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Benzothiazines in Synthesis. A Total Synthesis of Pseudopteroxazole

Michael Harmata* and Xuechuan Hong

Department of Chemistry, University of Missouri−Columbia, Columbia, Missouri 65211

harmatam@missouri.edu

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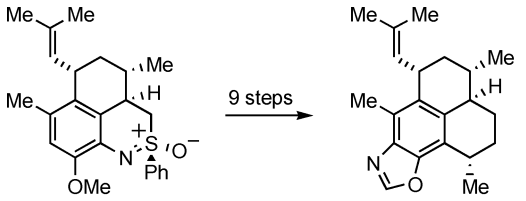
ABSTRACT



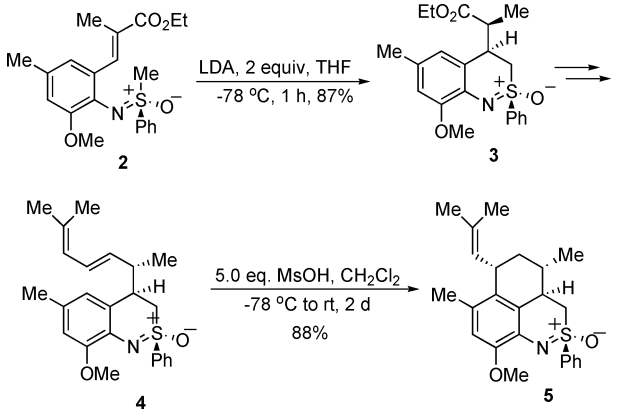
pseudopteroxazole

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* $H_{37}Rv$. 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 pseudoteroxazole 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 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.

Scheme 1



(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.

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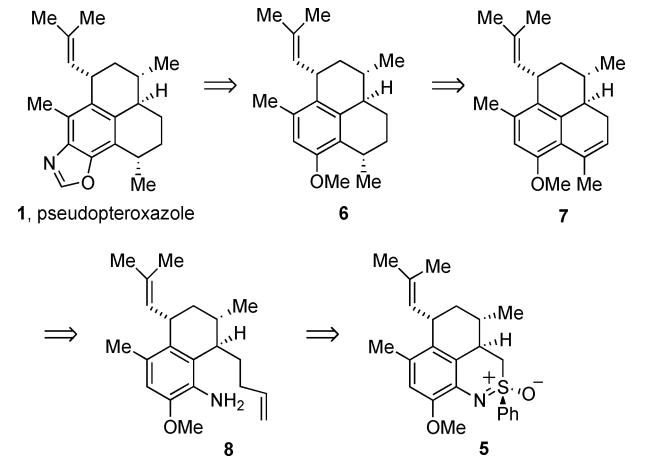
A retrosynthesis of pseudopteroxazole that leads to **5** is shown in Scheme 2. Alkylation and reductive desulfurization

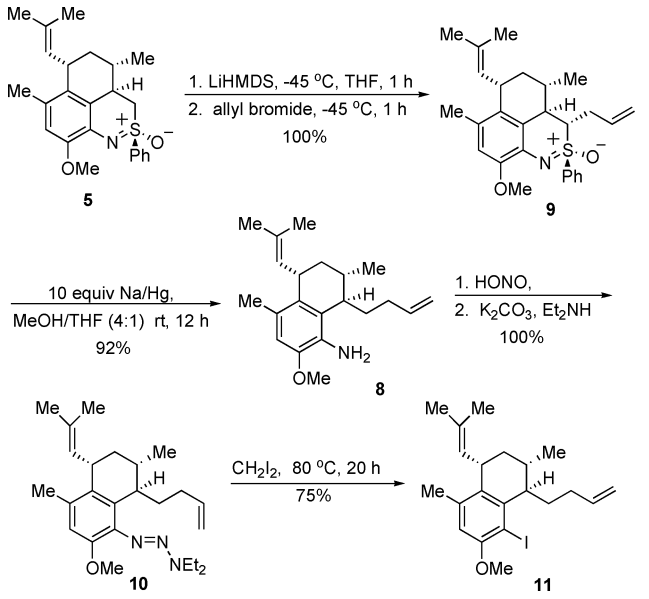
Scheme 2



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]

Scheme 3



Aniline **8** was converted to 1-aryl-3,3-diethyltriazene **10** in quantitative yield at 0−5 °C, in an Et_2O/THF/CH_3CN/H_2O solvent system, in the presence of K_2CO_3.[11] Subsequently, 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/NH_3 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

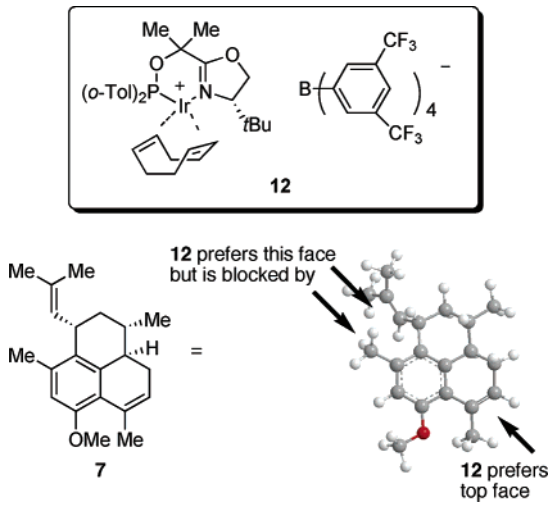
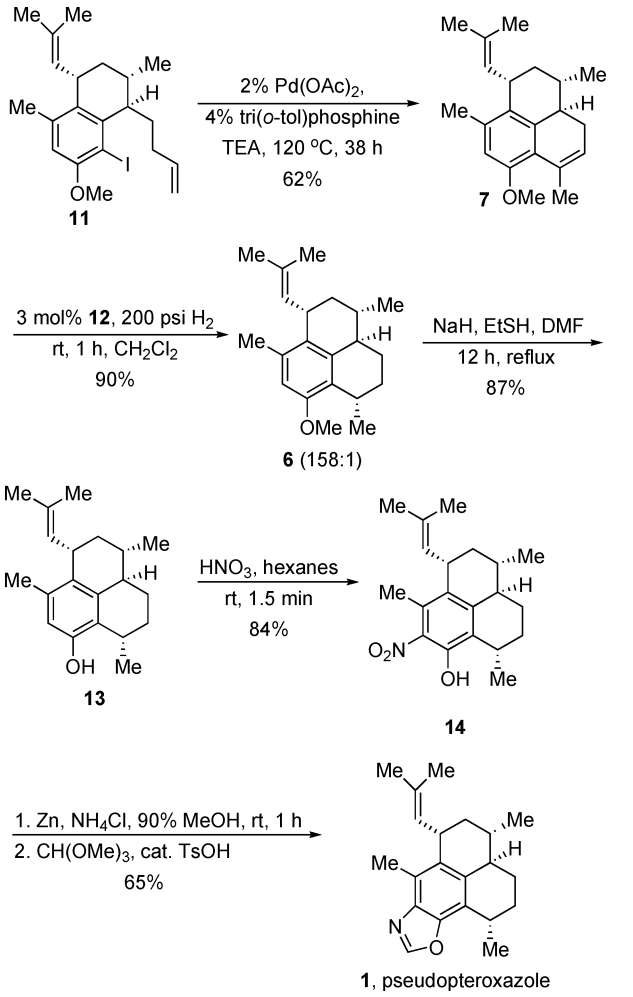


Figure 1.

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]

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 **15** 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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