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Benzothiazines in Synthesis. A Formal Total Synthesis of Pseudopteroxazole

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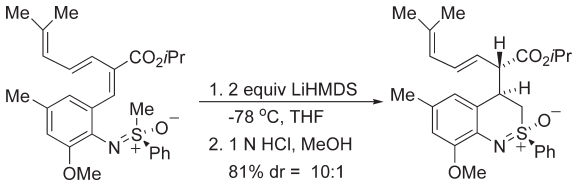


A formal total synthesis of the antitubercular natural product was accomplished. This work was undertaken to address certain stereochemical problems in our initial synthesis. By using an ester group as a surrogate for a methyl group, we were able to intercept a key intermediate in our first synthesis with better selectivity and greater convergence than had previously been the case.

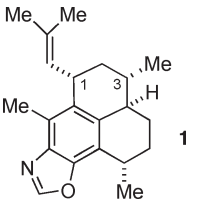
Introduction

The problem of tuberculosis has accompanied mankind for millennia.[1] At present, approximately one-third of the world's population is infected with the causative organism, *Mycobacterium tuberculosis*. Of this group, 5−10% proceed to active disease. Over two million people a year die worldwide due to tuberculosis.

Though still a disease that can be treated, tuberculosis often requires chemotherapy on the order of months or years to achieve a cure. This long course often results in noncompliance on the part of patients and this has led to the emergence of moderately drug resistant (MDR) and extensively drug resistant (XDR) strains of the disease. The latter are resistant to the typical first line of drugs used for the treatment of TB as well as at least two drugs comprising the second line of defense.

The persistence of this disease and in particular the rise of exceptionally resistant strains of the TB microorganism have made the discovery of new chemotherapies a priority. As is often the case, natural products can provide lead compounds for the development of new drugs, and a number of natural products with antitubercular properties have been identified.[2]

One such compound is pseudopteroxazole (**1**), which was isolated from the sea whip *Pseudopterogorgia elisabethae* by Rodriguez and co-workers.[3] This compound displayed significant activity against *M. tuberculosis* H37Rv and thus is a potential lead for the development of antitubercular agents. Corey corrected the stereochemical assignment originally given to **1** and also produced the first total synthesis of the compound.[4] We published a synthesis of **1** as well,[5] further demonstrating the synthetic utility of enantiomerically pure benzothiazines in synthesis.



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However, our first synthesis was not without some problems. A key step involved the intramolecular conjugate addition of the sulfoximine carbanion derived from **2** to

(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) *Handbook of tuberculosis; molecular biology and biochemistry*; Kaufmann, S. H. E., Rubin, E., Eds.; Wiley-VCH: Weinheim, Germany, 2008. (d) *Handbook of tuberculosis; immunology and cell biology*; Kaufmann, S. H. E., Britton, W. J., Eds.; Wiley-VCH: Weinheim, Germany, 2008. (e) *Handbook of tuberculosis; clinics, diagnostics, therapy and epidemiology*; Kaufmann, S. H. E., van Helden, P., Eds.; Wiley-VCH: Weinheim, Germany, 2008.

(2) (a) Gutierrez-Lugo, M.-T.; Bewley, C. A. *J. Med. Chem*. **2008**, *51*, 2606–2612. (b) Copp, B. R.; Pearce, A. N. *Nat. Prod. Rep*. **2007**, *24*, 278–297.

(3) Rodriguez, A. D.; Ramirez, C.; Rodriguez, I. I.; Gonzalez, E. *Org. Lett*. **1999**, *1*, 527–530.

(4) (a) Johnson, T. W.; Corey, E. J. *J. Am. Chem. Soc*. **2001**, *123*, 4475–4479. (b) Davidson, J. P.; Corey, E. J. *J. Am. Chem. Soc*. **2003**, *125*, 13486–13489.

