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Facile Construction of the Bicyclo[6.4.0]dodecane Ring System Via Intramolecular Cyclization of a Sulfone Stabilized Carbanion

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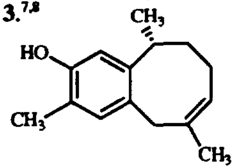
Abstract: A new synthetic approach to eight-membered rings has been accomplished via intramolecular cyclization of a sulfone stabilized carbanion.

Ring annulation has proven to be the most important transformation in synthesis. A plethora of five- and six-membered ring forming reactions has been developed, culminating in syntheses of a marvellous array of cyclopentane and cyclohexane annulated natural products.[1] In comparison, few methods for direct formation of medium-sized rings are available.[2] Intramolecular ring closure leading to eight-membered ring carbocycles is often the most difficult.[3] This letter describes a strategy applicable to the synthesis of eight-membered rings based on intramolecular cyclization of a sulfone-stabilized carbanion.

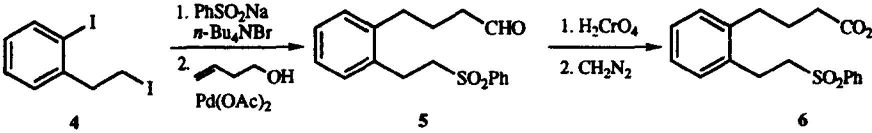
The general reaction under discussion is exemplified by the conversion of sulfone ester **1** into ketosulfone **2** upon treatment of **1** with base. *The desired sequence requires the generation of the α-sulfonyl anion in the presence of the reactive ester.* While this type of ring closure has previously been used for the construction of five-and six-membered carbocycles,[4,5,6] it has not found application in medium ring construction. At first, it would appear difficult because entropic factors and transannular interactions disfavour such processes from occurring. Herein we disclose our successful study on eight-membered ring construction, a strategy that augurs well for the total synthesis of Parvifoline **3**.[7,8]

1 2



3

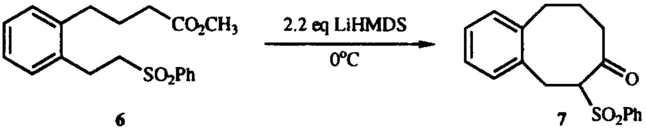
The required ester sulfone was readily obtained from 1-iodo-2-(2-iodoethyl)-benzene **4**[9] via sulfonylation[10] and palladium-catalyzed coupling of the aryl iodide with 3-buten-1-ol[11] to give aldehyde **5**.[12]



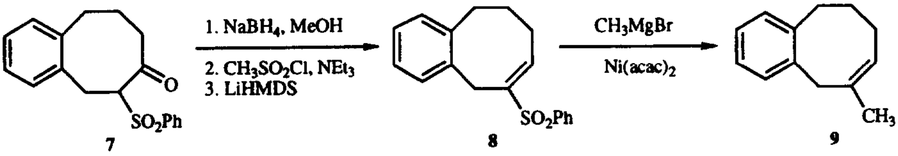
4 5 6

Jones oxidation and subsequent esterification with diazomethane provided sulfone ester **6** in excellent overall yield (86%). The critical ring closure was achieved by slow addition of 2.2 equiv. of lithium bis(trimethylsilyl)amide (LiHMDS, 1.0*M* in THF) to a solution of **6** ($5\cdot10^{-3}M$ in THF) and stirring at this temperature for 2 h in THF at 0°C for 2.5 h. After extractive isolation and chromatography on silica gel, ketosulfone **7** was obtained as a colourless solid in 67% yield (m.p. 159-161°C).

This paper is dedicated to Professor Peter T. Lansbury on the occasion of his 60th birthday



The rapid ring closure is a clear demonstration of the kinetic acidity of the phenylsulfonyl group,[13] an observation that has previously been noted with alkoxide bases.[14] Conversion of ketosulfone 7 into deconjugated olefin 9 was accomplished via reduction of the ketone with $NaBH_4$ in MeOH to give a single isomerically pure alcohol (94%, cis to the phenylsulfonyl group). Mesylation (CH_3SO_2Cl, NEt_3, 45%) and subsequent elimination with LiHMDS gave vinylsulfone 8 (75%). Transition-metal-catalyzed introduction of the methyl group (50%) was finally achieved by treating 8 with MeMgBr in the presence of $Ni(acac)_2$.[15]



The relative efficiency of cyclization of ester sulfone 6 is noteworthy. The strategically placed ketosulfone can easily be transformed into the structural features of Parvifoline. Investigations toward the total synthesis as well as other ring systems are ongoing and will be reported in due course.

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