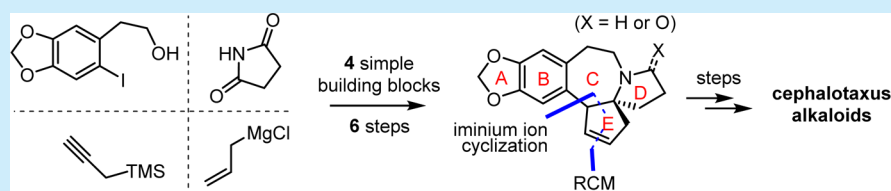


Stereoselectivity in *N*-Iminium Ion Cyclization: Development of an Efficient Synthesis of (±)-CephalotaxineHao Liu,<sup>†,§</sup> Jing Yu,<sup>†,‡,§</sup> Xinyu Li,<sup>†</sup> Rui Yan,<sup>†</sup> Ji-Chang Xiao,<sup>‡</sup> and Ran Hong<sup>\*,†</sup><sup>†</sup>CAS Key Laboratory of Synthetic Chemistry of Natural Substances and <sup>‡</sup>CAS Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

## Supporting Information



**ABSTRACT:** A stereoselective *N*-iminium ion cyclization with allylsilane to construct vicinal quaternary–tertiary carbon centers was developed for the concise synthesis of (±)-cephalotaxine. The current strategy features a  $\text{TiCl}_4$ -promoted cyclization and ring-closure metathesis to furnish the spiro-ring system. The stereochemical outcome in the *N*-acyliminium ion cyclization was rationalized by the stereoelectronic effect of the *Z*- or *E*-allylsilane. Two diastereomers arising from the cyclization were merged into the formal synthesis of (±)-cephalotaxine.

In 2012, the FDA approved the first protein translation inhibitor homoharringtonine (**1**, HHT) (omacetaxine mepesuccinate) as an adult orphan-drug for the treatment of chronic myeloid leukemia (CML) with resistance to tyrosine kinase inhibitors (TKIs).<sup>1</sup> HHT is a natural ester of cephalotaxine (**2**) manufactured by semi-synthesis via esterification.<sup>2,3</sup> Cephalotaxine was first reported by Paudlar and co-workers in 1963 from Chinese traditional medicine, *Cephalotaxus harringtonii*.<sup>4</sup> Its absolute stereochemistry was further validated by X-ray analysis of the corresponding *p*-bromobenzoate by Powell and co-workers in 1974.<sup>5</sup> Among all cephalotaxus alkaloids isolated from this plant, homoharringtonine (**1**) represents the most effective anticancer ingredient.<sup>6</sup> The limited natural resource to fulfill the clinical needs as well as the rare 1-azaspiro[4.4]nonane fused to a benzazepine rendered **2** as an intriguing synthetic target.

Since the first total synthesis of (±)-cephalotaxine by the Weinreb and Semmelhack groups in 1972,<sup>7</sup> over 30 racemic, formal, and enantioselective syntheses have been reported.<sup>8,9</sup> One generic and practical approach was based on the construction of a 1-azaspiro[4.4]nonane ring system. During our continuing interest to access biologically significant alkaloids, an embedded 1-azabicyclo[5.3.0]decane is clearly reminiscent of our previous endeavors in the syntheses of stemoamide and tetrapetalones.<sup>10</sup> Inspired by the definition of *pattern recognition* by Danishefsky and co-workers,<sup>11</sup> the azabicyclic motif would be a perfect illustration to explore *N*-acyliminium ion cyclization to establish the aza-containing vicinal quaternary–tertiary carbon stereogenic centers (C(5) and C(4) in Figure 1). Surprisingly, such structural challenge has not been fully explored via an iminium ion cyclization in literature precedents.<sup>12,13</sup>

