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Dehydrative Mannich-Type Reaction for the Synthesis of Azepinobisindole Alkaloid Iheyamine A

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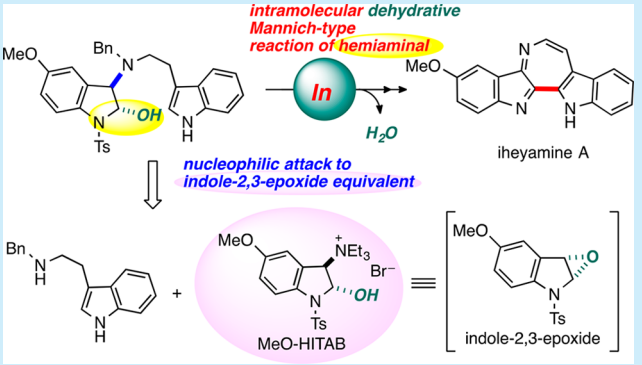
Supporting Information

ABSTRACT: A concise synthesis of the azepinobisindole alkaloid iheyamine A from an indole-2,3-epoxide equivalent has been achieved. This method features a formal C3 electrophilic reaction of an indole-2,3-epoxide equivalent with tryptamine to form a 3-aminoindoline and a novel In-catalyzed dehydrative Mannich-type reaction of the hemiaminal to give the azepinobisindole core.



Iheyamines A (**1**) and B were isolated from a colonial ascidian *Polycitorella* sp. by Higa and co-workers in 1999 (Figure 1),[1]

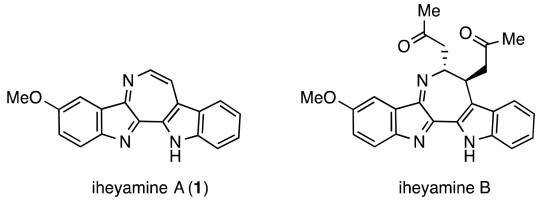
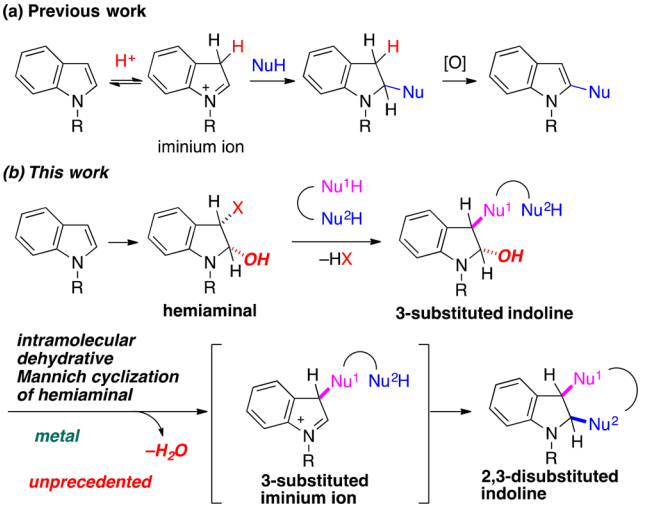


Figure 1. Azepinobisindole alkaloids iheyamines A (**1**) and B.

and their structure consists of a central azepane ring between two indole rings. These alkaloids have attracted considerable interest because of their intriguing structural features and cytotoxity against tumor cells.[2] The first elegant total synthesis of iheyamines A (**1**) was accomplished by Sperry and co-workers in 2016 via intermolecular cross-Mannich reaction between 5-methoxy-3-acetoxyindole and tryptamine to afford 2,2′-bisindole.[3] Recently, Sperry also reported the related synthetic studies toward iheyamine A, in which intramolecular Mannich cyclization occurred at the C4 position of 5-methoxyindole not the C2 position.[4]

The Mannich reaction of indoles with nucleophiles is a powerful tool to construct C−C bonds at the C2 position of indoles (Scheme 1).[5] However, only indoles, in which the enamine form is predominant over the required iminium form, was deployed in previous studies (Scheme 1a). Thus, the reaction of alternative, more reactive imine equivalents is highly desirable to introduce various nucleophiles at the C2 position of the indoles. We speculated that hemiaminals could be used in Mannich reactions as imine equivalents via dehydration. However, to date, Mannnich-type cyclizations of indole rings

