Total Synthesis of (-)-Mirabazole C

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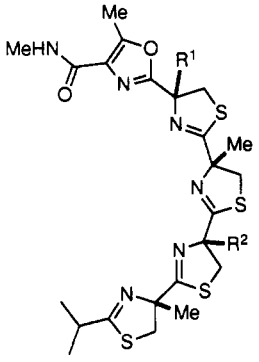
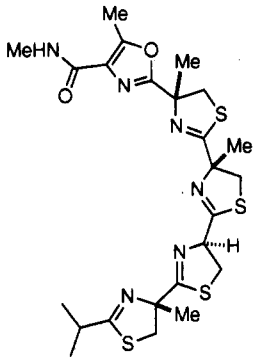
Summary: The tetrathiazoline marine alkaloid (-)-mirabazole C (7) has been synthesized by cyclization of a diamide derivative of the tripeptide derived from (*R*)-2-methylcysteine.

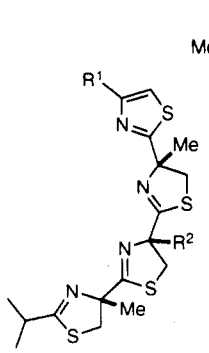
The tantazoles (1-4)[1] and mirabazoles (5-7)[2] comprise a new group of natural products that have in common a unique array of four consecutive thiazoline/thiazole rings. The two groups of compounds were each accompanied by compounds containing one additional thiazole ring (8 and 9), and it has been suggested that these more highly oxidized materials are artifacts of the isolation process, since tantazole A (1) and tantazole I (4) were both found to undergo facile air oxidation to didehydrotantazole A (8) during purification. Several of the compounds, including tantazole B (2) and didehydromirabazole A (9), possess selective cytotoxicity against murine solid tumors. The tantazoles have been degraded to (*R*)-2-methylcysteine, and the natural products are presumably biosynthesized from this unusual amino acid.[1] Although the absolute configurations of the mirabazoles have not been elucidated, their strong structural resemblance to the tantazoles makes it likely that they also are derived from (*R*)-2-methylcysteine.

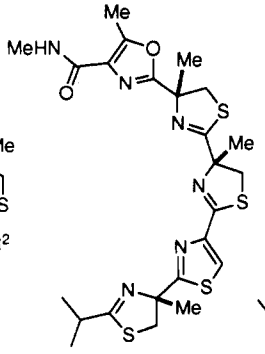


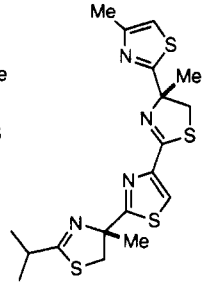


4

1: R^1 = H, R^2 = Me
2: R^1 = R^2 = Me
3: R^1 = Me, R^2 = H







5: R^1 = R^2 = Me
6: R^1 = Me, R^2 = H
7: R^1 = H, R^2 = Me

8 9

Pattenden and Thom have recently reported a synthesis of didehydromirabazole A (9) in which the thiazoline rings are formed by sequential cyclocondensations of imino ethers with (*R*)-2-methylcysteine.[3] This report prompts us to disclose our own synthesis of mirabazole C (7), which also employs (*R*)-2-methylcysteine, but which uses a completely different strategy for elaboration of the thiazoline rings.

(*R*)-*N*-(Carbobenzyloxy)-*S*-benzyl-2-methylcysteine (10)[4,5] and the hydrochloride salt of the corresponding methyl ester (11) were coupled using bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP)[6] as the condensation reagent to obtain the dipeptide (12). The carbobenzyloxy group was removed by treatment of 12 with HBr in acetic acid, and the resulting amine (13) was coupled with 10 to afford tripeptide 14. Once again, the carbobenzyloxy group was removed and the resulting amine was acylated with isobutyryl chloride to obtain 15. Saponification of the methyl ester gave the free acid, which was treated successively with *p*-toluenesulfonyl chloride and *S*-(benzylamino)ethanethiol to obtain 16. The benzyl groups were removed by treatment of 16 with sodium in ammonia and the resulting tetrathiol treated with titanium tetrachloride in CH_2Cl_2 to obtain dihydromirabazole C (17). The terminal thiazoline ring was oxidized by nickel peroxide[7] to (-)-mirabazole C (7).

