplykurodines have attracted considerable levels of attention from the synthetic community.[3] In 2010, Danishefsky and Zhang reported the first total synthesis of **1** in 22 steps, using an elegant anionic Diels−Alder reaction to construct the core. They also studied what they called the "C20 problem" (marked as C13 in Figure 1) with a suitable choice of vinyl cuprate nucleophile for the 1,4-addition and judicious selection of hydrogenation catalysts.[4] De Paolis et al. recently reported a formal synthesis of **1** using a Robinson annulation−reduction approach. They highlighted an aerobic oxidation of the Hajos−Parrish enone and controlled epimerization at C3.[5] In both syntheses, the stereochemical complexity of this small molecule required additional manipulation steps and protection−deprotection sequences, which led to the development of lengthy synthetic routes and limited yields. Due to the limited availability of these natural products, further synthetic studies are necessary to provide sufficient quantities for biological research, while simultaneously contributing to the development of new synthetic methods.

Protecting-group-free total syntheses display the step economy, atom economy, and redox economy philosophy that arose during the mid-1990s.[6] Achieving this simplicity requires both comprehensive rationalizations of the molecular structures and precise synthetic designs. The development of modern, highly selective, functional group tolerated synthetic methodologies takes this concept to a new height.[7,8] Our previous work has exhibited the viability of such syntheses and prompted us to explore this field further.[9a]

In our continuing efforts toward the syntheses of biologically active natural products, we endeavor to not only develop new strategies for the preparation of the natural products themselves but also develop new methodologies that are suitable for the preparation of analogous compounds and derivatives for the effective evaluation of their biological properties.[9] Herein we describe our recently developed novel strategy for the concise total synthesis of aplykurodinone-1 in 8 steps, featuring a unique $SmI_2$ mediated reductive cascade cyclization reaction.

Our retrosynthetic analysis centers on a $SmI_2$ cascade reaction and a direct 1,4-addition (Figure 2). Briefly, aplykurodinone-1 (**1**) can be disconnected to give **5**, which could be converted to **1** via the secondary alkyl cuprate-mediated 1,4-addition of Grignard reagent **4**.[10] Synthetically, aplykurodinone B (**2**) and aplykurodin B (**3**) could be constructed from **1** using reduction and lactone-transformation reactions. The advanced intermedi-

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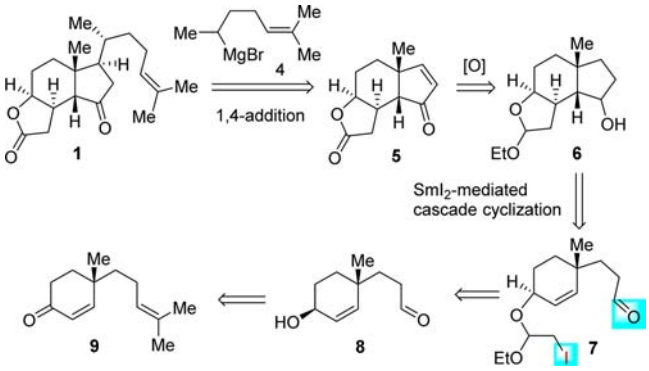



**Figure 2.** Retrosynthetic analysis.

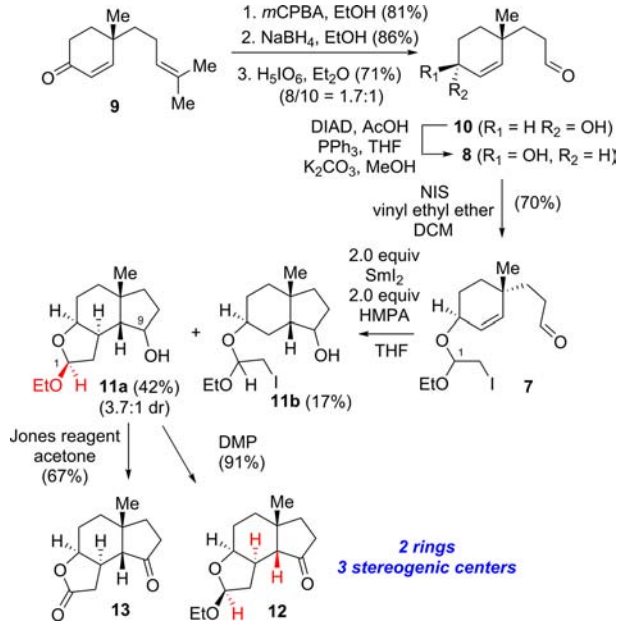
ate **5** could be disconnected to give **6**, which could be converted to **5** via an oxidation reaction. The tricyclic core structure of **6** could be stereoselectively constructed from the corresponding cyclohexene-aldehyde **7** via a $SmI_2$-mediated reductive cascade cyclization reaction.[11] We envision that the *trans* configuration between the hemiacetal group and aldehyde side chain in **7** would control the stereochemical outcome of the cyclization reaction. **7** could be accessed from the readily available ketone **9**[12] via the hydroxyl-aldehyde **8** according to a series of simple functional group transformations.

