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# Unified Total Synthesis of Five Gelsedine-Type Alkaloids: (−)-Gelsenicine, (−)-Gelsedine, (−)-Gelsedilam, (−)-14-Hydroxygelsenicine, and (−)-14,15-Dihydroxygelsenicine

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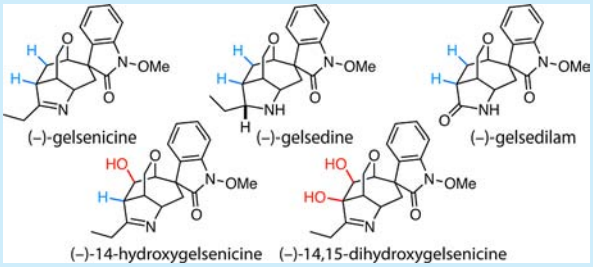
Supporting Information

**ABSTRACT:** The systematic arrangement of a two-carbon unit, hydrogen atom, and oxygen atom on the versatile enal moiety of a non-natural synthetic intermediate successfully led to the unified access to the gelsedine-type alkaloids. The development and use of this new synthetic hub and an array of site-selective transformations resulted in the asymmetric synthesis of (−)-gelsenicine, (−)-gelsedine, (−)-gelsedilam, (−)-14-hydroxygelsenicine, and (−)-14,15-dihydroxygelsenicine.




Biosynthesis of natural products has been a popular and inspiring guide for synthetic chemists in designing total syntheses. Biomimetic approaches that usually emulate the transformations developed in nature, however, do not necessarily represent the most efficient pathways in the realm of organic synthesis. It is imperative to customize the originally inspired strategy to follow the logic of modern organic synthesis. These abiotic approaches would also target a group of natural products accompanied by many structurally related congeners. Thus, our attention turned to the unified synthesis of natural products resembling each other, namely, gelsemium alkaloids.[1] These natural products have attracted a great deal of attention of synthetic chemists because of their complex structures, which hardly succumb to conventional synthetic approaches. These compounds are known as the toxic principles in the parent plant that has a rich therapeutic history in traditional Asian medicine over the past thousand years.[2] Among their interesting biological activities, we chose to focus on the prominent cytotoxic activity of the gelsedine-type[3] gelsemium alkaloids against A431 epidermoid carcinoma cells.[4] In order to obtain a more detailed understanding of the structure−activity relationship of these natural products and their congeners, we found it necessary to develop an efficient and unified strategy for the synthesis of these target molecules. Earlier synthetic studies of the gelsedine-type alkaloids were conducted by Baldwin,[5] Hamer,[6] and Kende.[7] Takayama and Sakai demonstrated remarkable transformations among the gelsemium alkaloids and reported a comprehensive semisynthesis based on the biogenetic pathway.[8] Hiemstra succeeded in the de novo synthesis of *ent*-gelsedine.[9] Recent achievements include the synthesis of gelsemoxonine by Fukuyama[10] and Carreira[11] and the synthesis of gelsenicine by Ferreira.[12]

Nevertheless, the biological profiles of these alkaloids remain unclear, partly because of the lack of a comprehensive library. Thus, we launched our synthetic campaign toward the development of a flexible and unified route to the gelsedine-type alkaloids. Our target compounds include gelsenicine (**1**),[13] gelsedine (**2**),[14] gelsedilam (**3**),[8e] 14-hydroxygelsenicine (humantenidine) (**4**),[15] and 14,15-dihydroxygelsenicine (**5**),[16] which are characterized by the common spiro-*N*-methoxyindolinone moiety, the oxabicyclo[3.2.2]nonane core skeleton, and the variably functionalized pyrrolidine moiety (Figure 1). Since these alkaloids were found in a single species, *Gelsemium elegans* Benth,[17] they are closely related to each other within the integrated biosynthetic pathway proposed by Takayama and Sakai.[15b] The C21 unit of the parent intermediate gelselegine (**6**) was proposed to be oxidatively removed to furnish the cyclic imine metabolite gelsenicine (**1**), which would then be selectively reduced to give gelsedine (**2**). Oxidation of gelsenicine (**1**) on the imine moiety and removal of a two-carbon unit[18] would afford the lactam derivative, gelsedilam (**3**). Oxygenation at C14 would give 14-hydroxygelsenicine (**4**), and repeated oxygenation at both the C14 and C15 positions would give 14,15-dihydroxygelsenicine (**5**), which would afford gelsemoxonine (**7**) by sequential ring opening and cyclization. Within the framework of the current state of organic synthesis, transformations that emulate this entire biosynthesis, especially C−H oxidations on C14 and C15, do not seem to be practical. Thus, we abandoned a biomimetic strategy and envisioned access to these targets through a single artificial intermediate bearing a versatile core structure (Scheme 1).[19] The ideal intermediate would be one that would allow regio- and diastereoselective introduction of different functional groups at C14 and C15 and flexible manipulation of the terminal two-

