Natural Product Synthesis

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

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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 α,β-epoxy-γ-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*,[1,2] are endowed with an intriguing structure based on a ten-membered ring fused to a α,β-epoxy-γ-butyrolactone and a benzoquinone or hydroquinone (Figure 1). Clavilactones A, B, and C (**1**, **2**, and **3**) exhibit antifungal and antibacterial activities[3] 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,[3] which might serve as potent molecularly targeted anticancer agents.[4,5]

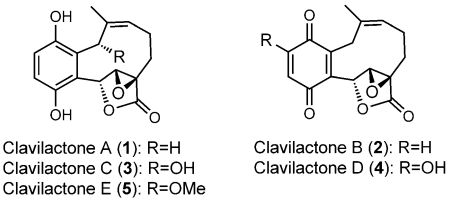
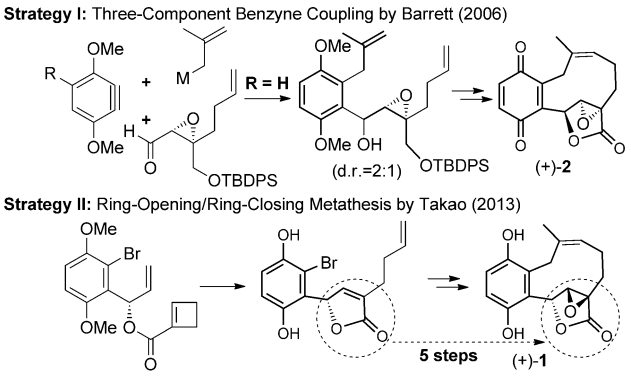


Figure 1. The clavilactone family.

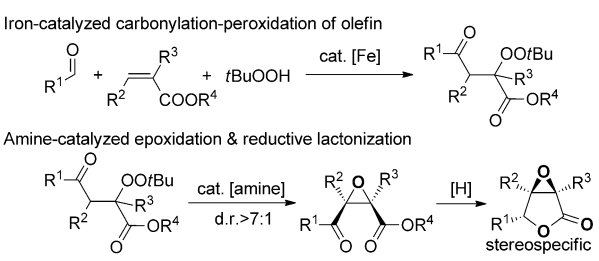
The significant biological properties of clavilactones have attracted the endeavors from synthetic community and, to date, the groups of Barrett[6] and Takao[7] have successfully achieved the total synthesis (Scheme 1), and several groups have made great efforts in semisynthesis of clavilactones.[8] The macrocycle of clavilactones were realized by ring-closing metathesis (RCM),[6,7,9] and the major difference is how to build the α,β-epoxy-γ-butyrolactone skeleton.[10] It is worth noting that clavilactone D (**4**, R = OH) is difficult to synthesize by strategy I owing to the selectivity of benzyne coupling,[11] and five synthetic steps were used to transform furan-2(5*H*)-one into α,β-epoxy-γ-butyrolactone unit in strategy II.



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 α,β-epoxy-γ-butyrolactones through base-catalyzed epoxidation followed by reductive lactonization (Scheme 2).[12] Considering the efficiency and high selectivity of the construction of the α,β-epoxy-γ-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.

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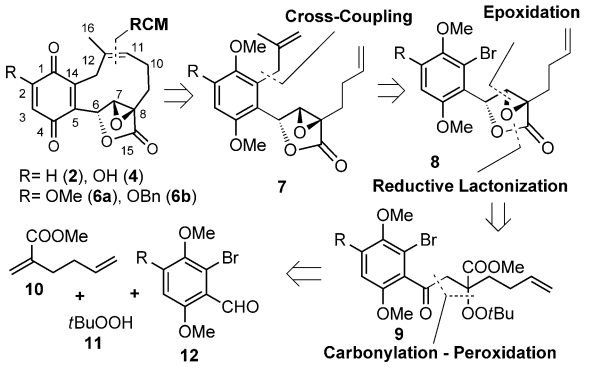
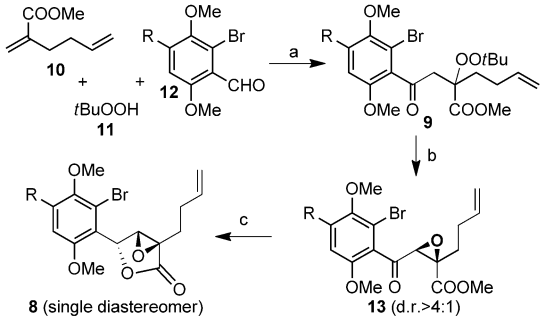