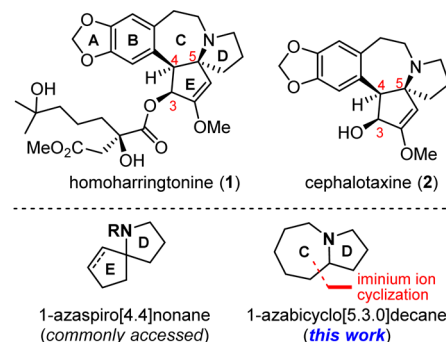
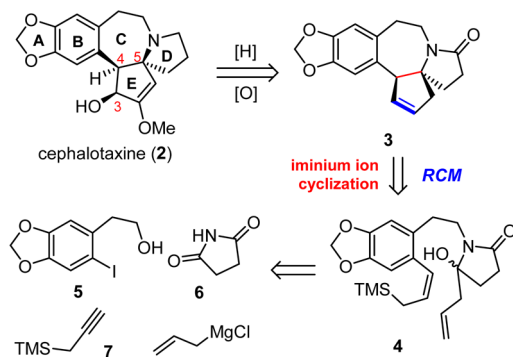


Figure 1. Cephalotaxus alkaloids and synthesis approaches.

In this communication, we devise a distinct approach featuring a new carbon–carbon bond disconnection between C(4) and C(5), two stereogenic centers within the C/E ring junction (Scheme 1). Cephalotaxine (**2**) is expected to be derived from Kuehne's intermediate **3** through a four-step sequence involving dihydroxylation, oxidation, methylation, and reduction, which was successfully established by Kuehne and co-workers.<sup>14</sup> The key iminium ion cyclization of hemiaminal **4** would furnish the C ring and the subsequent ring-closure metathesis (RCM) completes the spiro-ring system D/E in **3**. The hemiaminal **4** can be constructed from readily available materials such as 2-iodo-4,5-methylenedioxy-phenylethanol (**5**), succinimide (**6**), propargyl trimethylsilane (**7**), and allylmagnesium chloride.

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Scheme 1. Strategic Disconnection of (±)-Cephalotaxine



Iodinated phenylethanol **5** was prepared through a two-step protocol from 3,4-methylenedioxyphenylacetic acid by reduction and iodination (over 20 g scale).<sup>15</sup> Sonogashira coupling<sup>16</sup> of phenylethanol **5** with propargyl trimethylsilane (**7**) in the presence of palladium catalyst and copper iodide delivered alkyne **8** in excellent yield (97%). Partial hydrogenation with Lindlar catalyst resulted in the formation of the desired *Z*-alkene **9**, admixed with the overreduction product, the corresponding alkene, from which the desired product could not be separated. After screening several reducing reagents, the utilization of “P-2 Nickel” with ethylenediamine (Brown catalyst)<sup>17</sup> was fruitful and gave *Z*-**9** in quantitative yield (dr > 15/1).<sup>17</sup> The subsequent Mitsunobu reaction<sup>18</sup> with succinimide (**6**) afforded lactam **10** in 93% yield. After treatment of allylmagnesium chloride, the corresponding hemiaminal **4** was isolated in 86% yield.

Since compound **4** is prone to undergo facile elimination to form triene **11** (vide infra) during the storage in the refrigerator, the critical *N*-acyliminium ion cyclization was thus immediately carried out. For most of the conditions that were examined, only triene **11** was identified as a major product except  $\text{TiCl}_4$ , which led to the desired cyclization to give **12** in a combined 84% yield (entries 4 vs 1–3, Table 1).<sup>19</sup> However, a diastereomeric ratio of 1/1.2 favoring the *trans*-isomer resulted. To optimize the diastereoselectivity, different solvents and reaction temperatures were examined. Polar solvents (such as tetrahydrofuran and methyl *tert*-butyl ether) only resulted in compound **11** (entries 5 and 6). Other chloro hydrocarbons gave similar results (entries 7 and 8). When aromatic hydrocarbons were chosen, the *cis*/*trans* ratio was slightly improved (entry 10 vs 4). The best selectivity so far was achieved in mesitylene at  $-45^\circ\text{C}$ , in which the ratio of *cis*-**12**/*trans*-**12** was 2.5/1 and the isolated yield was 87% (entry 11).

