Total Synthesis of (−)-Tantazole B

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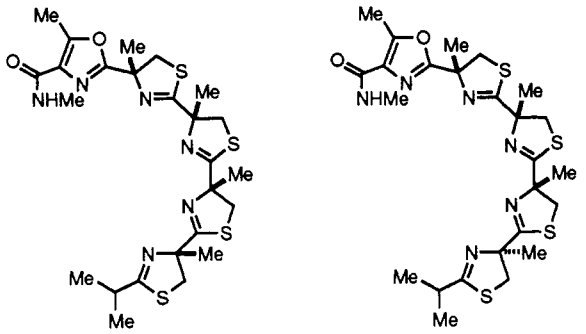
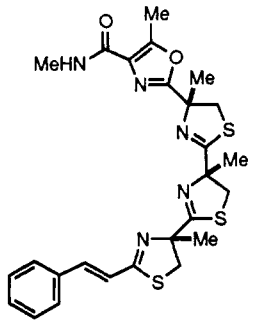
Received May 17, 1993

Tantazole B was recently isolated by Moore and co-workers from the terrestrial cyanophyte *Scytonema mirabile* (Dillwyn) Bornet (strain BY-8-1).[1] Tantazole B represents a novel class of natural products, including the tantazoles,[1] the mirabazoles,[2] and thiangazole (**3**),[3] that have in common a unique chain of thiazoline as well as oxazole and/or thiazole rings. Based on the extensive spectroscopic and degradation studies, the structure of natural tantazole B was originally assigned as formulated in **1**. While tantazole B and several other members of this family of alkaloids show selective cytotoxicity against murine solid tumors, thiangazole has been shown to exhibit unusually high inhibitory activity against HIV-1 in vitro.[4] Novel structural features as well as interesting biological activities have made the members of this family popular targets among synthetic chemists.[5] In this communication we report the first total synthesis of (−)-tantazole B and the revision of its structure to **2**.[6] Our highly efficient protocol can be readily applied to the synthesis of the other members of the tantazole family, including thiangazole.



1 (reported) **2** (revised)

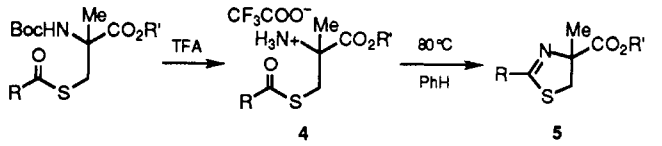
Tantazole B



3
Thiangazole

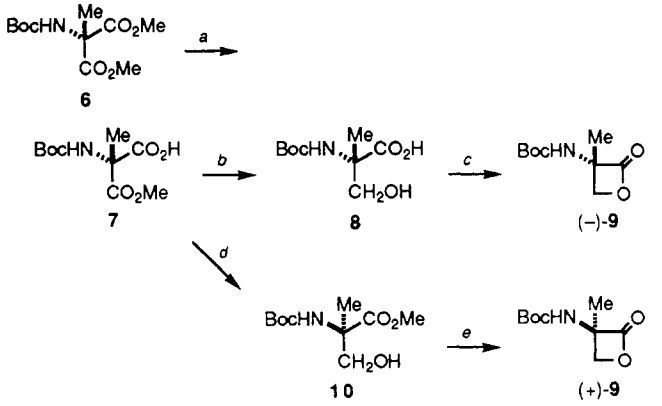
A successful total synthesis of tantazole B would require a novel and versatile method of constructing thiazolines in combination with an efficient means of concatenating the rings. During the search for such effective synthetic methods for thiazolines, we observed a facile transformation of ammonium thiol ester **4** into thiazoline **5** in hot benzene (Scheme I).[7]

Scheme I



4 **5**

Scheme II[a]



6 **7** **8** (−)-**9** **10** (+)-**9**

[a] Reagents and conditions: (a) PLE, pH 7.5, 0.1 M phosphate buffer, 23 °C (91%); (b) $NaBH_4$, THF–EtOH (10:1), 50 °C (90%); (c) Ph_3P, diethyl azodicarboxylate (DEAD), CH_2Cl_2, 0 °C (74%); (d) $ClCO_2Et$, Et_3N, THF, −5 °C, then $NaBH_4$ (86%); (e) 6 N HCl, 100 °C; Boc_2O, NaOH, THF–H_2O (74%, 2 steps); Ph_3P, DEAD, CH_2Cl_2, 0 °C (73%).

