

# Total Synthesis of (±)-Clavilactones A, B, and Proposed D through Iron-Catalyzed Carbonylation–Peroxidation of Olefin\*\*

Leiyang Lv, Baojian Shen, and Zhiping Li\*

**Abstract:** Biologically significant clavilactones A, B, and the previously proposed D have been synthesized through iron-catalyzed carbonylation–peroxidation of a 1,5-diene. Three steps from aldehydes, alkenes, and tert-butylhydroperoxide build up  $\alpha,\beta$ -epoxy- $\gamma$ -butyrolactone skeleton as a key building block for synthesis of clavilactone family and its derivatives. Based on our results, the structure of the proposed clavilactone D is not correct and requires revision.

Clavilactones A–E (1–5), isolated from cultures of the Basidiomycetous fungus *Clitocybe clavipes*,<sup>[1,2]</sup> are endowed with an intriguing structure based on a ten-membered ring fused to a  $\alpha,\beta$ -epoxy- $\gamma$ -butyrolactone and a benzoquinone or hydroquinone (Figure 1). Clavilactones A, B, and C (1, 2, and

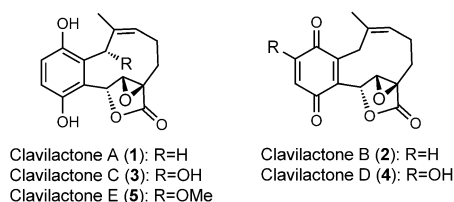


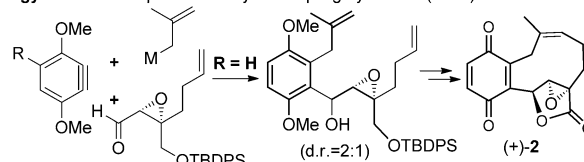
Figure 1. The clavilactone family.

3) exhibit antifungal and antibacterial activities<sup>[3]</sup> and inhibit the germination of *Lepidium sativum*. Clavilactone A, B, and D (1, 2, and 4) are potent kinase inhibitors against Ret/ptc1 and epidermal growth factor receptor (EGF-R) tyrosine kinases,<sup>[3]</sup> which might serve as potent molecularly targeted anticancer agents.<sup>[4,5]</sup>

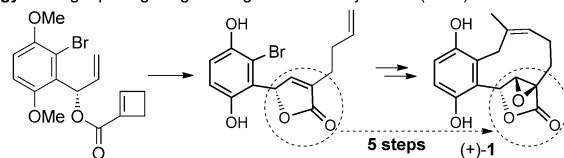
The significant biological properties of clavilactones have attracted the endeavors from synthetic community and, to date, the groups of Barrett<sup>[6]</sup> and Takao<sup>[7]</sup> have successfully

achieved the total synthesis (Scheme 1), and several groups have made great efforts in semisynthesis of clavilactones.<sup>[8]</sup> The macrocycle of clavilactones were realized by ring-closing metathesis (RCM),<sup>[6,7,9]</sup> and the major difference is how to build the  $\alpha,\beta$ -epoxy- $\gamma$ -butyrolactone skeleton.<sup>[10]</sup> It is worth noting that clavilactone D (4, R=OH) is difficult to synthesize by strategy I owing to the selectivity of benzyne coupling,<sup>[11]</sup> and five synthetic steps were used to transform furan-2(5H)-one into  $\alpha,\beta$ -epoxy- $\gamma$ -butyrolactone unit in strategy II.

Strategy I: Three-Component Benzyne Coupling by Barrett (2006)



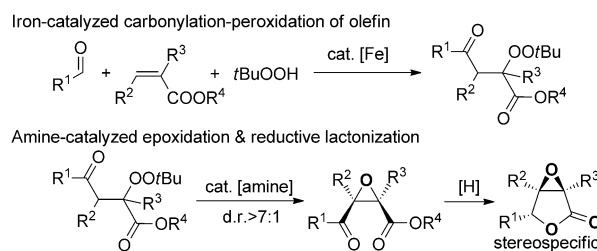
Strategy II: Ring-Opening/Ring-Closing Metathesis by Takao (2013)



Scheme 1. The developed strategies for clavilactones A and B.