The ^1H NMR spectrum of the synthetic alkaloid was identical to that reported for the natural product.[2] The specific rotation of the synthetic material ($[\alpha]_D$ = -113 (*c* = 0.024, $CHCl_3$)) is close to that reported for the natural product ($[\alpha]_D$ = -110 (*c* = 0.03, $CHCl_3$)).[2] The specific rotation of 7 is remarkably dependent on concentration. For example, we also observed a specific rotation of $[\alpha]_D$ = -178 (*c* = 0.19, $CHCl_3$). A similar concentration dependence is seen in the ^1H NMR spectrum of 7, suggesting that the alkaloid associates at higher concentrations. It is noteworthy that Pattenden and Thom report a much larger specific rotation for their synthetic (-)-didehydromirabazole A (9) ($[\alpha]_D$ = -289 (*c* = 1.78, $CHCl_3$)) than that reported for the natural product ($[\alpha]_D$ = -26 (*c* = 0.44, $CHCl_3$)).[3] A part of this discrepancy may be due to the difference in concentrations of the two measurements.

(1) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbett, T. H.; Valeriote, F. J. *J. Am. Chem. Soc.* **1990**, *112*, 8195.
(2) Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1991**, *32*, 2593.
(3) Pattenden, G.; Thom, S. M. *Synlett* **1992**, 533.
(4) Compound 10 was prepared from (*S*)-alanine by a modification of the method reported by Karaday and co-workers for the synthesis of 2-methylphenylalanine: Karady, S.; Amato, J. S.; Weinstock, L. M. *Tetrahedron Lett.* **1984**, *25*, 4337. Full details are given in the supplementary material.
(5) The *S*-benzyl derivative of (*S*)-2-methylcysteine methyl ester has been previously synthesized by Schöllkopf (who mistakenly refers to it as *R*): Groth, U.; Schöllkopf, U. *Synthesis* **1983**, 37. Schöllkopf reports a specific rotation of $[\alpha]_D$ = -32.7 (*c* = 1.1 ethanol). We observe a specific rotation of $[\alpha]_D$ = +36.1 (*c* = 1.1 ethanol) for (*R*)-*N*-(carbobenzyloxy)-*S*-benzyl-2-methylcysteine (10).
(6) Coste, J.; Frérot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967.