(5) (a) Harmata, M.; Hong, X. *Org. Lett*. **2004**, *6*, 2201–2203. (b) Harmata, M.; Hong, X. *Org. Lett*. **2005**, *7*, 3583–3583.

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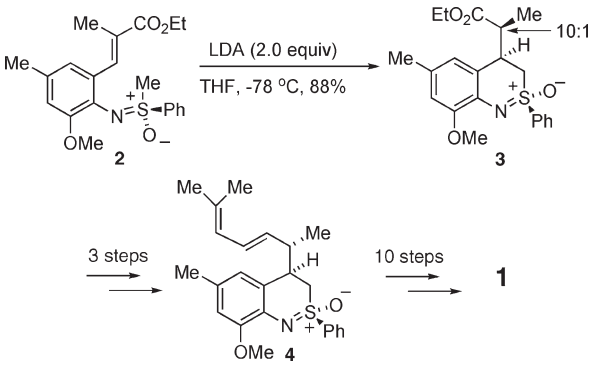
SCHEME 1. Summary of Our First Synthesis of Pseudopteroxazole



afford **3** (Scheme 1). This proceeded in high yield and diastereoselectivity. Unfortunately, the diastereoselection was in a direction opposite to that desired and ultimately the stereochemistry at the methyl-bearing carbon atom, the one that would be carbon 3 of pseudopteroxazole, had to be corrected. Once this was done, the synthesis of diene **4** proved to be straightforward, as did the conversion of the latter to pseudopteroxazole. We thus set out to prepare **4** via a modified route, and this report details the results of our efforts.

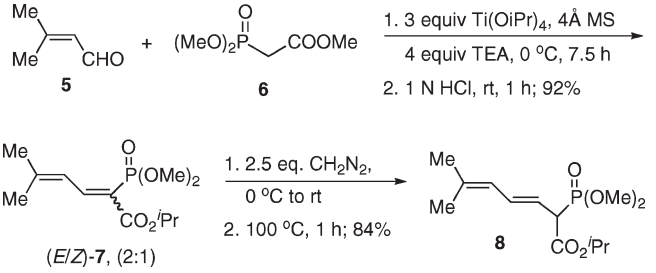
Results and Discussion

Our plan was to bring in all of the elements needed to construct **4** at a very early stage of the synthesis and use the inherent diastereoselectivity of the benzothiazine formation to our advantage. First, we made phosphonate **8** from commercially available 3-methyl-2-butenal **5** and trimethyl phosphonoacetate **6** in 4 steps (Scheme 2).[6] This reagent was then coupled with 2-bromo-3-methoxy-5-methylbenzaldehyde **9**[7] to give **10** with high stereoselectivity, using $Ba(OH)_2$ as base (Scheme 3).[8]

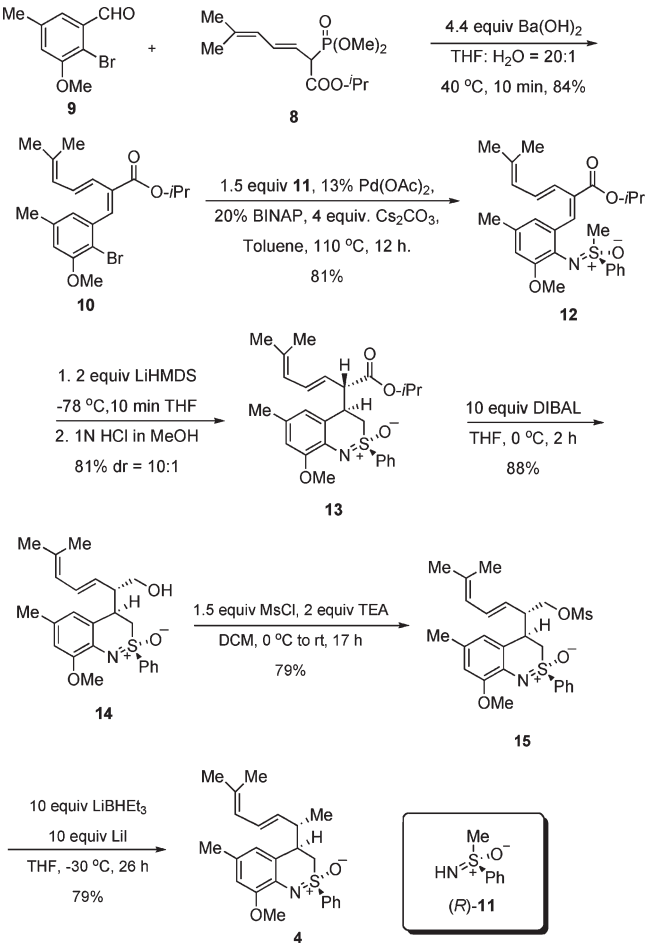
A key step was the Buchwald−Hartwig coupling of triene **10** with sulfoximine (*R*)-**11**.[9] We were pleased to find that the coupling product **12** could be obtained in 81% yield, with minimal complications due to Heck reactions, a side reaction that we feared might dash our hopes of using this strategy.[10]