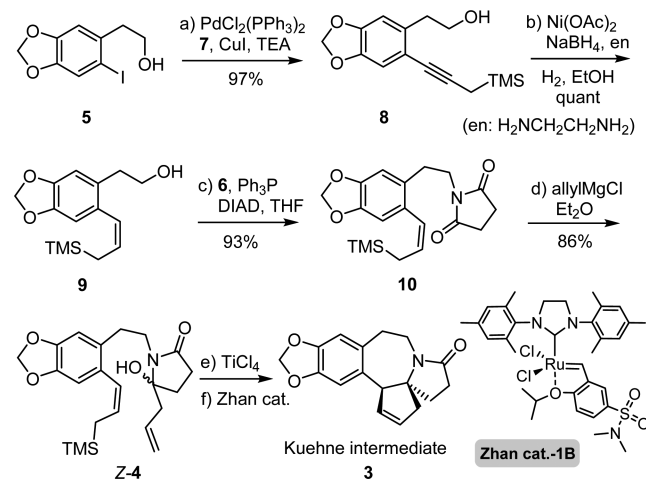
The following RCM reaction catalyzed by Grubbs-II<sup>20</sup> of **12** proceeded smoothly in refluxing toluene to give the requisite spiro compound **3**<sup>21</sup> as a single stereoisomer in 58% yield. Moreover, Zhan catalyst-1B (1 mol %) proved more effective to promote the RCM reaction at room temperature to deliver **3** in 70% yield along with the *trans*-isomer of **12** in 25% yield. The pentacyclic core of cephalotaxine (**2**), also known as Kuehne intermediate,<sup>14</sup> was thus furnished in a total of 6 steps and 47% overall yield from the readily available **5** (Scheme 2).

Although the aforementioned approach furnished the Kuehne intermediate (**3**) in a relatively short synthesis in high overall yield, moderate diastereoselectivity observed in the cyclization (*cis*/*trans* = 2.5/1) and the inability to separate two diastereomers of **12** by silica gel chromatography make the current route less attractive. We presumed the stereochemistry

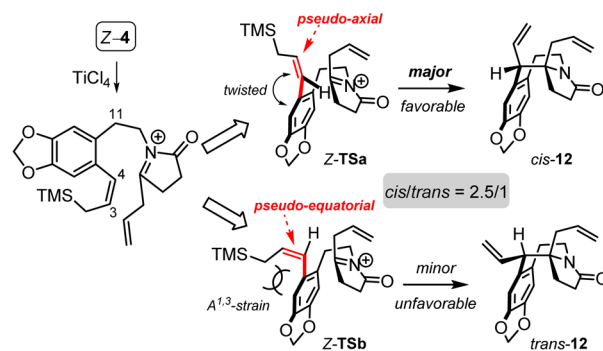
Table 1. *N*-Iminium Ion Cyclization<sup>a</sup>

| entry | promoter                         | solvent                  | temp ( $^\circ\text{C}$ ) | product (yield/%; dr) <sup>b</sup> |
|-------|----------------------------------|--------------------------|---------------------------|------------------------------------|
| 1     | $\text{CF}_3\text{CO}_2\text{H}$ | $\text{CH}_2\text{Cl}_2$ | 0                         | <b>11</b>                          |
| 2     | $\text{FeCl}_3$                  | $\text{CH}_2\text{Cl}_2$ | 0                         | <b>11</b>                          |
| 3     | $\text{Zn}(\text{OTf})_2$        | $\text{CH}_2\text{Cl}_2$ | 0                         | <b>11</b>                          |
| 4     | $\text{TiCl}_4$                  | $\text{CH}_2\text{Cl}_2$ | $-78$                     | <b>12</b> (84%; 1/1.2)             |
| 5     | $\text{TiCl}_4$                  | THF                      | $-78$                     | <b>11</b>                          |
| 6     | $\text{TiCl}_4$                  | $t\text{BuOMe}$          | $-78$                     | <b>11</b>                          |
| 7     | $\text{TiCl}_4$                  | $\text{CHCl}_3$          | $-60$                     | <b>12</b> (75%; 1/1.1)             |
| 8     | $\text{TiCl}_4$                  | $\text{CCl}_4$           | $-22$                     | <b>12</b> (56%; 1.3/1)             |
| 9     | $\text{TiCl}_4$                  | PhH                      | 0                         | <b>12</b> (50%; 1/1.7)             |
| 10    | $\text{TiCl}_4$                  | PhCH <sub>3</sub>        | $-78$                     | <b>12</b> (87%; 1.5/1)             |
| 11    | $\text{TiCl}_4$                  | mesitylene               | $-45$                     | <b>12</b> (87%; 2.5/1)             |