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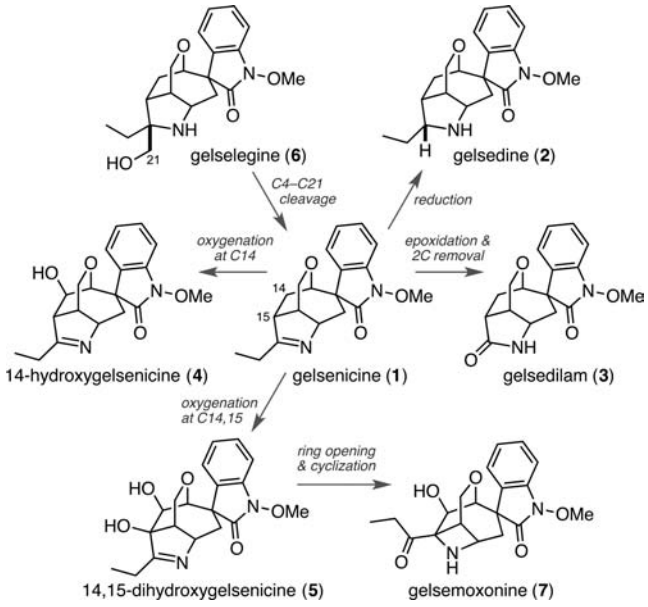
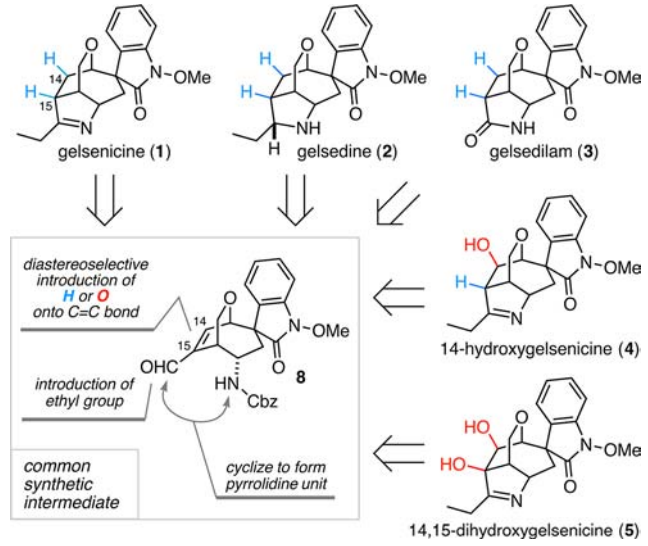