The $SmI_2$-mediated reductive cascade cyclization is a highly efficient process that generally occurs with a high level of stereoselectivity. Reactions of this category have been investigated extensively throughout the past 30 years and applied to the total synthesis of a broad range of natural products and synthetic materials.[11,13] Previous reports have shown a diverse substrate scope, including applications in the synthesis of carbocyclic compounds from alkyl halides and alkenes,[14] as well as the construction of polycyclic compounds via the reaction of carbonyl compounds with alkenes.[15] Recent reports in total synthesis have generally focused on the use of one "activated" alkene (as an unsaturated ketone/ester) to undergo the cascade sequence.[13a,b] However, to the best of our knowledge, the $SmI_2$-mediated reductive cyclization cascade reaction with a "halide-inactivated alkene−aldehyde" sequence in an intramolecular process (such as the system in **7**) remains unprecedented. Under the $SmI_2$ conditions, the halide and aldehyde could simultaneously form alkyl and ketyl radicals, respectively,[11] which would make it increasingly difficult to control the orientation of attack during the cyclization cascade reaction. The latent multiple reaction pathways[16] and potential versatility of this reaction inspired us to investigate this reaction in greater detail.

In order to evaluate the key reactions, the implementation of our synthetic strategy was first carried out with the preparation of the aldehyde **7** (Scheme 1). Sequential treatment of the readily available enone **9** with *m*CPBA, $NaBH_4$, and orthoperiodic acid provided diastereoisomers **8** and **10** in a ratio of 1.7:1, as compounds separable by flash column chromatography. The undesired allylic alcohol **10** could be converted into the desired compound **8** by sequential Mitsunobu and deacylation reactions in an overall yield of 65%. Treatment of alcohol **8** with NIS and vinyl ethyl ether gave the cyclization precursor **7**, as an inseparable 1:1 mixture of diastereomeric haloacetals.

With the haloacetal-aldehyde **7** in hand, we proceeded to investigate the $SmI_2$ mediated reductive cascade cyclization reaction for the rapid construction of the tricyclic core in compound **13**.

