

Highly Convergent Three Component Benzyne Coupling: The Total Synthesis of *ent*-Clavilactone B

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Clavilactones A, B, and C (1–3), first isolated by Arnone et al. from a culture of the nontoxic fungus *Clitocybe clavipes*,¹ show antifungal and antibacterial activities.² Clavilactones A, B, and D (1, 2, and 4) are potent kinase inhibitors against Ret/pt1 and epidermal growth factor receptor (EGF-R) tyrosine kinases. As such they represent a new structural class of tyrosine kinase inhibitors,³ which are key enzymes modulating the transduction pathway regulation of essential cellular processes such as growth, differentiation, and apoptosis^{4,5} (see Figure 1).

The constitution and relative configuration of the clavilactones were determined by ¹H and ¹³C NMR spectroscopy studies, chemical reactions, and single-crystal X-ray analysis of the dimethoxy derivative of 1. Their intriguing structures contain a constrained ten-membered ring fused to a 2,3-epoxy- γ -lactone and a benzoquinone or hydroquinone. A concise total synthesis of these antibiotics would be of considerable interest to further define structure–activity relationships. Herein, we describe the first total synthesis of *ent*-clavilactone B ((+)-2) and the assignment of absolute stereochemistry.

Our retrosynthetic strategy is outlined in Scheme 1. The trisubstituted alkene C11–C12 of clavilactone B (2) should be available by means of a ring closing metathesis reaction (RCM) from diene 5. Reductive disconnection of the lactone in 5 would lead to diol 6. As part of our ongoing interest in aryne chemistry,⁶ we considered that bonds C5–C6 and C13–C14 in 6 could be created in a single operation using a three-component benzyne coupling strategy.⁷ This key process would involve the reaction of benzyne 7 with the methylallyl organometallic 8 and epoxy-aldehyde 9.

Epoxy-aldehyde 9 was synthesized as depicted in Scheme 2. Silyl protection of propargylic alcohol 10 followed by lithiation and quenching with ethyl chloroformate gave propargylic ester 11. 1,4-Cuprate addition to ester 11 yielded exclusively the (*Z*)-unsaturated ester 12.⁸ DIBAL-H reduction of ester 12 followed by Sharpless epoxidation of the resultant allylic alcohol 13 using *L*-(+)-diethyl tartrate gave the (–)-epoxide 14 with excellent yield (89%, two steps) and enantioselectivity (97% ee).^{9,10} Finally, Swern oxidation gave the (+)-epoxy-aldehyde 9 in an overall yield of 77% and 97% ee after six steps.

After examination of several benzyne precursors we selected fluorobenzene 15 as the most effective for the three component coupling reaction.¹¹ Reaction with *n*-BuLi (1 equiv) gave the *o*-fluoroaryllithium, which was allowed to fragment to benzyne in the presence of methylallyl Grignard (16) at room temperature to afford the aryl Grignard species 17. Finally, reaction with epoxy-aldehyde 9 at –78 °C gave the two diastereomeric adducts 18a (25%) and 18b (40%) (Scheme 3).¹²

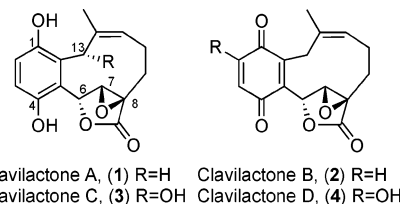
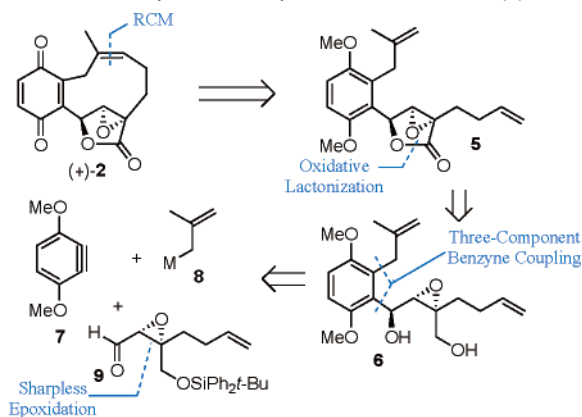
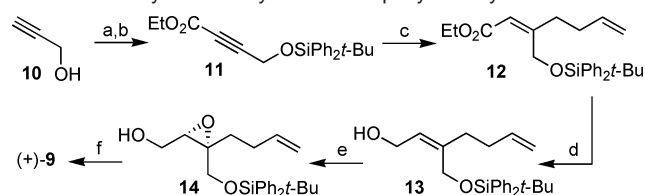


Figure 1. Clavilactone family.

Scheme 1. Retrosynthetic Analysis for Clavilactone B (2)



Scheme 2. Asymmetric Synthesis of Epoxy-Aldehyde 9^a



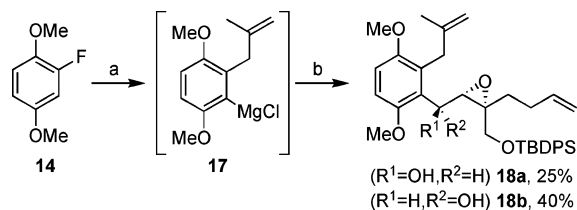
^a Conditions: (a) *t*-BuPh₂SiCl, imidazole, CH₂Cl₂, 96%; (b) *n*-BuLi; EtOCOCl, THF, –78 °C, 99%; (c) Mg, 4-bromo-1-butene, THF; CuBr·SMe₂, THF, –40 °C; 11, THF, –78 °C, 97%; (d) DIBAL-H, PhMe, –78 °C, 96%; (e) Ti(O-*i*-Pr)₄, *L*-(+)-DET, *t*-BuOOH, 4 Å MS, CH₂Cl₂, –20 °C, 93%, 97% ee; (f) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, –78 °C, 94%.