**Figure 1.** Gelsedine-type alkaloids and plausible biosynthetic relationship.

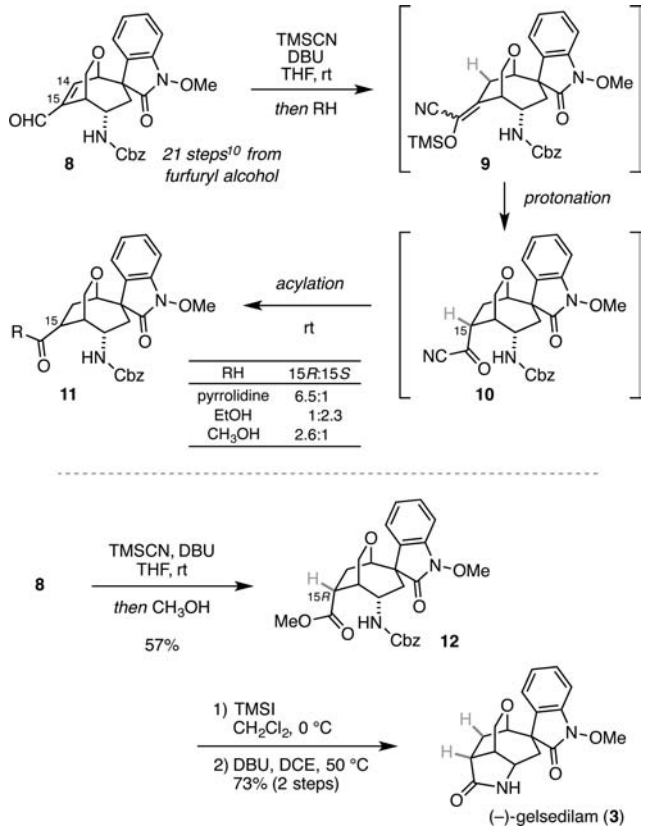
**Scheme 1. Retrosynthetic Analysis of Gelsedine-Type Alkaloids through the Introduction of an Ethyl Group and Hydrogen/Oxygen Atoms on the Enal Moiety of the Non-natural Intermediate 8**




carbon unit. We therefore focused on the key intermediate **8**, which we used for the total synthesis of gelsemoxonine.[10] This molecule bears the common spiro-*N*-methoxyindolinone moiety and a nitrogen functionality on the oxabicyclo[3.2.2]-nonane structure, which is also equipped with a versatile enal functionality. Introduction of the two-carbon unit and installation of two hydrogen or oxygen atoms on the C−C double bond could be envisioned through the transformation of this enal moiety. Ensuing cyclization from the nitrogen functionality is expected to afford all of the targeted gelsedine-type alkaloids.

Scheme 2 represents our total synthesis of gelsedilam (**3**). It was necessary to introduce two hydrogen atoms on the C14−C15 double bond as well as to oxidize the aldehyde moiety. A one-step conversion that might fulfill this requirement is the

**Scheme 2. Asymmetric Synthesis of Gelsedilam**




redox-neutral isomerization reaction using the TMSCN−DBU combination.[20] Submission of **8** to the reaction conditions initially formed a TMS cyanohydrin in situ, which subsequently underwent a double-bond migration to form **9**. The stereochemical outcome of the ensuing protonation and acylation steps, however, varied significantly depending on the reagents employed. The use of pyrrolidine as a reagent mainly yielded **11** with the desired 15*R* isomer (15*R*:15*S* = 6.5:1). This result indicated that protonation of the silyl enol ether intermediate **9** preferentially occurred from the less hindered *Si* face to afford (15*R*)-**10**. Because of the difficulties associated with further transformations of the pyrrolidine amide, ethanol was employed next. However, the use of ethanol reversed the stereoselectivity (15*R*:15*S* = 1:2.3), probably as a result of isomerization of the sterically congested acyl cyanide **10** to the thermodynamically more stable 15*S* isomer during the slow solvolysis stage. To expedite the solvolysis, methanol was employed as a smaller nucleophile. Methanol indeed gave an acceptable result (15*R*:15*S* = 2.6:1), and the desired 15*R* isomer **12** was isolated in 57% yield. Removal of the Cbz group by TMS iodide and subsequent cyclization under basic conditions completed the synthesis of (−)-gelsedilam (**3**).[8e] The intriguing stereochemical outcomes obtained here were consistent with our previous studies of this bicyclic system,[10] which could be explained by the fact that the *Re* face of the enolate is somewhat blocked by the bulky indolinone moiety.