<sup>a</sup>Reaction conditions: substrate **Z-4** (0.1 mmol), promoter (0.3 mmol), solvent (1.5 mL), 10 min ~2 h. <sup>b</sup>Isolated yield; diastereomeric ratio (dr) of *cis*/*trans* for **12** was determined by  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ).

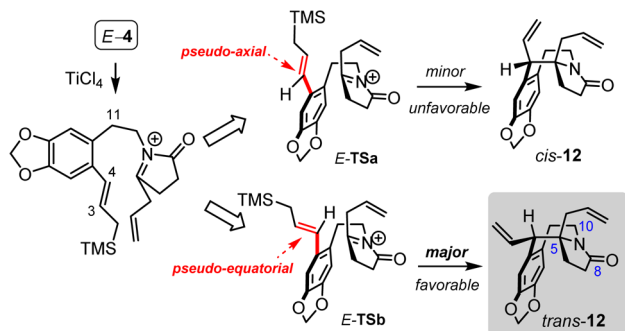
Scheme 2. 6-Step Synthesis of Kuehne Intermediate (**3**)

of the fused azepine ring system was determined by a boat-like transition state (TS) during the *N*-iminium ion cyclization as shown in Scheme 3. Due to the severe  $\text{A}^{1,3}$ -strain in conformer

Scheme 3. Proposed Model for the Cyclization of **Z-4**

of allylsilane **Z-TSb**, the reaction proceed through conformer **Z-TSa** resulting in *cis*-**12** as the major product. On the basis of this proposal, the alternative *E*-allylsilane may alleviate the steric repulsion, while also providing a more favorable transition state (*E*-**TSb**) since a pseudoequatorial vinyl group will be in optimal conjugation with the arene (Scheme 4). As a

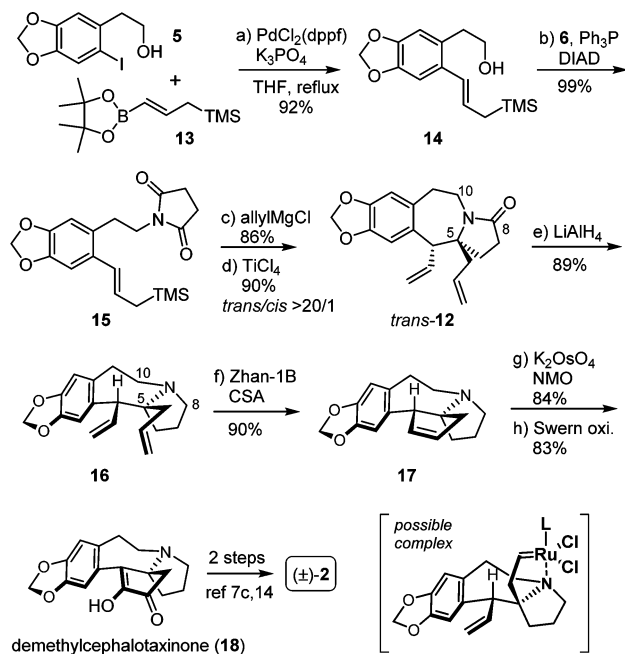
Scheme 4. Proposed Model for the Cyclization of *E*-4



consequence, the alignment of orbital interaction between allylsilane and the iminium ion makes this pathway favorable to generate *trans*-**12**, which may be feasible to access ( $\pm$ )-cephalotaxine.

