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Published on Web 10/11/2006

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 nontoxigenic 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/ptc1 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 ^{1}H and ^{13}C NMR spectroscopy studies, chemical reactions, and single-crystal X-ray analysis of the dimethoxy derivative of **1**.[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]

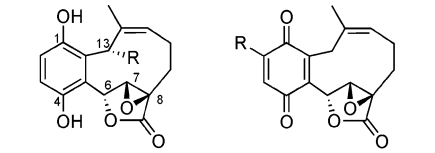
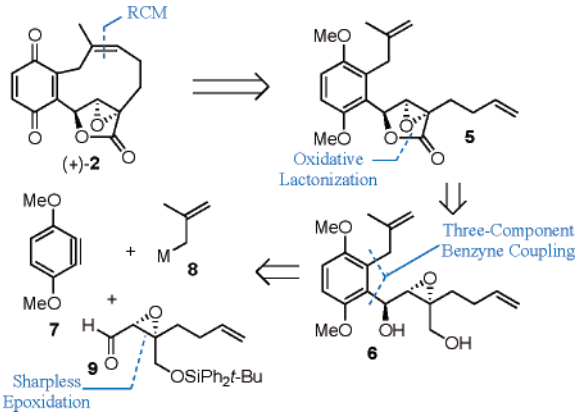
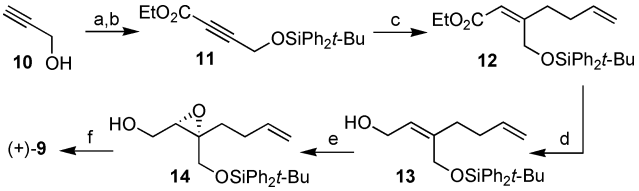


Figure 1. Clavilactone family.

Scheme 1. Retrosynthetic Analysis for Clavilactone B (**2**)



Scheme 2. Asymmetric Synthesis of Epoxy-Aldehyde **9**[a]



[a] Conditions: (a) *t*-BuPh$_2$SiCl, imidazole, CH_2Cl_2, 96%; (b) *n*-BuLi; EtOCOCl, THF, −78 °C, 99%; (c) Mg, 4-bromo-1-butene, THF; CuBr·SMe$_2$, 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, CH_2Cl_2, −20 °C, 93%, 97% ee; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −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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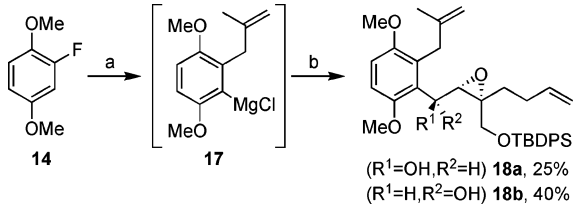
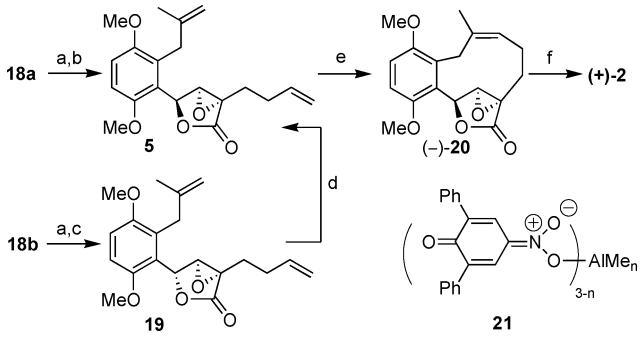
10.1021/ja0662671 CCC: $33.50

Scheme 3. Three-Component Benzyne Coupling[a]



[a] Conditions: (a) *n*-BuLi, THF, −78 °C; CH_2═C(Me)CH_2MgCl (**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 %), $PhI(OAc)_2$, 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) $Cl_2(Cy_3P)$(sIMes)Ru═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 $TiCl_n(Oi\text{-}Pr)_{4-n}$ (n = 0−4) or BX_3 (X = Br, F) led only to decomposition. In contrast, Yamamoto's bulky aluminum complex $MeAl(OAr)_2$ (Ar = 2,6-*t*-Bu-4-BrC_6H_2) 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 tetrafluorobenzoquinone[22] 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 ($[\alpha]_D$ = −105 (c 0.1, MeOH)) was of the same magnitude but opposite sign to that previously reported ($[\alpha]_D$ = +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.

Acknowledgment. We thank GlaxoSmithKline for the generous endowment (to A.G.M.B.), the Royal Society and the Wolfson Foundation for a Royal Society Wolfson Research Merit Award (to A.G.M.B.), the Wolfson Foundation for establishing the Wolfson Center for Organic Chemistry in Medical Sciences at Imperial College, the EPSRC, the Ministerio de Educacion y Ciencia (I.L.), and the Deutscher Akademischer Austausch Dienst (DAAD) (P.H.) for postdoctoral fellowships. We thank Prof. Gianluca Nasini for authentic samples of natural **5** and **20**.

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

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JA0662671