Other target gelsedine-type alkaloids are characterized by possessing two additional carbon atoms on the side chain. Thus, enal **8** was treated with an ethyl Grignard reagent followed by IBX oxidation to afford ethyl ketone intermediate **13** (Scheme 3a).[10] The synthesis of gelsenicine (**1**) required reduction of the double bond and deprotection of the amine



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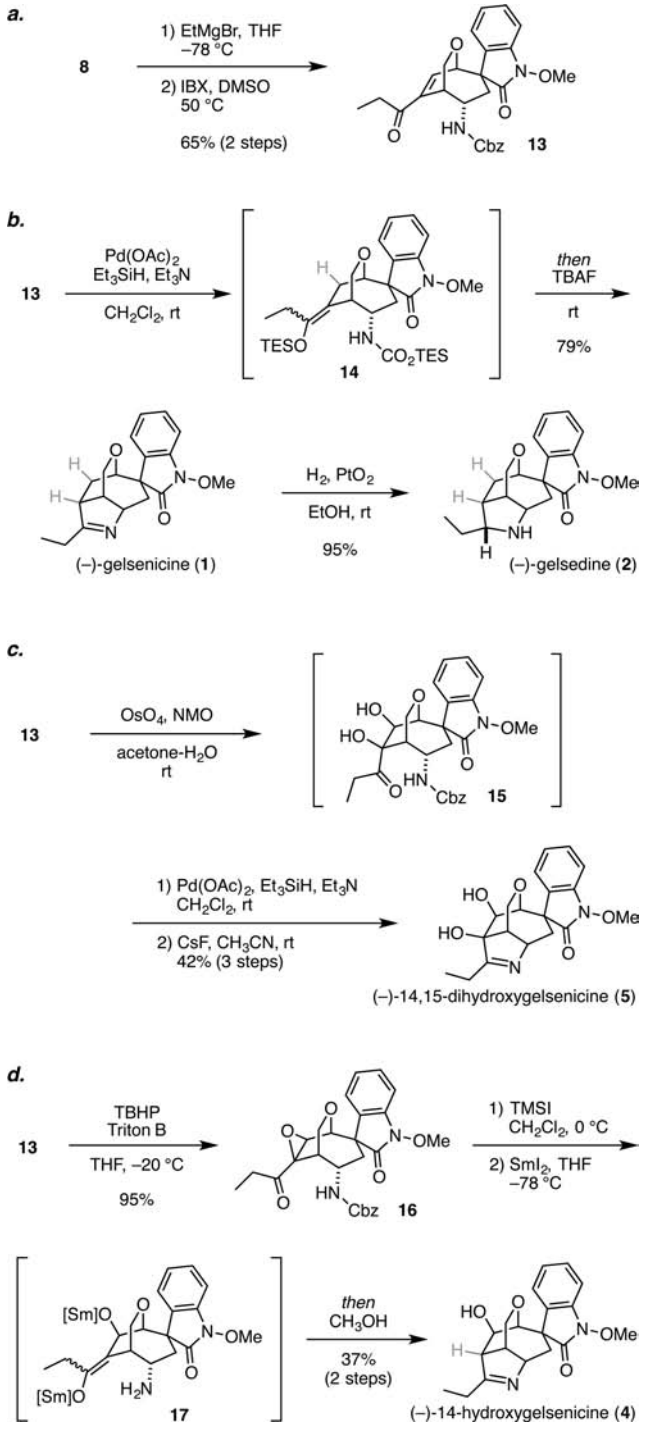
**Scheme 3. Asymmetric Syntheses of Gelsenicine, Gelsedine, 14,15-Dihydroxygelsenicine, and 14-Hydroxygelsenicine**




