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Benzothiazines in synthesis. Eight-membered ring formation in an intramolecular Friedel–Crafts reaction

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ABSTRACT

Treatment of certain benzothiazines bearing allylic bromides side chains with indium tribromide resulted in the formation of eight-membered rings in addition to the expected six-membered rings.

Elisapterosin B (**1**) is a complex natural product isolated by Rodriguez and co-workers.[1] The compound is not only structurally intriguing, but biologically as well, as it possesses significant antitubercular activity, inhibiting the growth of *M. tuberculosis* H37Rv. These factors have stimulated interest in the compound in the synthetic community and a number of syntheses have been reported.[2–6]

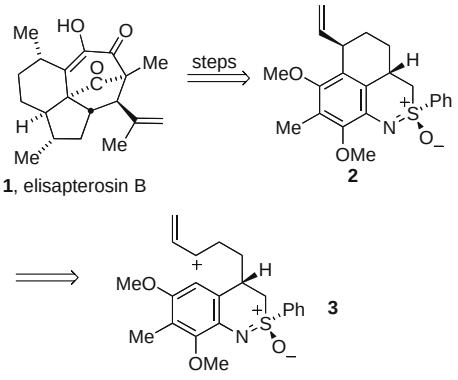
Our approach to this compound is centered on benzothiazine chemistry, with which we have had success in the synthesis of a number of natural products.[7,13]

Our plan in the synthesis of elisapterosin B depends on the stereoselective synthesis of **2**, which we anticipate can be converted to the natural product in short order (Scheme 1). One approach to **2** involves a stereoselective intramolecular Friedel–Crafts reaction of an allylic cation (**3**) or its equivalent. This Letter describes several approaches to **2** and the interesting observation of the formation of an eight-membered ring product in the Friedel–Crafts reaction of one of the precursors.

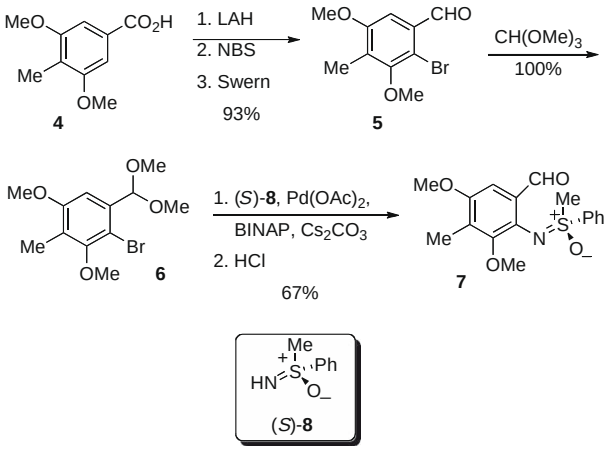
Our approach to precursors to **3** consisted of generating benzothiazines via the stereoselective conjugate addition of sulfoximine carbanions to alkenes bearing an electron-withdrawing group.[8] These electron-withdrawing groups would be removed at some point during the synthesis to afford **2**, which could be carried forward to the natural product.

The *N*-aryl sulfoximine needed for this study was prepared as shown in Scheme 2. The commercially available benzoic acid **4** was reduced with LAH, brominated with NBS, and oxidized to the corresponding aldehyde **5** in 93% overall yield. Protection of the aldehyde afforded acetal **6** quantitatively. A Buchwald–Hartwig reaction with (*S*)-**8**,[9] followed by hydrolysis gave aldehyde **7** in 67% overall yield.

Sulfoximine **7** was used as a substrate for the generation of two cyclization precursors. These were synthesized via a Horner–Em-



Scheme 1. Partial retrosynthesis of elisapterosin B.



Scheme 2. Synthesis of sulfoximine.

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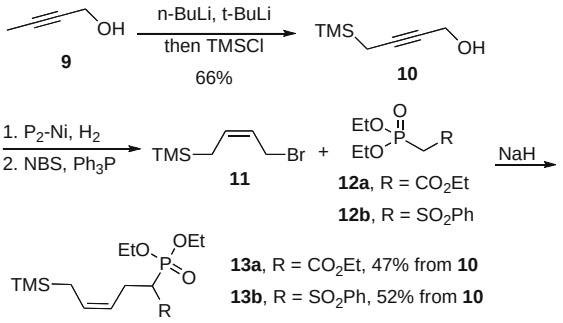


Scheme 3. Preparation of phosphonates **13a** and **13b**.

