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Synthetic Studies of the Tridentatols

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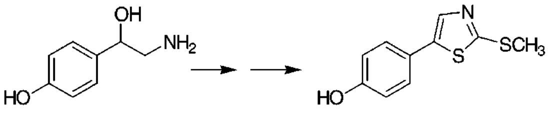
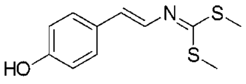
ABSTRACT



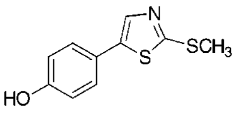
DL-Octopamine   Tridentatol C

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.[1] 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 (λ_{max} 313−337 nm), the tridentatols may serve the hydroid as natural sunscreens.[2] In an effort to study the potential of these compounds for use in sunscreen applications,[3] we have developed a preparation of tridentatol C and two tridentatol derivatives as model sunscreens. This is the first reported tridentatol synthesis.



Tridentatol A (**1**)

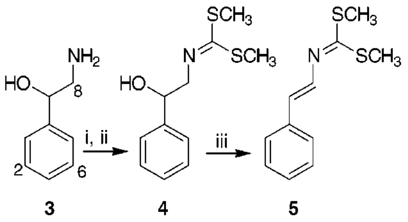


Tridentatol C (**2**)

N-Bis(alkylthio)methylene functional groups have been prepared from amines via the corresponding alkyl dithiocarbamate.[4] 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.[4] 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.[1] Our initial (unoptimized) efforts produced 20% of **5** from **3**.

Scheme 1



(i) CS$_2$, MeI; (ii) K$_2$CO$_3$, MeI; (iii) DAST

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

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[1] Lindquist, N.; Lobkovsky, E.; Clardy, J. *Tetrahedron Lett.* **1996**, *37*, 9131−9134.
[2] Stachowicz, J. J.; Lindquist, N. *Mar. Ecol. Prog. Ser.* **1997**, *155*, 115−126.
[3] Lindquist, N. U.S. Patent 5705146; *Chem. Abstr.* **1998**, *128*, 119431.
[4] Cativiela, C.; Diaz de Villegas, M. D. *Tetrahedron* **1993**, *49*, 497−506.

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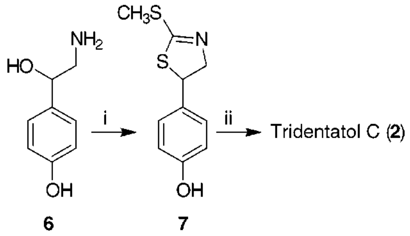
tridentatol A (**1**) from the corresponding phenol, DL-octopamine (**6**) (Scheme 2). On treatment with CS_2/MeI, rather than the expected dithiocarbamate, the cyclic product **7** was obtained; the increased benzylic electrophilicity induced by the phenol group apparently enabled nucleophilic attack of the thiocarbonyl, resulting in a 4,5-dihydrothiazole (thiazoline) ring. Although such nucleophilic substitution has been used in the construction of thiazoline rings,[5] 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**).

Scheme 2

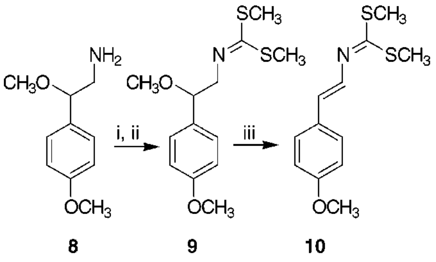


(i) CS_2, MeI; (ii) DDQ

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

Scheme 3



(i) CS_2, MeI; (ii) K_2CO_3, MeI; (iii) P_2O_5/H_2O

Thus tridentatol C (**2**), deoxytridentatol A (**5**), and methoxytridentatol A (**10**) have been prepared, the latter of which displays enhanced UVB absorption properties (λ_{max} 334, ϵ 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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[5] Crawhall, J. C.; Elliott, D. F. *J. Chem. Soc.* **1952**, 3094−3102.