To best utilize this finding for the synthesis of the eight diastereomers of tantazole B, enantiomerically pure β-lactones (−)-**9** and (+)-**9** have been prepared from the readily available malonate derivative **6**[8] (Scheme II). Enzymatic hydrolysis of malonate **6** by pig liver esterase (PLE)[9] gave the acid **7** in 91% yield (93% ee).[10,11] Selective reduction of the ester **7** with $NaBH_4$ provided (*S*)-*N*-(*t*-Boc)-2-methylserine (**8**), which was subjected to the Mitsunobu reaction conditions to give the β-lactone (−)-**9**.[12,13] Similarly, selective reduction of the acid group of **7** via a mixed anhydride gave **10**,[14] which was converted to the enantiomeric β-lactone (+)-**9** in a three-step sequence involving hydrolysis, reprotection of the amine, and the Mitsunobu reaction.

Upon treatment with thioisobutyric acid and K_2CO_3 at room temperature, β-lactone (+)-**9** underwent smooth cleavage to give

(1) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 8195.
(2) Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1991**, *32*, 2593.
(3) Jansen, R.; Kunze, B.; Reichenbach, H.; Jurkiewicz, E.; Hunsmann, G.; Höfle, G. *Liebigs Ann. Chem.* **1992**, 357.
(4) Thiangazole has been reported to show 100% inhibition of HIV-1 (HTLV-IIIB) at 4.7 pM (antiviral efficacy) and no cell toxicity at 4.7 mM.[3]
(5) Total synthesis of (−)-didehydromirabazole A: Pattenden, G.; Thom, S. M. *Synlett* **1992**, 533. Total synthesis of (−)-mirabazole C: Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 5566.
(6) Six out of eight possible diastereomers of tantazole B have been synthesized. Synthetic **1** and authentic tantazole B show the same R_f on TLC and MS and similar CD spectra except that **1** has much larger intensity at 230 nm. Specific rotations of synthetic **1** and natural tantazole B are $[\alpha]^{23}_D$ = −325° and −94°, respectively.
(7) Instantaneous acyl migration occurred from sulfur to nitrogen even under neutral workup conditions.
(8) Prepared from $BocNHCH(CO_2Me)_2$ in 97% yield (MeI, NaOMe, MeOH, reflux).
(9) For a review of enzymatic hydrolysis of esters with PLE, see: Ohno, M; Otsuka, M. *Org. React.* **1989**, *37*, 1.
(10) For predicting the specificity of PLE, see: Toone, E. J.; Werth, M. J.; Jones, R. B. *J. Am. Chem. Soc.* **1990**, *112*, 4946.
(11) The enantiomeric purity of **7** was determined by ^1H NMR of the amide derived from **7** and (*R*)-(+)-phenylethylamine. Enantiomerically pure **7** was obtained by recrystallization from CH_2Cl_2–*n*-hexane.
(12) (a) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105. (b) Pansare, S. V.; Huyer, G.; Arnold, L. D.; Vederas, J. C. *Org. Synth.* **1991**, *70*, 1 and references cited therein.
(13) The absolute configuration of β-lactone (−)-**9** was determined by comparison of the specific rotation of *N*,*S*-bis(2,4-dinitrophenyl)-2-methylcysteine methyl ester ($[\alpha]^{23}_D$ = +158° (*c* = 0.31, $CHCl_3$)), which was derived from (−)-**9** in a four-step sequence ((1) AcSH, K_2CO_3; (2) 6 N HCl; (3) 2,4-dinitrofluorobenzene; (4) CH_2N_2), with that of (2*S*)-*N*,*S*-bis(2,4-dinitrophenyl)-2-methylcysteine methyl ester ($[\alpha]^{23}_D$ = −162° (*c* = 0.5, $CHCl_3$)).[3]
(14) Minami, N.; Kijima, S. *Chem. Pharm. Bull.* **1979**, *27*, 816.

