

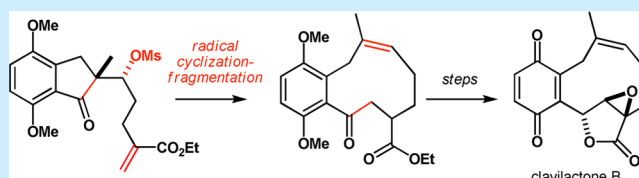
Total Synthesis of Clavilactone B: A Radical Cyclization–Fragmentation Strategy

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Supporting Information

ABSTRACT: A new synthetic route to clavilactone B, a naturally occurring inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase, is disclosed. The route features a sequential samarium-mediated radical cyclization–fragmentation of an indanone derivative, which provides rapid access to a 10-membered carbocyclic motif fused to an aromatic ring.



Arnone and co-workers identified in 1994 a series of cyclic bioactive compounds, clavilactones B (1), A (2), and C (3), as antifungal and antibacterial constituents in a culture of the nontoxic fungus *Clitocybe clavipes* (Figure 1).¹ There-

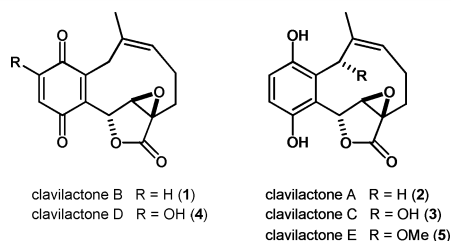


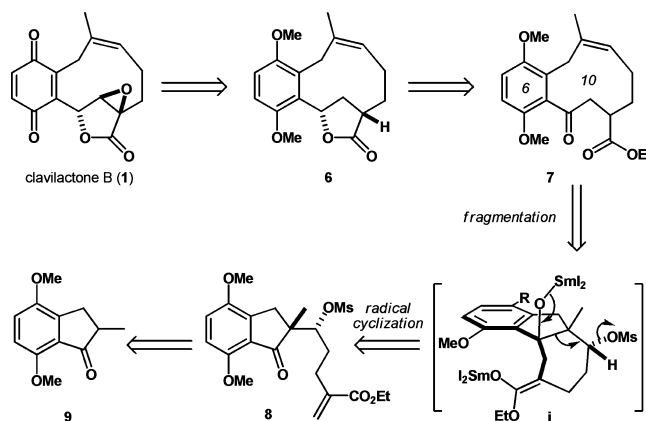
Figure 1. Structures of clavilactones.

after, Merlini and co-workers reported the isolation of structurally related clavilactones D (4) and E (5) from the same fungus grown in a different culture medium although it has recently been suggested that the originally proposed structure of clavilactone D (4) needs revision.² Clavilactones A (2), B (1), and D (4) have been shown to exhibit potent inhibitory activity toward epidermal growth factor receptor (EGFR) tyrosine kinase, which is responsible for cellular transduction pathways,³ thereby underscoring their relevance to medicinal applications.

The first total synthesis of clavilactone B (1) was accomplished by Barrett and co-workers, who devised an efficient strategy that enabled the rapid construction of a highly substituted aromatic ring by allylation–alkylation of an aryne followed by ring-closing metathesis (RCM) to furnish the 10-membered ring system of clavilactone B (1).⁴ The second synthesis of clavilactones B (1) and A (2) was developed by Takao and co-workers, who employed an elegant sequential ring-opening/ring-closing olefin metathesis to access the natural product.⁵ The most recent synthetic endeavor by Li and co-workers, who utilized an iron-catalyzed carbonylation–peroxidation and subsequent RCM, has uncovered a successful unified approach to clavilactones A (2), B (1), and proposed D

(4).⁶ Our group has also devised a ‘Lariat’ cyclization strategy that includes sequential iodo-etherification/Friedel–Crafts type cyclization and reductive olefination, and this strategy has yielded the core motif of clavilactone D.⁷ Here, we report a new synthetic approach to clavilactone B (1), which features a SmI₂-mediated radical cyclization–fragmentation of an indanone derivative to construct the 10-membered carbocycle of the target natural product (Scheme 1).

