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Asymmetric synthesis via optically active vinyl sulfoxides

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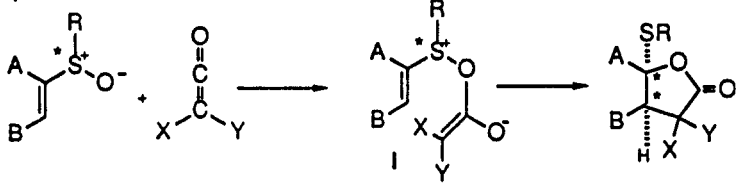
Abstract: The reaction of chiral vinyl sulfoxides with dichloroketene to yield optically active γ-butyrolactones provides the basis for enantioselective syntheses of heterocyclic natural products. In particular, 2-alkylsulfinylindoles are transformed into butyrolactones that serve as precursors to the physostigmine alkaloids. The total synthesis of physostigmine in optically active form has revealed the importance of the size of alkyl group of the sulfoxide in the 3,3-sigmatropic rearrangement leading to the chiral butyrolactone. In addition, an efficient synthesis of optically active benzohydrofuran lactones which are precursors to the aflatoxins is described.

The role of the sulfur atom in its various oxidation states in directing carbon-carbon bond formations is well documented in organic synthesis. From the time-honored Pummerer reaction[1] to the 2,3-sigmatropic rearrangements of allylic sulfoxides[2] and allyl sulfonium ylides[3], many advances in synthetic methodology have materialized in the last twenty years. To a lesser extent, chiral sulfur atoms have played a significant role in asymmetric synthesis[4]. The challenges of asymmetric synthesis have brought to the forefront numerous sulfur-containing chiral auxiliaries, and applications of chiral sulfoxonium species.

In 1981, we reported a new lactonization process involving chiral vinyl sulfoxides and haloketenes[5]. This reaction has proven to be a general enantioselective 3,3-sigmatropic rearrangement of an intermediate vinyl oxsulfonium enolate, I.

Scheme 1



Subsequent work in our laboratories revealed that with R=Aryl and A and/or B as carbon containing groups, the lactonization process generally produces a single enantiomer[6]. The conformational analysis of the reaction pathway confirms the intermediacy of a pseudochair conformation for the oxysulfonium species I with R=Aryl preferring a pseudoequitorial position.

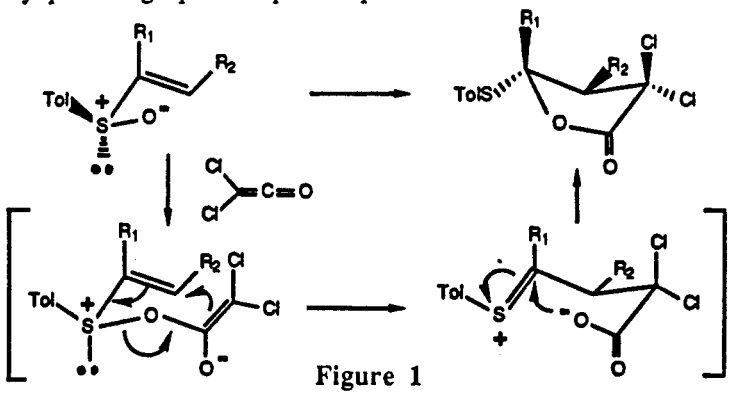
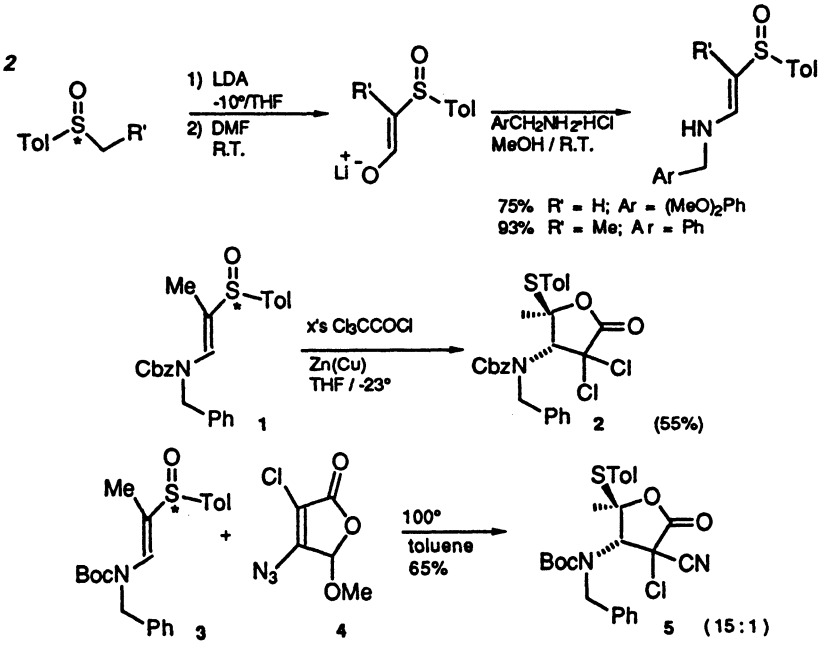


