ORGANIC LETTERS

2004
Vol. 6, No. 13
2201−2203

Benzothiazines in Synthesis. Toward the Synthesis of Pseudopteroxazole

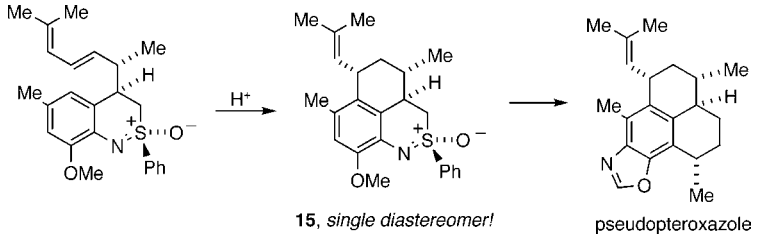
Michael Harmata,* Xuechuan Hong, and Charles L. Barnes

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

harmatam@missouri.edu

Received April 12, 2004

ABSTRACT

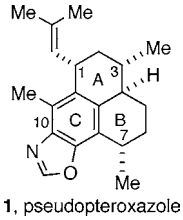


The tricyclic benzothiazine 15 was prepared in a straightforward fashion via a completely stereoselective intramolecular Friedel–Crafts alkylation. This compound represents a potential precursor to the antitubercular agent, pseudopteroxazole. Its synthesis proceeded via a completely selective, intramolecular addition of a sulfoximine-stabilized carbanion to an α,β-unsaturated ester, followed by functional group manipulations.

Tuberculosis is a disease whose history and present status suggest an insidious and significant threat to human health on a global scale. It is estimated that as many as 2 billion people are currently infected with *Mycobacterium tuberculosis*, the microorganism responsible for the disease. Many of these individuals will remain asymptomatic, but a significant portion will develop tuberculosis. Eight million new cases of TB appear annually. Three million people die from the disease each year. This number exceeds that caused by any other infectious agent, including the malarial parasite.[1]

A current problem associated with tuberculosis is the appearance of multidrug resistant variants. Up to 50 million people are infected with resistant forms of *M. tuberculosis*. This problem is exacerbated by the presence of the HIV pandemic. Individuals with HIV are significantly more susceptible to TB infection than the general population. Other factors associated with a compromised immune system as well as public health factors, including crowding, drug use, poor nutrition, and even aging, create increased risks for contracting the disease. This can occur either through new infection or transformation of latent disease into active TB.

Despite this picture, tuberculosis is generally highly curable and it is likely that progress made on the scientific front will not result in the realization of diminution of the disease without effective public policy. Current treatment for TB involves a "short course" of antibiotic treatment that can last for 10 months or more. Treating drug resistant variants can require two years of treatment. The cost and general difficulty of effectively maintaining such treatment regimens is one motivation for the continued search for new and more effective treatments for TB.



1, pseudopteroxazole

There is therefore high general interest in the pursuit of new chemotherapeutics for tuberculosis. As with other diseases, leads to effective drugs can often be found among natural products.[2] One such natural product is the amphilectane diterpene, pseudopteroxazole.

Pseudopteroxazole (**1**) was isolated from the sea whip *Pseudopterogorgia elisabethae* as part of a bioassay-guided

(1) See: (a) Mitscher, L. A.; Baker, W. *Med. Res. Rev.* **1998**, *18*, 363−374. (b) *Tuberculosis: Current Concepts and Treatment;* Friedman, L. N., Ed.; CRC: Boca Raton, FL, 2001. (c) The Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) website. http://www.taacf.org/.

