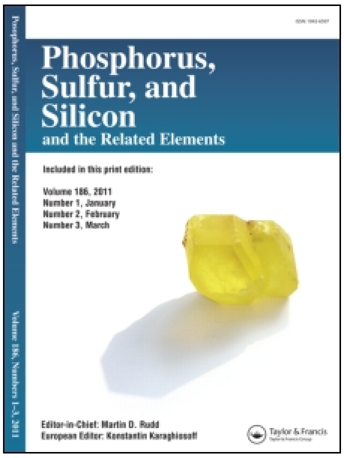

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Facile Construction of Medium-Sized Carbocycles, Total Synthesis of (±)-Parvifoline

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

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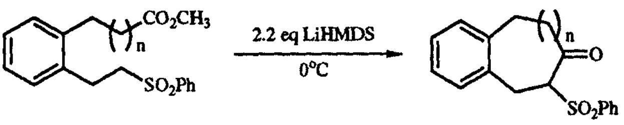
Abstract A new synthetic approach to medium-sized rings has been accomplished via intramolecular cyclization of a sulfone-stabilized carbanion. This strategy was applied to the total synthesis of (±)-parvifoline.

Few methods for direct formation of medium-sized rings are available.[1] 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**).[2]

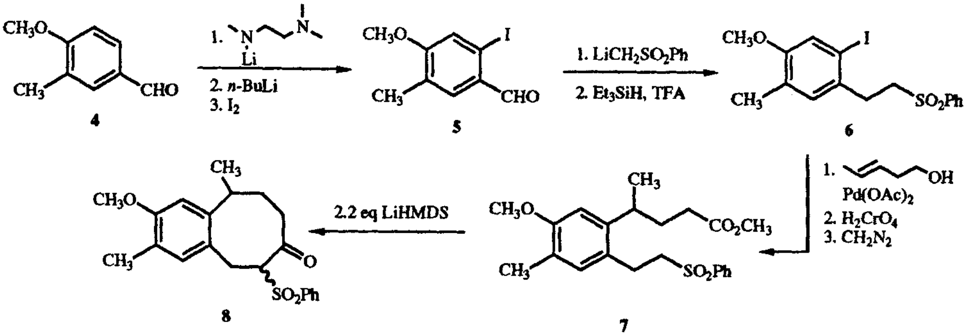
The general reaction under discussion is exemplified by the conversion of sulfone ester **2** into ketosulfone **3** upon treatment with base. *The desired sequence requires the generation of the α-sulfonyl anion in the presence of the reactive ester, followed by ring closure.* The relative efficiency 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.



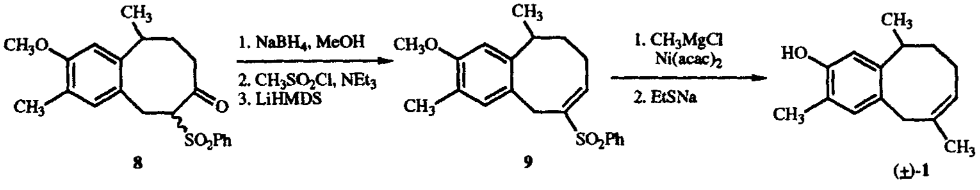
2 a,b,c **3 a,b,c**

	n	Yield (%)
a:	1	90
b:	2	67
c:	3	61

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.[3]



The stage was now set for the introduction of the deconjugated olefin. Thus reduction of **8** with $NaBH_4$ in MeOH (94%), mesylation of the alcohol (CH_3SO_2Cl, 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 MeMgCl in the presence of $Ni(acac)_2$ (75%). Smooth demethylation of the protected phenol was then accomplished without migration of the double bond under basic conditions (EtSNa, DMF, 150°C, 12h, 90%). ^1H and ^{13}C NMR, IR and MS data of synthetic (±)-**1** were in complete agreement with an authentic sample of natural parvifoline provided by Professor Joseph-Nathan.



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