(Scheme 3b). A hydrosilylative transformation was chosen for this purpose. When **13** was treated with triethylsilane in the presence of palladium acetate,[21] the desired hydrosilylation and hydrogenolysis of the Cbz group proceeded simultaneously to give silyl enol ether/silyl carbamate intermediate **14**. Subsequent treatment with TBAF liberated the amine and ketone to smoothly form (−)-gelsenicine (**1**).[8c,22] It is not quite clear whether the facile formation of the cyclic imine resulted from exclusive protonation of the enolate from the *Si* face or rapid epimerization of the ketone. Catalytic hydrogenation of **1** with Adams' catalyst following the report of Takayama and Sakai[8c] furnished (−)-gelsedine (**2**). With the successful reduction of the C−C double bond, we next focused on introduction of the oxygen functionalities on the double bond (Scheme 3c). Fortunately, dihydroxylation of **13** with catalytic osmium tetroxide and NMO occurred smoothly at the desired face to afford diol **15**. Removal of the Cbz group with triethylsilane/palladium acetate and subsequent desilylation of the resulting silyl carbamate and partially silylated secondary alcohol caused the spontaneous dehydrative cyclization, leading to the first total synthesis of (−)-14,15-dihydroxygelsenicine (**5**).[16] The last target, 14-hydroxygelsenicine (**4**), bears an oxygen atom at C14 and a hydrogen atom at C15. This task might be realized via the partial reduction of the C14−C15 epoxide (Scheme 3d). Diastereoselective introduction of the epoxide functionality in **16** was performed by treatment with TBHP and Triton B.[10] After removal of the Cbz group by TMS iodide, the reductive transformation was achieved by treatment with samarium(II) iodide, which mediated the reduction of the carbon−oxygen bond adjacent to the carbonyl group[23] while keeping the N−O bond on the indolinone intact. The samarium enolate **17** generated in situ might be protonated from the less hindered *Re* face, resulting in the formation of a cyclic imine. In this case again, rapid epimerization of the ketone cannot be ruled out. Formal *cis* hydration of the C14−C15 double bond eventually afforded (−)-14-hydroxygelsenicine (**4**).[24]

In summary, five gelsedine-type alkaloids have been synthesized from a common non-natural intermediate by manipulating the potentially divergent enal functional group. For (−)-14-hydroxygelsenicine (**4**) and (−)-14,15-dihydroxygelsenicine (**5**), this synthesis unequivocally established the structure and absolute configuration. The established synthetic route to a broad range of gelsedine-type alkaloids sets the stage for the synthesis of structurally similar unnatural analogues that could potentially stimulate medicinal research based on these alkaloids.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02263.

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

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

(1) (a) Saxton, J. E. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1965; Vol. 8, p 93. (b) Liu, Z.-J.; Lu, R.-R.



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*Org. Lett.* 2016, 18, 4622−4625