10.1021/ol049334+ CCC: $27.50
Published on Web 05/27/2004

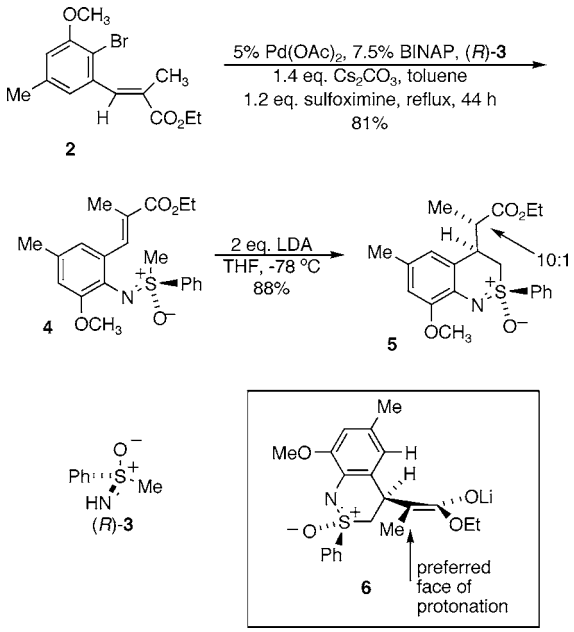
evaluation of extracts of this organism.[3] It was assigned as a member of the amphilectane class of diterpenes, and the appearance of the benzoxazole functionality was highlighted as particularly noteworthy, due to its rare occurrence in natural products. Biological evaluation of **1** demonstrated potent inhibitory activity (97% at 12.5 μg/mL) against *M. tuberculosis* H37Rv.

Recent synthetic studies by Corey and co-workers have established that the original structure assigned to **1** is incorrect.[4] The originally assigned structure had the incorrect configuration at C-7. It is the structure proposed by Corey that is shown in **1**. Recently, Corey and co-workers confirmed their assignment through the total synthesis of **1**.[5]

We considered pseudopteroxazole to be a target particularly suited to methodology we had developed involving the stereoselective, intramolecular addition of sulfoximine carbanions to α,β-unsaturated esters.[6] In this Letter, we report on our progress toward pseudopteroxazole and present a very highly selective intramolecular Friedel−Crafts alkylation reaction.

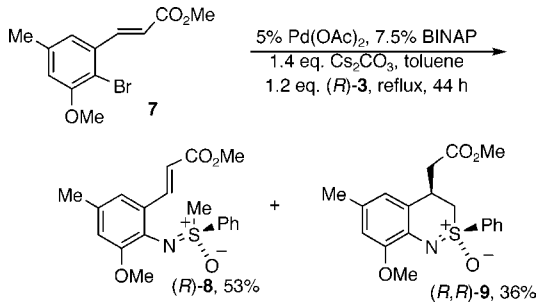
We began our study with the ester **2**,[7] whose coupling with sulfoximine **3** proceeded uneventfully (Scheme 1) to afford

Scheme 1



4.[8] Interestingly, we had reported that ester **7** reacted with sulfoximine **3** to afford both sulfoximine and benzothiazine products **8** and **9** under our standard coupling conditions (Scheme 2).[6] Apparently, the presence of the methyl group on **2** was sufficient to prevent benzothiazine formation. Treatment of **4** with LDA followed by protic quench afforded the benzothiazine **5** as a 10:1 mixture of diastereomers in 88% yield. We attribute the selectivity observed in the

Scheme 2



benzothiazine formation to protonation of the intermediate enolate on its less-hindered face.[9] As shown in **6**, models suggest that the enolate intermediate will adopt a conformation in which one face of the enolate is significantly more congested than the other. This model explains the stereochemistry of the major product of the reaction. Unfortunately, **5** has the wrong stereochemistry at the methyl-bearing carbon, at least with respect to a projected pseudopteroxazole synthesis. We nevertheless pushed this material forward in order to evaluate the viability of subsequent steps.