With this notion in mind, we examined the *E*-allyl silane in the iminium ion cyclization. The first task is the synthesis of alcohol **14** (Scheme 5). Our initial proposal on direct reduction

Scheme 5. 8-Step Synthesis of Demethylcephalotaxinone (**18**)



of the triple bond in **8** to an *E*-alkene and Heck-type reaction of **5** with allylsilane proved unsuccessful due to poor stereoselectivity and regioselectivity, respectively. Encouraged by Carboni's recent work,<sup>22</sup> an in situ generated 3-boryl trimethylsilyl propene (**13**) was subjected to Suzuki coupling with aryl iodide **5** by palladium catalyst. Following the established protocol as first shown in Scheme 2, Mitsunobu reaction and Grignard reaction resulted in the requisite *E*-

isomer of **4** in good overall yield. To our delight,  $\text{TiCl}_4$ -promoted iminium ion cyclization was effective in gram scale and delivered the cyclized product **12** in 90% yield with a ratio of 20/1 in favor of the *trans*-isomer.

In contrast to the previous RCM reaction of *cis*-diene **12**, the *trans*-isomer of **12** proved to be inert to the Zhan catalyst-1B. Several catalysts were screened without any success. We reasoned the negative result to be attributed to the farther spatial distance of the two terminal double bonds in *trans*-**12**. Moreover, the amide functional group forces the surrounding carbons (C(5), C(8), and C(10)) nearly into the same plane (as the conformation of *trans*-**12** in Scheme 4), which makes the structure more rigid. We reasoned that reduction of the amide to the corresponding tertiary amine would make the system more conformationally flexible and promote the desired cyclization. Accordingly, the amide in *trans*-**12** was treated with  $\text{LiAlH}_4$  to give amine **16** in 89% yield. The subsequent RCM reaction was realized in the presence of Zhan catalyst-1B (5 mol %) in refluxing toluene for 36 h to give the cyclized product **17** in 55% yield along with 15–20% yield of recovered **16**. The low reactivity of amine **16** may be attributed to the coordination of the free amine with the metal center (see the inserted possible complex in Scheme 5).<sup>23</sup> It was found that the metathesis proceeded smoothly in the presence of camphor-sulfonic acid (CSA, 1 equiv)<sup>24</sup> with 1 mol % of Zhan-1B to give the requisite **17** in 90% yield. The fused ring system was subjected to dihydroxylation and Swern oxidation to deliver demethylcephalotaxinone (**18**) in 70% in two steps and is identical with the literature data.<sup>7c,14</sup> The highly diastereoselective cyclization of allyl silane *E*-4 establishes the importance of the allylsilane stereochemistry in the success of this pathway for the stereoselective formation of the cephalotaxine core.<sup>25</sup> After known transformations, ( $\pm$ )-cephalotaxine could be obtained in a 10-step LLS (the longest linear steps) from alcohol **5**.

In summary, a novel *N*-iminium ion cyclization was developed for the efficient construction of the vicinal azabicyclic quaternary–tertiary chiral centers found in the 1-azabicyclo[5.3.0]decane core of the cephalotaxus alkaloids. The stereochemical outcome for the cationic cyclization was rationalized by the stereoelectronic effect of the conjugation event of *Z/E* allylsilane with the arene in the proposed boat-like model. The subsequent RCM converted both *cis*-**12** and *trans*-**16** into the pentacyclic ring system suitable for the completion of the target molecule. Future studies directed toward the development of the enantioselective variant of total synthesis as well as its application to the synthesis of other complex polycyclic ring systems are currently underway 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.5b02106.

Full experimental details; analytical data including NMR spectra and X-ray diffraction of compound **3** (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: rhong@sioc.ac.cn

## Author Contributions

<sup>§</sup>Hao Liu and Jing Yu contributed equally.

## Notes

The authors declare no competing financial interest.