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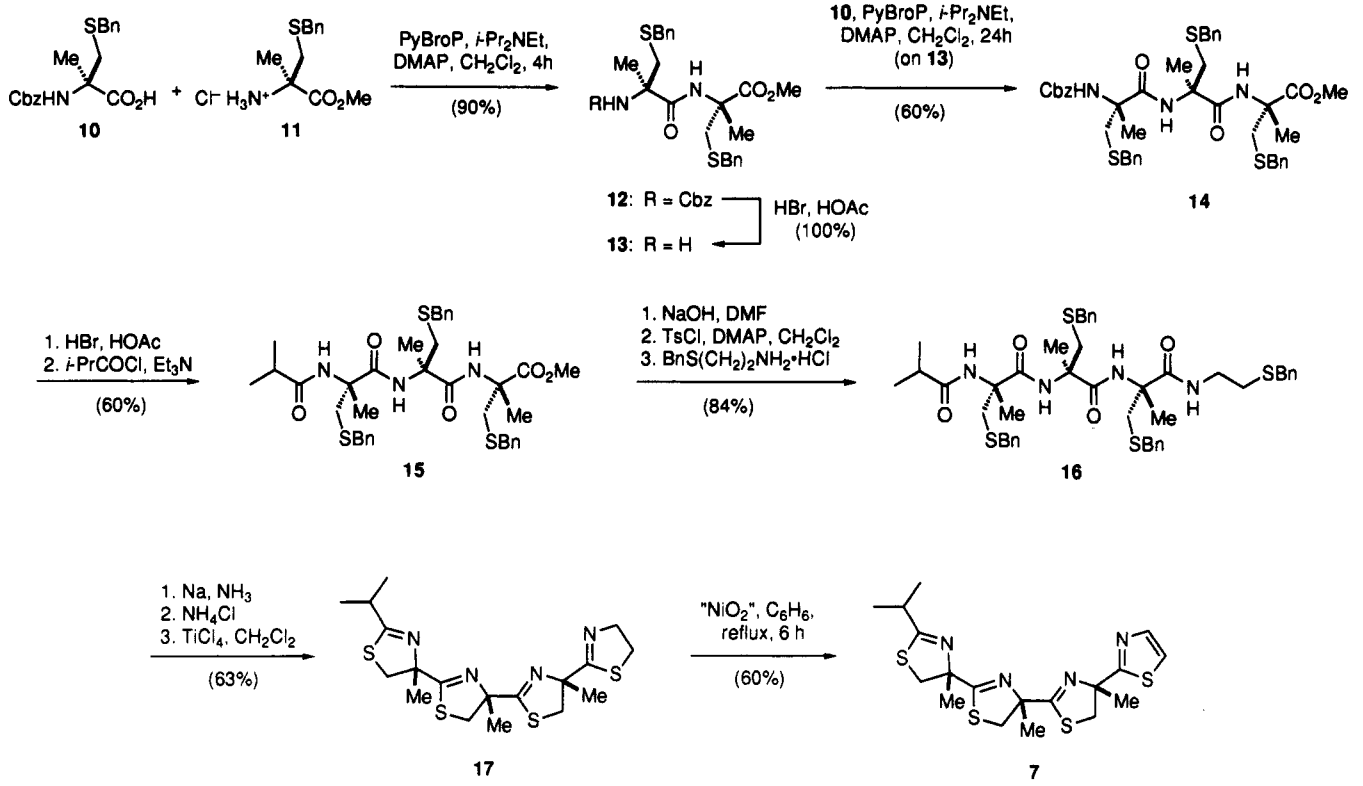
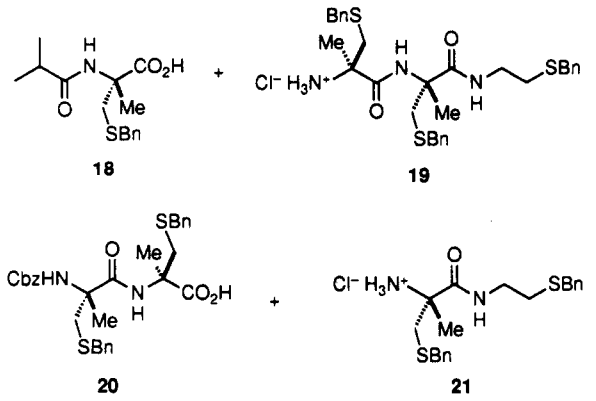
Scheme I

