Organic LETTERS

Letter

pubs.acs.org/OrgLett

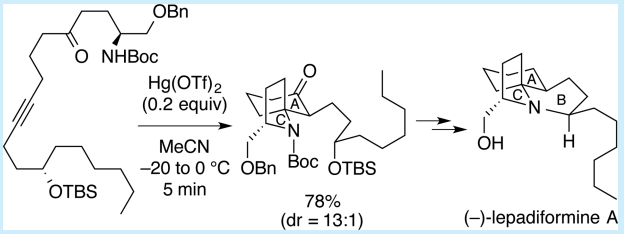
Total Synthesis of (−)-Lepadiformine A Utilizing $Hg(OTf)_2$-Catalyzed Cycloisomerization Reaction

Keisuke Nishikawa, Seiho Kikuchi, Shinnosuke Ezaki, Tomoyuki Koyama, Haruka Nokubo, Takeshi Kodama, Yoshimitsu Tachi, and Yoshiki Morimoto*

Department of Chemistry, Graduate School of Science, Osaka City University, Sumiyoshi-ku, Osaka 558-8585, Japan

Supporting Information

ABSTRACT: A cytotoxic marine alkaloid (−)-lepadiformine A (**1**) possesses a unique structure characterized by the *trans*-1-azadecalin AB ring system fused with the AC spiro-cyclic ring. In this research, we found that a cycloisomerization reaction from amino ynone **2** to a 1-azaspiro[4.5]decane skeleton **3**, corresponding to the AC ring system of **1**, is promoted by $Hg(OTf)_2$. Thus, we have accomplished the efficient total synthesis of (−)-lepadiformine A in 28% overall yield by featuring the novel $Hg(OTf)_2$-catalyzed cycloisomerization.



An azatricyclic alkaloid (−)-lepadiformine A (**1**) was isolated from the marine tunicate *Clavelina lepadiformis* Müller in the Mediterranean near Tunisia by Biard and co-workers in 1994 (Figure 1).[1] Compound **1** exhibits

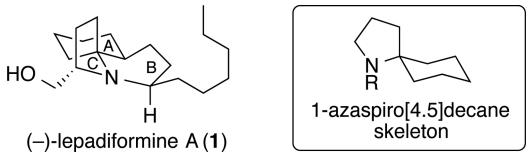
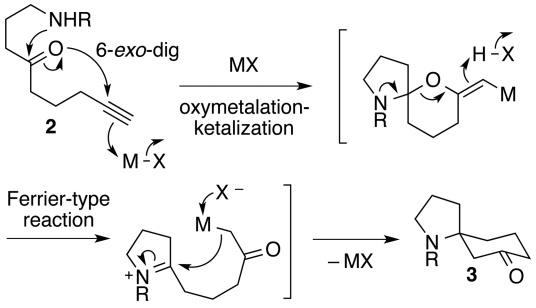


Figure 1. Structure of (−)-lepadiformine A (**1**).

cytotoxicities against various tumor cells [IC_{50} = 9.20 μg/mL (KB), 0.75 μg/mL (HT29), 3.10 μg/mL (P388), 6.30 μg/mL (P388 doxorubicin-resistant), and 6.10 μg/mL (NSCLS-N6)] and also possesses antiarrhythmic and antihypertensive properties. Although the structure different from **1** was first proposed based on spectroscopic and chemical methods, the original structure was finally revised to **1** through total synthesis by the Kibayashi and Weinreb groups.[2] The complex skeleton structure is characterized by the *trans*-1-azadecalin AB ring system fused with the AC spiro-cyclic ring, four asymmetric centers including a nitrogen-containing stereogenic tetrasubstituted carbon, and the B ring as a boat form. Although the specific skeleton structure and the interesting biological activities have prompted many synthetic organic chemists to promote the total synthesis so far,[2,3] we intended to carry out the efficient total synthesis of (−)-**1** based on our original synthetic methodology. In this contribution, we report the total synthesis of (−)-lepadiformine A (**1**) utilizing a $Hg(OTf)_2$-catalyzed cycloisomerization reaction as a key step.