Recently we reported a novel iron-catalyzed carbonylation–peroxidation of olefin, which provides a general and concise way to synthesize  $\alpha,\beta$ -epoxy- $\gamma$ -butyrolactones through base-catalyzed epoxidation followed by reductive lactonization (Scheme 2).<sup>[12]</sup> Considering the efficiency and high selectivity of the construction of the  $\alpha,\beta$ -epoxy- $\gamma$ -butyrolactone skeleton from simple alkenes, aldehydes, and hydroperoxides, we then decided to use the developed synthetic method to synthesize clavilactones.

Scheme 3 gives our retrosynthetic analysis to clavilactones. The tri-substituted alkene C11–C12 of clavilactones

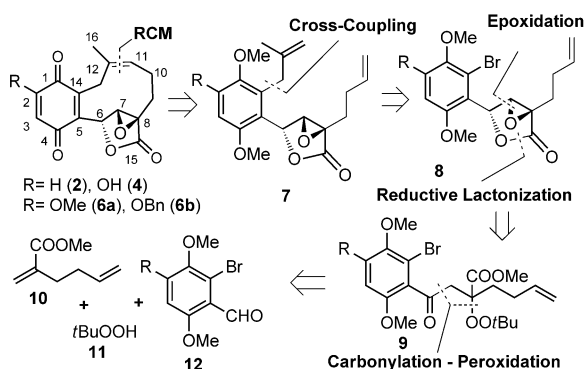


Scheme 2. Our developed methodologies.

[\*] L. Lv, Prof. Dr. Z. Li  
Department of Chemistry, Renmin University of China  
Beijing 100872 (China)  
E-mail: zhipingli@ruc.edu.cn  
Homepage: <http://chem.ruc.edu.cn/ligroup/index.html>  
Prof. Dr. B. Shen, Prof. Dr. Z. Li  
State Key Laboratory of Heavy Oil Processing  
China University of Petroleum, Beijing 102249 (China)

[\*\*] Financial support by the National Science Foundation of China (Nos. 21072223, 21272267) and State Key Laboratory of Heavy Oil Processing (2012-1-06). We are grateful to Prof. L. Merlini and Dr. L. Scaglioni for providing the original spectra and helpful discussions on the structure of clavilactone D.

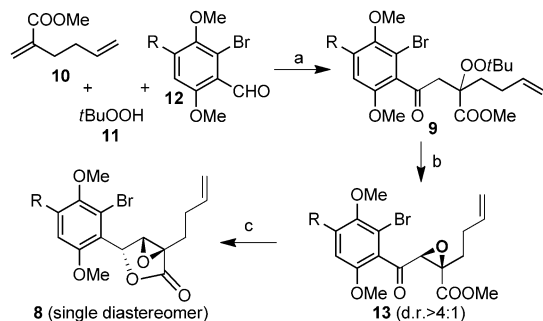
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201400326>.



**Scheme 3.** The retrosynthetic analysis for clavilactones.

can be constructed through RCM of diene **7**, which might be accessed by the cross-coupling reaction.<sup>[13]</sup> We envisioned that **8** can be constructed by a sequential steps of amine-catalyzed epoxidation of  $\alpha$ -ester- $\beta$ -keto peroxide **9** followed by reductive lactonization. The designed key intermediate **9** can be assembled by iron-catalyzed carbonylation-peroxidation of alkene **10** with aldehyde **12** and *tert*-butyl hydroperoxide (TBHP) **11**. Herein, we report our efforts for synthesis of clavilactones A, B, and D. The salient feature of our synthesis is a highly convergent, general, and concise strategy to accomplish the synthesis of diverse members of clavilactone family as well as its analogues.

