Total Synthesis of the Novel Benzopentathiepin Varacinium Trifluoroacetate: The Viability of "Varacin Free Base"

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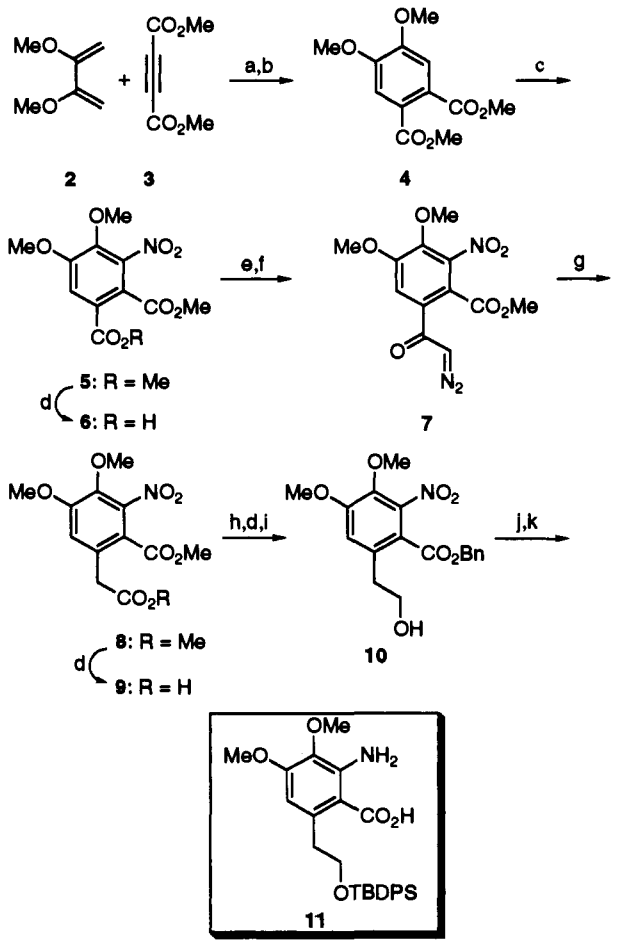
Varacin is a metabolite which was isolated from the marine ascidian *Lissoclinum vareau* in 1991 by Ireland and associates and assigned as structure **1a**.[1] The natural product exhibited potent antifungal activity against *Candida albicans* (14-mm zone of inhibition of 2 μg of varacin/disk) as well as potent antitumor activity against human colon tumor cell line HCT 116 (IC_{90} 0.05 μg/mL). Preliminary information suggested that varacin acts through damaging DNA.[1] Though the parent benzopentathiepin ring system is known,[2] **1a** would be the first naturally occurring benzopentathiepin.[3]

A proposal for the synthesis of varacin must deal with several interesting problems. Though the chemistry of benzopentathiepins has not been extensively elucidated, there have already been described complex reactions of such compounds with diethylamine.[2a] Thus, accommodation of the potentially incompatible primary amino and pentathiepin moieties found in varacin appeared to constitute a significant obstacle. Moreover, the incorporation of such a pentathiepin in a pentasubstituted aromatic ring added to the complexity of the goal. Given these challenges, as well as the potent biological activity of varacin, an undertaking directed at total synthesis seemed warranted. We note in passing that our interest in varacin was spurred by our broader interest in polysulfur-containing antitumor antibiotics.[4] Our results are reported herein.

The synthetic effort began with a Diels–Alder reaction of commercially available 2,3-dimethoxy-1,3-butadiene (**2**) and dimethylacetylene dicarboxylate (**3**, DMAD) (see Scheme I). Without benefit of full purification, this product was immediately oxidized with DDQ, affording diester **4** which, upon treatment with nitronium tetrafluoroborate (NO_2BF_4)[5] in sulfolane, gave nitrodiester **5**.[6a,b] Having exploited the symmetry of **4** to simplify the nitration step, it was now necessary to distinguish the nonequivalent methyl ester groups in **5**. Fortunately, this was readily accomplished. Hydrolysis of the less-hindered methyl ester provided carboxylic acid **6**, which was homologated via the Arndt–Eistert[7] sequence. Thus, conversion of **6** to its acid chloride and subsequent treatment with excess diazomethane provided diazoketone **7**. Wolff rearrangement, effected with silver benzoate,[8] led to methyl ester **8** and thence to acid **9**, as shown.[6a,b]