Scheme 1. Retrosynthesis of Clavilactone B (1)



In our retrosynthetic analysis of clavilactone B (1), we envisioned that functionalized 10-membered ring 7 with the clavilactone core would be constructed from indanone derivative 8 by a SmI₂-mediated radical cyclization and a subsequent ring opening of intermediate i bearing a good leaving group (Scheme 1).^{8,9} One of the key issues of the present approach was the stereoselective installation of an aldol unit suitable for the ionic fragmentation that requires an antiperiplanar orientation between the leaving group and the

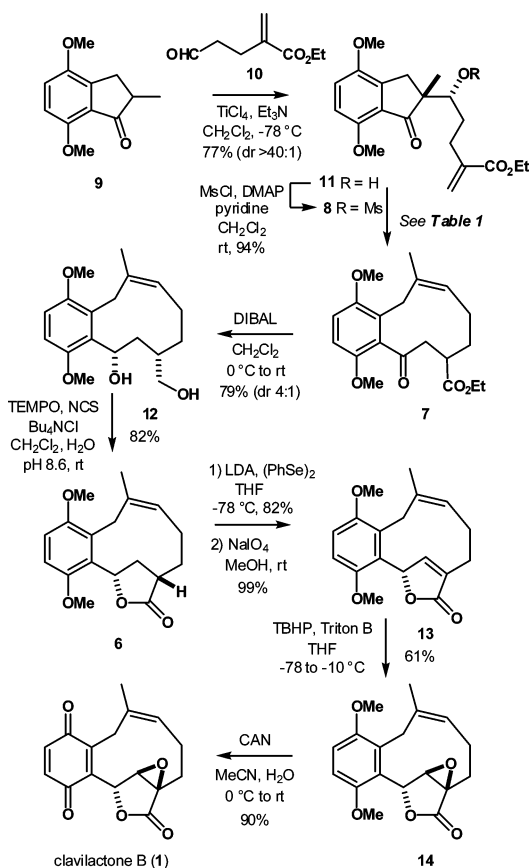
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internal cleaving C–C bond ($8 \rightarrow i \rightarrow 7$). We expected that the configuration of key indanone **8** would be available by the stereoselective aldol reaction of indanone **9**. Resultant compound **7** would be converted by manipulating the γ -keto ester functionality into γ -lactone **6**, which, upon several oxidative transformations, would produce clavilactone B (**1**).

The aldolization of indanone **9**¹⁰ was carried out with aldehyde **10**¹¹ using titanium chloride¹² in the presence of triethylamine to provide aldol **11** in 77% yield with excellent diastereoselectivity (dr >40:1) (Scheme 2). The high

Scheme 2. Total Synthesis of Clavilactone B (**1**)



diastereoselectivity yielded by this process was likely due to the intermediacy of rigid six-membered transition state **ii** generated by a titanium enolate (Figure 2). Resultant aldol **11**

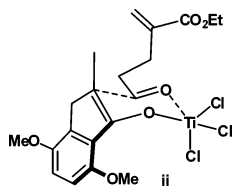


Figure 2. Plausible intermediate **ii** leading to highly stereocontrolled aldolization of **9** with **10**.

was then converted into mesylate **8** in 94% yield, with which we examined the key radical cyclization–fragmentation reaction using samarium reagents.¹³ Initial attempts to convert mesylate **8** with SmI_2 in THF afforded 10-membered motif **7** (21%) along with tetracyclic compound **15** (19%)¹⁴ and lactone **16** (15%)¹⁵ as identifiable products (Table 1, entry 1). The

Table 1. Samarium(II)-Mediated Radical Cyclization–Fragmentation of Mesylate **8**

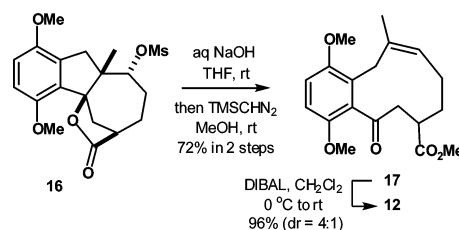
entry	additive (equiv)	product (%) ^a		
		7	15	16
1	—	21	19	15
2	Et_3N (20)	41	— ^b	29

^aIsolated yield after purification by SiO_2 column chromatography.

^bNot detected.

production of tetracyclic byproduct **15** suggested the intervention of intramolecular alkylation of enolate **i** shown in Scheme 1. With a view to improving the chemical yield of desired **7**, we envisaged that Lewis bases that likely coordinate to samarium alkoxide **i** would weaken the oxygen–samarium bond to facilitate the fragmentation. After making numerous attempts to optimize the conditions with such prospects in mind, we were pleased to find that the use of SmI_2 in combination with triethylamine increased the yield of **7** while attenuating the production of undesired tetracyclic compound **15** (entry 2). In this particular transformation, neither HMPA nor water was effective, and both gave complicated undesired products possibly by over-reduction. It is worth mentioning that, whereas lactone **16** was generated under the mentioned conditions,¹⁶ it could be converted into advanced intermediate **12** (vide infra) in good overall yield in three steps: its hydrolytic fragmentation, methyl esterification of resultant γ -keto carboxylic acid, and reduction of keto ester **17** with DIBAL (Scheme 3).

