

Benzothiazines in Synthesis. A Total Synthesis of Pseudopteroxazole

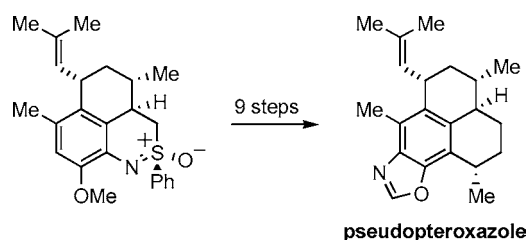
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ABSTRACT

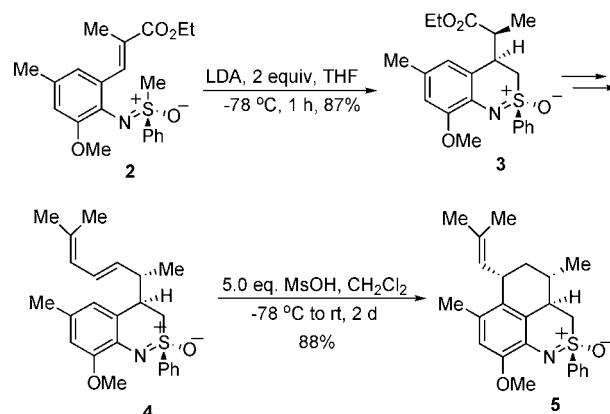


An enantioselective total synthesis of the naturally occurring antitubercular agent pseudopteroxazole is described. The synthesis is organized around the use of a stereoselective, intramolecular addition of a sulfoximine carbanion to an α,β -unsaturated ester to form an enantiomerically pure benzothiazine. Other important processes include a completely stereoselective intramolecular Friedel–Crafts alkylation and a stereoselective and regioselective hydrogenation.

Pseudopteroxazole (**1**) is an amphilectane diterpene recently isolated from the marine soft coral *Pseudopterogorgia elisabethae* as part of a bioassay-guided evaluation of extracts of this organism.¹ It is one of a series of compounds isolated from this organism that shows activity against *Mycobacterium tuberculosis* H₃₇Rv. The structure of **1** was initially elucidated by extensive NMR studies and comparisons with known amphilectane models. Subsequently, the structure was reassigned by Corey and co-workers through the total synthesis of **1**.^{2,3} The promising biological activity of pseudopteroxazole and related compounds has stimulated considerable interest in their synthesis.^{2–4} However, since its reported isolation, only one synthesis of **1** has appeared.³

Recently, we have established a novel way to introduce benzylic stereocenters with high selectivity through a completely stereoselective, intramolecular Michael addition of sulfoximine carbanions to α,β -unsaturated esters.⁵ The benzothiazines thus formed can serve as templates around which various functional groups and structural features can

Scheme 1



be stereoselectively introduced. We have applied this methodology to the formal total syntheses of (+)-curcuphenol, (+)-curcumene, and erogorgiaene.^{6,7} We have also published an approach to the synthesis of pseudopteroxazole that culminated with the stereoselective synthesis of **5** (Scheme 1).⁸ We now wish to report that we have successfully converted this compound to pseudopteroxazole.

(1) Rodriguez, A. D.; Ramirez, C.; Rodriguez, I. I.; Gonzalez, E. *Org. Lett.* **1999**, *1*, 527.

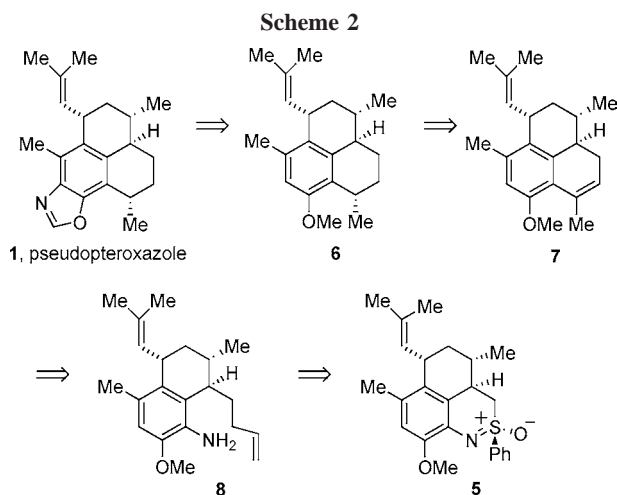
(2) Johnson, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2001**, *123*, 4475.

(3) Davidson, J. P.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 13486.

(4) Heckrodt, T. J.; Mulzer, J. *Top. Curr. Chem.* **2005**, *244*, 1.

