A New Route to the Synthesis of the Naturally Occurring Benzopentathiepin Varacin

F. Dean Toste and Ian W. J. Still*

J. Tuzo Wilson Research Laboratories, Erindale College
University of Toronto in Mississauga
Mississauga, Ontario, Canada L5L 1C6

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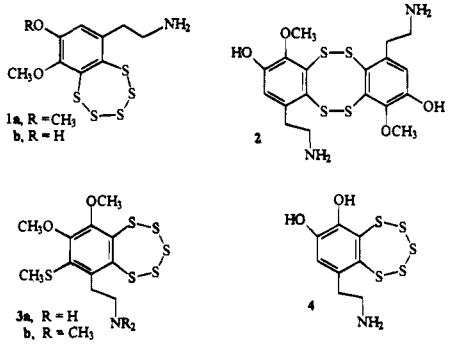
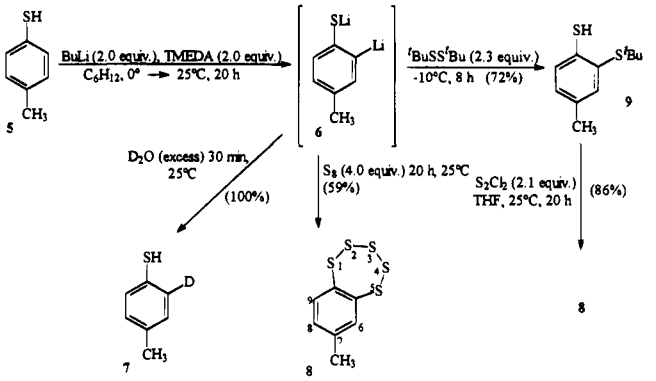
Since it was first isolated from marine organisms in 1991,[1] the cyclic pentasulfide varacin (**1a**) has been the focus of great synthetic[2] and structural[3] interest. As well as possessing a highly unusual pentathiepin ring, varacin exhibits potent antifungal and antitumor activity.[1] Davidson and co-workers[3b] have very recently attributed a novel type of conformational stability to this benzopentathiepin system and have raised the possibility of the existence of (natural) varacin in enantiomerically pure form. A closely related benzopentathiepin, lissoclinotoxin A, the structure of which was at first wrongly assigned as that of the related trithiole, was also isolated in 1991 by Guyot and Litaudon[4] and was assigned the correct structure **1b** more recently.[5]



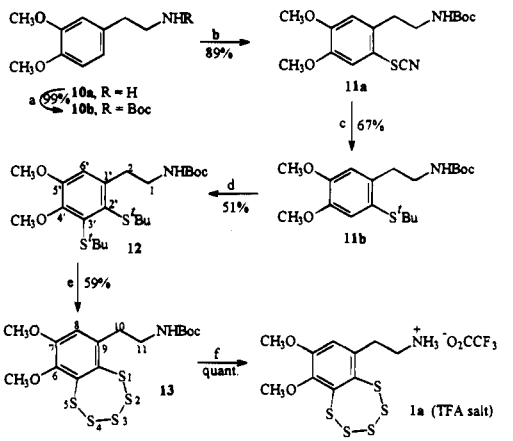
Searle and Molinski[6] have very recently isolated a group of five new alkaloids from the tropical ascidian, *Lissoclinum* sp. One of these, the dibenzotetrathiocin lissoclinotoxin D (**2**), as well as **1b**, which was also found to be present, had potent antifungal activity. These workers made the interesting claim that lissoclinotoxin A (**1b**) is *chiral* but that its optical activity may be lost during isolation. Faulkner, Carté, and co-workers[7] have described the isolation of some structurally related benzopentathiepins from two *Lissoclinum* species. These include the 5-methylsulfanyl varacins **3a,b**, two very similar benzotrithiole analogues, and 3,4-desmethylvaracin (**4**) from a *Eudistoma* species. We now describe an efficient synthetic route to varacin and related compounds.

Until very recently, synthetic procedures for reliably constructing the pentathiepin ring have been distinguished only by their paucity. Before embarking upon our synthesis, we tested

Scheme 1



Scheme 2[a]



[a] (a) $(Boc)_2O$, DMF, TEA, 60 °C, 2 h; (b) NTS, HOAc, 25 °C, 4 h; (c) $^tBu_2Cu(CN)Li_2$ (3.0 equiv), THF, −78 °C, 4 h; (d) BuLi (4.0 equiv), TMEDA (4.0 equiv), hexanes, 50 °C, 18 h, followed by $^tBuSS^tBu$ (5.0 equiv), −10 → 25 °C, 18 h; (e) S_2Cl_2 (5.0 equiv), $BaCO_3$, THF, 25 °C, 18 h; (f) CH_2Cl_2, TFA, 25 °C, 2 h.

an approach which relied upon the introduction of only a *single* sulfur substituent, as shown by our model system in Scheme 1, and a final step (**9** → **8**) using S_2Cl_2, as first reported by Chenard and co-workers,[8] for the construction of the pentathiepin ring. Regioselective double lithiation of *p*-toluenethiol (**5**) by a literature procedure[9] afforded **6**, verified by quantitative deuteration to produce **7**. In an initial attempt at the thiation of **6**, using S_8, we were gratified to find that 7-methylbenzopentathiepin (**8**) had been formed in 59% yield, accompanied, however, by some di-*p*-tolyl disulfide. A more reliable route to **8** was afforded by prior conversion of the dilithiated intermediate **6** to **9** by treatment with di-*tert*-butyl disulfide. Subsequent thiation of **9** with S_2Cl_2 yielded the pentathiepin **8** in 86% yield, after chromatography.