Scheme 3. The retrosynthetic analysis for clavilactones.

can be constructed through RCM of diene **7**, which might be accessed by the cross-coupling reaction.[13] We envisioned that **8** can be constructed by a sequential steps of amine-catalyzed epoxidation of α-ester-β-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.

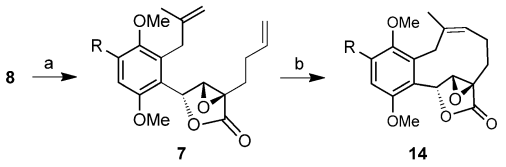
The synthesis began with three-component reactions of **10**, **11**, and **12** by the use of $FeCl_2$ as catalyst (Scheme 4). The desired transformation underwent smoothly by using



Scheme 4. Reagents and conditions: a) $FeCl_2$, 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) $NaBH_4$, EtOH, 0 °C, 3 h, R = H (**8a**, 73%), OMe (**8b**, 71%), OBn (**8c**, 78%).

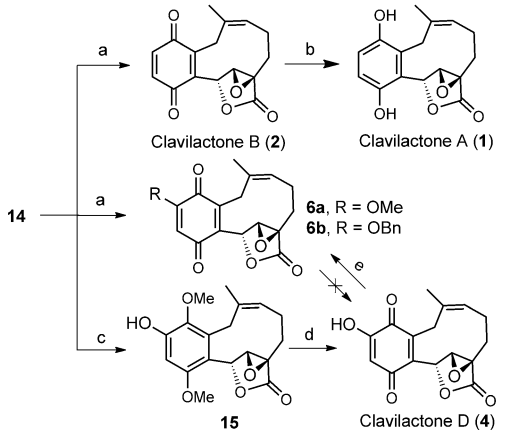
2.5 mol% $FeCl_2$ for syntheses of **9a** and **9b**. However, a reduced amount of catalyst (0.1 mol%) had to be used for synthesis of **9c** to avoid some unknown side reactions. Subsequently, pyrrolidine-catalyzed epoxidation of **9** followed by $NaBH_4$-mediated reductive lactonization of **13** furnished α,β-epoxy-γ-butyrolactones **8**. The chelation between the carbonyl and epoxy group with boron atom allows hydride to attack the less hindered side of the carbonyl.[12a]

The Stille coupling[14] of highly hindered **8** with tributyl(2-methylallyl)stannane proved to be challenging. When 1,4-dioxane was employed as the solvent,[7] 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.[8b] Gratifyingly, MeCN was found as effective solvent for the present Stille coupling, and the expected dienes **7** were obtained in excellent yields (Scheme 5).[15] 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, $[Pd(PPh_3)_4]$, CsF, MeCN, 100 °C, 12 h, R = H (**7a**, 87%), OMe (**7b**, 82%), OBn (**7c**, 88%); b) $[Cl_2(Cy_3P)(sIMes)Ru{=}CHPh]$, tetrafluorobenzoquinone, 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[6,16] of **14a** in 70% yield. The reduction of clavilactone B by $NaBH_4$ 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 α,β-epoxy-γ-butyrolactone skeleton and the feasible reduc-

