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Benzothiazines in synthesis. Formal syntheses of (+)-curcumene and (+)-curcuphenol

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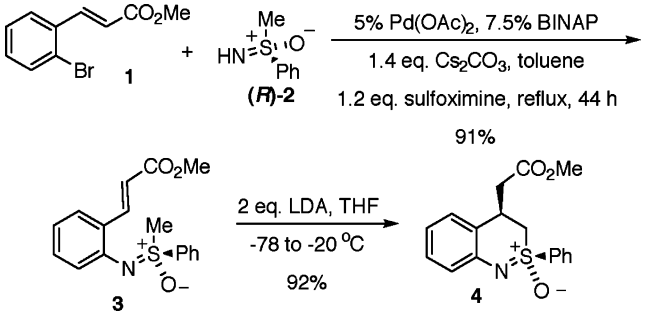
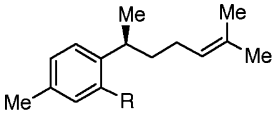
Abstract—A benzothiazine readily available in enantiomerically pure form via a stereoselective, intramolecular Michael addition reaction could be converted to a precursor to (+)-curcuphenol and to (+)-curcumene.

We recently reported the completely stereoselective, intramolecular Michael addition of sulfoximine carbanions to α,β-unsaturated esters as exemplified in Scheme 1.[1] Preparation of sulfoximine **3** was conducted via the methodology introduced by Bolm and co-workers.[2] Subsequent treatment of sulfoximine **3** with LDA afforded **4** as a single stereoisomer in high yield. The reaction is stereospecific, and offers a way of establishing benzylic stereocenters with high fidelity and as such should be applicable to many synthetic problems.

Our initial efforts in developing applications for the chemistry have focused on relatively simple bisabolane sesquiterpenes, represented by (+)-curcumene (**5**) and (+)-curcuphenol (**6**). These compounds, and a large number of other terpenoids of related structure have often been targeted as a means of demonstrating a particular methodology.[3] Curcumene was isolated from the rhizomes of *Curcuma aromatica* Salisb.[4] (+)-Curcuphenol was isolated from a marine sponge (*Epipolasis* and *Didiscus flavus*) and is an inhibitor of gastric H,K-ATPase and has antitumor and antifungal acitivity.[5,6] Interestingly, its enantiomer, which has been isolated from the gorgonian coral *Pseduopterogorgia rigida* and the plant *Lasianthaea podocephata*, exhibits antibacterial activity against *Staphylococcus aureus*.[6,7]



Scheme 1.



5: R = H, *S*-(+)-curcumene
6: R = OH, *S*-(+)-curcuphenol

Our approach to these compounds began with the commercially available aniline **7**. This was converted via a known procedure to the *ortho*-bromobenzaldehyde **8**[8] (Scheme 2). The reaction of **8** with the anion of the phosphonate **9** afforded the ester **10** in 82% yield. Use of the corresponding Wittig reagent gave **10** in a 72% yield. This ester was then coupled with (*S*)-**2** under our standard reaction conditions[1] for this coupling to afford the sulfoximine **11** in excellent yield. Ring closure to afford the corresponding benzothiazine resulted in the formation of **12** as a single stereoisomer. The structure of **11** and **12** were unequivocally established by X-ray analysis.[9] Treatment of **12** with lithium aluminium hydride smoothly led to benzothiazine **13**, the precursor to both **5** and **6**.

The conversion of **13** to a known precursor to (+)-curcumene began with the reductive desulfurization of **13** with sodium/amalgam to afford **14** in 85% yield[10]