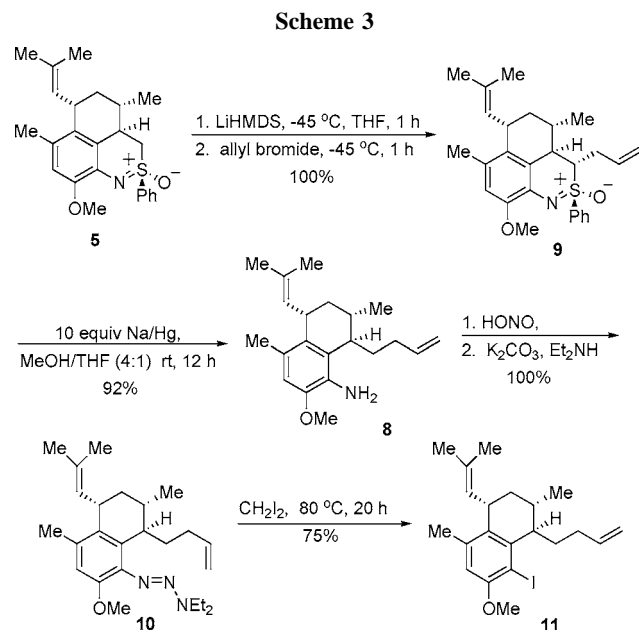
(5) Harmata, M.; Hong, X. *J. Am. Chem. Soc.* **2003**, *125*, 5754.

A retrosynthesis of pseudopteroxazole that leads to **5** is shown in Scheme 2. Alkylation and reductive desulfurization



of **5** would give **8**. Activation of the aniline nitrogen followed by an intramolecular Heck reaction would afford **7**. A stereoselective reduction of the conjugated double bond and installation of the oxazole ring would give **1**.

Thus, the elaboration of **5** into pseudopteroxazole started with deprotonation with LiHMDS followed by alkylation with allyl bromide to deliver compound **9** as a single diastereoisomer in quantitative yield.⁹ A reductive desulfurization of **9** was then accomplished with Na/Hg to provide aniline **8** in 92% yield (Scheme 3).¹⁰



Aniline **8** was converted to 1-aryl-3,3-diethyltriazeno **10** in quantitative yield at 0–5 °C, in an Et₂O/THF/CH₃CN/H₂O solvent system, in the presence of K₂CO₃.¹¹ Subse-

quently, upon treatment with diiodomethane in a sealed tube at 80 °C for 20 h, triazene **10** was smoothly converted to aryl iodide **11** in 75% yield.¹²

We then began to investigate possibilities to synthesize **7** directly from **11** by a Pd-catalyzed intramolecular Heck coupling reaction. After a systematic literature evaluation, we found that a catalytic system consisting of Pd(OAc)₂, tri(*o*-tol) phosphine, and triethylamine (TEA) would probably lead to the desired product.¹³ In the event, exposure of **11** to these reagents for 38 h at 120 °C in TEA afforded **7** in 62% yield.¹⁴

Our first attempt at the reduction of **7** consisted of subjecting this compound to dissolving metal conditions (Li/NH₃ at -78 °C). This afforded two diastereoisomers in 77% yield in a ratio of 1:1.¹⁵ The lack of stereoselectivity was a problem, but we found a solution that turned out to be both highly regio- and stereoselective.

In considering a solution, we were drawn to work by Pfaltz, who showed that catalyst **12** was highly effective for the enantioselective reduction of trisubstituted alkenes, with facial selectivity commensurate with our goals.¹⁶ We thus anticipated reduction of the styryl double bond in **7** to take place from the top face. Further, we expected the conformation of the remaining trisubstituted double bond to be such as to minimize 1,3-allylic strain.¹⁷ In this conformation, the methyl group on the benzene ring blocks the face of the olefin that should be preferred by **12** (Figure 1). This should

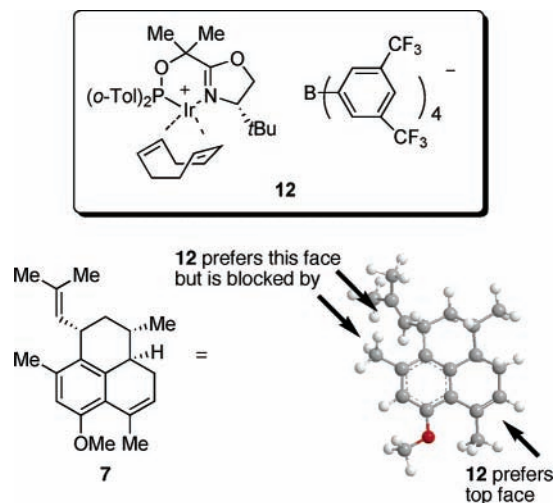


Figure 1.

inhibit reduction of this double bond and make the reaction regioselective.