**Scheme 1. Synthesis of the Tricyclic Core 13**




Our initial investigation of the $SmI_2$-mediated reductive cascade cyclization reaction of **7** with $SmI_2$ in THF provided only trace quantities of the desired product. A variety of different additives were then evaluated in the reaction in an attempt to modulate the reactivity of the $SmI_2$ (see Supporting Information (SI)). Following a period of optimization, the cascade cyclization reaction of **7** with 2.0 equiv of $SmI_2$ was ultimately performed in THF in the presence of 2.0 equiv of HMPA.[16d,e] These conditions provided the desired cyclization product **11a** in 42% yield as a mixture of C9-diastereoisomers (3.7:1 dr), together with the formation of byproduct **11b** in 17% yield (Scheme 2). If both C1-diastereoisomers **7** could undergo cyclization, we would obtain multiple C1 isomers as the products. Interestingly, only product **11a** was observed as the cascade-ring-closing product, along with the monocyclization product **11b**. Consequently, it is possible that only one of the diastereoisomers of **7** can undergo cyclization. To probe the mechanism further, we oxidized compound **11a** with DMP and Jones reagent, generating compounds **12** and **13**, respectively. Tricyclic core **13** was also reported as an advanced intermediate in Danishefsky and Zhang's total synthesis.[4] This precedent confirmed that the reaction could provide the desired product with the correct stereoselectivity at the desired position. The structure of **12** was determined by 2D-NMR (see SI), which showed one single C1-isomer. The observation of byproduct **11b** accompanied by a failure to isolate the isomer **11c** (Scheme 3) supports a preferred reaction pathway in which the reaction initiates from the aldehyde group (**7** → **7a** → **7b**). This pathway explains that the diastereoselectivity observed in **11a** results from the outcome of the cyclization reaction that provided the 2-ethoxytetrahydrofuran ring, most likely via intermediate **7c** (anion cyclization) or **7d** (diradical cyclization). Cyclization of **7b** to **11a** depended heavily on the C1-stereochemistry of the haloacetals in **7b**, as the reaction required a specific conformation at the reaction site. Due to the delicate nature of $SmI_2$, this preliminary explanation is not sufficient to eliminate the possibility of the iodide-initiated pathway. Further studies utilizing this reaction in total synthesis as well as mechanistic study are currently underway in our lab.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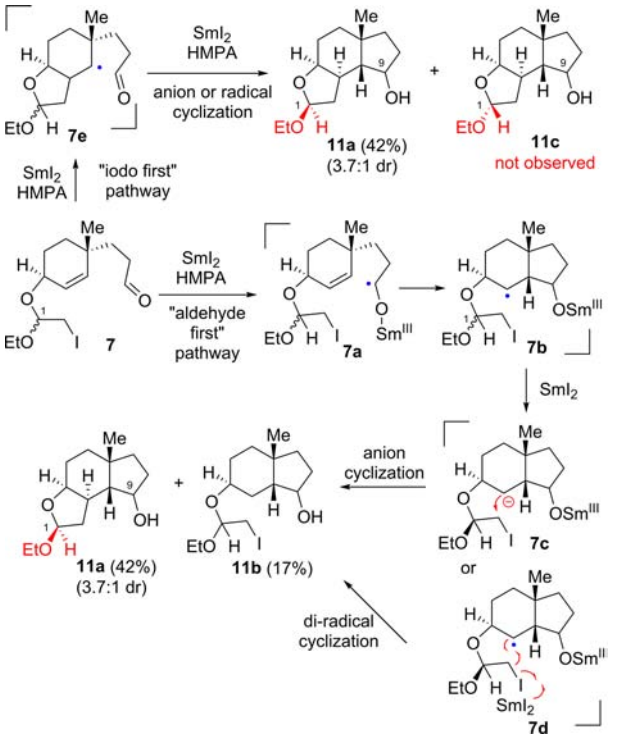
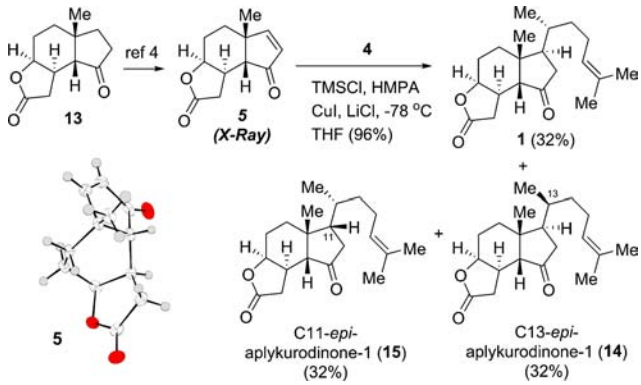
**Scheme 2. Possible Pathways for the $SmI_2$ Reaction**




**Scheme 3. Total Synthesis of 1**




To complete the total synthesis of aplykurodinone-1 (**1**), compound **13** was subjected to the reported[4] Saegusa oxidation reaction to give enone **5**, and the structure of this compound was unambiguously confirmed by X-ray crystallographic analysis (Scheme 3). With **5** in hand, we continued toward the final stage of the synthesis involving the installation of the C11 side chain. The TMSCl-mediated 1,4-addition of the organocuprate derived from Grignard reagent **4** proceeded smoothly to give **1**, as well as C13-*epi*-aplykurodinone-1 (**14**) and C11-*epi*-aplykurodinone-1 (**15**) in high yield. As expected, **1** and **14** were formed in equimolar amounts in a combined yield of 64%, whereas the undesired facial isomer **15** was formed rather unexpectedly in 32% yield (see SI). This approach could be invoked to obtain the structurally diverse analogues for their structure−activity relationship (SAR) studies. This reaction differed from the previously reported example, where the 1,4-addition of the vinyl cuprate reagent was followed by a reduction sequence.[4] Furthermore, we demonstrated that the stereochemistry at C13 could be addressed by the direct addition of a secondary alkyl-cuprate reagent, with the desired product being formed in a relatively good yield. It is noteworthy that due to the "C20 problem" addressed by Danishefsky and Zhang,[4] five additional steps were required for the stereoselective construction of **1** from **5**, with an overall yield of 20%. Our current strategy represents a reevaluation of this complication, subsequently paving the way for a step and redox economical approach for the construction of similar structures.