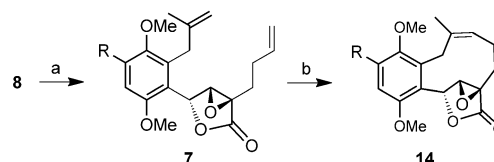
The synthesis began with three-component reactions of **10**, **11**, and **12** by the use of  $\text{FeCl}_2$  as catalyst (Scheme 4). The desired transformation underwent smoothly by using



**Scheme 4.** Reagents and conditions: a)  $\text{FeCl}_2$ , MeCN, 85 °C, 3 h, R = H (**9a**, 60%), OMe (**9b**, 74%), OBn (**9c**, 70%); b) pyrrolidine, MeCN, 0 °C, 3 h, R = H (**13a**, 87%, d.r. 5:1), OMe (**13b**, 90%, d.r. 4:1), OBn (**13c**, 91%, d.r. 4:1); c)  $\text{NaBH}_4$ , EtOH, 0 °C, 3 h, R = H (**8a**, 73%), OMe (**8b**, 71%), OBn (**8c**, 78%).

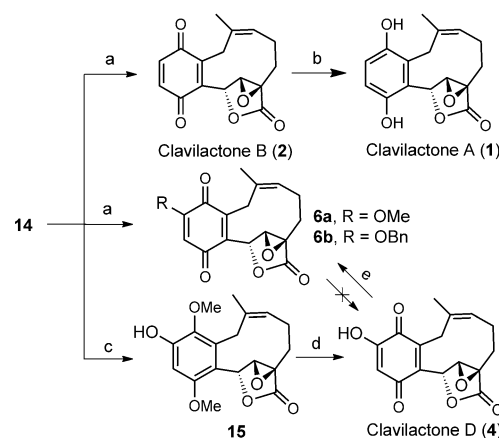
2.5 mol%  $\text{FeCl}_2$  for syntheses of **9a** and **9b**. However, a reduced amount of catalyst (0.1 mol%) had to be used for synthesis of **9c** to avoid some unknown side reactions. Subsequently, pyrrolidine-catalyzed reductive epoxidation of **9** followed by  $\text{NaBH}_4$ -mediated reductive lactonization of **13** furnished  $\alpha,\beta$ -epoxy- $\gamma$ -butyrolactones **8**. The chelation between the carbonyl and epoxy group with boron atom allows hydride to attack the less hindered side of the carbonyl.<sup>[12a]</sup>

The Stille coupling<sup>[14]</sup> of highly hindered **8** with tributyl(2-methylallyl)stannane proved to be challenging. When 1,4-dioxane was employed as the solvent,<sup>[7]</sup> the yield of the diene **7a** was very poor and the debromination product was also present. The desired products **7b** and **7c** were not observed if 1,2-dichloroethane was applied as the solvent.<sup>[8b]</sup> Gratifyingly, MeCN was found as effective solvent for the present Stille coupling, and the expected dienes **7** were obtained in excellent yields (Scheme 5).<sup>[15]</sup> Finally, RCM reactions successfully generated the ten-membered products **14** by Grubbs's second-generation catalyst.



**Scheme 5.** Reagents and conditions: a) tributyl(2-methyl-allyl)stannane,  $[\text{Pd}(\text{PPh}_3)_4]$ , CsF, MeCN, 100 °C, 12 h, R = H (**7a**, 87%), OMe (**7b**, 82%), OBn (**7c**, 88%); b)  $[\text{Cl}_2(\text{Cy}_3\text{P})(\text{sImes})\text{Ru}=\text{CHPh}]$ , tetrafluorobenzquinone, toluene, 80 °C, 18 h, R = H (**14a**, 65%), OMe (**14b**, 43%), OBn (**14c**, 42%).