Figure 1

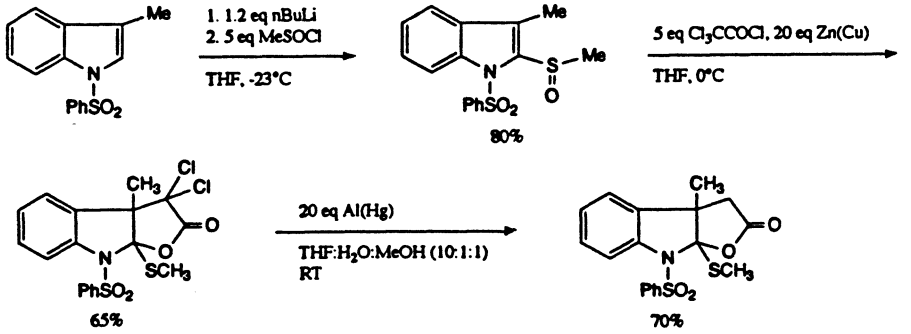
The focus of this paper is the utilization of the above lactonization process in the enantioselective synthesis of physostigmine[7] and chiral precursors for the aflatoxins B_1 and G_1. Implicit in our approach to physostigmine is the ability of carrying out the asymmetric lactonization on an α-amido vinyl sulfoxide

(A≡N, Scheme 1). Unpublished work[8] in our laboratory on β-amidovinylsulfoxides (B=N) indicated that this class of compounds could easily be prepared by modifications of literature procedures[9] using the sequence shown in Scheme 2. Furthermore, reactions of the protected β-aminovinylsulfoxides **1** and **3** with dichloroketene and chlorocyanoketene yield the respective butyrolactones **2** and **5**. It is important to note that the zinc method for generating a haloketene is not a requirement for the success of the lactonization. In the case of sulfoxide **3**, the azidobutenolide **4** serves as a presursor to the chlorocyanoketene[10].

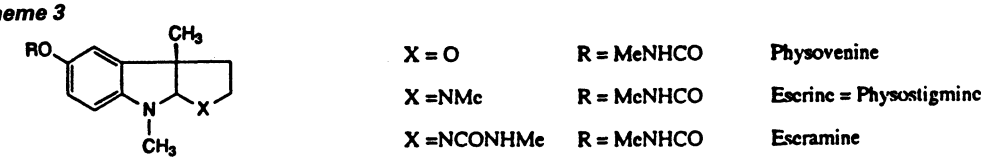
Scheme 2



Having established the compatibility of a protected nitrogen atom as part of the vinyl sulfoxide system, the nature of the vinyl unit of the vinyl sulfoxide led us to explore the possibility of incorporating the double bond in a hetrocyclic ring. To this end, we initially examined the reactions of 2-alkylsulfinyl indoles. Scheme **3** outlines the preparation and lactonization of N-phenylsulfonyl-3-methyl-2-methylsulfinylindole[11]. The realization of the formation of indoline-fused butyrolactones stimulated our interest in the total synthesis of the alkaloids physostigmine, physovenine and the related flustramines (Figure 2).