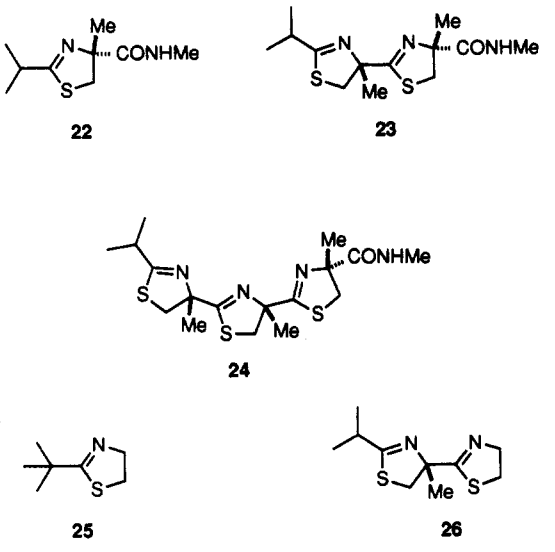


Scheme II



Coupling of *S*-benzyl-2-methylcysteine is difficult, with PyBroP being the only reagent to give either the dipeptide or tripeptide in reasonable yield.[8] The coupling to give the tripeptide is more difficult than formation of the dipeptide and requires a longer reaction time (24 h instead of 4 h). Several attempted couplings which would give a more convergent synthesis of intermediate **16** were unsuccessful even with PyBroP. Two of these unsuccessful couplings (**18** + **19**; **20** + **21**) are shown in Scheme II.

The $TiCl_4$-mediated cyclization that provides **17** was studied with several other substrates, leading to **22–24**. Each of these cyclizations proceeds smoothly, with the reaction leading to trithiazoline **24** being a little more sluggish than the reactions leading to monothiazoline **22** or dithiazoline **23**. However, cyclizations leading to products in which the terminal thiazoline ring is not substituted at C-4 (e.g., monothiazoline **25**, dithiazoline **26**, tetrathiazoline **17**) are difficult. These compounds give mixtures of the fully cyclized product and a related material in which all but the terminal unsubstituted thiazoline ring have been formed. With these substrates, acceptable cyclization yields are obtained by resubmitting the initial product mixture to the $TiCl_4/CH_2Cl_2$ reaction conditions.



The strategy that we have worked out for the synthesis of **7** is precedented conceptually by Hecht's biomimetic synthesis of the bithiazole unit of bleomycin[9] and should be applicable for the synthesis of other members of the tantazole–mirabazole family of natural products; efforts in this direction are underway.

(7) Minster, D. K.; Jordis, U.; Evans, D. L.; Hecht, S. M. *J. Org. Chem.* **1978**, *43*, 1624.

(8) The following methods were unsuccessful: (a) generation of the acid chloride with PCl_5 or $SOCl_2$, (b) BOP (Castro, B.; Dormoy, J.-R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, 1219), (c) BOP-Cl (Tung, R. D.; Rich, D. H. *J. Am. Chem. Soc.* **1985**, *107*, 4342) (d) DPPA (Shioiri, T.; Ninumiya, K.; Yamada, S.-I. *J. Am. Chem. Soc.* **1972**, *94*, 6203), and (e) DCC (Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067).

(9) McGowan, D. A.; Jordis, U.; Minster, D. K.; Hecht, S. M. *J. Am. Chem. Soc.* **1977**, *99*, 8078.

Acknowledgment. This research was supported by a research grant from the United States Public Health Service (GM 46057).

Supplementary Material Available: Experimental procedures and analytical data for all new compounds reported in this manuscript and a reproduction of the 400-MHz ^{1}H NMR spectrum of synthetic **7** (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Articles

Thermal and Photochemical Rearrangements of Cyclopropyl Ethers of *p*-Quinols. Competing Reaction Pathways Leading to Five- and Six-Membered Ring Spirocyclic Ketones