The next critical step was the intramolecular Michael addition.[11] Treatment of **12** with LiHMDS followed by quenching with HCl in cold methanol afforded **13** with

SCHEME 2. Preparation of Phosphonate 8



SCHEME 3. Formal Synthesis of Pseudopteroxazole



a diastereoselectivity that was as high as 10:1.[12] The stereochemical outcome of the reaction could be rationalized on the basis of a model we presented earlier[4] and, in fact, was the same stereochemical outcome observed for the formation of **3**. However, the key difference is that we planned to convert the ester group in **13** to a methyl group en route to **4**.

Thus treatment of **13** with DIBAL afforded the corresponding alcohol **14** in 88% yield. Mesylation afforded the corresponding mesylate **15**. Attempted reduction of this mesylate with various reducing agents did not proceed very successfully. After numerous attempts at reduction of this and related sulfonates, we ultimately used a procedure that presumably resulted in the in situ formation of the corresponding iodide with concomitant reduction. Thus, treatment of **15** with excess lithium iodide and excess lithium

(6) Minami, T.; Tokumasu, S.; Mimasu, R.; Hirao, I. *Chem. Lett*. **1985**, 1099–1102.

(7) Koyama, H.; Kamikawa, T. *J. Chem. Soc., Perkin Trans. 1* 1998, *1*, 203−209.

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(9) (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. (c) Bolm, C.; Hildebrand, J. P. *J. Org. Chem*. **2000**, *65*, 169–175.

(10) Only trace amounts of a compound assigned as an intramolecular Heck reaction product were isolated whenever this reaction was performed. This product **16** was characterized and details on it are reported in the Supporting Information. The enantiopurity of **12** is considered to be the same as that of (*R*)-**11**, which was established by both optical rotation and HPLC to be 100%, within experimental error.

(11) Harmata, M.; Hong, X. *J. Am. Chem. Soc*. **2003**, *125*, 5754–5756.

(12) Diastereomeric ratios were determined based on proton NMR analysis of crude reaction mixtures. The diastereoselectivity varied from 7 to 10:1. The minor isomer was not characterized but could be separated from the desired diastereomer by column chromatography.

triethylborohydride at −30 °C for 26 h resulted in the formation of **4** in 79% yield, thereby completing a formal total synthesis of **1**.

Conclusion

This approach to **4** required 6 steps from aldehyde **9** (conversion of **12** to **13** shows the workup as step 2). The old procedure (Scheme 1) required 7 steps from the same aldehyde, but suffered from the need to separate a significant amount of undesired stereoisomer en route to the synthesis of **4**. Further, in this new approach, we have demonstrated that the palladium-catalyzed coupling of a sulfoximine to a highly unsaturated compound is possible in high yield, without loss of material due to other palladium-catalyzed processes. The reaction time for the coupling is significantly shorter than what has been typically reported and only a slight excess of **11** was needed to produce a very high yield of **12**.