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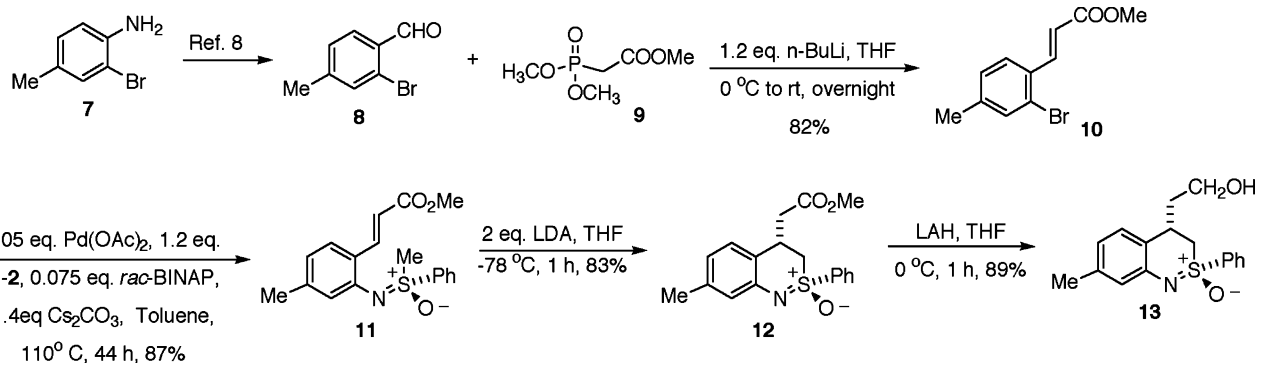
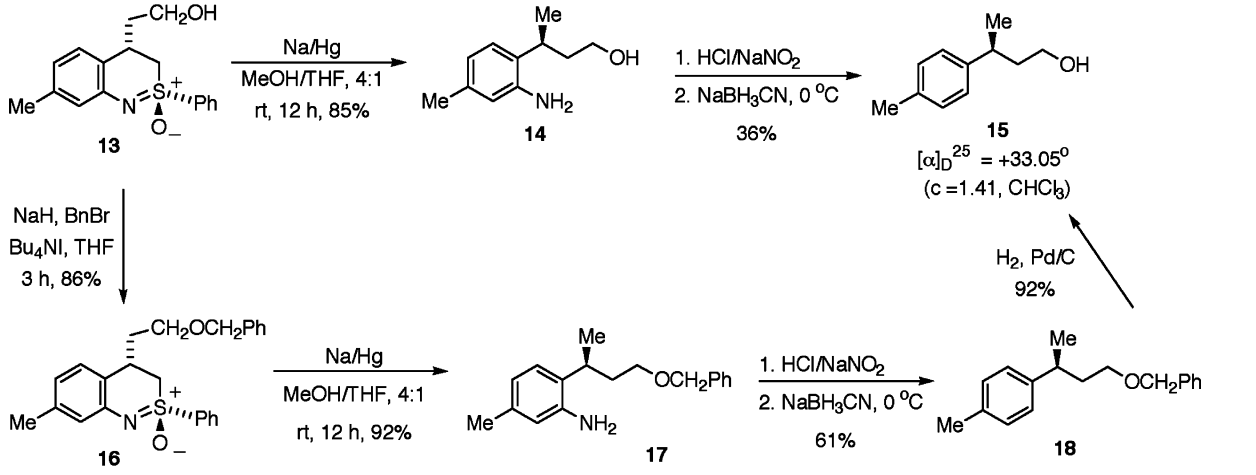


Scheme 2.

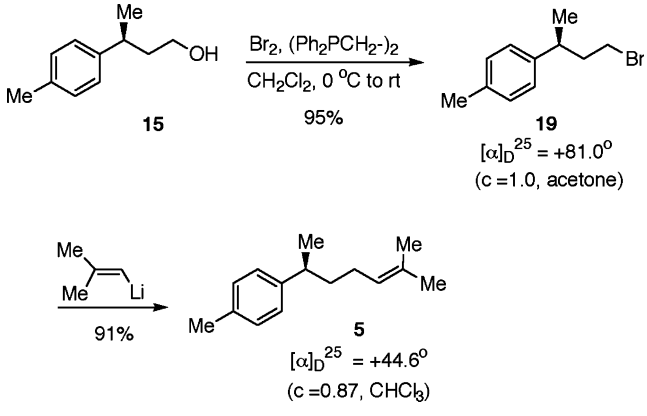


Scheme 3.