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## REFERENCES

- (1) (a) Wetzler, M.; Segal, D. *Curr. Pharm. Des.* **2011**, *17*, 59. (b) Kantarjian, H. M.; O'Brien, S. M.; Cortes, J. *Clin. Lymphoma, Myeloma Leuk.* **2013**, *13*, 530.
- (2) (a) Robin, J.; Dhal, R.; Dujardin, G.; Girodier, L.; Mevellec, L.; Poutot, S. *Tetrahedron Lett.* **1999**, *40*, 2931. (b) Ding, H.-X.; Leverett, C. A.; Kyne, R. E., Jr.; Liu, K. K.-C.; Sakya, S. M.; Flick, A. C.; O'Donnell, C. J. *Bioorg. Med. Chem.* **2014**, *22*, 2005. and references cited therein. (c) A large-scale preparation of racemic cephalotaxine (2) for chemical resolution was carried out by Merck chemists (see the footnote 19 in ref 7c). However, the detailed information was not disclosed. A resolution of *rac*-cephalotaxinone with L-tartaric acid was appeared, see: (l) Zhong, S. B.; Liu, W.; Ling, Y.; Li, R. *Zhongguo Yaowu Huaxue Zazhi* **1994**, *4*, 84.
- (3) Early attempts on semisynthesis of cephalotaxine derivatives, see: (a) Huang, W.-K.; Li, Y.-L.; Pan, X.-F. *Lanzhou Daxue Xuebao* **1974**, *148*. (b) Mikolajczak, K. L.; Smith, C. R., Jr.; Weisleder, D.; Kelly, T. R.; McKenna, J. C.; Christenson, P. A. *Tetrahedron Lett.* **1974**, *15*, 283. (c) Huang, W.-K.; Li, Y.-L.; Pan, X.-F. *Lanzhou Daxue Xuebao* **1975**, *44*. (d) Department of Pharmacology, Institute of Materia Medica, Chinese Academy of Medical Sciences, *Chin. Sci. Bull.* **1975**, *20*, 437. (e) Huang, W.-K.; Li, Y.-L.; Pan, X.-F. *Chin. Sci. Bull.* **1976**, *21*, 178. (f) Huang, W.-K.; Li, Y.-L.; Pan, X.-F. *Sci. Sin.* **1979**, *9*, 1171. (g) Huang, L.; Xi, Y.-L.; Guo, J.-Y.; Liu, D.-K.; Xu, S.-P.; Wu, K.-M.; Cheng, J.-H.; Jiang, Y.-Z.; Guo, Z.-R.; Gao, Y.-S.; Li, L.-M.; Zhang, M.-Y.; Chu, F.-M. *Sci. Sin.* **1979**, *9*, 1028. (h) Kelly, T. R.; McNutt, R. W., Jr.; Montury, M.; Tosches, N. P.; Mikolajczak, K. L.; Smith, C. R., Jr.; Weisleder, D. *J. Org. Chem.* **1979**, *44*, 63. (i) More references were discussed in ref 8a..
- (4) Paudler, W. W.; Kerley, G. I.; McKay, J. *J. Org. Chem.* **1963**, *28*, 2194.
- (5) Arora, S. K.; Bates, R. B.; Grady, R. A.; Powell, R. G. *J. Org. Chem.* **1974**, *39*, 1269.
- (6) (a) Powell, R. G.; Weisleder, D.; Smith, C. R., Jr. *J. Pharm. Sci.* **1972**, *61*, 1227. (b) Kantarjian, H. M.; Talpaz, M.; Santini, V.; Murgo, A.; Cheson, B.; O'Brien, S. M. *Cancer* **2001**, *92*, 1591. (c) Li, Y. F.; Deng, Z. K.; Xuan, H. B.; Zhu, J. B.; Ding, B. H.; Liu, X. N.; Chen, B. A. *Chin. Med. J.* **2009**, *122*, 1413. (d) Quintás-Cardama, A.; Kantarjian, H.; Cortes, J. *Cancer* **2009**, *115*, 5382.
- (7) (a) Auerbach, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1972**, *94*, 7172. (b) Semmelhack, M. F.; Chong, B. P.; Jones, L. D. *J. Am. Chem. Soc.* **1972**, *94*, 8629. (c) Weinreb, S. M.; Auerbach, J. *J. Am. Chem. Soc.* **1975**, *97*, 2503. (d) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507. (e) Weinreb, S. M.; Semmelhack, M. F. *Acc. Chem. Res.* **1975**, *8*, 158.