We focused on construction of a 1-azaspiro[4.5]decane skeleton corresponding to the AC spiro-cyclic ring system of **1**, because the skeleton is embedded in a number of complex alkaloids such as lepadiformines,[1,4] cylindricines,[5] polycitorols,[6] FR901483,[7] and *Kopsia* alkaloids.[8] It was envisioned that the desired azaspiro compound **3** could be obtained from an acyclic amino ynone **2** in one step if 6-*exo*-dig oxymetalation and aminoketalization for the substrate **2** with metal catalysis and subsequent Ferrier-type cyclization[9] consecutively proceeded as shown in Scheme 1. It was investigated using substrate **4** whether or not such a cycloisomerization reaction takes place (Table 1).

Scheme 1. Metal-Catalyzed Cycloisomerization Reaction

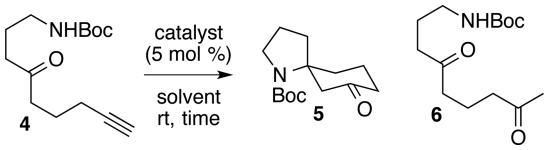


First, gold catalysts known as a good ynophile[10] were examined. Although AuCl and $AuCl_3$ showed little reactivity, recovering only starting material **4** (entries 1 and 2), it was found that $Ph_3PAuOTf$ and Ph_3PAuBF_4 brought about the cycloisomerization[12] to afford desired spiro product **5** albeit in modest yields (entries 3 and 4). Only AgOTf required for preparation of $Ph_3PAuOTf$ resulted in no reaction (entry 5). Platinum catalysts (entries 6 and 7) afforded compound **5** in low yields along with alkyne hydration byproduct **6**, which was

Received: October 3, 2015

DOI: 10.1021/acs.orglett.5b02867
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Conditions for the Cycloisomerization Reaction



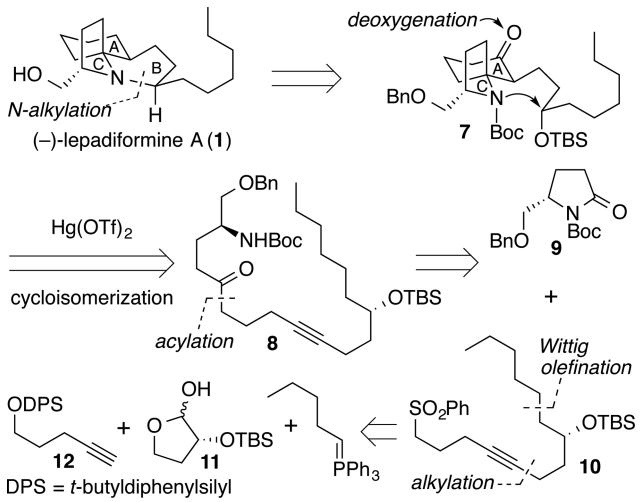
				yield (%)[a]		
entry	catalyst	solvent	time	5	4	6
1	AuCl	MeCN	14 h		65	
2	$AuCl_3$	MeCN	22 h		57	
3	$Ph_3PAuOTf$[b]	CH_2Cl_2	30 min	53		
4	Ph_3PAuBF_4[b]	MeCN	30 h	47		
5	AgOTf	MeCN	23 h		73	
6	$PtCl_2$	CH_2Cl_2	42 h	21	11	40
7	$PtCl_4$[c]	CH_2Cl_2	5 h	22		23
8	$Pd(TFA)_2$	MeCN	13 h		21	12
9	$Hg(OTf)_2$	CH_2Cl_2	40 min	71		16
10	$Hg(OTf)_2$	MeCN	40 min	74	10	
11	$Hg(OTf)_2$	toluene	1 h	64		33
12[d]	$Hg(OTf)_2$	MeCN	25 min	61		

[a]Isolated yield. [b]These catalysts were prepared in situ from Ph_3PAuCl and AgOTf or $AgBF_4$ (ref 11). [c]10 mol %. [d]MS4A (100 wt %) was added.