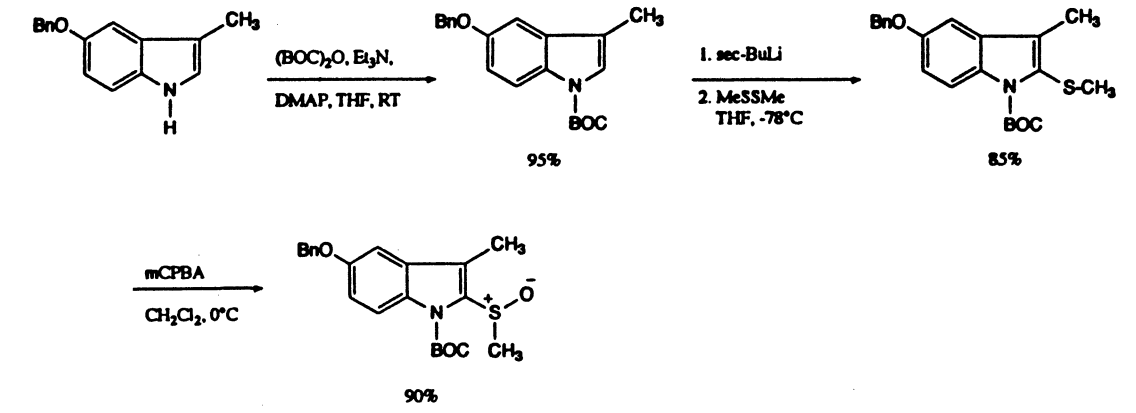
Scheme 3



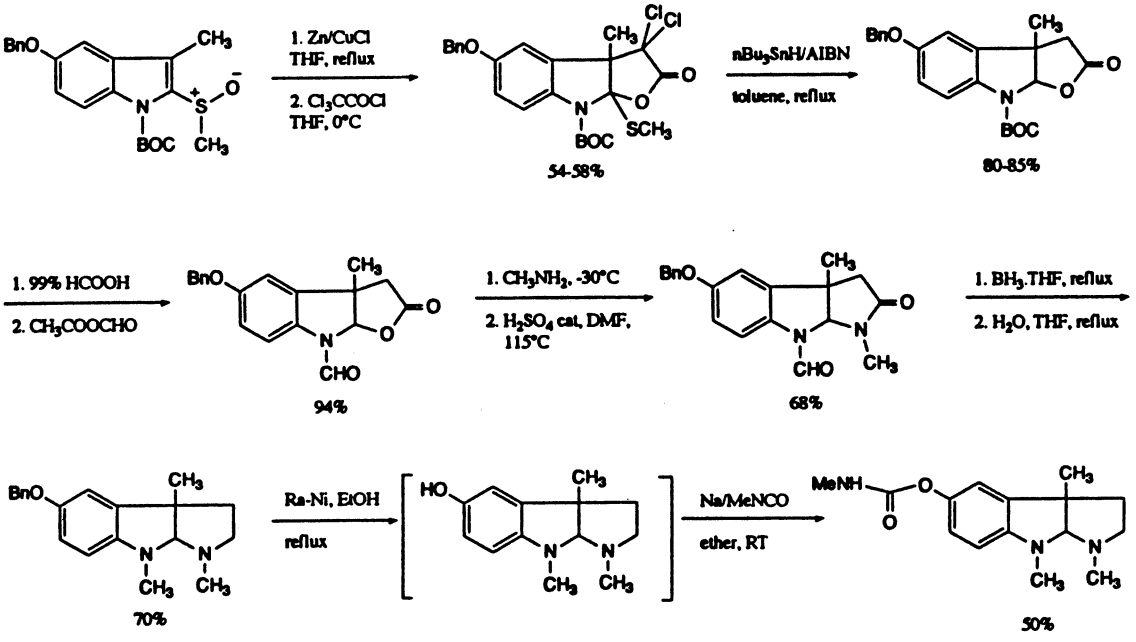
While our initial studies utilized the Niphenylsulfonyl protecting group, a more readily removable group proved to be the t-butyloxycarbonyl (t-BOC) unit. The synthesis of the racemic indole-2-sulfoxide is outlined in Scheme 4 starting from commercially available 5-benzyloxyindole. Scheme **5** summarizes the production of racemic physostigmine in less than ten operations from the sulfoxide. The lactonization product is readily dechlorinated and desulfurized with tri-n-butylstannyl hydride. It was most efficient to exchange the t-BOC protecting group for an N-formyl group which will ultimately be transformed into the

N-methyl group. Transformation of the butyrolactone into an N-methylpyrrolidone was straightforward. The double reduction of the pyrrolidone carbonyl and the N-formyl group are efficiently accomplished with diborane in THF. The final steps of debenzylation and carbamoylation can be best performed as shown.