Scheme I[a]



[a] (a) PhMe, $CHCl_3$, reflux; (b) DDQ, PhH, 78% for two steps; (c) NO_2BF_4, sulfolane, 77%; (d) LiOH, THF-H_2O, quantitative; (e) $(COCl)_2$, catalyst DMF, PhH; (f) excess CH_2N_2, Et_2O, 79% from **5**; (g) silver benzoate, TEA, MeOH, 76%; (h) BH_3·THF, THF; (i) BnBr, $NaHCO_3$, TBAI, DMF, 92% from **8**; (j) TBDPSCl, TEA, DMAP, CH_2Cl_2, 90%; (k) H_2, $Pd(OH)_2$, THF; H_2, Pd–C, EtOH, 94%.

Borane reduction of **9** followed by the action of LiOH[9] provided a hydroxy acid, which upon esterification afforded benzyl ester **10**.[6a,b] Silylation of the free hydroxyl group was followed by reduction of the nitro and benzyl ester functions, providing anthranilic acid **11**.[6a,b]

The stage was set for installation of sulfur. Accordingly, compound **11** was treated with isoamyl nitrite in the presence of carbon disulfide and isoamyl alcohol.[10,11] Thermal decomposition of the presumed diazonium carboxylate salt gave rise to **14**[6a] in 40% yield, perhaps via intermediates **12** and **13** (Scheme II).

Nitrogen installation was achieved by removal of the silyl protecting group, followed by Mitsunobu reaction of the resultant alcohol **15** with phthalimide.[12] Protection of the amino group in a manner where it could be deblocked under mildly acidic conditions was eventually shown to be necessary for maintaining the pentathiepin ring. Accordingly, the phthalimide function was cleaved by hydrazinolysis, and the amino group was immediately treated with di-*tert*-butyl dicarbonate, affording *tert*-butyl carbamate **16**.[6a]

Introduction of the pentathiepin array proved to be difficult by the established methods, which involve prior formation of an

(1) Davidson, B. S.; Molinski, T. F.; Barrows, L. R.; Ireland, C. M. *J. Am. Chem. Soc.* **1991**, *113*, 4709.
(2) (a) Chenard, B. L.; Harlow, R. L.; Johnson, A. L.; Vladuchick, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 3871. (b) Sato, R.; Onodera, A.; Goto, T.; Saito, M. *Heterocycles* **1988**, *27*, 2563. (c) Sato, R.; Chino, K. *Tetrahedron Lett.* **1991**, *32*, 6345.
(3) For a similar natural product containing a benzotrithiole ring, see: Litaudon, M.; Guyot, M. *Tetrahedron Lett.* **1991**, *32*, 911.
(4) (a) Haseltine, J. N.; Cabal, M. P.; Mantlo, N. B.; Iwasawa, N.; Yamashita, D. S.; Coleman, R. S.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 3850. See also: (b) Nicolaou, K. C.; Hummel, C. W.; Pitsinos, E. N.; Nakada, M.; Smith, A. L.; Shibayama, K.; Saimoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 10082. (c) Nakatsuka, S.; Fukuyama, T.; Kishi, Y. *Tetrahedron Lett.* **1974**, 1549. (d) Kishi, Y.; Nakatsuka, S.; Fukuyama, T.; Havel, M. *J. Am. Chem. Soc.* **1975**, *95*, 6493. (e) Kishi, Y.; Fukuyama, T.; Nakatsuka, S. *J. Am. Chem. Soc.* **1973**, *95*, 6490, 6492.
(5) Kuhn, S. J.; Olah, G. A. *J. Am. Chem. Soc.* **1961**, *83*, 4564.
(6) Characterized by (a) ^1H NMR, ^{13}C NMR, IR, HRMS spectra and (b) combustion analysis.
(7) Bachmann, W. E.; Struve, W. S. *Org. React.* **1942**, *1*, 38.
(8) Newman, M. S.; Beal, P. F. *J. Am. Chem. Soc.* **1950**, *72*, 5163.
(9) Borane reduction gave a mixture of hydroxy ester and lactone.
(10) Nakayama, J. *Synthesis* **1975**, 38.
(11) Friedman, L.; Logullo, F. M. *J. Org. Chem.* **1969**, *34*, 3089.
(12) Mitsunobu, O. *Synthesis* **1981**, 1.