also generated in a palladium-catalyzed reaction (entry 8). Next, mercury(II) triflate,[13] as a good ynophile as a gold(I) catalyst, was tested. To our delight, it was found that $Hg(OTf)_2$ effected the cycloisomerization reaction in better yields than gold(I) catalysts (entries 9–11). As the alkyne hydration byproduct **6** was observed, the reaction was conducted in the presence of molecular sieves (MS); however, the yield of **5** could not be improved (entry 12). Thus, we could develop the $Hg(OTf)_2$-catalyzed cycloisomerization reaction from acyclic amino ynone **2** to spiro compound **3**, a 1-azaspiro[4.5]decane skeleton frequently occurring in the aforementioned complex alkaloids. With this method in hand, we embarked on the total synthesis of (−)-lepadiformine A (**1**).

The retrosynthetic analysis of **1** was outlined in Scheme 2. We planned to construct the AC spiro-cyclic ring system **7** by applying the $Hg(OTf)_2$-catalyzed cycloisomerization reaction

Scheme 2. Retrosynthetic Analysis of (−)-Lepadiformine A (1)



to functionalized amino ynone precursor **8** bearing all carbon numbers required for the synthesis of **1**. The product **7** could be converted into (−)-lepadiformine A (**1**) via deoxygenation and the B ring formation according to Kibayashi's and Zhao's precedents.[3c,i] The precursor **8** would be prepared by acylation of sulfone **10**, which should be assembled from the known hemiacetal **11**[14] and alkyne **12**,[15] with the known pyrrolidinone **9**.[16]

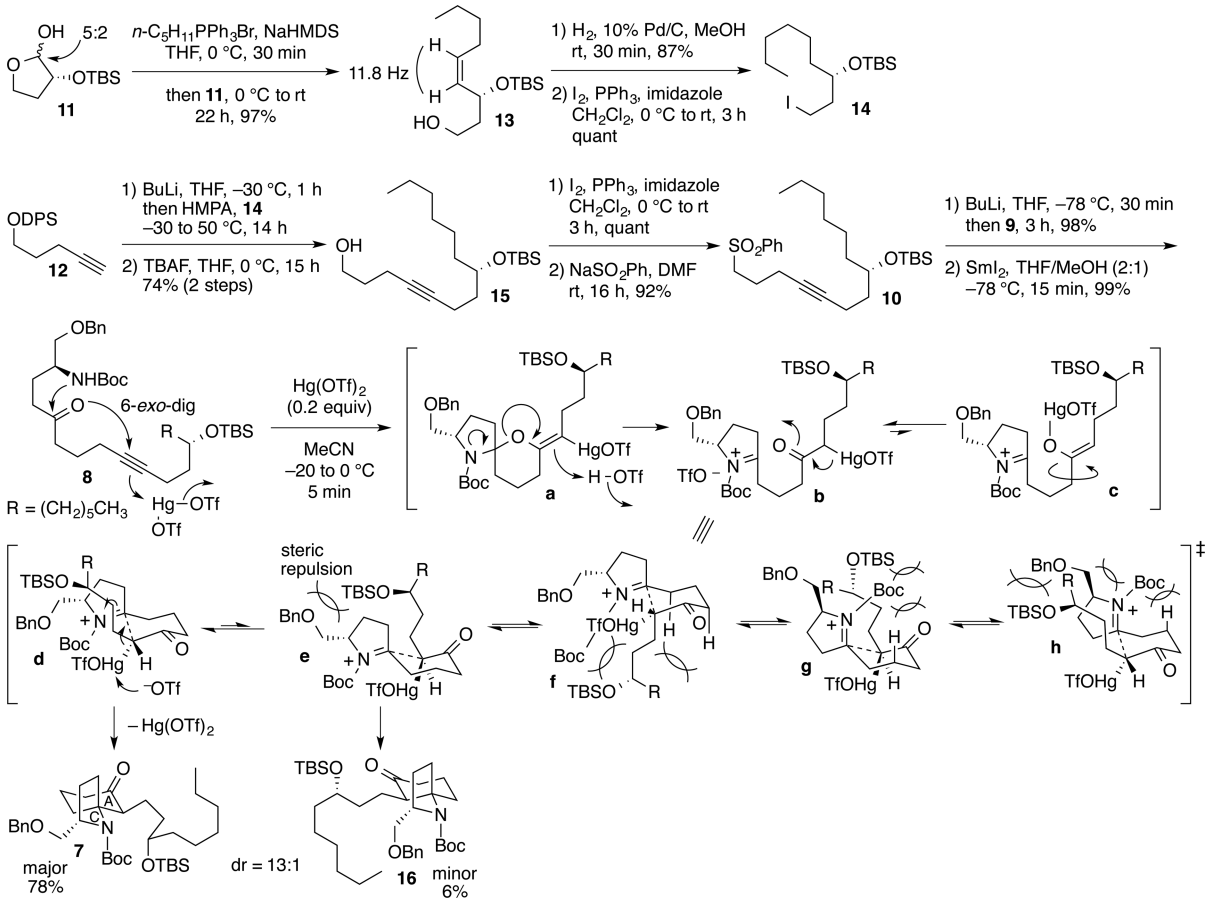
The synthesis of the cyclization precursor **8** began with Wittig olefination of the hemiacetal **11** with pentylidene-triphenylphosphorane to provide *Z*-selective alkene **13** (Scheme 3). After hydrogenation of the alkene **13** and subsequent iodination of the alcohol, alkylation of the lithium acetylide of **12** with iodide **14** and selective deprotection[17] of the DPS group afforded alcohol **15**. Conversion of the alcohol **15** to sulfone **10** was carried out via iodination and sulfonylation, and acylation of an α-anion of sulfone **10** with pyrrolidinone **9** followed by desulfonylation[18] prepared the functionalized cyclization substrate **8** in high overall yield. After optimization of the reaction conditions, ynone **8** was treated with 0.2 equiv of $Hg(OTf)_2$ in MeCN at −20 to 0 °C for 5 min to give the desired AC spiro-cyclic ring system **7** in 78% yield and good diastereoselectivity (dr = 13:1).[19]