Scheme 1. Mannich Reaction of Indoles with Nucleophiles



at the hemiaminal moiety have not yet been explored because of their instability.[6] As a part of our interest in the total synthesis of azepinoindole alkaloids by the C4 Pictet−Spengler reaction of serotonins[7a] or tryptophans,[7b,c] we next set out to synthesize **1** by an intramolecular dehydrative Mannich-type cyclization of hemiaminals (Scheme 1b). We recognized the potential utility of bench-stable and weighable-in-air indole-containing hemiaminals as C2 electrophiles to react with various nucleophiles via dehydration and Mannich-type reaction. In connection with our work on the total synthesis of indole alkaloids,[8] we have

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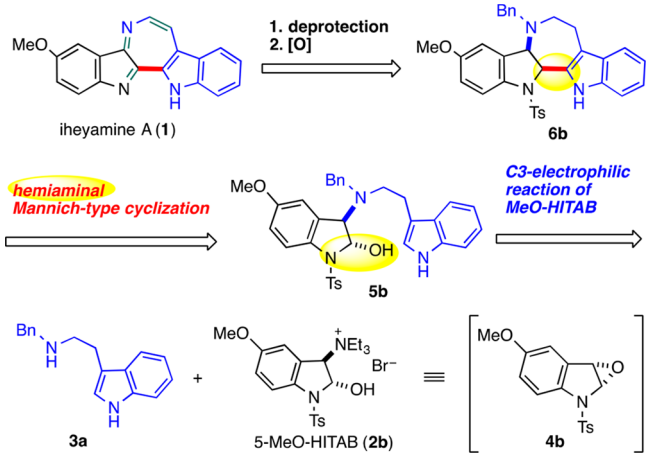
previously described the use of a novel indole-2,3-epoxide equivalent, namely, 2-hydroxyindoline-3-triethylammonium bromide (HITAB), as a convenient reagent for formal C3 electrophilic reactions of indoles with nucleophiles.[9] In addition, we found that the hemiaminals derived from HITAB are isolable. Hence, we envisioned that HITAB could be used as the starting material for the synthesis of **1**. Herein, we report a concise synthesis of iheyamine A by the intramolecular dehydrative Mannich-type reaction of the corresponding hemiaminal.

According to our retrosynthetic analysis of **1** (Scheme 2), 3-amino-2-hydroxyindoline **5b** was envisioned to arise from MeO-

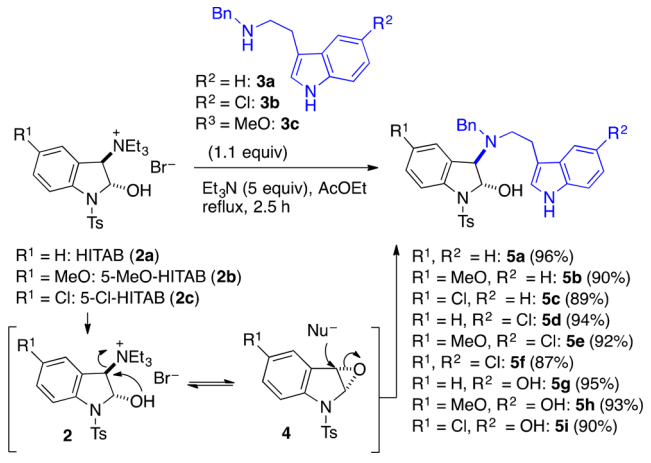
Scheme 2. Retrosynthesis of Iheyamine A (1)



HITAB (**2b**), which is an equivalent of indole-2,3-epoxide **4**, and tryptamine **3** by C3 electrophilic reaction. Intramolecular dehydrative Mannich-type reaction of **5b** would afford azepinoindole **6b**, which would be easily transformed into iheyamine A (**1**) by deprotection and oxidation.

Our investigation began with the synthesis of 3-amino-2-hydroxyindoline **5** (Scheme 3). HITAB (**2a**),[9] 5-MeO-HITAB

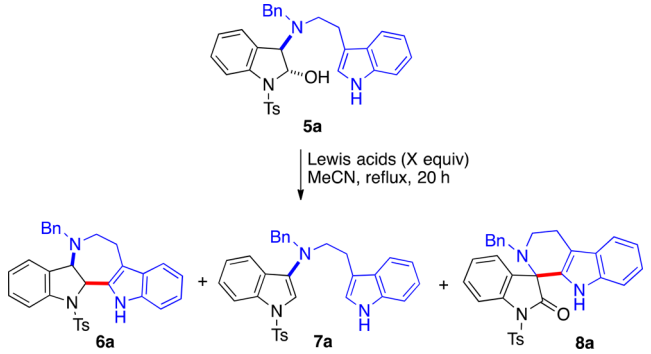
Scheme 3. Synthesis of 5 from 2



(**2b**), and 5-Cl-HITAB (**2c**) were prepared from commercially available indoles in one-pot, gram quantity and without column chromatography purification. A C3 electrophilic reaction of **2a**–**c** with tryptamines **3a**–**c** afforded **5a**–**i** via indole-2,3-epoxide **4a**–**c** in 87–96% yields with *trans* selectivity.