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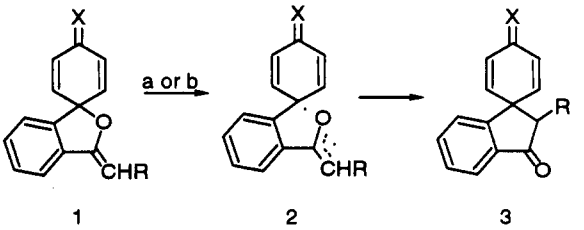
Cyclopropyl ethers of *p*-quinols were prepared by reaction of 3″-methylenedispiro[1,3-dioxolone-2,1′-[2,5]-cyclohexadiene-4′,1″(3″*H*)-isobenzofuran] and the associated ketone with ethyl diazoacetate/rhodium(II) acetate and diethylzinc/methylene iodide, respectively, and their thermal and photochemical rearrangements were studied. One major process at 180–200 °C is cleavage of the carbon–oxygen bond at the spiro center of the quinol to give a phenoxy and cyclopropoxy radical pair. A cyclopropylcarbinyl-like opening of the latter radical followed by recombination of the ring-opened radical with the phenoxy radical resulted in formation of a six-membered ring spirocyclic ketone. The other major thermal process for the cyclopropyl ether is conveniently viewed as ring-opening of the cyclopropane ring without breakage of the quinol carbon–oxygen bond followed by a hydrogen shift to afford a functionalized vinyl ether. This compound reacts under the thermal conditions to afford as the final product the five-membered ring spirocyclic ketone. Interestingly, the importance of these two competing pathways is influenced by the stereochemistry of ester substituents on the cyclopropane ring. Two major processes have been established in the photochemistry of these cyclopropyl ethers of *p*-quinols. One is rearrangement to the same six-membered ring spirocyclic ketone as discussed above. The second process is photolysis to a styrene derivative and a carbene.

Introduction. The thermal[1] and photochemical[2] [1,3]-oxygen-to-carbon migrations of vinyl ethers of *p*-quinols lead to spirocyclic ketones in high yield, Scheme I. Since the starting vinyl ethers are readily available from quinone monoketals,[3] this serves as a useful route to these spiro-fused compounds containing the cyclopentanone moiety. The reaction is most conveniently viewed as involving homolytic cleavage of the carbon–oxygen bond of the *p*-quinol followed by reclosure of the phenoxy–allyloxy biradical, **2**, at the carbon of the latter radical, Scheme I. If a similar bond homolysis occurs for cyclopropyl ethers of *p*-quinols, then a convenient route to spiro-fused dienones containing a six-membered ring could result. We report here the preparation of cyclopropyl ethers of *p*-quinols and a study of their thermal and photochemical rearrangements.

Synthesis and Rearrangement Studies. The most direct route to the cyclopropyl ethers required for study would be reaction of carbenoid reagents with the readily available vinyl ether **4**.[2b] There are two different types of double bonds available for cyclopropanation in **4** in addition to a vinyl ether and ketal function which could be unstable in the presence of Lewis acid catalysts. Thus, we first investigated the rhodium(II)[4]-catalyzed reaction of ethyl diazoacetate with **4**. The mild conditions for the reaction together with the selectivity of the carbenoid species for an electron-rich double bond offered the best chance for a high-yield cyclopropanation reaction. As shown below, reaction of **4** under these conditions gave in 63% yield a ca. 1:1 mixture of **5a** and **5b**.[5] These compounds could be separated by chromatography, but hy-

Scheme I. [1,3]-Oxygen-to-Carbon Migrations in Spirocyclic Vinyl Ethers[a]



1 2 3

[a] Key: (a) X = O, 120–160 °C; (b) X = $(OR)_2$, *hν*.

(1) (a) Morrow, G. W.; Wang, S.; Swenton, J. S. *Tetrahedron Lett.* **1988**, *29*, 3441. (b) Wang, S.; Morrow, G.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 5364.

(2) (a) Wang, S.; Callinan, A.; Swenton, J. S. *J. Org. Chem.* **1990**, *55*, 2272. (b) Swenton, J. S.; Callinan, A. C.; Wang, S. *J. Org. Chem.* **1992**, *57*, 78.

(3) For reviews and leading references, see: Swenton, J. S. *Acc. Chem. Res.* **1983**, *16*, 74. Swenton, J. S. In *Chemistry of Quinonoid Compounds, Part 2*; Rappoport, Z., Patai, S., Eds.; John Wiley: New York, 1988; p 899.

(4) For a review, see: Doyle, M. *Chem. Rev.* **1986**, *86*, 919.

(5) The cyclopropyl hydrogens in both **5a** and **5b** showed nearly identical patterns to those of **7a** and **7b**, so the stereochemistries for **5a** and **5b** were assigned based on this similarity (see supplementary material for spectra).

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