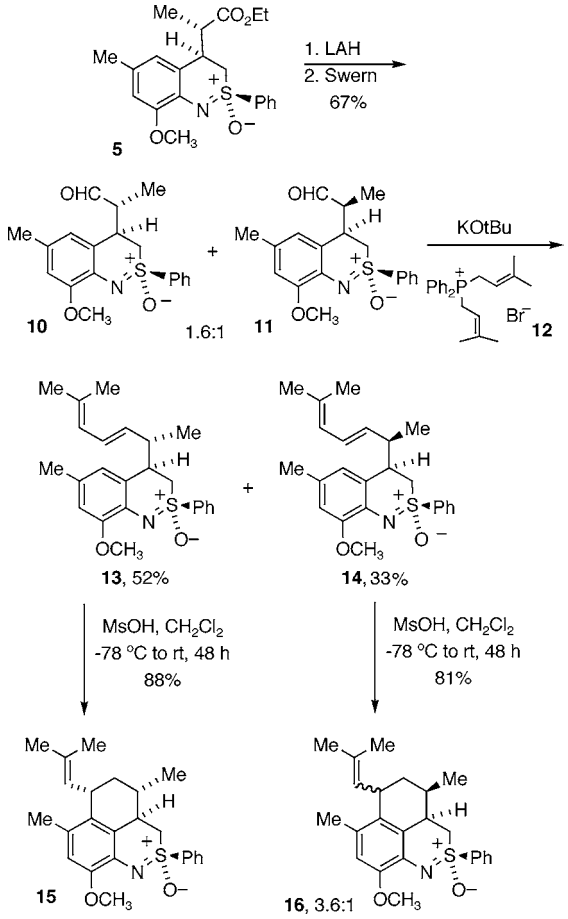
We therefore addressed this problem through reduction, oxidation, and epimerization. Thus, reduction and a "long" Swern oxidation of **5** afforded aldehydes **10** and **11** in a 1.6:1 ratio (Scheme 3). We simply allowed the basic reaction mixture to stir after the oxidation was complete to effect epimerization. Without separation, these compounds were treated with the Wittig reagent derived from **12** to give **13** and **14** in 52 and 33% yields, respectively, as single stereoisomers. These compounds were separable. Each was treated individually with methanesulfonic acid.[5] The results are intriguing. Diene **13** afforded **15** as a *single diastereomer* in 88% yield. The structure of this compound was confirmed by X-ray analysis. When **14** was treated under the same reaction conditions, **16** was formed in 81% yield as a 3.6:1 ratio of diastereomers.

This last result is very significant. Related cyclizations reported in the literature are often not selective or selective in the opposite stereochemical sense.[4,5,9,10] One exception to this generalization was reported by Corey and co-workers, who demonstrated a stereochemical divergence in the reaction of **17a** and **17b** with methanesulfonic acid.[10d] While compound **17a** afforded **20** and **21** with a diastereoselectivity of 25:1, **17b** afforded the corresponding compounds in a ratio of 1:8.

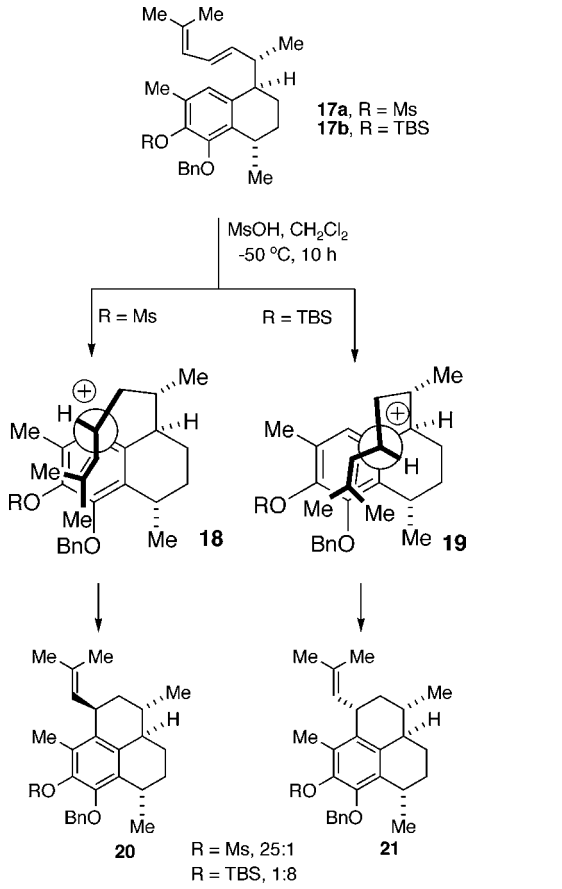
This result was rationalized on the basis of the different directing effects of the substituents on the aromatic ring of