With **5** in hand, we tested the feasibility of the key dehydrative Mannich-type reaction to form the azepinobisindole core (Table 1). Initially, **5a**, used as a model substrate, was refluxed in MeCN (entry 1). However, under these conditions, the desired product

Table 1. Dehydrative Mannich-Type Reaction of 5a[a]



		yield (%)[b]		
entry	Lewis acids (X equiv)	**6a**	**7a**	**8a**
1		0	0	0
2	ZnI_2 (1)	10	3	10
3	$ZnCl_2$ (1)	13	4	8
4	$ZnBr_2$ (1)	15	0	13
5	$Zn(OTf)_2$ (1)	20	4	11
6	$Cu(OTf)_2$ (1)	37	13	0
7	$Yb(OTf)_3$ (1)	59	24	0
8	$La(OTf)_3$ (1)	52	17	5
9	$FeCl_3$ (1)	28	24	0
10	$In(OTf)_3$ (1)	60	1	3
11	$In(OTf)_3$ (0.5)	59	6	0
12	$In(acac)_3$ (0.5)	0	0	0
13	$InF{\cdot}3H_2O$ (0.5)	0	0	0
14	$InBr_3$ (0.5)	57	26	0
15	$InCl_3$ (0.5)	60	23	0
16	$InCl_3{\cdot}4H_2O$ (0.5)	61	26	0
17	$InCl_3{\cdot}4H_2O$ (0.3)	51	12	10
18	$InCl_3{\cdot}4H_2O$ (0.1)	31	0	5

[a]**6a** (0.2 mmol), Lewis acid (X equiv), solvent (4 mL). [b]Isolated yields.

6a was not obtained. When the reaction was performed in the presence of ZnI_2 as Lewis acid, **6a** was obtained in 10% yield along with byproducts **7a** and **8a** (entry 2). The Ciamician–Plancher rearrangement is known to give 2,3-disubstituted indoles from 3,3-disubstituted indolenines via 1,2-migration.[10] In our cases, the Ciamician–Plancher rearrangement formed spiro compound **8a** along with small amounts of the desired **6a**. Although **6a** was obtained in low yield, this result showed the feasibility of our strategy. A variety of zinc complexes were screened, but no improvement was observed (entries 3–5). To our delight, the use of $Yb(OTf)_3$ or $In(OTf)_3$ dramatically increased the yield of **6a** (entries 6–10).[11] Interestingly, the dehydrative Mannich-type reaction was found to proceed also with a catalytic amount of the indium complex (entries 11). Because of the high cost of $Yb(OTf)_3$ and $In(OTf)_3$, other Lewis acids were investigated (entries 12–16), and the best results (61% yield) were achieved using $InCl_3{\cdot}4H_2O$ (0.5 equiv) (Table 1, entry 16). It is noteworthy that the dehydrative Mannich-type reaction could be performed in the presence of water and under air atmosphere. Decreasing the catalyst loading below 50 mol % resulted in significantly lower yields (entries 16–18). To the best of our knowledge, this is the first example of an indium-catalyzed