Scheme 4



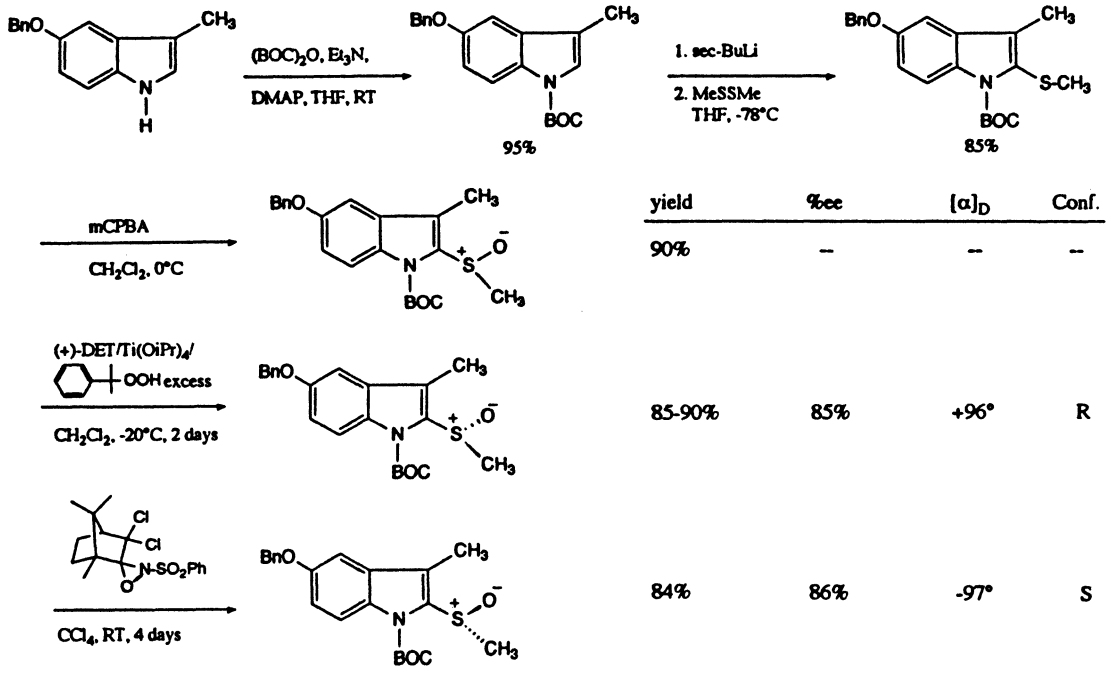
Scheme 5



The extension of the above synthesis to optically active physostigmine presented several unforeseen challenges. The initial objective of preparing the requisite optically active 2-methylsulfinyl indole proved to be non-trivial. The obvious approach of the reaction of the 2-lithioindole with the chiral methyl menthylsulfinate was not effective at low temperatures. Clearly, new strategies for the preparation of optically active alkyl sulfoxides were necessary.

In this regard, we initially explored the asymmetric oxidation of the 2-methylsulfenyl-indole precursor. After much unsuccessful probing of the Kagan modification[12] of the Sharpless oxidation, we were successful in preparing the optically active methyl sulfoxide in 90% yield, with 85% ee, using the standard Sharpless oxidation conditions. In addition, we found that oxidation of the indole sulfide with the dichloro oxaziridine Davis reagent[13] also produced the enantiomeric chiral (S) sulfoxide with 86% ee. These oxidations are summarized in Scheme 6.