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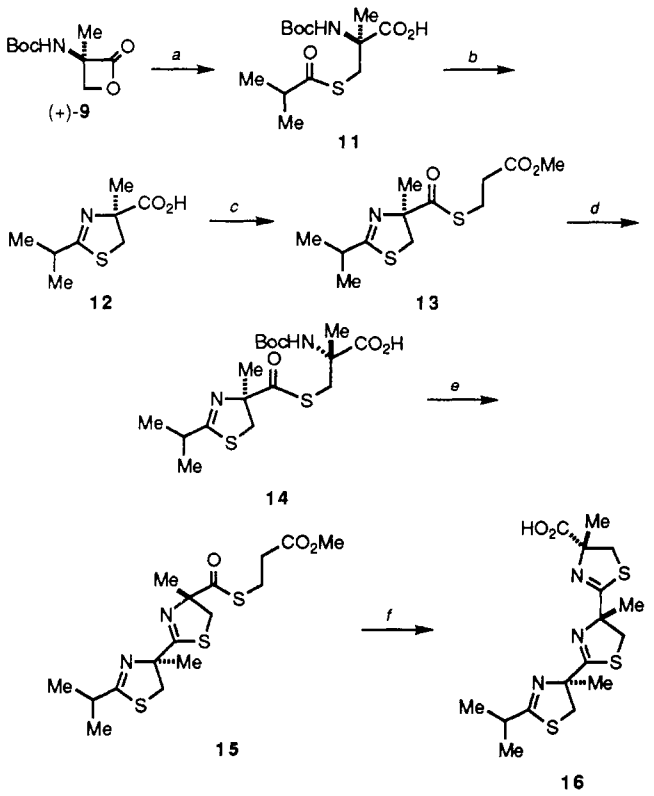
Scheme III[a]



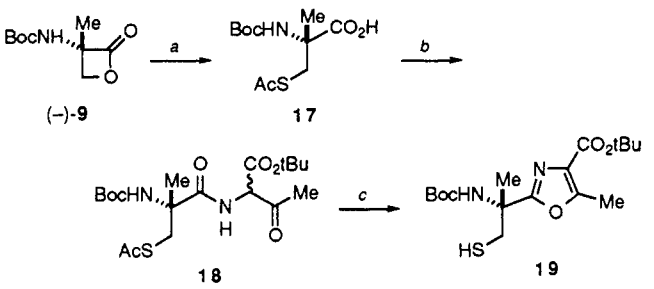
[a] Reagents and conditions: (a) $Me_2CHCOSH$, K_2CO_3, THF, 23 °C, 1 h (87%); (b) TFA, 23 °C, 10 min, then evaporate to dryness on a rotary evaporator; benzene, 80 °C, 2 h; (c) $HSCH_2CH_2CO_2Me$, BOP-Cl, Et_3N, CH_2Cl_2, 23 °C, 5 h (77% from **11**); (d) *t*-BuOK/*t*-BuOH (1 equiv), THF, 0 °C, 30 min, then (–)-**9** (1.05 equiv), 23 °C, 30 min (87%); (e) steps b and c (74%, 2 steps); (f) steps d (86%) and b (73%).

the thiol ester **11** (Scheme III). Deprotection of the *t*-Boc group of **11** with trifluoroacetic acid followed by heating at 80 °C in benzene furnished the desired thiazoline **12**. Since thiocarboxylic acids are somewhat unstable to handle, the acid **12** was first converted to the thiol ester **13** using methyl 3-mercaptopropionate and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl).[15] The retro-Michael reaction of **13** was effected by treatment with 1 equiv of *t*-BuOK to give the corresponding potassium thiocarboxylate, which was subsequently trapped in situ with β-lactone (–)-**9** to give the acid **14**. The second thiazoline ring was formed by following exactly the same procedure established for the conversion of **11** to **13**. The bithiazoline **15** was further converted to the trithiazoline **16** by iterative application of the protocol.

In light of the instability of the thiazoline rings under harsh reaction conditions, we opted to prepare the oxazole **19** with the requisite functionalities prior to the formation of the fourth thiazoline ring (Scheme IV). Thus, β-lactone (–)-**9** was cleaved with thiolacetic acid to give acid **17**. Condensation of the acid **17** with a diastereomeric mixture of threonine *tert*-butyl esters followed by Jones oxidation afforded amide **18**. The desired oxazole ring was formed by treatment with $SOCl_2$ and pyridine,[16] and subsequent base hydrolysis of the thiolacetate gave the thiol oxazole **19**.