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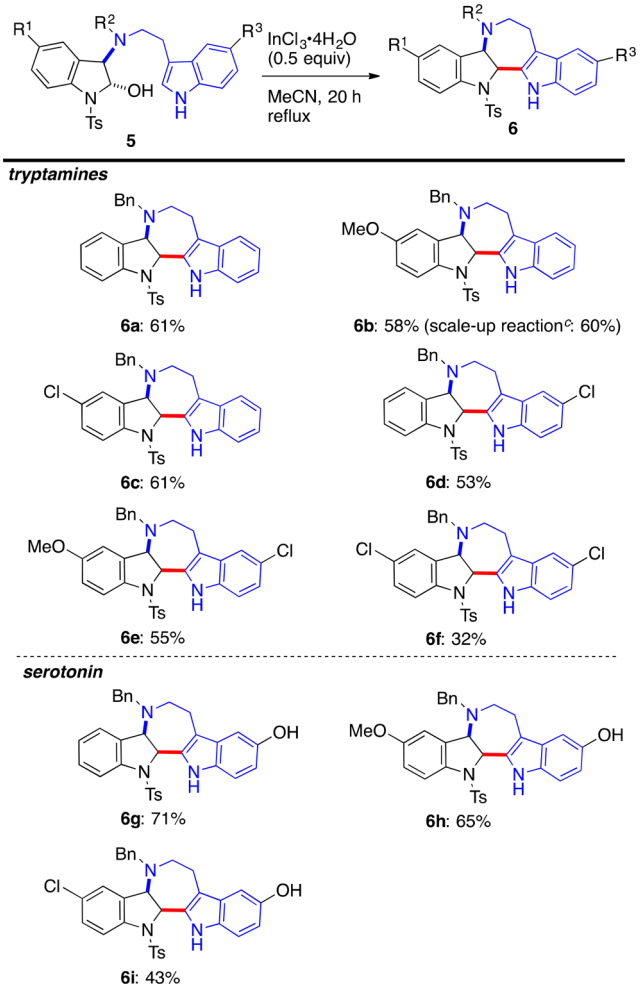
intramolecular Mannich-type reaction of a hemiaminal with release of water.[6]

With the optimized conditions in hand, we then explored the substrate scope of the reaction. As shown in Scheme 4,

Scheme 4. Substrate Scope[a,b]

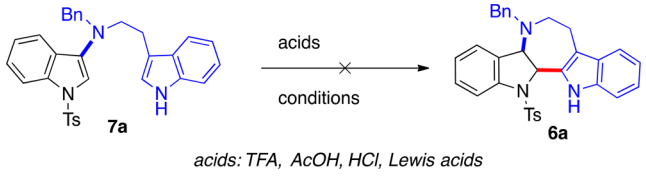


[a] **5** (0.2 mmol), $InCl_3·4H_2O$ (0.1 mmol), MeCN (4 mL). [b] Isolated yields. [c] **5** (1 mmol), $InCl_3·4H_2O$ (0.5 mmol), MeCN (20 mL).

tryptamine derivatives **5a–f** reacted smoothly to produce azepinoindoles **6a–f** in 32–61% yields. Notably, the dehydrative Mannich-type reaction was also amenable to scale up (**5b**, 1 mmol). Further investigations showed that serotonin derivatives **5g–i** could also be employed, affording **6g–i** in 43–71% yields. Because straightforward methods to access these azepinoindoles are limited to intermolecular 2,2′-bisindole synthesis,[2−4] the present protocol is of great synthetic significance.

For comparison, intramolecular Mannich reactions of indole **7a** were carried out in the presence of various acids (Scheme 5).

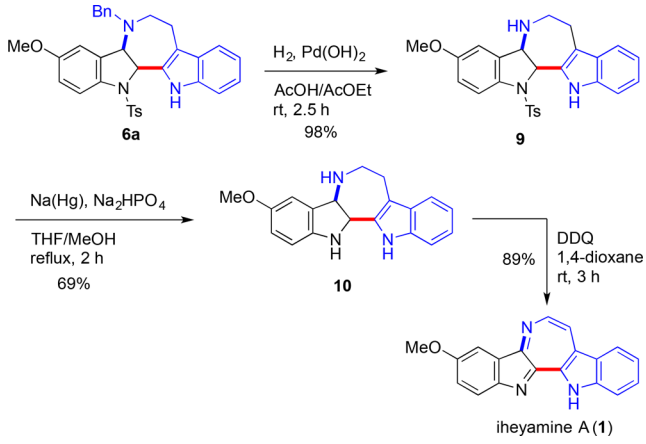
Scheme 5. Attempted Synthesis of 6a from 7a



However, no desired product **6a** was obtained under all conditions. Given the difficulties reported in the pioneering study by Sperry and co-workers,[4] it was not surprising that the intramolecular Mannich reaction of indoles to form 2,2′-bisindoles was challenging. Thus, it is noteworthy that the hemiaminal **5a** was highly suitable as a pivotal intermediate in the construction of 2,2′-bisindoles containing an azepane ring.

