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Benzothiazines in synthesis. Formal synthesis of erogorgiaene

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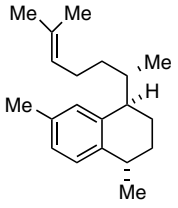
Abstract—A benzothiazine, readily available in enantiomerically pure form via a completely selective, intramolecular addition of a sulfoximine-stabilized carbanion to an α,β-unsaturated ester, could be converted to a precursor to erogorgiaene in good overall yield.

Introducing a stereogenic center at the benzylic position is very important in asymmetric synthesis. A very large number of natural and man-made structures are known that bear such a stereogenic center.[1,2] Such compounds exhibit a diversity of biological activities including anti-viral, analgesic, anti-inflammatory, and anti-mycobacterial properties.[3] Their importance in medicinal chemistry and limited availability has brought enormous attention to their synthesis in the recent past.

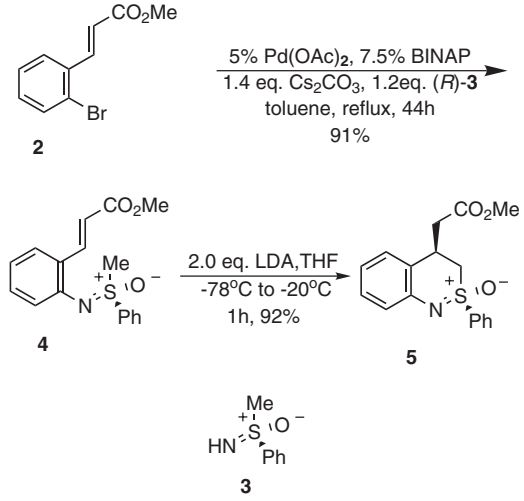


1: erogorgiaene

Erogorgiaene (**1**) is a new type of anti-mycobacterial serrulatane diterpene, which was first isolated from the sea whip, the West Indian gorgonian octocoral, *Pseudopterogorgia elisabethae* Bayer, as part of a bioassay-guided evaluation of extracts of this organism by Rodriguez and co-workers in 2001.[4] Biological evaluation of erogorgiaene **1** showed that it can inhibit 96% of *Mycobacterium tuberculosis* $H_{37}Rv$ growth at 12.5 ug/mL, making it of interest as a lead in the synthesis of new anti-tubercular agents. Since its reported isolation, only two syntheses of erogorgiaene have appeared in the literature.

The first, by Hoveyda and co-workers, utilized catalytic, asymmetric conjugate addition chemistry to install a stereogenic center.[5a] The second, by Davies and co-workers, made use of an elegant carbene insertion/Cope rearrangement strategy to rapidly establish all of the stereocenters of the natural product.[5b]

Recently, we reported a completely stereoselective, intramolecular Michael addition of sulfoximine carbanions to α,β-unsaturated esters as exemplified in Scheme 1.[1b] Based on the methodology introduced by Bolm and



Scheme 1.

Keywords: Benzothiazine; Sulfoximine; Anti-tubercular; Stereoselective; Erogorgiaene.
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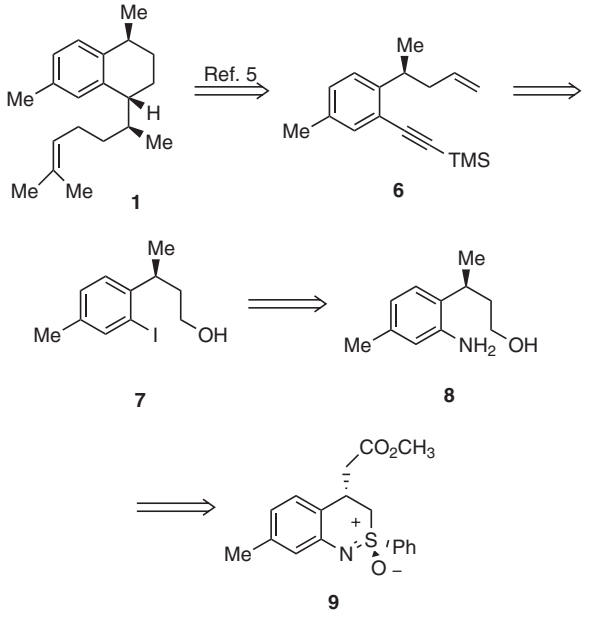
co-workers sulfoximines such as **4** were prepared (Scheme 1).[6] Subsequent treatment of sulfoximine **4** with LDA (or LiHMDS) afforded **5** as a single stereoisomer in high yield. The reaction is stereospecific and offers a way to establish benzylic stereocenters with high selectivity. We applied this methodology to the formal total syntheses of (+)-curcuphenol, (+)-curcumene,[2b] and are pursuing the synthesis of pseudopteroxazole.[7]