With the key precursor **14** in hand, we subsequently investigated synthesis of diverse members of clavilactone family (Scheme 6). Clavilactone B (**2**) was obtained by the oxidative demethylation<sup>[6,16]</sup> of **14a** in 70% yield. The reduction of clavilactone B by  $\text{NaBH}_4$  afforded clavilactone A (**1**) in a quantitative yield. Initially, we expected that clavilactone D could be generated by the deprotection of **6a** or **6b**, which were obtained by the oxidation of **14b** or **14c**, respectively. However, removal of the methyl group in **6a** and the benzyl group in **6b** turned out to be more difficult than anticipated, which is mainly due to the frangible structure of  $\alpha,\beta$ -epoxy- $\gamma$ -butyrolactone skeleton and the feasible reduc-



**Scheme 6.** Reagents and conditions: a) CAN, MeCN/H<sub>2</sub>O (2:1), 0 °C, R = H (**2**, 70%), OMe (**6a**, 65%), OBn (**6b**, 60%); b)  $\text{NaBH}_4$ , EtOH, 0 °C, 5 min, (**1**, 99%); c) 10 wt% Pd/C, 1,4-cyclohexadiene, EtOH, 25 °C, 1 h, (**15**, 99%); d) CAN, MeCN/H<sub>2</sub>O (2/1), 0 °C, 10 min (**4**, 85%); e)  $\text{K}_2\text{CO}_3$ ,  $\text{Me}_2\text{SO}_4$ , 25 °C, 3 h, (**6a**, 70%). CAN = ceric ammonium nitrate.

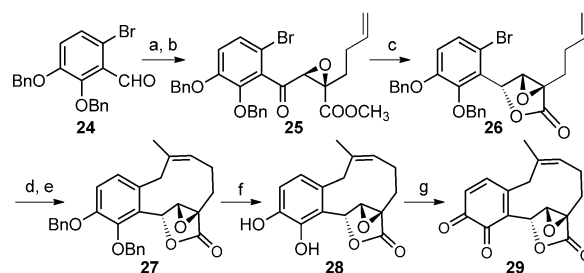
tion of 2-hydroxyquinone to 2-hydroxyhydroquinone simultaneously. With extensive efforts, we found that benzyl protecting group of **14c** could be first removed in the presence of 10 wt % Pd/C and 1,4-cyclohexadiene as the hydrogen donor.<sup>[17]</sup> Followed by oxidative demethylation of **15**, clavilactone D (**4**) was successfully achieved for the first time. To verify the structure of our synthesized clavilactone D (**4**), the methylation of the obtained **4** gave **6a**, which is identical to that synthesized from **14b**.

Surprisingly, it turned out that NMR spectroscopic data of synthesized **4** is not identical with the data of clavilactone D published by Merlini et al.<sup>[18]</sup> The only difference ( $\Delta\delta = 0.25$  ppm) in the  $^1\text{H}$  NMR chemical shifts was observed for 3-H, which appears at 6.15 ppm for our synthesized **4**, while 5.90 ppm for the naturally isolated clavilactone D. Moreover, significant deviations ( $\Delta\delta > 5.5$  ppm) were also detected in the  $^{13}\text{C}$  NMR chemical shifts for C2, C3, and C5. On the basis of NMR spectroscopic data analysis, we rationalized that: 1) the proposed structure for the natural clavilactone D does not concur with NMR spectroscopic data; and 2) one of possible structures for the natural clavilactone D is most likely the other regioisomer of the proposed structure of clavilactone D, in which the OH group is on 3-position of the quinone ring instead of 2-position.

Guided by our established synthetic strategy, the newly proposed structure of clavilactone D (**22**) was synthesized (Scheme 7). The iron-catalyzed carbonylation–peroxidation of alkene **10** with aldehyde **16** and *tert*-butyl hydroperoxide **11** gave the corresponding peroxide intermediate, which was smoothly converted into the desired epoxide **17** by pyrrolidine.  $\text{NaBH}_4$ -mediated reduction delivered the lactone **18**. The Stille coupling and RCM offered the macrolide **19**. The debenzoylation of **19** by 10 wt % Pd/C gave 3-hydroxy intermediate **20**. Unexpectedly, various oxidative demethylation

methods failed to give the desired 3-hydroxy clavilactone D (**22**) directly, while an *ortho*-quinone intermediate **21** was generated. Fortunately, **21** could be transformed into the desired product **22** through acid-catalyzed isomerization.<sup>[19]</sup> Furthermore, the methylation of **22** led to the corresponding methylated product **23**.