Our synthesis of **1** commenced with **6a** (Scheme 6). Upon treatment with H_2/Pd–C in AcOH/AcOEt, deprotection of the

Scheme 6. Completion of the Synthesis of Iheyamine A (1)



benzyl group of **6a** was achieved, affording **9** in 98% yield. The reaction of **9** with sodium amalgam gave the detosylated compound **10** in 69% yield. Finally, DDQ oxidation of **10** afforded iheyamine A (**1**) in 89% yield. The identity of synthetic **1** was confirmed by comparison of the spectral data with those of the natural product.[1,3]

In conclusion, a concise synthesis of azepinobisindole alkaloid iheyamine A was achieved by a formal C3 electrophilic reaction of HITAB with tryptamine and an indium-mediated dehydrative Mannich-type reaction of a hemiaminal. A key feature of our strategy is the use of stable hemiaminals for the construction of 2,2′-bisindoles containing an azepane ring. As previous studies of the Mannich reaction are limited to indoles,[4,5] the reaction developed herein represents a significant advance in synthetic chemistry. The hemiaminals in this route could potentially be used to synthesize other related azepinobisindole alkaloids, such as iheyamine B[1] and trigonolimine C.[12] The total synthesis of these alkaloids by dehydrative Mannich-type reaction of hemiaminals is currently being investigated in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00330.