The reaction mechanism and the diastereoselectivity of the cycloisomerization that we propose at present are shown in Scheme 3. As predicted in Scheme 1, a 6-*exo*-dig intramolecular oxymercuration initiated by coordination of $Hg(OTf)_2$ to the alkyne π-electron and nucleophilic addition of the nitrogen function to the carbonyl carbon would produce aminoketal **a**. The aminoketal could be cleaved by protonation of the enol ether with TfOH generated to afford iminium ion intermediate **b**.[20] Although an α-mercury carbonyl in **b** would be in equilibrium with the enolate form **c**, we think that the α-mercury carbonyl would predominate due to the stability of a C−Hg bond.[21] The spiro-cyclic products could be obtained by reforming a carbocycle via Ferrier-type cyclization with regeneration of a $Hg(OTf)_2$ catalyst, yielding diastereoselectively **7** along with a minor product **16**. Considering chairlike transition states **d**–**h** in the cyclization, **d**–**f** could be more stable than **g** and **h** because in **g** and **h** a bulky NBoc iminium moiety is disposed in an axial position. In transition states **d**–**f**, **f** with a bulky TBSO-containing alkyl group in an axial position[22] and **e** with steric repulsion between benzyloxymethyl and the TBSO-containing alkyl groups would be less stable than **d** without such steric repulsion.[3c] Thus, **7** would be selectively produced by way of the transition state **d**.