This work further establishes that benzothiazines are easily prepared templates that are useful for total synthesis. Further studies of their synthesis and applications will be reported in due course.

Experimental Section

(2*E*,3*E*)-Isopropyl 2-(2-Bromo-3-methoxy-5-methylbenzylidene)-6-methylhepta-3,5-dienoate (10). To a solution of bromo aldehyde **9** (2.22 g, 9.7 mmol) and phosphonoacetate **8** (3.43 g, 11.8 mmol) in 120 mL of THF and 6 mL of H_2O was added $Ba(OH)_2$ (7.35 g, 43 mmol) in portions with vigorous stirring at 40 °C. After 10 min, the reaction was allowed to reach rt and was diluted with 200 mL of CH_2Cl_2. The solution was washed with 1 × 100 mL of saturated $NaHCO_3$ and 1 × 100 mL of brine and then dried with $MgSO_4$, filtered through Celite, and concentrated in vacuo. After flash chromatography (1% TEA, 10% ethyl acetate in hexane), 3.2 g (84%) of the brom oester was obtained as a viscous oil. IR (neat) 2974, 2930, 1714, 1234, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33(s, 1H), 7.16 (dd, 1H, J = 11.0, 15.6), 6.79 (s, 1H), 6.67 (s, 1H), 6.22 (d, 1H, J = 15.6 Hz), 5.82 (d, 1H, J = 11.0 Hz), 5.22 (septet, 1H, d = 6.0 Hz), 3.90 (s, 3H), 2.33 (s, 3H), 1.79 (s, 6H), 1.38 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.0, 155.8, 138.3, 137.6, 137.4, 135.8, 132.2, 131.8, 126.2, 123.9, 122.2, 112.2, 110.1, 68.4, 56.2, 26.2, 21.8, 21.4, 18.6; HRMS calcd for $C_{20}H_{25}O_3BrNa$ $[M + Na]^+$ 415.0879, found 415.0875.

Isopropyl (2*E*,3*E*)-2-(2-{[*R*-methylphenyl(oxido)-λ^6-sulfanylidene]amino}benzylidene)-6-methylhepta-3,5-dienoate(12). A 100 mL round-bottomed flask with condenser was charged with palladium acetate (15 mg, 0.065 mmol) and *rac*-BINAP (60 mg, 0.1 mmol) in 35 mL of toluene. The mixture was stirred for 15 min at rt. The bromoester **10** (510 mg, 0.5 mmol) and (*R*)-**11** (220 mg, 0.77 mmol) in 5 mL of toluene were added, followed by addition of Cs_2CO_3 (1.17 g, 2 mmol). The solution was refluxed at 110 °C for 12 h, then diluted with 40 mL of CH_2Cl_2, filtered through Celite, which was washed with 3 × 50 mL CH_2Cl_2, and concentrated in vacuo. After flash chromatography (25% ethyl acetate in hexanes), 491 mg (81%) of **12** was obtained as a pale yellow semisolid. IR (film) 3064, 2974, 2925, 1703, 1560, 1454, 1336, 1270, 1233, 1094, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.00 (dd, 2H, J = 1.5, 10.0 Hz), 7.77 (s, 1H), 7.56−7.50 (m, 3H), 7.20 (dd, 1H, J = 11.0, 15.5 Hz), 6.80 (s, 1H), 6.60 (s, 1H), 6.40 (d, 1H, J = 15.5 Hz), 5.87 (d, 1H, J = 11.0 Hz), 5.21 (m, 1H, J = 6.0 Hz), 3.59 (s, 3H), 3.10 (s, 3H), 2.28 (s, 3H), 1.81 (s, 6H), 1.36 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 152.2, 142.4, 137.2, 136.9, 132.3, 132.0, 131.6, 130.7, 130.2, 129.8, 128.9, 127.5, 126.6, 123.4, 113.1, 67.8, 55.6, 46.0, 26.2, 22.0, 21.2, 18.6; HRMS calcd for $C_{27}H_{33}NO_4SNa$ $[M + Na]^+$ 490.2022, found 490.2016; $[\alpha]_D^{25}$ 77.975 (c 0.79, $CHCl_3$).