With this encouraging result in hand, we returned to the main synthetic objective (see Scheme 2). The readily available, inexpensive 3,4-dimethoxyphenethylamine (**10a**) was chosen as the starting material. After quantitative protection of the NH_2 group, we were able to regioselectively introduce a thiocyanate group in excellent yield by an electrophilic thiocyanation procedure which we have recently developed, using *N*-thiocy-

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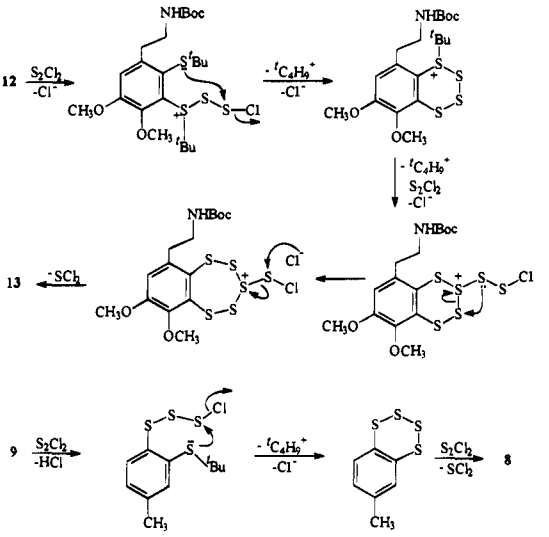
anatosuccinimide (NTS).[10] Conversion of the thiocyanate **11a** to the analogous *tert*-butyl sulfide **11b** was achieved by a novel ligand-exchange reaction which we also discovered very recently,[11] using the higher order cuprate $^tBu_2Cu(CN)Li_2$.[12] (We have found S^{t}Bu to be a more convenient ortho-directing group than SH in the target series.) Regioselective lithiation[13] and reaction with di-*tert*-butyl disulfide afforded the desired bis-sulfide **12** in good yield. Some loss of the Boc group was observed during this process; this was easily restored by brief treatment with di-*tert*-butyl dicarbonate prior to workup. The key step, construction of the pentathiepin ring of varacin, was at first problematic. By addition of $BaCO_3$ to the reaction mixture with S_2Cl_2, however, we obtained the Boc-protected varacin **13** in 59% yield, after chromatographic purification to remove S_8 as contaminant.[14] As noted by others,[2c] no trithiole or other cyclic polysulfide contaminant could be detected in the product mixture.[15] Removal of the Boc group was routinely achieved.

Our S_2Cl_2 procedure, modified by the use of $BaCO_3$, gives significantly higher yields for this step than previous procedures[2c] and avoids the need to reductively cleave the bis-sulfide, which has been problematic.[2b,3a] In Scheme 3, we suggest plausible mechanistic pathways for the conversions of **12** to **13** and **9** to **8**.

This synthesis of varacin is significantly shorter (six steps, including the protection–deprotection steps), and the overall yield of 18% is much higher than has been achieved previously.[2,3a] Our synthetic route is unique in that the aminoethyl side chain of varacin is present throughout and in that the introduction of the key sulfur substituent is effected by a relatively mild *electrophilic*, rather than by a decidedly forcing nucleophilic, reaction. We plan to extend the synthetic approach described here to the synthesis of lissoclinotoxin A and related pentathiepins.

Scheme 3



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Supporting Information Available: Experimental procedures for compounds **7**–**9** and intermediate **6**, as well as for the preparation of **11b**, **12**, **13**, and **1a**; spectroscopic details (^{1}H- and ^{13}C-NMR, FT-IR, UV, and EIMS) for these compounds, as well as HR-EIMS data in most cases (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet: see any current masthead page for ordering information and Internet access instructions.

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(14) Somewhat confusingly, different numbering systems for varacin[2b,3b] and lissoclinotoxin A[4,5] have been used previously by different authors. We have reverted to a numbering system for these compounds consistent with the *pentathiepin*, rather than the benzenoid ring, as the major ring, as used originally by Chenard and co-workers.[8] see **13** and **8**.

(15) Compound **13** shows the (single) aromatic proton in the ^{1}H-NMR spectrum at δ 6.77; the aromatic proton in the related trithiole is found at δ 6.44.[2b]