Unexpectedly, the stereochemical bias of epoxy-aldehyde 9 was opposite to that reported for similar substrates.^{13,14} Although the key three component coupling reaction proceeded with a modest stereochemical bias favoring the wrong isomer, this was ultimately irrelevant with the development of a method for the C6 epimerization reaction at a later stage (vide supra).

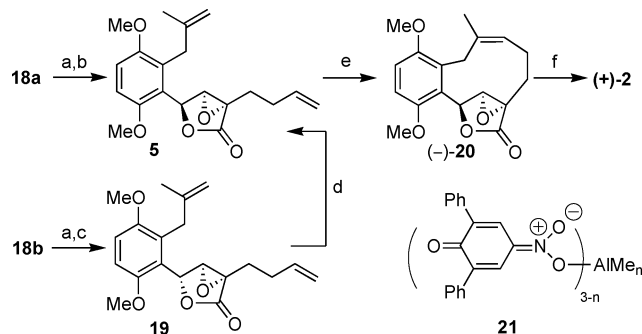
Deprotection of the silyl ethers 18a and 18b using TBAF in THF gave the corresponding *anti*-6 and *syn*-6-epi-6 diols, respectively, which were selectively oxidized to yield lactones 5 and 19 (Scheme 4). Interestingly, TPAP oxidation proceeded in superior yield for the *syn* lactone 19 (74% yield from the *syn*-diol 6-epi-6),¹⁵ whereas

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Scheme 3. Three-Component Benzyne Coupling^a

^a Conditions: (a) *n*-BuLi, THF, -78 °C; $\text{CH}_2=\text{C}(\text{Me})\text{CH}_2\text{MgCl}$ (**16**), -78 to 25 °C; (b) **9**, -78 to -35 °C, 65% (dr 2:1).

Scheme 4. Synthesis of (+)-Clavilactone B (**2**)^a

^a Conditions: (a) Bu_4NF (TBAF), THF, 87% (**6**), 86% (6-epi-**6**); (b) TEMPO (20 mol %), $\text{PhI}(\text{OAc})_2$, CH_2Cl_2 , 80%; (c) Pr_4NRuO_4 (TPAP) (15 mol %), NMO, 4 Å MS, MeCN, 74%; (d) **21** (60 mol %), CH_2Cl_2 , 80%; (e) $\text{Cl}_2(\text{Cy}_3\text{P})(\text{sImes})\text{Ru}=\text{CHPh}$ (40 mol %), tetrafluorobenzoquinone (80 mol %), PhMe, 80 °C, 65%; (f) CAN, MeCN, H_2O , 74%.

the use of TEMPO and iodobenzene diacetate was better for the anti lactone **5** from **6** (80%).¹⁶ At this point, we sought to isomerize lactone **19** into **5** by reversible Lewis acid catalyzed benzylic C—O bond scission.¹⁷ Attempted isomerization of **19** using $\text{TiCl}_n(\text{O}i\text{-Pr})_{4-n}$ ($n = 0-4$) or BX_3 ($\text{X} = \text{Br}, \text{F}$) led only to decomposition. In contrast, Yamamoto's bulky aluminum complex $\text{MeAl}(\text{OAr})_2$ ($\text{Ar} = 2,6\text{-}t\text{-Bu-4-BrC}_6\text{H}_4$) mediated the clean, albeit incomplete, epimerization of **19** into **5** (40% conversion in 3 days).^{18,19} Gratifyingly, a novel Lewis acid whose structure has been tentatively assigned as **21** was found to induce complete and clean conversion of **19** to **5** (80%).²⁰ Conveniently, this sequence of reactions can be performed on the mixture of diastereoisomers obtained from the benzyne coupling reaction. Therefore, the crude mixture of **18a** and **18b** was deprotected, and the resultant diol mixture (59%, two steps) directly oxidized to a mixture of **5** and **19** with TEMPO and iodobenzene diacetate (65% yield). The resultant mixture of lactones **5** and **19** were treated with the aluminum complex **21** to obtain pure (+)-**5** in 80% yield.

RCM reactions to form macrocycles with trisubstituted alkenes, such as **20**, are known to be very difficult.²¹ Gratifyingly, after extensive optimization it was found that the slow addition of Grubbs' second generation catalyst and tetrafluorobenzoquinone²² to a 0.03 M solution of the diene in toluene at 80 °C, with concomitant removal of the ethylene formed during the reaction, gave the clavilactone A dimethyl ether (-)-**20**, in 65% yield (Scheme 4). The NMR spectra of the compound obtained were compared with those of a sample derived from the natural product and a complete correlation was found. The optical rotation ($[\alpha]_{\text{D}} = -105$ (c 0.1, MeOH)) was of the same magnitude but opposite sign to that previously reported ($[\alpha]_{\text{D}} = +111$ (c 0.1, MeOH)).¹ Consequently, the absolute configuration of the natural product was unambiguously assigned as 6*R*, 7*R*, 8*R*. Finally, oxidative demethylation of **20** gave (*ent*)-clavilactone B ((+)-**2**) (74%).^{23,12}

In conclusion, we have developed the first asymmetric synthesis of clavilactone **B** (**2**), a potent antifungal agent and determined its absolute configuration. Our strategy employs a powerful and convergent three-component benzyne coupling and an RCM reaction to generate the whole carbon skeleton of the molecule. In addition, a new mild and selective method for the epimerization of delicate polyfunctional benzylic lactones has been developed. On the basis of this approach, the synthesis and bioassay of several derivatives of clavilactone are underway.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ¹H and ¹³C NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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