Synthesis procedures and spectral and characterization data, including ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Sasaki, T.; Ohtani, I. I.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1999**, *40*, 303.
(2) Bremner, J. B.; Sengpracha, W.; Skelton, B. W. *Synth. Commun.* **2008**, *38*, 1931.
(3) Lindsay, A. C.; Leung, I. K. H.; Sperry, J. *Org. Lett.* **2016**, *18*, 5404.
(4) Lindsay, A. C.; Sperry, J. *Tetrahedron* **2017**, *73*, 4355.
(5) For selected examples of the Mannich-type reaction of indoles, see: (a) Smith, G. F.; Walters, A. E. *J. Chem. Soc.* **1961**, 940. (b) Bergman, J.; Koch, E.; Pelcman, B. *Tetrahedron Lett.* **1995**, *36*, 3945. (c) Gilbert, E. J.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 5500. (d) Chisholm, J. D.; Van Vranken, D. *J. Org. Chem.* **2000**, *65*, 7541. (e) Bergman, J.; Koch, E.; Pelcman, B. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 2609. (f) Hao, X.; Liu, S. *Tetrahedron Lett.* **2011**, *52*, 5640. (g) Xu, M.; An, R.; Huang, T.; Hao, X.; Liu, S. *Tetrahedron Lett.* **2016**, *57*, 1247. For selected examples of the C2 functionalization of indoles, see: (h) Morimoto, N.; Morioku, K.; Suzuki, H.; Takeuchi, Y.; Nishina, Y. *Org. Lett.* **2016**, *18*, 2020. (i) Nandi, R. K.; Ratsch, F.; Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Chem. Commun.* **2016**, *52*, 5328. (j) Nowrouzi, F.; Batey, R. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 892. (k) Alam, R.; Diner, C.; Jonker, S.; Eriksson, L.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 14417.
(6) For selected examples of the dehydrated Mannich-type reaction of hemiaminals, see: (a) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717. (b) Aggarwal, V. K.; Astle, C. J.; Rogers-Evans, M. *Org. Lett.* **2004**, *6*, 1469. (c) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (d) Lesma, G.; Colombo, A.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 590. (e) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030. (f) Shi, S.; Wei, X.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2012**, *134*, 17019. (g) Koley, D.; Srinivas, K.; Krishna, Y.; Gupta, A. *RSC Adv.* **2014**, *4*, 3934. (h) Koley, D.; Krishna, Y.; Srinivas, K.; Khan, A. A.; Kant, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 13196. (i) Zhang, S.; Li, L.; Hu, Y.; Li, Y.; Yang, Y.; Zha, Z.; Wang, Z. *Org. Lett.* **2015**, *17*, 5036. (j) Srinivas, K.; Singh, N.; Das, D.; Koley, D. *Org. Lett.* **2017**, *19*, 274. For reviews of reactions with hemiaminals, see: (k) Huang, Y.-Y.; Cai, C.; Yang, X.; Lv, Z.-C.; Schneider, U. *ACS Catal.* **2016**, *6*, 5747. (l) Wu, P.; Nielsen, T. E. *Chem. Rev.* **2017**, *117*, 7811.
(7) (a) Yamada, K.; Namerikawa, Y.; Haruyama, T.; Miwa, Y.; Yanada, R.; Ishikura, M. *Eur. J. Org. Chem.* **2009**, *2009*, 5752. (b) Yamada, K.; Yamaguchi, S.; Hatae, N.; Abe, T.; Iwamura, T.; Ishikura, M. *Heterocycles* **2011**, *83*, 815. (c) Abe, T.; Yamada, K. *J. Nat. Prod.* **2017**, *80*, 241. (d) Abe, T.; Haruyama, T.; Yamada, K. *Synthesis* **2017**, *49*, 4141.
(8) (a) Abe, T.; Ikeda, T.; Yanada, R.; Ishikura, M. *Org. Lett.* **2011**, *13*, 3356. (b) Abe, T.; Ikeda, T.; Yanada, R.; Ishikura, M. *Eur. J. Org. Chem.* **2012**, *2012*, 5018. (c) Abe, T.; Nakamura, S.; Yanada, R.; Choshi, T.; Hibino, S.; Ishikura, M. *Org. Lett.* **2013**, *15*, 3622. (d) Abe, T.; Itoh, T.; Choshi, T.; Hibino, S.; Ishikura, M. *Tetrahedron Lett.* **2014**, *55*, 5268. (e) Itoh, T.; Abe, T.; Choshi, T.; Nishiyama, T.; Yanada, R.; Ishikura, M. *Eur. J. Org. Chem.* **2016**, *2016*, 2290. (f) Abe, T.; Yamada, K. *Org. Lett.* **2016**, *18*, 6504. (g) Itoh, T.; Abe, T.; Choshi, T.; Ishikura, M. *Heterocycles* **2016**, *92*, 1132. (h) Itoh, T.; Abe, T.; Choshi, T.; Nishiyama, T.; Ishikura, M. *Heterocycles* **2017**, *95*, 507. (i) Abe, T.; Takahashi, U.; Matsubara, Y.; Yamada, K. *Org. Chem. Front.* **2017**, *4*, 2124. (j) Abe, T.; Kida, K.; Yamada, K. *Chem. Commun.* **2017**, *53*, 4362.
(9) Abe, T.; Suzuki, T.; Anada, M.; Matsunaga, S.; Yamada, K. *Org. Lett.* **2017**, *19*, 4275.
(10) For pioneering reports of the Ciamician−Plancher rearrangement, see: (a) Ciamician, G.; Plancher, G. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 2475. (b) Plancher, G. *Gazz. Chim. Ital.* **1898**, *28*, 374. (c) Plancher, G. *Atti. Accad. Lincei.* **1900**, *9*, 115. (d) Boyd-Barrett, H. S. *J. Chem. Soc.* **1932**, 321 . For recent examples, see:. (e) Eisenbeis, S. A.; Phillips, J. R.; Rescek, D.; Oyola-Cintron, Y. *Tetrahedron Lett.* **2010**, *51*, 4303. (f) Loh, C. C. J.; Raabe, G.; Enders, D. *Chem. - Eur. J.* **2012**, *18*, 13250.
(11) (a) Frost, C. G.; Hartley, J. P. *Mini-Rev. Org. Chem.* **2004**, *1*, 1. (b) Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1414. (c) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793. (d) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462. (e) Yanada, R.; Hashimoto, K.; Tokizane, R.; Miwa, Y.; Minami, H.; Yanada, K.; Ishikura, M.; Takemoto, Y. *J. Org. Chem.* **2008**, *73*, 5135. (f) Yanai, H.; Oguchi, T.; Taguchi, T. *J. Org. Chem.* **2009**, *74*, 3927. (g) Kuninobu, Y.; Tatsuzaki, T.; Matsuki, T.; Takai, K. *J. Org. Chem.* **2011**, *76*, 7005.
(12) (a) Tan, C.-J.; Di, Y.-T.; Wang, Y.-H.; Zhang, Y.; Si, Y.-K.; Zhang, Q.; Gao, S.; Hu, X.-J.; Fang, X.; Li, S.-F.; Hao, X.-J. *Org. Lett.* **2010**, *12*, 2370. (b) Qi, X.; Bao, H.; Tambar, U. K. *J. Am. Chem. Soc.* **2011**, *133*, 10050 . For a report of total synthesis of (−)-trigonolimine C and stereochemical revision, see:. (c) Han, S.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 10768. (d) Reddy, N. B.; Ramana, C. V. *Chem. Commun.* **2013**, *49*, 9767.

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