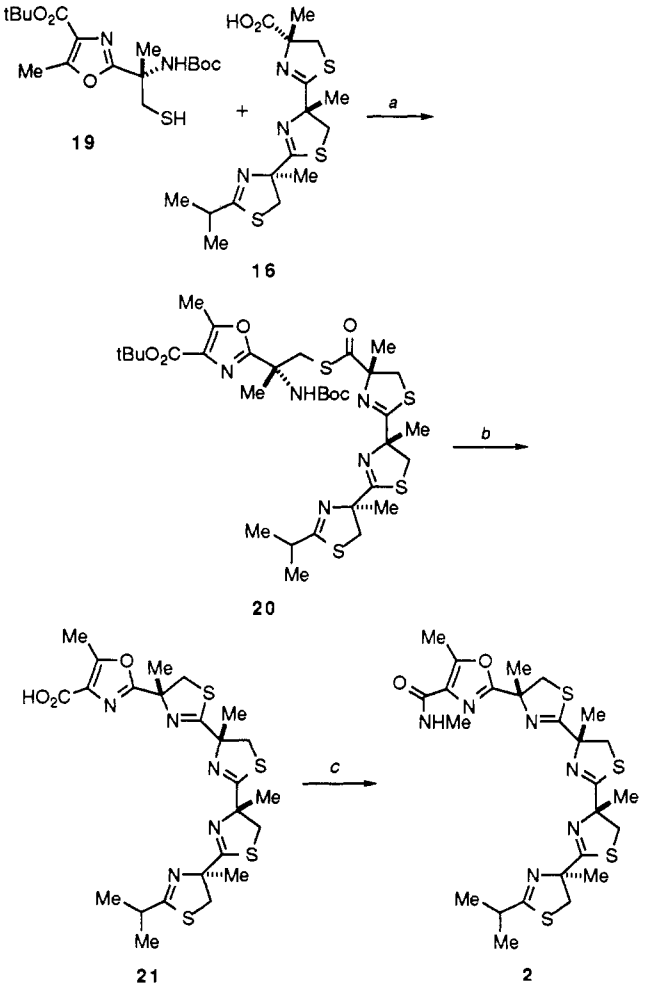
Condensation of the trithiazoline acid **16** with the thiol oxazole **19** was achieved by means of BOP-Cl to give the thiol ester **20** (Scheme V). Deprotection of both the *t*-Boc and the *tert*-butyl ester groups with trifluoroacetic acid and subsequent heating at 80 °C in benzene completed the construction of the fourth thiazoline ring. Finally, the acid **21** was converted to (–)-tantazole

Scheme IV[a]



[a] Reagents and conditions: (a) AcSH, K_2CO_3, THF, 23 °C, 1 h (87%); (b) (±)-threonine and (±)-*allo*-threonine *tert*-butyl esters, BOP-Cl, Et_3N, CH_2Cl_2, 23 °C; Jones oxidation (60%, 2 steps); (c) $SOCl_2$, pyridine, CH_2Cl_2, 23 °C, 24 h (53%); NaOH, MeOH, 23 °C, then quenched with AcOH (75%).

Scheme V[a]



[a] Reagents and conditions: (a) BOP-Cl, Et_3N, CH_2Cl_2, 23 °C, 4 h (80%); (b) TFA, 23 °C, 30 min, then evaporated to dryness on a rotary evaporator; benzene, 80 °C, 4 h (74%); (c) $ClCO_2Et$, Et_3N, THF, 0 °C; 40% $MeNH_2$ in H_2O, 10 min (86%).

B (**2**) in a conventional manner. The synthetic sample was identical with an authentic sample in HPLC behavior and spectroscopic properties (500 MHz ^1H NMR, MS, $[\alpha]_D$, CD).[17]

Acknowledgment. This work was supported by the National Institutes of Health (Grant CA 28119). We also thank Professor Richard E. Moore for valuable discussions regarding the stereochemistry of tantazole B.

Supplementary Material Available: Spectroscopic data for key intermediates and synthetic (–)-tantazole B (**2**) (6 pages). Ordering information is given on any current masthead page.

(15) Cabre, J.; Palomo, A. L. *Synthesis* **1984**, 413.
(16) Korte, F.; Störiko, K. *Chem. Ber.* **1960**, *93*, 1033.
(17) We are indebted to Professor Richard E. Moore of the University of Hawaii for a direct comparison of our synthetic sample with the natural tantazole B.