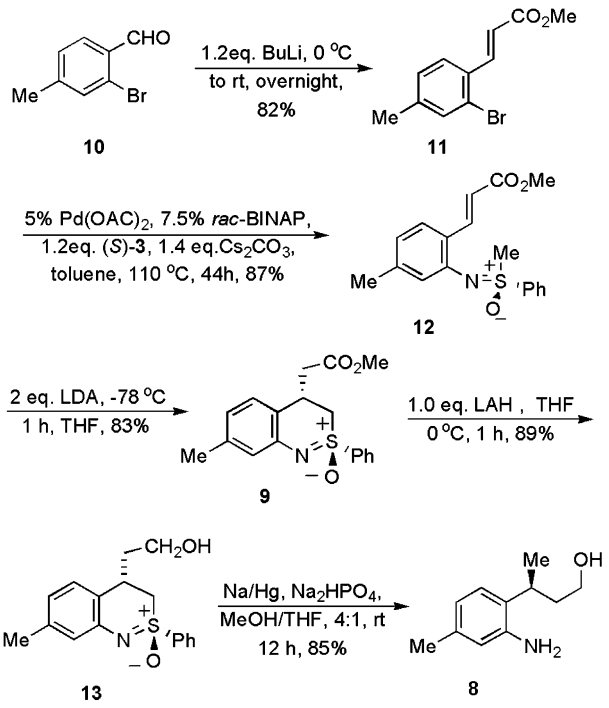
In an effort to expand the scope of this process, we decided to explore the synthesis of erogorgiaene, using our methodology to construct the benzylic stereocenter of the target. With the appearance of the total synthesis of erogorgiaene by Hoveyda, our short-term goal became a formal total synthesis. A retrosynthesis based on this approach is shown in Scheme 2.

The aniline (**8**) needed for this process was prepared as shown in Scheme 3. We began with Horner–Wadsworth–Emmons reaction of the commercially available *ortho*-bromobenzaldehyde **10**. This was then coupled with (*S*)-methylphenylsulfoximine **3** using the Buchwald–Hartwig reaction as modified by Bolm and Hildebrand[6b] to give the sulfoximine **12** in 87% yield. Treatment of the sulfoximine **12** with LDA resulted in the formation of benzothiazine **9** with complete diastereoselectivity in 83% yield. The ester functional group was reduced with lithium aluminum hydride to afford the alcohol **13** in 89% yield. The alcohol **13** was then treated with Na/Hg to provide the aniline **8** in 85% yield via a reductive desulfurization.[8]

Several attempts to do direct iodination of the diazonium ion corresponding to **8** using KI were unsuccessful. In order to introduce iodide into the aromatic ring, we utilized triazene chemistry. Though direct iodination of a diazonium species might save a step, the ease with which triazenes are formed, as well as their stability, were attractive. Diazotization of aniline **8** with sodium



Scheme 2. Retrosynthesis of erogorgiaene.

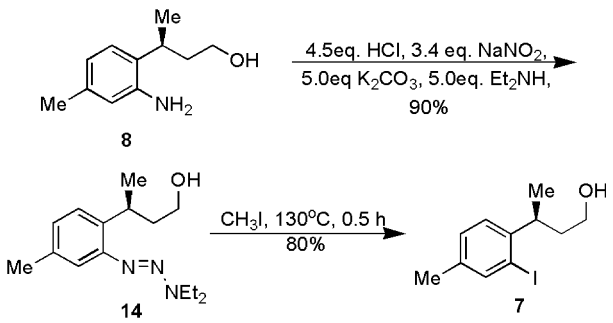


Scheme 3.