In summary, we have successfully developed a unique and concise strategy for the total synthesis of aplykurodinone-1 (8 steps from known **9**), without the requirement for any protecting group chemistry. A $SmI_2$-mediated reductive cyclization cascade reaction was used as the key step in this strategy for the diastereoselective construction of the tricyclic core in the advanced intermediate **13**. This strategy also involved the use of a secondary alkyl cuprate mediated 1,4-addition reaction, which allowed for the direct installation of the C11 side chain. To the best of our knowledge, this work represents the first example of the use of a $SmI_2$-mediated intramolecular cascade cyclization reaction between "halide, normal alkene and aldehyde" groups. It was envisaged that the use of the chiral ketone (+)-**9**[12c] would permit asymmetric transformation into aplykurodinone-1. We believe that this new strategy will provide a platform for the straightforward and asymmetric synthesis of natural products containing the unusual *cis*-fused hydrindane framework.

## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedure, $^1H$ and $^{13}C$ NMR spectra, and X-ray data information. This material is available free of charge via the Internet at http://pubs.acs.org.

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§G.L. and G.M. contributed equally to the work.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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## ■ REFERENCES

(1) (a) Ortega, M. J.; Zubia, E.; Salva, J. *J. Nat. Prod.* **1997**, *60*, 488−489. (b) Spinella, A.; Gavagnin, M.; Crispino, A.; Cimino, G.; Martinez, E.; Ortea, J.; Sodano, G. *J. Nat. Prod.* **1992**, *55*, 989−993. (c) Miyamoto, T.; Higuchi, R.; Komori, T. *Tetrahedron Lett.* **1986**, *27*, 1153−1156.

(2) Gavagnin, M.; Carbone, M.; Nappo, M.; Mollo, E.; Roussis, V.; Cimino, G. *Tetrahedron* **2005**, *61*, 617−621.

(3) (a) Izzo, I.; Meduri, G.; Avallone, E.; De Riccardis, F.; Sodano, G. *Eur. J. Org. Chem.* **2000**, 439−448. (b) De Riecardis, F.; Spinella, A.; Izzo, I.; Giordano, A.; Sodano, G. *Tetrahedron Lett.* **1995**, *36*, 4303−4306.

