## Synthetic Studies of the Tridentatols

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The tridentatols are conjugated tyramine derivatives isolated from the Atlantic hydroid *Tridentata marginata* and have potentially useful properties in sunscreen applications. Preparations of tridentatol C and two tridentatol A analogues bearing the unusual *N*-[bis(methylthio)methylene] functional group are described.

The tridentatols are N-[(dialkylthio)methylene] tyramine derivatives isolated from hydroids found among the floating *Sargassum* patches off the coast of North Carolina by Lindquist et al.<sup>1</sup> Tridentatol A (1) displays a linear arrangement of the unusual N-[bis(methylthio)methylene] functional group while in tridentatol C (2) the group has cyclized to form a thiazole ring. Because of their UV absorption



properties ( $\lambda_{max}$  313–337 nm), the tridentatols may serve the hydroid as natural sunscreens.<sup>2</sup> In an effort to study the potential of these compounds for use in sunscreen applications,<sup>3</sup> we have developed a preparation of tridentatol C and two tridentatol derivatives as model sunscreens. This is the first reported tridentatol synthesis.

*N*-Bis(alkylthio)methylene functional groups have been prepared from amines via the corresponding alkyl dithiocarbamate.<sup>4</sup> Therefore, we envisioned a synthesis of tridentatol A (1) based on trapping an enamine as the methyl dithiocarbamate for elaboration into the desired functional group.<sup>4</sup> In studies toward a model tridentatol phenyl derivative, the dithiocarbamate adduct proved elusive, suggesting an unfavorable enamine/imine equilibrium. The inaccessibility of the methyl dithiocarbamate from the enamine necessitated introduction of the *N*-[bis(methylthio)methylene] group separately from the vinyl group.

Amino alcohol **3** (Scheme 1) was converted via the dithiocarbamate to intermediate **4**. Several attempts at dehydration of the benzylic alcohol **4** were made; best results were obtained by the use of diethylaminosulfur trifluoride (DAST), yielding a 2:1 mixture of *E* and *Z* isomers of **5** which could be separated by HPLC.<sup>1</sup> Our initial (unoptimized) efforts produced 20% of **5** from **3**.



Having established a method to the vinyl *N*-[bis(methylthio)methylene] functional group, we attempted to elaborate

<sup>(1)</sup> Lindquist, N.; Lobkovsky, E.; Clardy, J. Tetrahedron Lett. 1996, 37, 9131–9134.

<sup>(2)</sup> Stachowicz, J. J.; Lindquist, N. Mar. Ecol. Prog. Ser. 1997, 155, 115–126.

<sup>(3)</sup> Lindquist, N. U.S. Patent 5705146; *Chem. Abstr.* 1998, *128*, 119431.
(4) Cativiela, C.; Diaz de Villegas, M. D. *Tetrahedron* 1993, *49*, 497–506.

tridentatol A (1) from the corresponding phenol, DL-octopamine (6) (Scheme 2). On treatment with  $CS_2/MeI$ , rather



than the expected dithiocarbamate, the cyclic product **7** was obtained; the increased benzylic electrophilicity induced by the phenol group apparently enabled nucleophilic attack of the thiocarbonyl, resulting in a 4,5-dihydrothiazole (thiazoline) ring. Although such nucleophilic substitution has been used in the construction of thiazoline rings,<sup>5</sup> this result is interesting to contrast to the work of Cativiela and Diaz de Villegas who found that the C-8 carboxylate of **4** cyclizes to the oxazoline. This unexpected cyclization provided a route to the skeleton of tridentatol C (**2**). Aromatization of the thiazoline ring was carried out by treatment of **7** with DDQ to yield tridentatol C (**2**).

A scheme to the linear tridentatols therefore had to moderate the benzylic electrophilicity induced by the phenol group. The methyl ether was chosen for this task, and a suitable candidate (8) was prepared in three steps from p-methoxybenzaldehyde in 40% overall yield.

Treatment of **8** (Scheme 3) under conditions developed above for the introduction of the vinyl *N*-[bis(methylthio)methylene] functional group produced intermediate **9** in 60% yield. Elimination of the benzylic methoxy group could be

(5) Crawhall, J. C.; Elliott, D. F. J. Chem. Soc. 1952, 3094-3102.



achieved with phosphorus pentoxide, resulting in the E isomer of methoxy tridentatol A (10) in 70% yield.

Thus tridentatol C (2), deoxytridentatol A (5), and methoxytridentatol A (10) have been prepared, the latter of which displays enhanced UVB absorption properties ( $\lambda_{max}$  334,  $\epsilon$ 31 500) relative to the natural product. We are currently engaged in optimizing these synthetic pathways and in the preparation of additional derivatives for a systematic study of the physical properties of the extended conjugated system. We evaluated tridentatol C in the NCI 60 cell line panel and found it to be devoid of cytotoxicity, an important consideration for a potential sunscreen.

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**Supporting Information Available:** Experimental procedures and characterization of compounds **4**, **5**, **7-10**. This material is available free of charge via the Internet at http://www.pubs.acs.org.

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