(2) Newton S. M.; Lau, C.; Wright, C. W. *Phytother. Res.* **2000**, *14*, 303−322.
(3) Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I.; González, E. *Org. Lett.* **1999**, *1*, 527−530.
(4) Johnson, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2001**, *123*, 4475−4479.
(5) Davidson, J. P.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 13486-13489.
(6) Harmata, M.; Hong, X. *J. Am. Chem. Soc.* **2003**, *125*, 5754−5756.
(7) See Supporting Information.
(8) (a) Harmata, M.; Pavri, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2419−2422. (b) Bolm, C.; Hildebrand, J. P. *Tetrahedron Lett.* **1998**, *39*, 5731−5734.
(9) A very similar transition state model has been proposed to rationalize the stereochemical outcome of the reaction of a related enolate. See: Chow, R.; Kocienski, P. J.; Kuhl, A.; LeBrazidec, J.-Y.; Muir, K.; Fish, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2344−2355.

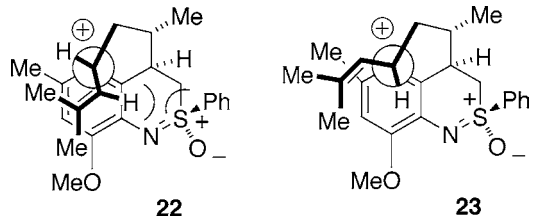
Scheme 3



Scheme 4



17a and **17b**. In the case of **17a**, the benzyloxy group served to direct the cyclization, and minimization of untoward steric interactions favored an approach of the allylic cation to the benzene ring as illustrated in **18**. In the case of **17b**, the −OTBS groups served to direct the regiochemistry of allylic cation attack as shown in **19**.



22 **23**

Applying these and related concepts to **13** and assuming the methoxy group is a better directing group than the sulfoximine group, we can formulate two possible approaches of the allylic cation to the benzene ring, as shown in **22** and **23**. The former suffers from steric interactions between the allylic cation and the sulfoximine phenyl substituent. The latter approach should thus be preferred, and this in fact leads to **15**.

In summary, we have developed a succinct route to a potential precursor to pseudopteroxazole, including a completely stereoselective intramolecular Friedel−Crafts allylation. Tasks at hand include the development of a better route to **10**, firmly establishing the basis for selectivity in the formation of **15** and converting **15** to pseudopteroxazole. Progress in these areas will be reported in due course.

Acknowledgment. This work was funded by the Petroleum Research Fund, administered by the American Chemical Society, to whom we are grateful. Some of the lithium reagents used in this work were a gift from FMC Lithium.

Supporting Information Available: X-ray structure data for **15** and the alcohol derived from **5** and detailed experimental procedures, copies of ^{1}H and ^{13}C NMR, and other characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049334+

(10) (a) Harrowven, M. C.; Tyte, M. J. *Tetrahedron Lett.* **2004**, 45, 2089−2091. (b) Kocienski, P. J.; Pontiroli, A.; Qun, L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2356−2366. (c) Lazerwith, S. E.; Johnson, T. W.; Corey, E. J. *Org. Lett.* **2000**, *2*, 2389−2392. (d) Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 12777−12782. (e) LeBrazidec, J.; Kocienski, P. J.; C., Joseph D.; Muir, K. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2475−2478. (f) Majdalani, A., Schmalz, H. *Synlett* **1997**, 1303−1305. (g) Gill, S.; Kocienski, P.; Kohler, A.; Pontiroli, A.; Qun, L. *J. Chem. Soc., Chem. Commun.***1996**, 1743−1744.