Isopropyl (2*S*,3*E*)-6-Methyl-2-[(2*R*,4*R*)-2-methyl-2-oxido-3,4-dihydro-2λ^4,1-benzothiazin-4-yl]hepta-3,5-dienoate (13). A 100 mL round-bottomed flask was charged with bromo ester (1.58 g, 3.38 mmol) in 40 mL of THF. LiHMDS (6 mL, 1 M in toluene, 6 mmol) was added dropwise to the mixture at −78 °C. After 10 min at −78 °C, the reaction was quenched with 1 N HCl in methanol at −78 °C, then poured into water, extracted with 3 × 20 mL of CH_2Cl_2, dried with $MgSO_4$, and concentrated in vacuo. After flash chromatography (30% ethyl acetate in hexanes), 1.28 g (81%) of **13** was obtained as the main isomer. IR (film) 2970, 2921, 2868, 1720, 1462, 1245, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.10−8.12 (m, 2H), 7.62−7.66 (m, 1H), 7.54−7.57 (m, 2H), 6.68 (s, 1H), 6.64 (s, 1H), 6.26 (dd, 1H, J = 11.0, 15.0 Hz), 5.77 (d, 1H, J = 11.0 Hz), 5.49 (dd, 1H, J = 7.5, 15.0 Hz), 4.89 (septet, 1H, J = 6.0 Hz), 3.96 (t, 1H, J = 7.0 Hz), 3.88 (s, 3H), 3.60−3.64 (m, 1H), 3.52−3.56 (m, 2H), 2.30 (s, 3H), 1.75 (s, 3H), 1.69 (s, 3H), 1.15 (d, 3H, J = 6.5 Hz), 1.05 (d, 3H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 152.6, 139.4, 136.8, 133.8, 132.1, 131.1, 129.9, 129.5, 129.4, 124.9, 124.9, 124.3, 119.4, 111.9, 68.4, 56.2, 51.1, 49.2, 38.4, 26.2, 21.8, 21.6, 18.6; HRMS calcd for $C_{27}H_{33}NO_4SNa$ $[M + Na]^+$ 490.2022, found 490.2012; $[\alpha]_D^{25}$ −60.48 (c 1.66, $CHCl_3$).

(2*R*,4*R*)-4-[(1*S*,2*E*)-1,5-Dimethyl-2,4-hexadienyl]-3,4-dihydro-8-methoxy-6-methyl-2-phenyl-2γ^4-2,1-benzothiazine 2-Oxide (4). To a solution of mesylate **15** (71 mg, 0.15 mmol) and LiI (201 mg, 1.5 mmol) in 7.5 mL of dry THF at −30 °C was added 1.5 mL of 1 M $LiBHEt_3$ in THF slowly. After the reaction was kept at −30 °C for 26 h, it was diluted with 15 mL of DCM and quenched with 10 mL of 10% NaOH and 5 mL of 30% H_2O_2. After the solution was stirred for 30 min at rt, it was washed with 10 mL of saturated $Na_2S_2O_3$ solution, followed by 30 mL of brine. After drying with Na_2SO_4, it was concentrated under vacuum. Chromatography (20% ethyl acetate in hexanes) afforded 45 mg (79%) of **4** as a colorless oil. The NMR data matched the published data.[4]

Acknowledgment. This work was supported by the NIH (1R01-AI59000-01A1) to whom we are grateful.

Supporting Information Available: Characterization data for compound **16** and copies of proton and carbon spectra for previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.