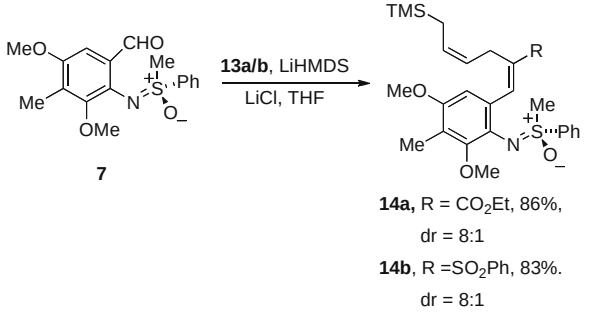
mons reaction. The preparation of the appropriate reagents is shown in Scheme 3. The conversion of 2-butyn-1-ol (**9**) into **10**,[10] followed by hydrogenation with *P*2-nickel,[11] afforded alcohol **12** in good yield. Alcohol **12** was converted into the corresponding allylic bromide **11**, which served as an electrophile to furnish phosphonates **13a** and **13b**.

Benzothiazines were prepared by coupling **13a/b** with **7** followed by intramolecular conjugate addition. The coupling sequence is shown in Scheme 4. Stereoselectivity in the formation of **14a** and **14b** was acceptable.[12] The *E* and *Z* isomers of each compound were separable and only the *E* isomers were taken forward.

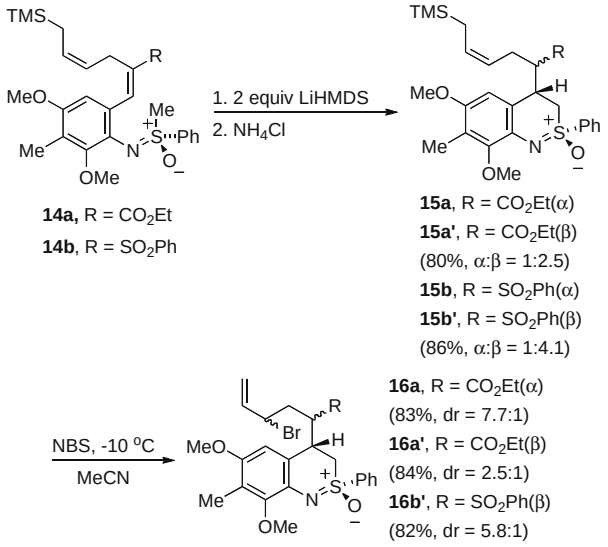
Diastereomeric mixtures were obtained when **14a** and **14b** were treated with base (Scheme 5). All of our results to date demonstrate that diastereomers result from non-selective protonation of the anions that arise from the intramolecular conjugate addition. We have had success in achieving relatively high diastereoselectivity in some cases,[13] but the selectivity in this study was low. Stereochemical assignments of the individual stereoisomers were based on several factors, including the idea that the major stereoisomers would bear the stereochemistry of similar compounds prepared in other studies.

Treatment of the individual benzothiazine diastereomers with NBS resulted in the formation of the corresponding secondary allylic bromides in low to good diastereoselectivities.[14] The exact stereochemistry of the bromide-bearing carbon was not ascertained. Rather, the compounds were treated with $InBr_3$ in refluxing CH_2Cl_2 in the presence of molecular sieves (Scheme 6).[15] The stereochemistry of the major isomer **17b** in the cyclization of **16a** was assigned by NOESY, a correlation being seen between the methylene group of the ethyl ester and one hydrogen on the methylene of the vinyl group. The major isomer obtained from the cyclization of **16a′** was crystalline and the stereochemistry was established by X-ray analysis. These data imply the stereochemistry of the other products and of the starting materials as well.