Unfortunately, NMR spectroscopic data of 3-hydroxycavilactone D (**22**) is still not identical with the data of clavilactone D (**4**). To exclude the possibility of an *ortho*-quinone skeleton for clavilactone D, **29** was synthesized by our strategy (Scheme 8). Based on the chemical shift of two carbonyl groups on the quinone ring by  $^{13}\text{C}$  NMR spectrum,<sup>[20]</sup> the possibility of an *ortho*-quinone structure of clavilactone D could be ruled out.



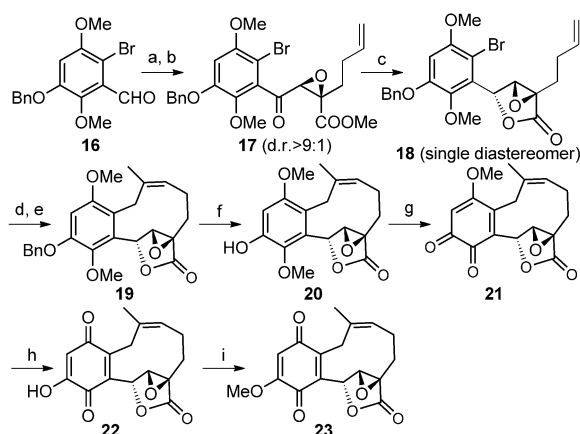
**Scheme 8.** Reagents and conditions: a)  $\text{FeCl}_2$ , MeCN, 85 °C, 3 h; b) pyrrolidine, MeCN, 0 °C, 3 h, (**25**, 32%, over 2 steps); c)  $\text{NaBH}_4$ , EtOH, 0 °C, 3 h, (**26**, 76%); d) tributyl(2-methyl-allyl)stannane,  $[\text{Pd}(\text{PPh}_3)_4]$ , CsF, MeCN, 100 °C, 12 h; e)  $[\text{Cl}_2(\text{Cy}_3\text{P})(\text{sImes})\text{Ru}=\text{CHPh}]$ , tetrafluorobenzoquinone, toluene, 80 °C, 18 h, (**27**, 47%, over 2 steps); f) 10 wt % Pd/C, cyclohexene, EtOH/THF (3:1), 50 °C, 1 h, (**28**, 81%); g) PIFA, MeCN/acetone/ $\text{H}_2\text{O}$  (30:10:1),  $-10^\circ\text{C}$ , 30 min, (**29**, 78%). PIFA = phenyliodonium bis(trifluoroacetate).

If the details of the NMR spectroscopic data of the natural clavilactone D are considered, the current spectral differences with our synthesized products might plausibly arise from the different stereoconfiguration of  $\alpha,\beta$ -epoxy- $\gamma$ -butyrolactone skeleton. To accomplish the structure elucidation and synthesis of the natural clavilactone D, new methods for the construction of other diastereomers of  $\alpha,\beta$ -epoxy- $\gamma$ -butyrolactone skeleton are needed.

In conclusion, we established a general, concise, and efficient approach for synthesis of clavilactone family and its derivatives. For examples, the total synthesis of ( $\pm$ ) clavilactone B was completed in 6 steps with 15.1 % yield, 7 steps with 14.9 % yield for ( $\pm$ ) clavilactone A, and 7 steps with 15.5 % yield for ( $\pm$ ) the proposed clavilactone D. This step-economical approach features a key iron-catalyzed carbonylation–peroxidation of olefin leading to  $\alpha$ -ester- $\beta$ -carbonyl peroxides, which can be transformed efficiently and selectively into  $\alpha,\beta$ -epoxy- $\gamma$ -butyrolactone skeleton as the key building block.