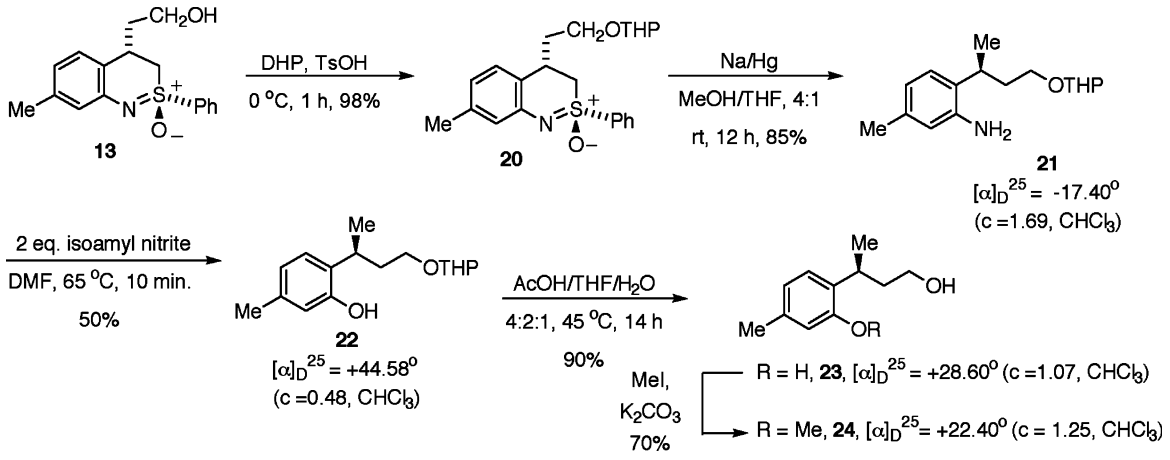
(Scheme 3). Reductive deamination using a protocol introduced by Corey and co-workers[11] afforded the alcohol **15**, but only in 36% yield. We hoped that protection of the hydroxy group in **13** would improve the yield in this reaction. Thus, **13** was reacted with sodium hydride and benzyl bromide to give **16** in good yield. Desulfurization afforded the aniline **17** in 92% yield. Reductive deamination of **17** afforded the ether **18** in 61% yield. Finally, deprotection of the hydroxy group afforded **15**. Spectral and rotation data for **15** corresponded to that reported in the literature.[12]

Compound **15** has been converted to curcumene via a sequence shown in Scheme 4.[3j] Bromination afforded the bromide **19** in 96% yield. Displacement of the bromide with the appropriate organolithium led to (+)-curcumene in excellent yield.[13]

The formal synthesis of (+)-cucurphenol involved a similar approach to that of (+)-curcumene and was the result of serendipity. Thus, the hydroxy group of benzothiazine **13** was protected as a THP ether to give **20** in nearly quantitative yield (Scheme 5). Desulfurization then afforded the aniline **21** in 85% yield. This aniline was then treated with isoamyl nitrite in DMF and heated for 10 minutes. This protocol was published by Doyle and co-workers as a means of reductively deaminating anilines.[14] In our particular case, the product we isolated was one of formal hydrolysis of the diazonium ion derived from the aniline. This compound was obtained in 50% yield. No effort has been made to determine the origin of the phenolic hydroxy group in **22**. However, it should be noted that we were able to perform reductive deaminations on simple anilines using the same procedure without observing the formation of phenols.[15] Removal of the THP group in **22** afforded **23**, which has been converted to curcuphe-



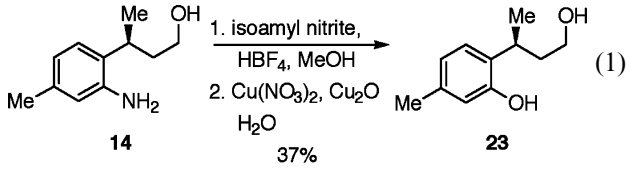
Scheme 4.



Scheme 5.

nol.[16] To further verify the stereochemistry of **23**, it was converted to the corresponding methyl ether **24**, also a known compound.[17]

Finally, several attempts were made to convert **14** to **23**. In the best case, diazotization of **14** followed by treatment of the resulting diazonium ion with copper nitrate/copper oxide according to a procedure introduced by Boger and co-workers afforded **23** in 37% yield (Eq. (1)).[18]



(1)

In summary, we have completed formal syntheses of (+)-curcumene and (+)-curcuphenol. These applications help to verify stereochemical assignments in the formation of benzothiazines via intramolecular Michael additions, which have heretofore been based largely on analogy. Further, this work demonstrates that sulfoximines can serve as ammonia equivalents in the Buchwald–Hartwig reaction. The work also lays the foundation for more complex applications. Details of these studies will be the focus of future reports.

Acknowledgements

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