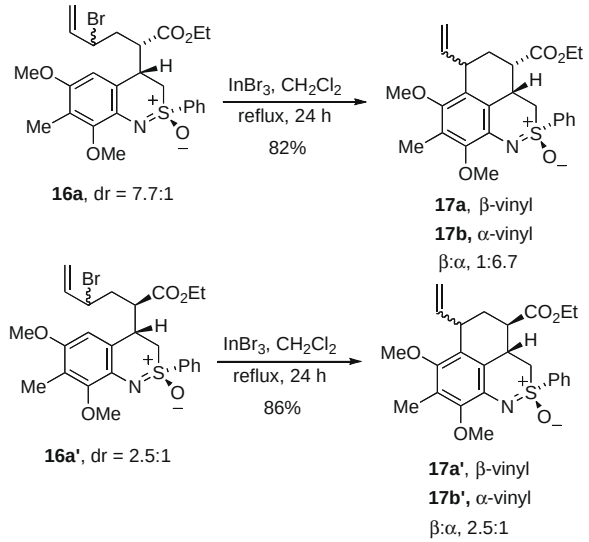
It is interesting to note that there is a close correlation between the diastereomeric ratios of the bromides and the corresponding



Scheme 4. Horner–Wadsworth–Emmons reactions of **7**.



Scheme 5. Synthesis of allylic bromides.

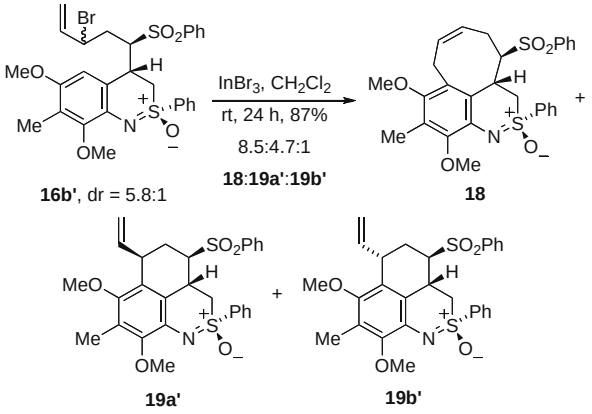


Scheme 6. Intramolecular Friedel–Crafts reaction of **16** and **16a′**.

cyclization products. The implication is that the substitution process occurs in an S_N2 fashion, though we have by no means rigorously established this.

Interestingly, when **16b′** was treated with excess indium bromide in CH_2Cl_2 for 24 h at room temperature, an eight-membered ring product (**18**) was obtained, in addition to the two expected six-membered ring diastereomers. A brief investigation of reaction conditions demonstrated some variability in product distribution as a function of temperature. Thus, the ratio of the three products formed changed from 8.5:4.7:1 (**18**:**19a′**:**19b′**) at room temperature to 9.1:4.8:1 in refluxing dichloroethane. In a reaction run at −78 °C to room temperature, the product ratio was 5.1:5.5:1.[16] Exposure of the product mixture from a low temperature experiment to reagent and heat did not result in equilibration to a new product mixture. This suggests a larger entropy of activation (less negative) for the formation of **18** vis-à-vis the six-membered ring regioisomer (Scheme 7).

Interestingly, the formation of the six-membered ring products from **16a′** proceeded with moderate diastereoselectivity in the direction desired for the synthesis of elisapterosin B, but also clo-



Scheme 7. Intramolecular Friedel–Crafts reaction of **16b**′.

sely reflected the diastereomer ratio of the precursor allylic bromides.

In conclusion, we have discovered that it is possible to prepare potential precursors to elisapterosin B as well as a unique cyclooctanoid via an intramolecular Friedel–Crafts alkylation process. The basis of substituent effects on this process with respect to both regiochemistry and stereochemistry is presently not clear and further work is necessary to determine it. Such studies and application of the method to the synthesis of various targets will be reported in due course.[17]

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.227.

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16. Other experiments we have performed show that the reaction does not take place to any significant extent at −10 °C.
17. Crystallographic data (excluding structure factors) for some structures reported in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 716164 (**17a**′) and 716143 (**18**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)336033; Email: deposit@ccdc.ac.uk].