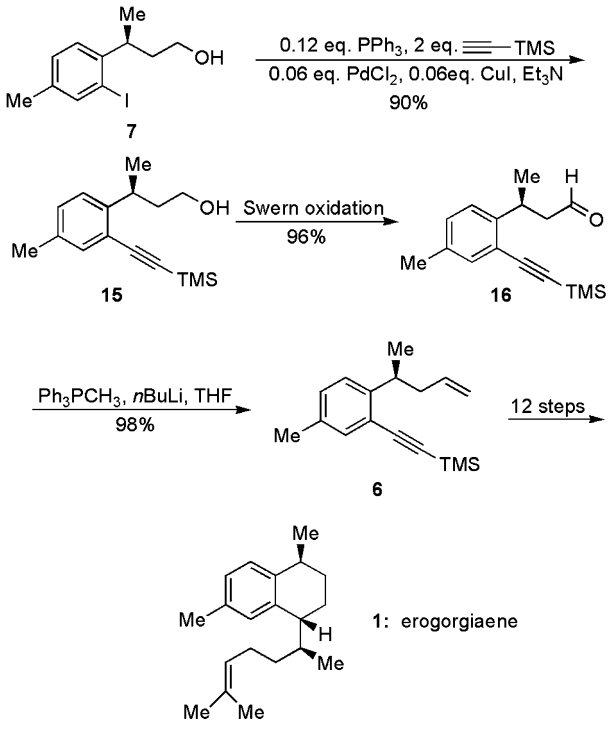
nitrite and HCl followed by reaction of the resulting diazonium salt with diethylamine in the presence of K_2CO_3 led to triazene **14** in 90% yield.[9] Subsequently, triazene **14** was directly converted to the key intermediate, iodide **7**, by refluxing in a sealed tube at 130 °C for 30 min.[9,10] This afforded **7** in 80% yield (Scheme 4).

Application of iodide **7** toward the formal synthesis of erogorgiaene required a Sonogashira coupling reaction to construct the alkyne **15**. We found that treatment of **7** with (trimethylsilyl)acetylene in the presence of $PdCl_2$, PPh_3, CuI, and triethylamine afforded compound **15** in 90% yield (Scheme 5).[11] Swern oxidation of **15** gave aldehyde **16** in 96% yield. Finally, aldehyde **16** was converted to compound **6** in 98% yield via a Wittig reaction. Hoveyda and co-workers reported that this compound could be converted to erogorgiaene in 12 steps. The proton and carbon NMR data as well as rotation value for compound **6** matched those reported by Hoveyda.[12]

In conclusion, we have accomplished a formal synthesis of the serrulatane diterpene, erogorgiaene (**1**), using our benzothiazine synthesis as a key step. The 10-step



Scheme 4.



Scheme 5.

process proceeds in a 27% overall yield from the commercially available benzaldehyde **10**. Hoveyda's route required six steps from commercially available starting materials and proceeded in an overall yield of 48%. This means that both routes had essentially the same average yield per step, but functional group manipulations inherently required in our approach increase the number of steps. Thus, it would behoove us to examine methods to develop productive sulfoximine excision chemistry. Future studies will include an independent approach to erogorgiaene as well as the synthesis of pseudopteroxazole and related compounds.[13]

Acknowledgments

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12. Data for **6**: colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.29–7.27 (m, 1H), 7.10–7.09 (m, 2H), 5.80–5.67 (m, 1H), 5.04–4.94 (m, 2H), 3.36 (dq, J = 14.3, 6.9 Hz, 1H), 2.46–2.38 (m, 1H), 2.27 (s, 3H), 2.29–2.23 (m, 1H), 1.23 (d, J = 7.0 Hz, 3H), 0.25 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 146.2, 137.2, 135.0, 133.0, 129.6, 125.5, 122.0, 115.8, 104.2, 97.7, 41.8, 36.2, 20.6, 20.0, 0.00(3); $[\alpha]_D^{25}$ −60.6 (c 0.66, $CHCl_3$). Reported rotation values for **16**: $[\alpha]_D^{25}$ −60; Ref. 5.
13. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR and IR spectra as well as HRMS data.