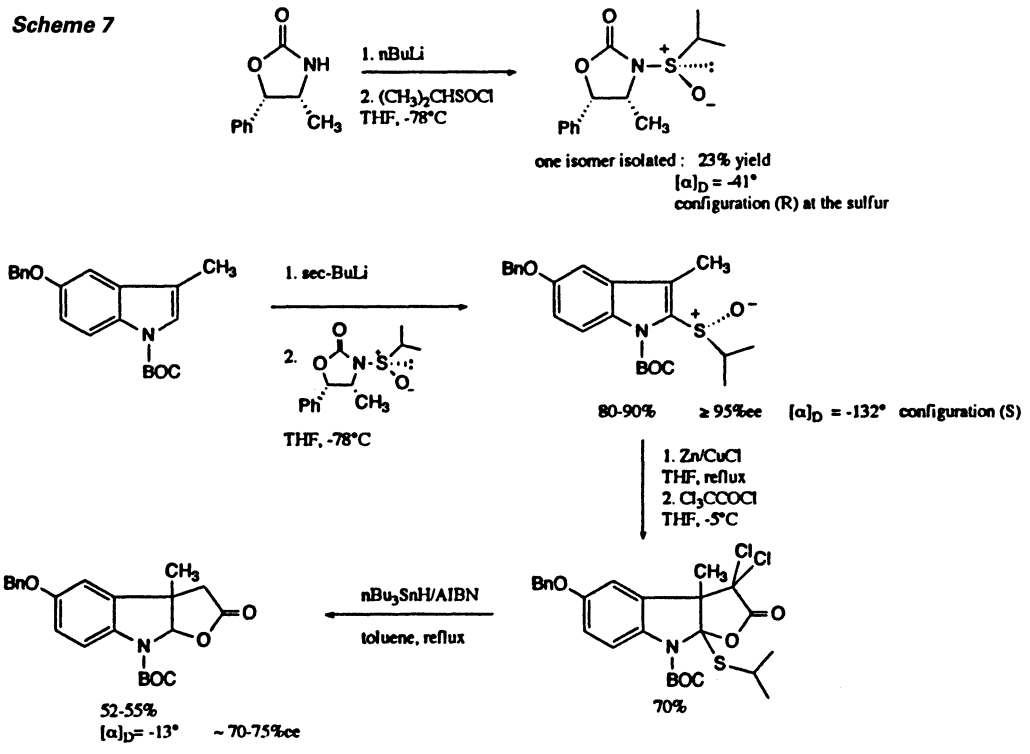
Scheme 6



	yield	%ee	$[\alpha]_D$	Conf.
	90%	--	--	--
	85-90%	85%	+96°	R
	84%	86%	-97°	S

With the optically active methyl sulfoxide in hand, the crucial lactonization with dichloroketene was carried out. To our great surprise, the observed butyrolactone product was essentially racemic. Since this was the first example of a chiral alkyl vinyl sulfoxide undergoing our lactonization process, we were expecting variations in the degree of asymmetric induction as a function of the size of the group on the chiral sulfoxide. As indicated in Figure 1, the p-tolyl sulfoxides usually had the tolyl group disposed in an equitorial disposition with sufficient bias to produce a single conformer and hence a single enantiomer. The much smaller methyl group clearly did not provide sufficient conformational preference to yield a major enantiomer. The clear test for this steric phenomenon would be the use of a bulkier alkyl group on the sulfoxide. This presented new problems since the aforementioned asymmetric oxidations were

Scheme 7



ineffectual for the analogous 2-isopropylsulfenyl indole. Thus, a new process for preparing higher alkyl sulfoxides of indoles was required. A solution was found in the development of a new class of N-sulfinyl oxazolidines reagents derived from the work of Evan's[14]. The N-isopropylsulfinyloxazolidine derived from ephedrine was prepared as a single diastereomer, and then reacted with the 2-lithio species of the indole to yield the optically active sulfoxide (95%ee). Subsequent lactonization of this isopropyl sulfoxide gave the desired butyrolactone in optical purities as high as 75% (Scheme 7). We were gratified that the simple substitution of a larger alkyl group resulted in greater asymmetric induction for the lactonization process.

Subsequent conversion of the lactone in Scheme 7 from the (S) sulfoxide into physostigmine confirmed the final synthesis of the naturally occurring enantiomer of physostigmine. Further extrapolations to larger alkyl groups for the sulfoxide (t-butyl) did not result in higher asymmetric induction because of alternative reaction pathways of the sulfoxide.

An equally challenging class of heterocyclic natural products to the physostigmines is the aflatoxins. Since the pioneering work of Büchi[15], few improvements on the synthesis of aflatoxins have appeared. Notwithstanding Büchi's accomplishments, there are no general syntheses of optically active aflatoxins. For this and other reasons, we sought to apply our asymmetric lactonization reaction to the synthesis of optically active precursors to aflatoxins. In addition to the aflatoxins, other metabolites such as versicolorin A, austocysins and sterigmatocystin all contain a benzodihydorfuran fused to another dihydrofuran as shown in Figure 3.

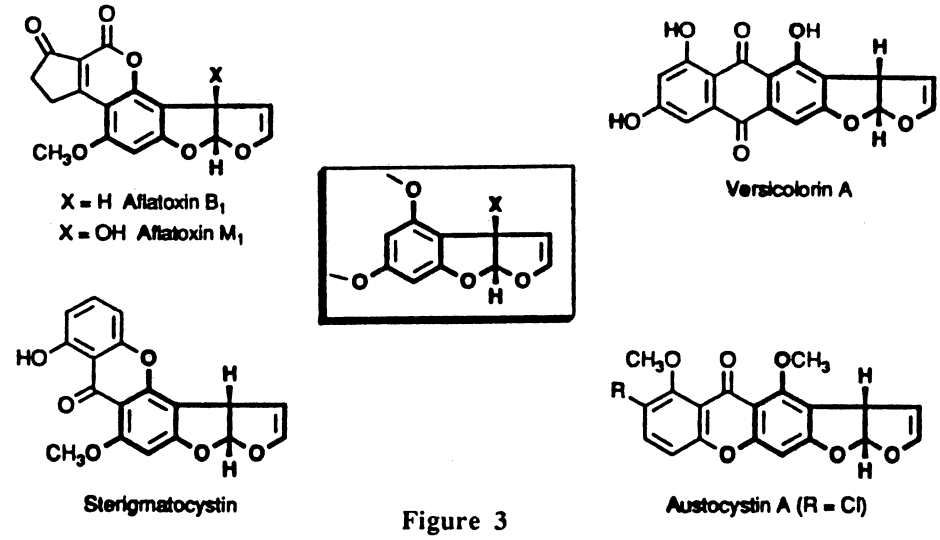
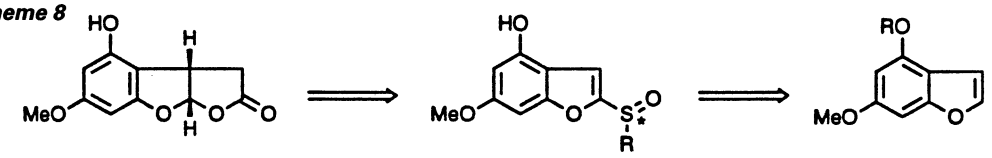