Received: January 12, 2014

Published online: March 11, 2014



**Scheme 7.** Reagents and conditions: a)  $\text{FeCl}_2$ , MeCN, 85 °C, 3 h; b) pyrrolidine, MeCN, 0 °C, 6 h, (**17**, 51%, over 2 steps); c)  $\text{NaBH}_4$ , EtOH, 0 °C, 4.5 h, (**18**, 72%); d) tributyl(2-methyl-allyl)stannane,  $[\text{Pd}(\text{PPh}_3)_4]$ , CsF, MeCN, 100 °C, 9 h; e)  $[\text{Cl}_2(\text{Cy}_3\text{P})(\text{sImes})\text{Ru}=\text{CHPh}]$ , tetrafluorobenzoquinone, toluene, 80 °C, 18 h, (**19**, 58%, over 2 steps); f) 10 wt % Pd/C, cyclohexene, EtOH/THF (3:1), 50 °C, 1 h, (**20**, 90%); g) CAN, MeCN/ $\text{H}_2\text{O}$  (2:1), 0 °C, 10 min, (**21**, 81%); h) MeCN,  $\text{H}_2\text{SO}_4$  (10% aqueous), RT, 9 h, (**22**, 99%); i)  $\text{K}_2\text{CO}_3$ ,  $\text{Me}_2\text{SO}$ , 25 °C, 3 h, (**23**, 82%).