(4) Zhang, Y. D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 9567−9569.
(5) Peixoto, P. A.; Jean, A.; Maddaluno, J.; De Paolis, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6971−6973.
(6) (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281. Recent review on the economies of synthesis: (b) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010−3021.
(7) Recent reviews on the protecting-group-free syntheses: (a) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193−205. (b) Hoffmann, R. W. *Synthesis* **2006**, 3531−3541.
(8) Representative recent syntheses using a protecting-group-free strategy: (a) Peng, Q.-L.; Luo, S.-P.; Xia, X.-E.; Liu, L.-X.; Huang, P.-Q. *Chem. Commun.* **2014**, *50*, 1986−1988. (b) Xiao, Q.; Jackson, J. J.; Basak, A.; Bowler, J. M.; Miller, B. G.; Zakarian, A. *Nat. Chem.* **2013**, *5*, 410−416. (c) Hayashi, Y.; Umemiya, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3450−3452. (d) Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7507−7510. (e) Xu, J.; Caro-Diaz, E. J. E.; Trzoss, L.; Theodorakis, E. A. *J. Am. Chem. Soc.* **2012**, *134*, 5072−5075. (f) Noutsias, D.; Vassilikogiannakis, G. *Org. Lett.* **2012**, *14*, 3565−3567. (g) Ge, H. M.; Zhang, L.-D.; Tan, R. X.; Yao, Z.-J. *J. Am. Chem. Soc.* **2012**, *134*, 12323−12325. (h) Hickmann, V.; Kondoh, A.; Gabor, B.; Alcarazo, M.; Fürstner, A. *J. Am. Chem. Soc.* **2011**, *133*, 13471−13480. (i) Liu, G.; Romo, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 7537−7540. (J) Gerfaud, T.; Xie, C. S.; Neuville, L.; Zhu, J. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 3954−3957. (k) Li, C.; Yu, X.; Lei, X. *Org. Lett.* **2010**, *12*, 4284−4287. (l) Zhou, Q.; Chen, X.; Ma, D.-W. *Angew. Chem., Int. Ed.* **2010**, *49*, 3513−3516. (m) Chen, P.; Cao, L.; Li, C. *J. Org. Chem.* **2009**, *74*, 7533−7535.
(9) (a) Han, J. C.; Liu, L. Z.; Li, C. C.; Yang, Z. *Chem.—Asian J.* **2013**, *8*, 1972−1975. (b) Wei, H.; Qiao, C.; Liu, G.; Yang, Z.; Li, C.-C. *Angew. Chem., Int. Ed.* **2013**, *52*, 620−624. (c) Liu, Q.; Yue, G.; Wu, N.; Lin, G.; Li, Y.; Quan, J.; Li, C.-C.; Wang, G.; Yang, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 12072−12076. (d) Shi, H.; Fang, L.; Tan, C.; Shi, L.; Zhang, W.; Li, C.-C.; Luo, T.; Yang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 14944−14947. (e) Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745−16746. (f) Liu, L.-Z.; Han, J.-C.; Yue, G.-Z.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 13608−13609.
(10) For the synthesis of the Grignard reagent **4**, see SI. The synthesis of the corresponding bromide: (a) Vyvyan, J.; Loitz, C.; Looper, R.; Mattingly, C.; Peterson, E.; Staben, S. *J. Org. Chem.* **2004**, *69*, 2461−2468. (b) Singh, V.; Khurana, A.; Kaur, I.; Sapehiyia, V.; Kad, G. L.; Singh, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1766−1768.
(11) (a) Szostak, M.; Fazakerley, N.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014**, *114*, 5959−6039. (b) Procter, D. J.; Flowers, R. A.; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; The Royal Society of Chemistry: Cambridge, 2009; p 204. (c) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140−7165. (d) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371−3404. (e) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351−10372. (f) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338.
(12) Racemic ketone **9** was prepared by an enamine Robinson annulation in good yield from the commercially available aldehyde: (a) Lau, S. Y. W. *Org. Lett.* **2011**, *13*, 347−349. (b) Ireland, R. E.; McKenzie, T. C.; Trust, R. I. *J. Org. Chem.* **1975**, *40*, 1007−1017. For enantioselective synthesis of **9**, see: (c) Das, P. P.; Lysenko, I.; Cha, J. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 9459−9461.
(13) Representative recent syntheses using $SmI_2$ mediated reductive cascade cyclization reaction: (a) Fazakerley, N. J.; Helm, M. D.; Procter, D. J. *Chem.—Eur. J.* **2013**, *19*, 6718−6723. (b) Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964−14967. (c) Parmar, D.; Price, K.; Spain, M.; Matsubara, H.; Bradley, P. A.; Procter, D. J. *J. Am. Chem. Soc.* **2011**, *133*, 2418−2420. (d) Beemelmanns, C.; Reissig, H. U. *Angew. Chem., Int. Ed.* **2010**, *49*, 8021−8025. (e) Helm, M. D.; Da Silva, M.; Sucunza, D.; Findley, T. J.; Procter, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9315−9317. (f) Nicolaou, K. C.; Zhang, H.; Ortiz, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 5642−5647. (g) Nicolaou, K. C.; Ortiz, A.; Zhang, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 5648−5652. (h) Shenvi, R.; Guerrero, C.; Shi, J.; Li, C.-C.; Baran, P. *J. Am. Chem. Soc.* **2008**, *130*, 7241−7243. (i) Shipe, W. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 7025−7035.
(14) For a $SmI_2$ mediated Barbier-type reaction cascade: (a) Rivkin, A.; Gonzalez-Lopez de Turiso, F.; Nagashima, T.; Curran, D. P. *J. Org. Chem.* **2004**, *69*, 3719−3725. (b) Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050−6058. (c) Curran, D. P.; Wolin, R. L. *Synlett* **1991**, 317−318. For a $SmI_2$ mediated reductive cyclization reaction of a haloacetal with an alkene to generate cyclic hemiketal, see: (d) Fukuzawa, S.-I.; Tsuchimoto, T. *Synlett* **1993**, 803−804.
(15) (a) Boffey, R. J.; Santagostino, M.; Whittingham, W. G.; Kilburn, J. D. *Chem. Commun.* **1998**, 1875−1876. (b) Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064−5067.
(16) (a) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943−961. (b) Molander, G.; Mckie, J. *J. Org. Chem.* **1992**, *57*, 3132−3139. (c) Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett* **1990**, 773−774. For the mechanistic role of HMPA in $SmI_2$ reactions, see: (d) Choquette, K.; Sadasivam, D.; Flowers, R. *J. Am. Chem. Soc.* **2010**, *132*, 17396−17398. (e) Sadasivam, D.; Antharjanam, P.; Prasad, E.; Flowers, R. *J. Am. Chem. Soc.* **2008**, *130*, 7228−7229 and references therein.