Figure 3

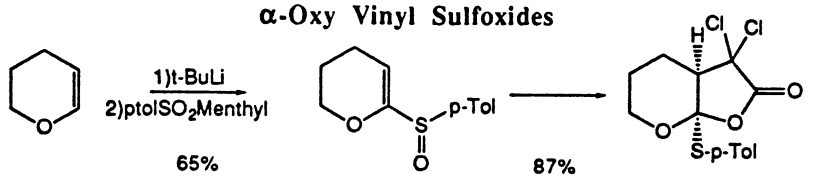
By analogy to Büchi's original synthesis of a key lactone precursor to aflatoxin we sought to convert a benzofuran-2-sulfoxide into the ring-fused lactone shown in Scheme 8.

Scheme 8

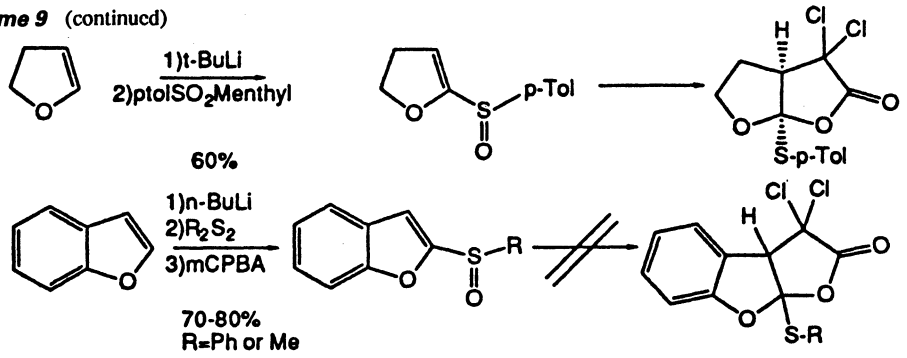


With this objective in mind, we proceeded to study the lactonization reactions of α-oxy vinyl sulfoxides. As can be seen in Scheme 9, α-sulfoxides of tetrahydropyran and dihydrofuran readily yielded the expected ring-fused butyrolactones with dichloroketene. In stark contrast, the 2-sulfoxide of benzofuran did not yield any lactone under identical conditions up to temperatures of 100°C. It is our conclusion that the furan double bond is too involved in the aromatic system to allow for the 3,3-sigmatropic rearrangement.

Scheme 9

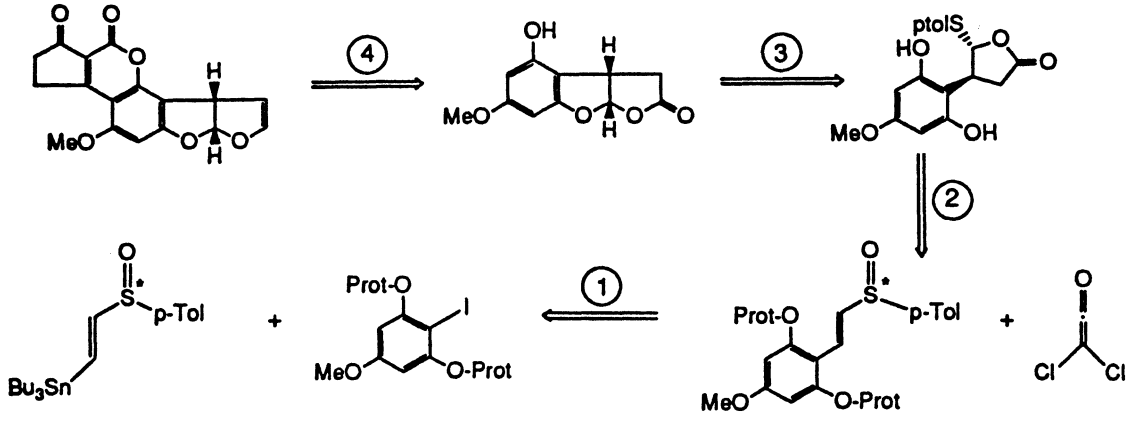


Scheme 9 (continued)