**Keywords:** carbonylation–peroxidation · clavilactone · epoxides · iron catalysis · natural product synthesis

- [1] A. Arnone, R. Cardillo, S. V. Meille, G. Nasini, M. Tolazzi, *J. Chem. Soc. Perkin Trans. 1* **1994**, 2165–2168.
- [2] L. Merlini, G. Nasini, L. Scaglioni, G. Cassinelli, C. Lanzi, *Pythtochemistry* **2000**, 53, 1039–1041.
- [3] G. Cassinelli, C. Lanzi, T. Pensa, R. A. Gambetta, G. Nasini, G. Cuccuru, M. Cassinis, G. Pratesi, D. Polizzi, M. Tortoreto, F. Zunino, *Biochem. Pharmacol.* **2000**, 59, 1539–1547.
- [4] S. A. Courtneidge, *Semin. Cancer Biol.* **1994**, 5, 239–246.
- [5] For reviews, see: a) I. C. F. R. Ferreira, J. A. Vaz, M. H. Vasconcelos, A. Martins, *Anti-Cancer Agents Med. Chem.* **2010**, 10, 424–436; b) B. Z. Zaidman, M. Yassin, J. Mahajana, S. P. Wasser, *Appl. Microbiol. Biotechnol.* **2005**, 67, 453–468.
- [6] I. Larrosa, M. I. Da Silva, P. M. Gómez, P. Hannen, E. Ko, S. R. Lenger, S. R. Linke, A. J. P. White, D. Wilton, A. G. M. Barrett, *J. Am. Chem. Soc.* **2006**, 128, 14042–14043.
- [7] K. Takao, R. Nanamiya, Y. Fukushima, A. Namba, K. Yoshida, K. Tadano, *Org. Lett.* **2013**, 15, 5582–5585.
- [8] a) T. Yoshimitsu, S. Nojima, M. Hashimoto, K. Tsukamoto, T. Tanaka, *Synthesis* **2009**, 2963–2969; b) H. Yasui, S. Yamamoto, K. Takao, K. Tadano, *Heterocycles* **2006**, 70, 135–141.
- [9] For selected reviews on olefin metathesis, see: a) G. C. Vougioukalakis, R. H. Grubbs, *Chem. Rev.* **2010**, 110, 1746–1787; b) S. P. Nolan, H. Clavier, *Chem. Soc. Rev.* **2010**, 39, 3305–3316; c) S. Monfette, D. E. Fogg, *Chem. Rev.* **2009**, 109, 3783–3816; d) H. Villar, M. Fringsa, C. Bolm, *Chem. Soc. Rev.* **2007**, 36, 55–66; e) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, 117, 4564–4601; *Angew. Chem. Int. Ed.* **2005**, 44, 4490–4527.
- [10] For examples for the formation of  $\alpha,\beta$ -epoxy- $\gamma$ -butyrolactones, see: a) T. J. Kimbrough, P. A. Roethle, P. Mayer, D. Trauner, *Angew. Chem.* **2010**, 122, 2675–2678; *Angew. Chem. Int. Ed.* **2010**, 49, 2619–2621; b) P. A. Roethle, D. Trauner, *Org. Lett.* **2006**, 8, 345–347; c) P. A. Roethle, P. T. Hernandez, D. Trauner, *Org. Lett.* **2006**, 8, 5901–5904; d) Q. Huang, V. H. Rawal, *Org. Lett.* **2006**, 8, 543–545; e) V. Capriati, L. Degennaro, R. Favia, S. Florio, R. Luisi, *Org. Lett.* **2002**, 4, 1551–1554.
- [11] For recent reviews on aryne chemistry, see: a) P. M. Tadross, B. M. Stoltz, *Chem. Rev.* **2012**, 112, 3550–3577; b) C. M. Gampe, E. M. Carreira, *Angew. Chem.* **2012**, 124, 3829–3842; *Angew. Chem. Int. Ed.* **2012**, 51, 3766–3778; c) A. Bhunia, S. R. Yetra, A. T. Biju, *Chem. Soc. Rev.* **2012**, 41, 3140–3152.
- [12] a) K. Liu, Y. Li, W. Liu, X. Zheng, Z. Zong, Z. Li, *Chem. Asian J.* **2013**, 8, 359–363; b) K. Liu, Y. Li, X. Zheng, W. Liu, Z. Li, *Tetrahedron* **2012**, 68, 10333–10337; c) W. Liu, Y. Li, K. Liu, Z. Li, *J. Am. Chem. Soc.* **2011**, 133, 10756–10759.
- [13] For a review on cross-coupling reactions in total synthesis, see: K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, 117, 4516–4563; *Angew. Chem. Int. Ed.* **2005**, 44, 4442–4489.
- [14] For reviews on the Stille coupling, see: a) V. Farina, V. Krishnamurthy, W. J. Scott, *Org. React.* **1997**, 50, 1–652; b) J. K. Stille, *Angew. Chem.* **1986**, 98, 504–519; *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 508–524.
- [15] For a review on the mechanisms of the Stille reaction, see: P. Espinet, A. M. Echavarren, *Angew. Chem.* **2004**, 116, 4808–4839; *Angew. Chem. Int. Ed.* **2004**, 43, 4704–4734.
- [16] P. Jacob, P. S. Callery, A. T. Shulgin, N. Castagnoli, *J. Org. Chem.* **1976**, 41, 3627–3629.
- [17] a) Y. Suzuki, Y. Fukuta, S. Ota, M. Kamiya, M. Sato, *J. Org. Chem.* **2011**, 76, 3960–3967; b) T. Gillich, E. M. Benetti, E. Rakhmatullina, R. Konradi, W. Li, A. Zhang, A. D. Schlüter, M. Textor, *J. Am. Chem. Soc.* **2011**, 133, 10940–10950.
- [18] We communicated this issue with the authors who isolated and characterized clavilactone D (Ref. [2]). We are very grateful to Prof. L. Merlini and Dr. L. Scaglioni for offering the original NMR spectra of clavilactone D and helpful discussions on the structure of clavilactone D.
- [19] a) E. Malamidou-Xenikaki, S. Spyroudis, M. Tsanakopoulou, *J. Org. Chem.* **2003**, 68, 5627–5631; b) G. Majetich, Y. Zhang, *J. Am. Chem. Soc.* **1994**, 116, 4979–4980.
- [20] a) R. H. Munday, R. M. Denton, J. C. Anderson, *J. Org. Chem.* **2008**, 73, 8033–8038; b) L. Guillonnet, D. Taddei, C. J. Moody, *Org. Lett.* **2008**, 10, 4505–4508; c) H. M. L. Davies, X. Dai, *Tetrahedron* **2006**, 62, 10477–10484.