Scheme 3. Transformation of Lactone **16** into Diol **12**



Compound **7** was then subjected to reduction with DIBAL to afford diol **12** (79%) in a diastereomeric ratio of *syn/anti* = 4:1. The relative stereochemistry of major *syn*-diol **12** was unambiguously established by X-ray crystallographic analysis (Figure 3).¹⁷ Regioselective oxidation of the primary hydroxyl group of diol **12** under TEMPO–NCS conditions¹⁸ successfully produced lactone **6** in 82% yield. The corresponding *anti*-diol (structure not shown) could also be transformed into lactone **6** by the same TEMPO oxidation protocol through epimerization of the aldehyde intermediate.¹⁹

Further efforts were made with lactone **6** to install an oxidation state relevant to clavilactone B. Lactone **6** was first treated with LDA followed by diphenyldiselenide to give an α -selenylated lactone, which, upon oxidation with NaIO_4 , gave butenolide **13** in 81% overall yield. The installation of an epoxide functionality into butenolide **13** was carried out as

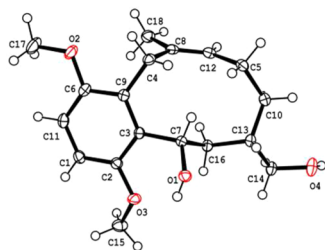


Figure 3. X-ray crystallographic structure of *syn*-diol **12**.

reported previously⁷ by using *tert*-butylhydroperoxide (TBHP) under basic conditions to provide epoxide **14** in 61% yield. Final oxidation of the aryl motif of compound **14** with ceric ammonium nitrate (CAN) in aqueous MeCN allowed us to furnish clavilactone B (**1**). The spectroscopic and analytical data of synthetic clavilactone B (**1**) were identical with those reported in the literature.^{4–6}

In conclusion, we have established a new route to access clavilactone B, which features a SmI₂-mediated radical cyclization–fragmentation of an indanone derivative. This approach has allowed for the facile construction of the key 10-membered ring system fused to an aromatic ring. The approach would provide an alternative to the RCM-based routes that have been successfully developed so far to synthesize this class of attractive natural products.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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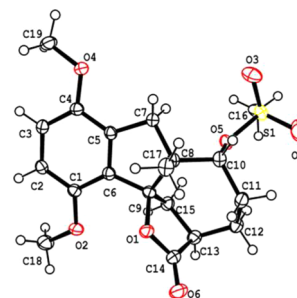
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(15) The structure of compound **16** was unambiguously determined by X-ray crystallographic analysis. CCDC 1023173 contains the supplementary X-ray crystallographic data for this compound. These data are available free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.



(16) We initially assumed that lactone **16** was formed by protonation of intermediate **i** and subsequent cyclization of the resultant ester during aqueous workup or on silica gel TLC (when monitoring by TLC). If this is the case, the elongation of reaction time would increase fragmentation product **7** while decreasing lactone **16**. However, prolonged reaction times did not facilitate the formation of **7** and led to no further consumption of lactone **16**, suggesting that lactone **16** was generated in situ via rapid protonation of Sm(III) enolate followed by lactonization. We suspected that intra- or intermolecular protonation of enolate **i** by the acidic motifs such as the methyl substituent of the methanesulfonyl group of the substrate or intermediate **i** and the acidic methylene protons of product **7** might be responsible for such phenomena. Attempted experimentations where the reaction was quenched by deuterium oxide, however,

showed no deuterium incorporation into the products. In the presence of *t*-BuOH (1 equiv) and Et₃N (10 equiv), lactone **16** was yielded (50%) along with fragmented compound **7** (19%), suggesting that the added proton source accelerated lactone formation. The aforementioned observations indicate that adventitious moisture in the reaction mixture might serve as the proton donor. Despite our efforts to adapt rigorous anhydrous conditions, the formation of lactone **16**, however, could not be suppressed. No further attempts were made to optimize the conditions.

(17) CCDC 1022864 contains the supplementary X-ray crystallographic data for this compound. These data are available free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. For details, see Supporting Information.

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