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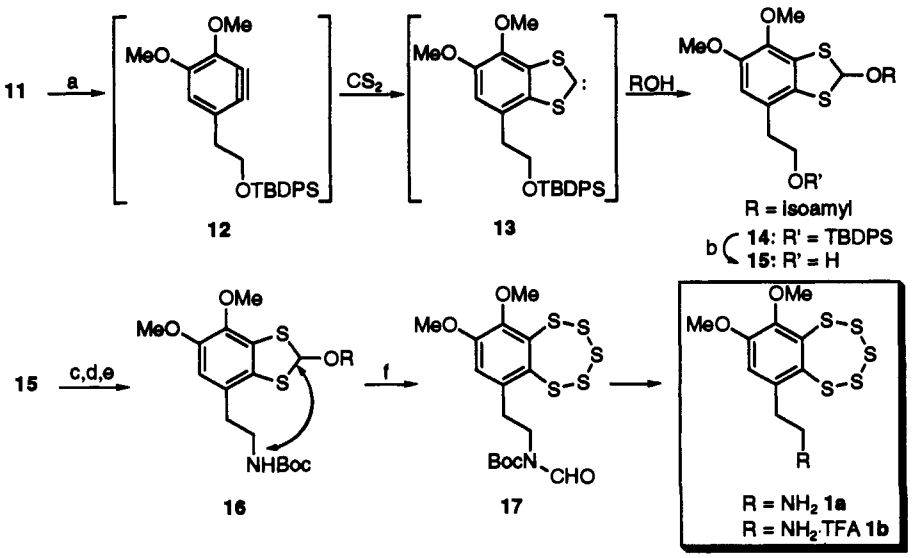
Scheme II[a]



[a] (a) Isoamyl nitrite, isoamyl alcohol, CS_2, 1,2-dichloroethane, 75 °C, 40%; (b) TBAF, THF, 93%; (c) phthalimide, DEAD, PPh_3, THF; (d) hydrazine, EtOH; (e) $(Boc)_2O$, DMAP, CH_2Cl_2, 55% from **15**; (f) S_2Cl_2, THF; MeOH, HCl, 46%.

ortho dithiol system.[2a,13] After considerable experimentation, a very direct solution to this problem was devised. *Thus, treatment of* **16** with S_2Cl_2 *effected removal of the ortho ester and installation of the pentathiepin moiety.* Not the least interesting feature of the remarkable conversion of **16** to **17** is the transfer of the formyl equivalent from sulfur to nitrogen (see arrows).[14] Elucidation of the precise nature of this step awaits further experimentation.

Removal of the nitrogen protecting groups was carried out in methanolic HCl. Purification by reverse-phase HPLC (CH_3CN:0.1% aqueous TFA, 45:55) afforded varacin as its trifluoroacetate salt **1b** in 46% yield from **16**. The ^1H NMR, ^{13}C NMR, and IR spectra of synthetic **1b** were identical to those of an authentic sample of **1b**, which was kindly provided by Professor C. M. Ireland.

In light of literature precedent for the reaction of pentathiepins with diethylamine,[2a] it was of particular interest to attempt to complete the synthesis of free varacin **1a** and to probe the stability of the pentathiepin substructure in the context of the free amine. Unfortunately, no stable free amine **1a** was obtained upon subjection of **1b** to a variety of desalting conditions.[15] Such treatments resulted in rapid decomposition. These observations lead us to suspect that at physiological pH varacin exists in the protonated form, and it is only in this state that the amino and pentathiepin functionalities coexist. Further studies of the varacin system, now readily available as **1b** by total synthesis, are in progress.

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(13) (a) Fehér, F.; Langer, M. *Tetrahedron Lett.* **1971**, 2125. (b) Degani, I.; Fochi, R. *Synthesis* **1976**, 471.

(14) ^1H NMR ($CDCl_3$, 300 MHz) δ 9.18 (s, 1H), 6.77 (s, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.79 (m, 2H), 3.14 (m, 2H), 1.49 (s, 9H); LRMS (EI) 467 (parent); FTIR (thin film) 2900, 1736, 1703, 1689, 1463, 1369, 1343, 1247, 1195, 1147 cm^{-1}.

(15) Among these attempts were reactions with propylene oxide, polyvinylpyridine, AG1-X8 anion exchange resin (HCO_3^- form), and partition between 5% $NaHCO_3$/EtOAc.