- (8) (a) Huang, L.; Xue, Z. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1984; Vol. 23, p 157. (b) Hudlicky, T.; Kwart, L. D.; Reed, J. W. In *The Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley and Sons: New York, 1987; Vol. 5, p 639. (c) Jalil Miah, M. A.; Hudlicky, T.; Reed, J. W. In *The Alkaloids: Chemistry and Biology*, Brossi, A., Ed.; Academic Press: New York, 1998; Vol. 51, p 199. (d) Abdelkafi, H.; Nay, B. *Nat. Prod. Rep.* **2012**, *29*, 845 and references cited therein.
- (9) For recent synthesis works, see: (a) Gonçalves-Martin, M. G.; Zigmantas, S.; Renaud, P. *Helv. Chim. Acta* **2012**, *95*, 2502. (b) Zhang, Q.-W.; Xiang, K.; Tu, Y.-Q.; Zhang, S.-Y.; Zhang, X.-M.; Zhao, Y.-M.; Zhang, T.-C. *Chem. - Asian J.* **2012**, *7*, 894. (c) Zhang, Z.-W.; Zhang, X.-F.; Feng, J.; Yang, Y.-H.; Wang, C.-C.; Feng, J.-C.; Liu, S.-X. *J. Org. Chem.* **2013**, *78*, 786. (d) Xing, P.; Huang, Z.-G.; Jin, Y.; Jiang, B. *Synthesis* **2013**, *45*, 596. (e) Xiao, K.-J.; Luo, J.-M.; Xia, X.-E.; Wang, Y.; Huang, P.-Q. *Chem. - Eur. J.* **2013**, *19*, 13075.
- (10) (a) Li, C.; Li, X.; Hong, R. *Org. Lett.* **2009**, *11*, 4036. (b) Wang, Y.; Zhu, L.; Zhang, Y.; Hong, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 2787. (c) Mi, X.; Wang, Y.; Zhu, L.; Wang, R.; Hong, R. *Synthesis* **2012**, *44*, 3432.
- (11) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2007**, *72*, 4293.
- (12) For recent reviews: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221. (c) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (d) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311. (e) Huang, P.-Q. *Synlett* **2006**, 2006, 1133.
- (13) (a) Duncan, D.; Livinghouse, T. *J. Org. Chem.* **2001**, *66*, 5237. (b) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507. (c) Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3017. (d) Liu, J.; Hsung, R. P.; Peters, S. D. *Org. Lett.* **2004**, *6*, 3989.
- (14) Kuehne, M. E.; Bornmann, W. G.; Parsons, W. H.; Spitzer, T. D.; Blount, J. F.; Zubietta, J. *J. Org. Chem.* **1988**, *53*, 3439.
- (15) Molander, G. A.; Hiersemann, M. *Tetrahedron Lett.* **1997**, *38*, 4347.
- (16) Yao, T.; Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3511.
- (17) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, 553.
- (18) (a) Mitsunobu, O. *Synthesis* **1981**, 1981, 1. (b) A similar transformation was also adopted in Huang's synthesis, see ref 9e..
- (19) The elimination product **11** was tested for the cationic cyclization with several Lewis acids and Brønsted acids; however, no appreciable cyclization product **12** was isolated.
- (20) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
- (21) CCDC 1408956 (3) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk](http://www.ccdc.cam.ac.uk).
- (22) Macé, A.; Tripoteau, F.; Zhao, Q.; Gayon, E.; Vrancken, E.; Campagne, J. M.; Carboni, B. *Org. Lett.* **2013**, *15*, 906.
- (23) The dark brown product **17** was isolated after purification on silica gel. This indicates a serious transition-metal contamination.
- (24) Verhelst, S. H. L.; Paez Martinez, B.; Timmer, M. S. M.; Lodder, G.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Org. Chem.* **2003**, *68*, 9598.
- (25) (a) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 2931. (b) An appendix to epimerization at C(4) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2009**, *11*, 1865.