In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, CA, 1988; Vol. *33*, p 83. (c) Takayama, H.; Sakai, S.-i. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1997; Vol. *49*, p 1.
(2) Kitajima, M.; Arai, Y.; Takayama, H.; Aimi, N. *Proc. Jpn. Acad., Ser. B* **1998**, *74*, 159.
(3) Kitajima, M. *J. Nat. Med.* **2007**, *61*, 14.
(4) (a) Kitajima, M.; Nakamura, T.; Kogure, N.; Ogawa, M.; Mitsuno, Y.; Ono, K.; Yano, S.; Aimi, N.; Takayama, H. *J. Nat. Prod.* **2006**, *69*, 715. (b) Kitajima, M.; Nakamura, T.; Kogure, N.; Ogawa, M.; Mitsuno, Y.; Ono, K.; Yano, S.; Aimi, N.; Takayama, H. *J. Nat. Prod.* **2007**, *70*, 142.
(5) Baldwin, S. W.; Doll, R. J. *Tetrahedron Lett.* **1979**, *20*, 3275.
(6) Hamer, N. K. *J. Chem. Soc., Chem. Commun.* **1990**, 102.
(7) Kende, A. S.; Luzzio, M. J.; Mendoza, J. S. *J. Org. Chem.* **1990**, *55*, 918.
(8) (a) Takayama, H.; Odaka, H.; Aimi, N.; Sakai, S.-i. *Tetrahedron Lett.* **1990**, *31*, 5483. (b) Takayama, H.; Kitajima, M.; Ogata, K.; Sakai, S.-i. *J. Org. Chem.* **1992**, *57*, 4583. (c) Takayama, H.; Tominaga, Y.; Kitajima, M.; Aimi, N.; Sakai, S.-i. *J. Org. Chem.* **1994**, *59*, 4381. (d) Kitajima, M.; Takayama, H.; Sakai, S.-i. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1573. (e) Kogure, N.; Ishii, N.; Kitajima, M.; Wongseripipatana, S.; Takayama, H. *Org. Lett.* **2006**, *8*, 3085. (f) Yamada, Y.; Kitajima, M.; Kogure, N.; Wongseripipatana, S.; Takayama, H. *Tetrahedron Lett.* **2009**, *50*, 3341. (g) Yamada, Y.; Kitajima, M.; Kogure, N.; Takayama, H. *Tetrahedron* **2008**, *64*, 7690. (h) Yamada, Y.; Kitajima, M.; Kogure, N.; Wongseripipatana, S.; Takayama, H. *Chem. - Asian J.* **2011**, *6*, 166.
(9) (a) Beyersbergen van Henegouwen, W. G.; Fieseler, R. M.; Rutjes, F. P. J. T.; Hiemstra, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2214. (b) Beyersbergen van Henegouwen, W. G.; Fieseler, R. M.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Org. Chem.* **2000**, *65*, 8317.
(10) (a) Shimokawa, J.; Harada, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 17634. (b) Shimokawa, J.; Harada, T.; Yokoshima, S.; Fukuyama, T. *Pure Appl. Chem.* **2012**, *84*, 1643.
(11) (a) Diethelm, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 8500. (b) Diethelm, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2015**, *137*, 6084.
(12) Newcomb, E. T.; Knutson, P. C.; Pedersen, B. A.; Ferreira, E. M. *J. Am. Chem. Soc.* **2016**, *138*, 108.
(13) (a) Du, X.-B.; Dai, Y.-H.; Zhang, C.-L.; Lu, S.-L.; Liu, Z.-G. *Acta Chim. Sin.* **1982**, *40*, 1137. (b) Yang, J.-S.; Chen, Y.-W. *Acta Pharm. Sin.* **1983**, *18*, 104. (c) Lin, L.-Z.; Cordell, G. A.; Ni, C.-Z.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 3199.
(14) (a) Schwarz, H.; Marion, L. *Can. J. Chem.* **1953**, *31*, 958. (b) Wenkert, E.; Orr, J. C.; Garratt, S.; Hansen, J. H.; Wickberg, B.; Leicht, C. L. *J. Org. Chem.* **1962**, *27*, 4123. (c) Jin, H.-L.; Xu, R.-S. *Acta Chim. Sin.* **1982**, *40*, 1129.
(15) (a) Yang, J.-S.; Chen, Y.-W. *Acta Pharm. Sin.* **1984**, *19*, 437. (b) Ponglux, D.; Wongseripipatana, S.; Subhadhirasakul, S.; Takayama, H.; Yokota, M.; Ogata, K.; Phisalaphong, C.; Aimi, N.; Sakai, S.-i. *Tetrahedron* **1988**, *44*, 5075.
(16) Kitajima, M.; Kogure, N.; Yamaguchi, K.; Takayama, H.; Aimi, N. *Org. Lett.* **2003**, *5*, 2075.
(17) Gelsedine was originally isolated from *Gelsemium sempervirens*[14a] and later from *Gelsemium elegans* Benth.[14c]
(18) Ouyang, S.; Wang, L.; Zhang, Q.-W.; Wang, G.-C.; Wang, Y.; Huang, X.-J.; Zhang, X.-Q.; Jiang, R.-W.; Yao, X.-S.; Che, C.-T.; Ye, W.-C. *Tetrahedron* **2011**, *67*, 4807.
(19) Shimokawa, J. *Tetrahedron Lett.* **2014**, *55*, 6156.
(20) (a) Kawabata, H.; Hayashi, M. *Tetrahedron Lett.* **2002**, *43*, 5645. (b) Kaise, H.; Shimokawa, J.; Fukuyama, T. *Org. Lett.* **2014**, *16*, 727.
(21) (a) Sakaitani, M.; Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett.* **1986**, *27*, 3753. (b) Fujiwara, H.; Kurogi, T.; Okaya, S.; Okano, K.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 13062.
(22) Takayama, H.; Sakai, S.-i. *Stud. Nat. Prod. Chem.* **1995**, *15*, 465.
(23) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596.
(24) Kogure, N. Ph.D. Dissertation, Chiba University, Chiba, Japan, 2008.



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