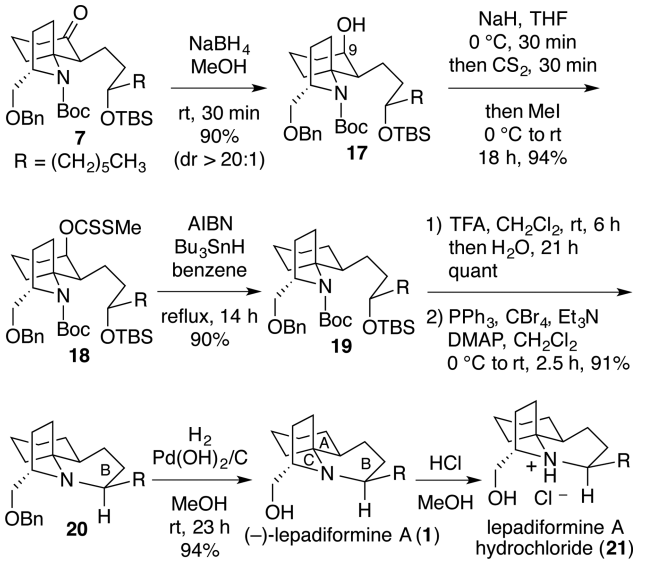
The residual tasks toward the total synthesis are deoxygenation in the A ring and formation of the B ring. Deoxygenation of **7** was performed according to Barton's method[23] after diastereoselective reduction to axial alcohol **17**[24] to furnish **19** in good yield (Scheme 4). After removal of both the Boc and TBS protective groups in **19** with TFA, the resulting amino alcohol was subjected to Kibayashi's and Zhao's procedure[3c,i] to provide azatricyclic ring system **20** via the B ring formation accompanied by inversion of configuration. Finally, deprotection of a Bn group in **20** gave synthetic (−)-lepadiformine A (**1**), the spectral data (^1H and ^{13}C NMR) and the optical rotation of which, $[\alpha]_D^{30}$ −14.6 (*c* 0.38, MeOH), were consistent with those reported for the previous synthetic one, lit.[2c] $[\alpha]_D^{20}$ −15 (*c* 0.45, MeOH). We confirmed that the spectral data and the optical rotation of the hydrochloride salt **21**, $[\alpha]_D^{30}$ +2.2 (*c* 0.70, $CHCl_3$), are also

DOI: 10.1021/acs.orglett.5b02867
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Synthesis of the AC Spiro-cyclic Ring System 7



Scheme 4. Total Synthesis of (−)-Lepadiformine A (1)



comparable to those reported for the authentic one, lit.[2c] $[\alpha]_D^{20}$ +2.5 (*c* 0.51, $CHCl_3$).

In conclusion, we have developed the novel construction method of a 1-azaspiro[4.5]decane skeleton, frequently occurring in many complex polycyclic alkaloids, by using a $Hg(OTf)_2$-catalyzed cycloisomerization reaction from an acyclic amino ynone substrate and accomplished the total synthesis of an azatricyclic alkaloid (−)-lepadiformine A (**1**) utilizing the cycloisomerization of **8** to **7** as a key step. The synthesis has been efficiently achieved in 28% overall yield and 16 steps based on the known hemiacetal **11**.[14] This novel $Hg(OTf)_2$-catalyzed cycloisomerization reaction could be useful for the construction of complex polycyclic alkaloids. A detailed reaction mechanism of the cycloisomerization and its application to other natural products are under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02867.

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: morimoto@sci.osaka-cu.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Astellas Foundation.