(6) Harmata, M.; Hong, X.; Barnes, C. L. *Tetrahedron Lett.* **2003**, 44, 7261.

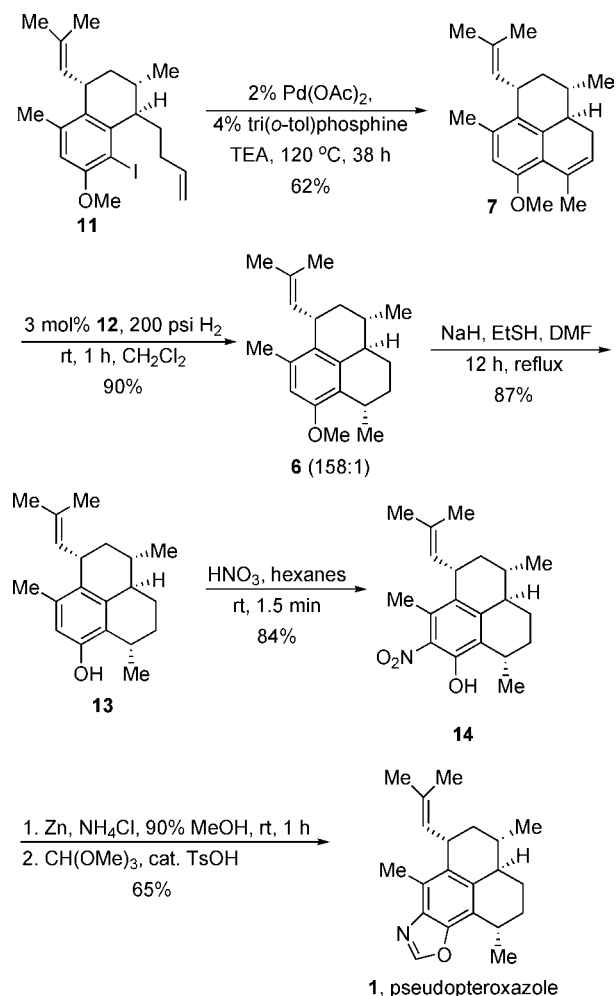
(7) Harmata, M.; Hong, X. *Tetrahedron Lett.* **2005**, 46, 3847.

(8) Harmata, M.; Hong, X.; Barnes, C. L. *Org. Lett.* **2004**, 6, 2201.

(9) Stereochemistry of this compound was not established rigorously but is consistent with stereochemical outcomes for alkylations of other, related benzothiazines.

(10) Harmata, M.; Kahraman, M. *Synthesis* **1994**, 142.

Scheme 4



We conducted reductions of **7** with 3 mol % **12** in CH_2Cl_2 at 200 psi of hydrogen for 1 h and found that compound **6** was obtained with complete stereoselectivity in 90% yield, along with only trace amounts of over-hydrogenated product (Scheme 4).¹⁸

(11) Cary, J. M.; Moore, J. S. *Org. Lett.* **2002**, 4, 4663.

(12) Moore, J. S.; Weinstein, E. J.; Wu, Z. *Tetrahedron Lett.* **1991**, 32, 2465.

With **6** in hand, the last stage of the synthesis involved establishing the benzoxazole ring. We followed the procedures introduced by Corey in his synthesis of isomers of pseudopteroxazole.² First, **6** was demethylated by NaSEt in DMF at reflux to give the phenol **13** in 87% yield.¹⁹ Subsequent nitration of **13** with concentrated HNO_3 in hexanes for 1.5 min produced the corresponding nitrophenol **14** in 84% yield. Finally, reduction of **14** with Zn dust, followed by treatment with methyl orthoformate and a catalytic amount of TsOH, completed the synthesis of pseudopteroxazole (**1**) in 65% yield over the last two steps (Scheme 4). The proton and carbon spectra of synthetic pseudopteroxazole were identical in all aspects to those reported previously by Rodriguez and Corey.^{1,3}

In conclusion, we have accomplished a total synthesis of pseudopteroxazole that proceeds in nine steps from **5** in an overall yield of 18%. Further studies of benzothiazine chemistry are in progress, and results will be reported in due course.

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Supporting Information Available: Experimental procedures, as well as characterization and copies of proton and carbon spectra for all previously unreported compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, 48, 3894.

(14) A 14% yield of the exocyclic alkene isomer of **7** was also produced. This isomerized to **7** in 82% yield upon column chromatography.

(15) Cesati, R. R.; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, 126, 96.

(16) Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, 6, 2023.

(17) Hoffmann, R. W. *Chem. Rev.* **1989**, 89, 1841.

(18) Ratio was 158:1 by GC.

(19) Smith, A. B.; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, 104, 4015.