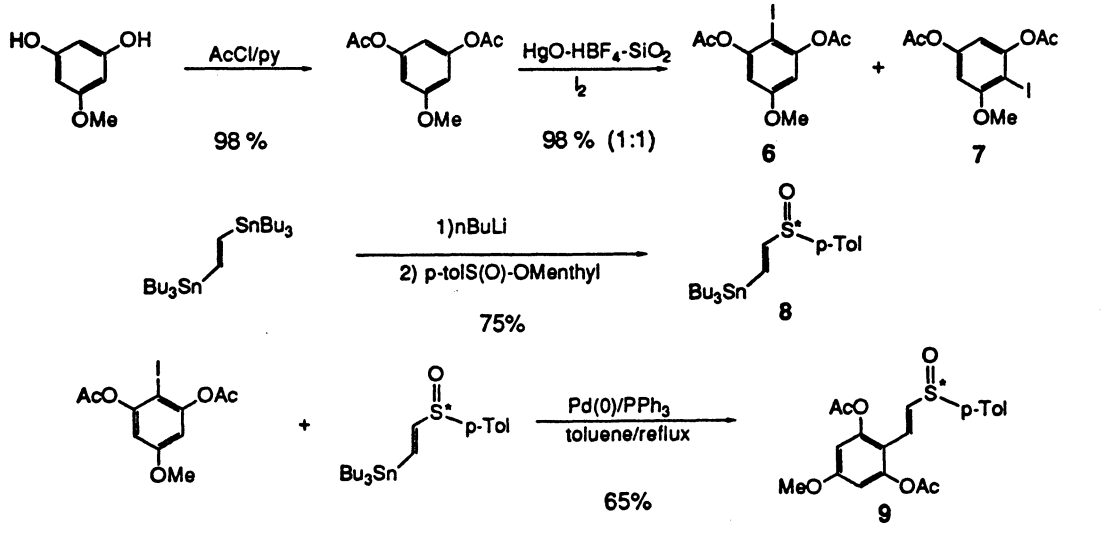
Faced with this dilemma, we chose to follow an alternative pathway which relied on a initial lactonization of an aryl vinyl sulfoxide followed by an intramolecular ring closure to the Büchi lactone. A retrosynthetic plan is outlined in Scheme 10 shown below.

Scheme 10 **Retrosynthetic Analysis**



Methoxyresorcinol was diacetylated and iodinated[16] to give the regioisomers **6** and **7** in high yield. The desired regioisomer **6** selectively crystallized from the mixture, and it was subjected to a Stille coupling[17] with the chiral synthon **8** which was prepared from the trans-1,2-n-butylstannyl-ethene. The coupled product **9**, when subjected to the dichloroketene lactonization, produced the trans-disubstituted butyrolactone[10] in 70% yield (100%ee) after zinc promoted dechlorinations. The optical purity of lactone **10** was confirmed by NMR studies with chiral shift reagents. A crucial ring closure of lactone **10** could be effected under acidic conditions, which first hydrolyzed the acetates and then catalyzed the acetal