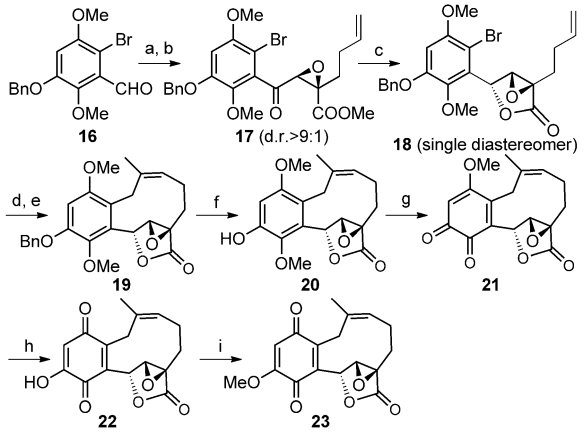


Scheme 6. Reagents and conditions: a) CAN, $MeCN/H_2O$ (2:1), 0 °C, R = H (**2**, 70%), OMe (**6a**, 65%), (**6b**, 60%); b) $NaBH_4$, EtOH, 0 °C, 5 min, (**1**, 99%); c) 10 wt% Pd/C, 1,4-cyclohexadiene, EtOH, 25 °C, 1 h, (**15**, 99%); d) CAN, $MeCN/H_2O$ (2/1), 0 °C, 10 min (**4**, 85%); e) K_2CO_3, Me_2SO_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.[17] 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**.

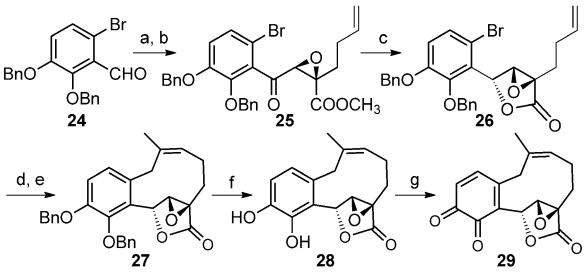
Surprisingly, it turned out that NMR spectroscopic data of synthesized **4** is not identical with the data of clavilactone D published by Merlini et al.[18] The only difference ($\Delta\delta = 0.25$ ppm) in the ^{1}H NMR chemical shifts was observed for 3-H, which appears at 6.15 ppm for our synthesized **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}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. $NaBH_4$-mediated reduction delivered the lactone **18**. The Stille coupling and RCM offered the macrolide **19**. The debenzylation 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.[19] Furthermore, the methylation of **22** led to the corresponding methylated product **23**.



Scheme 7. Reagents and conditions: a) $FeCl_2$, MeCN, 85 °C, 3 h; b) pyrrolidine, MeCN, 0 °C, 6 h, (**17**, 51%, over 2 steps); c) $NaBH_4$, EtOH, 0 °C, 4.5 h, (**18**, 72%); d) tributyl(2-methyl-allyl)stannane, [Pd(PPh_3)$_4$], CsF, MeCN, 100 °C, 9 h; e) [Cl_2(Cy_3P)(sIMes)Ru=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/H_2O (2:1), 0 °C, 10 min, (**21**, 81%); h) MeCN, H_2SO_4 (10% aqueous), RT, 9 h, (**22**, 99%); i) K_2CO_3, Me_2SO_4, 25 °C, 3 h, (**23**, 82%).

Unfortunately, NMR spectroscopic data of 3-hydroxyclavilactone 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 quinine ring by ^{13}C NMR spectrum,[20] the possibility of an *ortho*-quinone structure of clavilactone D could be ruled out.



Scheme 8. Reagents and conditions: a) $FeCl_2$, MeCN, 85 °C, 3 h; b) pyrrolidine, MeCN, 0 °C, 3 h, (**25**, 32%, over 2 steps); c) $NaBH_4$, EtOH, 0 °C, 3 h, (**26**, 76%); d) tributyl(2-methyl-allyl)stannane, [Pd(PPh_3)$_4$], CsF, MeCN, 100 °C, 12 h; e) [Cl_2(Cy_3P)(sIMes)Ru=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/H_2O (30:10:1), −10 °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 α,β-epoxy-γ-butyrolactone skeleton. To accomplish the structure elucidation and synthesis of the natural clavilactone D, new methods for the construction of other diastereomers of α,β-epoxy-γ-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 (±) clavilactone B was completed in 6 steps with 15.1% yield, 7 steps with 14.9% yield for (±) clavilactone A, and 7 steps with 15.5% yield for (±) the proposed clavilactone D. This step-economical approach features a key iron-catalyzed carbonylation–peroxidation of olefin leading to α-ester-β-carbonyl peroxides, which can be transformed efficiently and selectively into α,β-epoxy-γ-butyrolactone skeleton as the key building block.

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