■ REFERENCES

(1) (a) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*,

DOI: 10.1021/acs.orglett.5b02867
Org. Lett. XXXX, XXX, XXX−XXX

2691−2694. (b) Jugé, M.; Grimaud, N.; Biard, J. F.; Sauviat, M. P.; Nabil, M.; Verbist, J. F.; Petit, J. Y. *Toxicon* **2001**, *39*, 1231−1237.
(2) (a) For a review, see: Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531−2549. (b) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583−4592. (c) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337−4345.
(3) (a) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511−3514. (b) Liu, J.; Hsung, R. P.; Peters, S. D. *Org. Lett.* **2004**, *6*, 3989−3992. (c) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473−1480. (d) Lee, M.; Lee, T.; Kim, E.-Y.; Ko, H.; Kim, D.; Kim, S. *Org. Lett.* **2006**, *8*, 745−748. (e) Schär, P.; Renaud, P. *Org. Lett.* **2006**, *8*, 1569−1571. (f) Caldwell, J. J.; Craig, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2631−2634. (g) Fujitani, M.; Tsuchiya, M.; Okano, K.; Takasu, K.; Ihara, M.; Tokuyama, H. *Synlett* **2010**, *2010*, 822−826. (h) Meyer, A. M.; Katz, C. E.; Li, S.-W.; Velde, D. V.; Aubé, J. *Org. Lett.* **2010**, *12*, 1244−1247. (i) Mei, S.-L.; Zhao, G. *Eur. J. Org. Chem.* **2010**, *2010*, 1660−1668. (j) Perry, M. A.; Morin, M. D.; Slafer, B. W.; Rychnovsky, S. D. *J. Org. Chem.* **2012**, *77*, 3390−3400. (k) In, J.; Lee, S.; Kwon, Y.; Kim, S. *Chem. - Eur. J.* **2014**, *20*, 17433−17442. (l) Pandey, G.; Janakiram, V. *Chem. - Eur. J.* **2015**, *21*, 13120−13126.
(4) Sauviat, M.-P.; Vercauteren, J.; Grimaud, N.; Jugé, M.; Nabil, M.; Petit, J.-Y.; Biard, J.-F. *J. Nat. Prod.* **2006**, *69*, 558−562.
(5) Li, C. P.; Blackman, A. J. *Aust. J. Chem.* **1995**, *48*, 955−965.
(6) Issa, H. H.; Tanaka, J.; Rachmat, R.; Setiawan, A.; Trianto, A.; Higa, T. *Mar. Drugs* **2005**, *3*, 78−83.
(7) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37−44.
(8) Kam, T. S.; Lim, K. H. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: Amsterdam, 2008; Vol. *66*, pp 1−111.
(9) (a) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455−1458. (b) Chida, N.; Ohtsuka, M.; Ogura, K.; Ogawa, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2118−2121.
(10) (a) For a review, see: Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395−403. (b) Liu, Y.; Liu, M.; Guo, S.; Tu, H.; Zhou, Y.; Gao, H. *Org. Lett.* **2006**, *8*, 3445−3448.
(11) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133−4136.
(12) For a similar catalysis with gold(I) catalysts, see: (a) Zi, W.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 12600−12603. (b) Kim, H.; Rhee, Y. H. *J. Am. Chem. Soc.* **2012**, *134*, 4011−4014.
(13) For a review, see: Nishizawa, M.; Imagawa, H.; Yamamoto, H. *Org. Biomol. Chem.* **2010**, *8*, 511−521.
(14) Prévost, M.; St-Jean, O.; Guindon, Y. *J. Am. Chem. Soc.* **2010**, *132*, 12433−12439.
(15) Clark, R. C.; Lee, S. Y.; Boger, D. L. *J. Am. Chem. Soc.* **2008**, *130*, 12355−12369.
(16) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron* **1994**, *50*, 6221−6238.
(17) BouzBouz, S.; Cossy, J. *Org. Lett.* **2004**, *6*, 3469−3472.
(18) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135−1138.
(19) The stereochemistry of products **7** and **16** was unambiguously assigned based on their NOESY spectra. See the Supporting Information.
(20) Although the stereochemistry of the spiro ring system and the face selectivity of the protonation step in intermediate **a** have been unknown, we think that the intermediate **b** can have both *R* and *S* configurations of the C−Hg bond via the enolate form **c**.
(21) House, H. O.; Auerbach, R. A.; Gall, M.; Peet, N. P. *J. Org. Chem.* **1973**, *38*, 514−522.
(22) Like the transition state **f**, transition states with the bulky TBSO-containing alkyl group in an axial position in **e**, **g**, and **h** should also be disfavored due to steric hindrance.
(23) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.
(24) In this ketone reduction, an equatorial hydride attack could predominate as a result of avoiding the axial alkyl group. In the ^{1}H NMR spectrum of a major rotamer of **17**, the coupling pattern of C9−H at 4.12 ppm was observed as a doublet with J = 2.2 Hz showing an equatorial proton.

DOI: 10.1021/acs.orglett.5b02867
Org. Lett. XXXX, XXX, XXX−XXX