Scheme 11

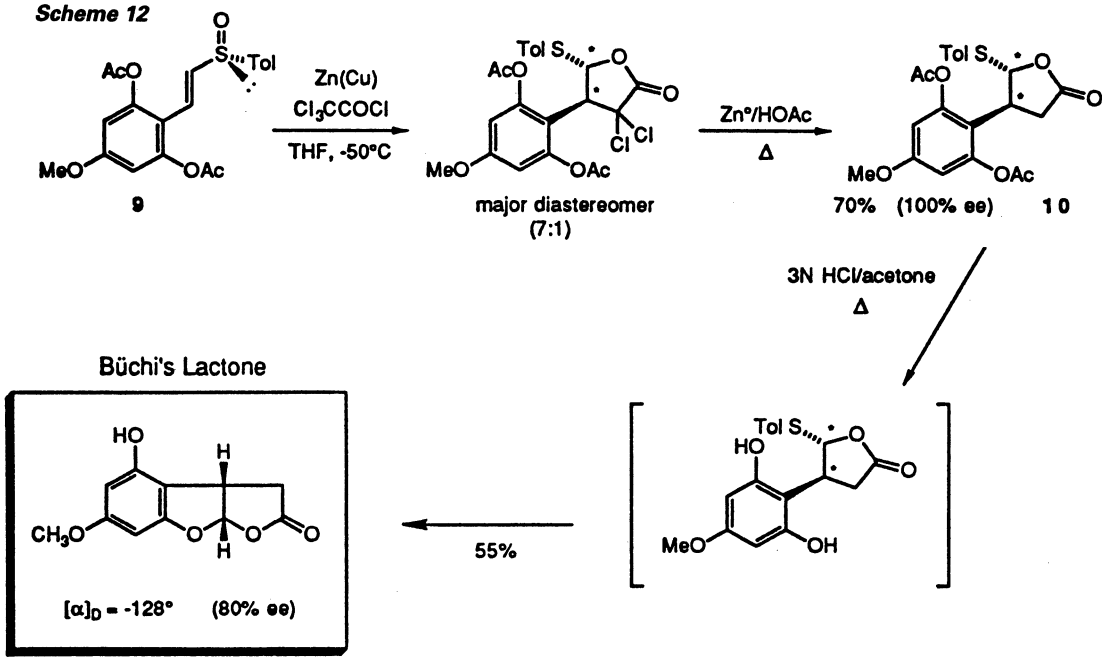


formation. Unfortunately, these aqueous acid conditions also resulted in partial racemization of a potential aldehyde intermediate. Nevertheless, the Büchi lactone was produced in good yield with 80%ee. The optical purity was determined by NMR analysis of a Mosher's ester of the phenol.

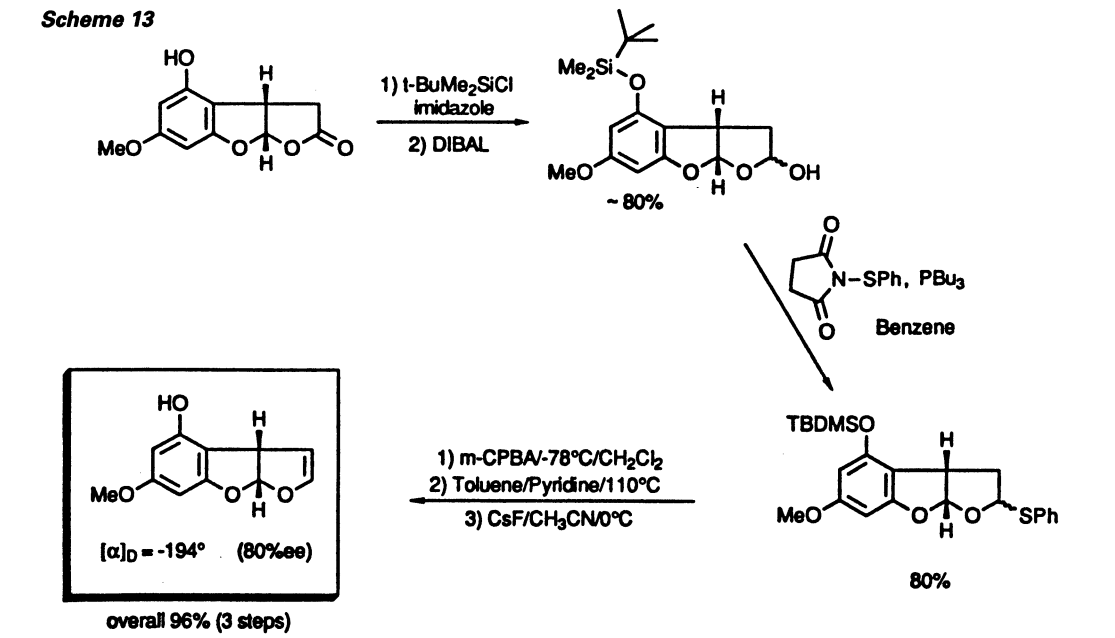
In order to effect the conversion of the Büchi lactone of Scheme 12 into the dihydrofuran system of aflatoxins, we carried out the literature precedented sequence shown in Scheme 13. Reduction of the lactone, and selective transformation to the hemithioacetal under the mildest of conditions prevented any further racemization. Oxidation and thermal elimination of the sulfoxide yielded the dihydrofuran in excellent yield. While this protocol did not provide aflatoxin precursors with 100%ee, the significant optical purities obtained are the first successful enantioselective syntheses of this class of natural products.

In conclusion, the lactonization reaction of chiral vinyl sulfoxides has been put to a challenging test in the synthesis of optically active heterocyclic natural products. New insights in the steric and substitution requirements for this process have been delineated.

Scheme 12



Scheme 13



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