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### Facile Construction of Medium-Sized Carbocycles, Total Synthesis of ( $\pm$ )-Parvifoline

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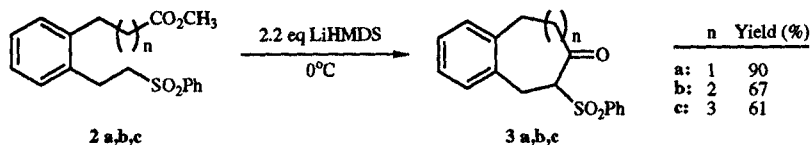
## FACILE CONSTRUCTION OF MEDIUM-SIZED CARBOCYCLES, TOTAL SYNTHESIS OF (±)-PARVIFOLINE

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**Abstract** A new synthetic approach to medium-sized rings has been accomplished via intramolecular cyclization of a sulfone-stabilized carbanion. This strategy was applied to the total synthesis of (±)-parvifoline.

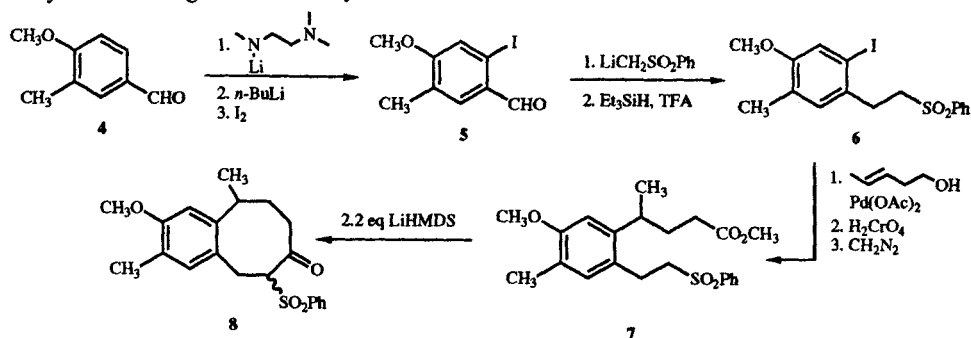
Few methods for direct formation of medium-sized rings are available.<sup>1</sup> Herein we describe a strategy applicable to the synthesis of medium-sized rings based on intramolecular cyclization of a sulfone-stabilized carbanion and its application to the total synthesis of (±)-parvifoline (**1**).<sup>2</sup>

The general reaction under discussion is exemplified by the conversion of sulfone ester **2** into ketosulfone **3** upon treatment with base. *The desired sequence requires the generation of the α-sulfonyl anion in the presence of the reactive ester, followed by ring closure.* The relative efficiency of cyclization leading to seven-, eight-, and nine-membered rings is noteworthy. We have applied this methodology to the total synthesis of (±)-parvifoline as shown below.

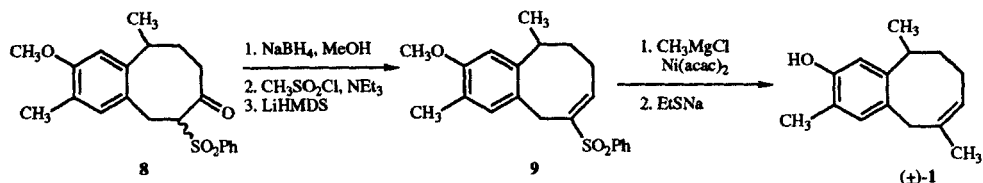


α-Amino alkoxide directed lithiation of **4** followed by reaction with iodine provided aldehyde **5** in 53% isolated yield, together with unreacted starting material. Treatment of **5** with the anion of methyl phenyl sulfone followed by reduction of the crude product with triethylsilane and trifluoroacetic acid in dichloromethane afforded iodosulfone **6** in 80% overall yield. Introduction of the ester side chain was readily

accomplished using a palladium-catalyzed coupling protocol. Thus reaction of aryl iodide **6** with *trans*-3-penten-1-ol, subsequent Jones oxidation of the resultant aldehyde and esterification with diazomethane yielded **7** (44% overall) as light yellow crystals. The critical ring closure was achieved by using the above conditions for cyclization to give **8** in 67% yield as a 9:1 mixture of diastereomers.<sup>3</sup>



The stage was now set for the introduction of the deconjugated olefin. Thus reduction of **8** with  $\text{NaBH}_4$  in MeOH (94%), mesylation of the alcohol ( $\text{CH}_3\text{SO}_2\text{Cl}$ ,  $\text{NEt}_3$ ) and immediate elimination with LiHMDS gave vinylsulfone **9** in 75% overall yield. Transition-metal-catalyzed introduction of the methyl group was achieved by treating **9** with  $\text{MeMgCl}$  in the presence of  $\text{Ni}(\text{acac})_2$  (75%). Smooth demethylation of the protected phenol was then accomplished without migration of the double bond under basic conditions ( $\text{EtSNa}$ , DMF,  $150^\circ\text{C}$ , 12h, 90%).  $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR and MS data of synthetic ( $\pm$ )-**1** were in complete agreement with an authentic sample of natural parvifoline provided by Professor Joseph-Nathan.



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