Stereocontrolled Total Synthesis of (+)-Paraherquamide B

Timothy D. Cushing, Juan F. Sanz-Cervera,† and Robert M. Williams*

Department of Chemistry
Colorado State University
Fort Collins, Colorado 80523

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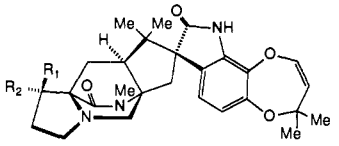
The paraherquamides are complex, heptacyclic, toxic mold metabolites with potent anthelmintic activity isolated from various *Penicillium* sp. The parent and most potent derivative, paraherquamide A (**1**), was first isolated from *Penicillium paraherquei* in 1980 by Yamazaki.[1] The simplest member, paraherquamide B (**2**), plus five other structurally related paraherquamides (C–G) were isolated from *Pencillium charlesii* (*ATCC* 20841) in 1990 at Merck & Co.[2,3] and concomitantly at SmithKline Beecham.[4]



1, (-)-PARAHERQUAMIDE A, R_1 = OH, R_2 = Me
2, (-)-PARAHERQUAMIDE B, R1 = R2 = H

Recent interest in the paraherquamides has come from the finding that this class of alkaloids displays potent anthelmintic and antinematodal properties.[2,4–6] There are essentially three classes of broad spectrum anthelmintics currently in use: the benzimidazoles, the levamisoles/morantels, and the avermectins/milbemycins. Unfortunately, the first two groups have lost much of their utility due to the appearance of drug resistance built up by the helminths.[6a,7] More recently, drug resistance to the avermectins has been observed in various parasites.[8] The paraherquamides represent an entirely new structural class of antiparasitic agents that promise to play a significant role in the near future. The relatively low culture yields of obtaining paraherquamides for biological study have slowed the development of these agents.

In connection with our ongoing studies on the biosynthesis of the structurally related metabolites the brevianamides,[9] we wish to report the first total synthesis of (+)-paraherquamide B. Key features of this synthesis include a unique application of the Somei/Kametani reaction;[10] an entirely stereocontrolled intramolecular S_N2' reaction; a Pd(II)-mediated indole cyclization reaction;[11] a chemoselective 3° amide reduction; and a regioselective indole-to-oxindole oxidative pinacol-type rearrangement. In particular, the key intramolecular S_N2' cyclization reaction[12] (**9** to **10**) appears to proceed via a closed transition state[13] where the developing chloride anion and sodium cation form a contact ion pair favoring cyclization from the "endo" (closed) conformer, giving the desired stereochemistry of the core bicyclo[2.2.2] ring system. This situation is reminiscient of the closed-transition-state model first advanced by Denmark[13] for the aldol condensation reaction. The piperazinone portion of the molecule starts with enal **3**, easily made on large scale in seven steps from L-proline as previously reported.[12]

Enal **3** was treated with ceric ammonium nitrate (CAN) to remove the *p*-methoxybenzyl group (79%). The resulting amide was reduced to the alcohol with $NaBH_4$ and protected with *tert*-butyldiphenylsilyl chloride to give **4**. This compound was treated in a two-step, one-pot procedure with methyl chloroformate, yielding the desired imidocarbamate **5** as a variable mixture of epimers (epimerization occurs on silica gel, Scheme I).

Gramine derivative **6** was synthesized in three steps[14] from the corresponding oxindole as previously reported.[15a] When **6** and **5** were refluxed with 0.5 equiv of *n*-Bu_3P in acetonitrile, the desired alkylation occurred[10] together with an unexpected and fortuitous decarbomethoxylation of the imidocarbamate. Indole **7** was treated with LiCl in wet HMPA at 100 °C, effecting decarbomethoxylation (obtained as a 3:1 *syn*:*anti* mixture that proved easy to separate by chromatography); both products were separately treated to the next series of manipulations. Lactim ether formation was accomplished by treating the amides with Me_3OBF_4 in CH_2Cl_2/Na_2CO_3. The lactim ethers were then treated with $(BOC)_2O$ followed by *n*-Bu_4NF to give the diols **8a** and **8b**. The sensitive allylic chlorides were prepared according to Corey[16] (NCS and Me_2S), and the secondary alcohols carefully reprotected with *tert*-butyldimethylsilyl triflate to furnish the key S_N2' cyclization substrates **9a**/**9b**. Individual treatment of **9a**/**9b** with 20 equiv of washed NaH in refluxing benzene effected stereoselective intramolecular S_N2' cyclization,[12] giving the desired bicyclo[2.2.2] product **10** (93% from **9a**; 85% from **9b**). Numerous attempts to effect the proton-mediated cationic cyclization of **10** to **11** were unsuccessful; strong protic acids, Lewis acids,[17] or TMSOTf failed to give even a trace of any heptacyclic indole. Treatment of **10** with Pd(II) according to Trost[11] [(1) $PdCl_2$, $AgBF_4$, MeCN; (2) $NaBH_4$, EtOH] gave the desired heptacycle

† On leave from the Department of Organic Chemistry, University of Valencia, Spain.

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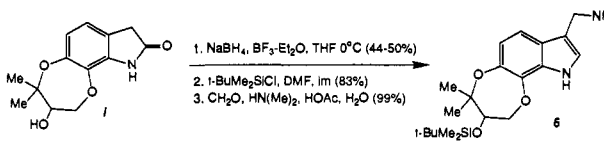
(14) The oxindole *i* was prepared as described in ref 15a from vanillin and transformed into **6**:



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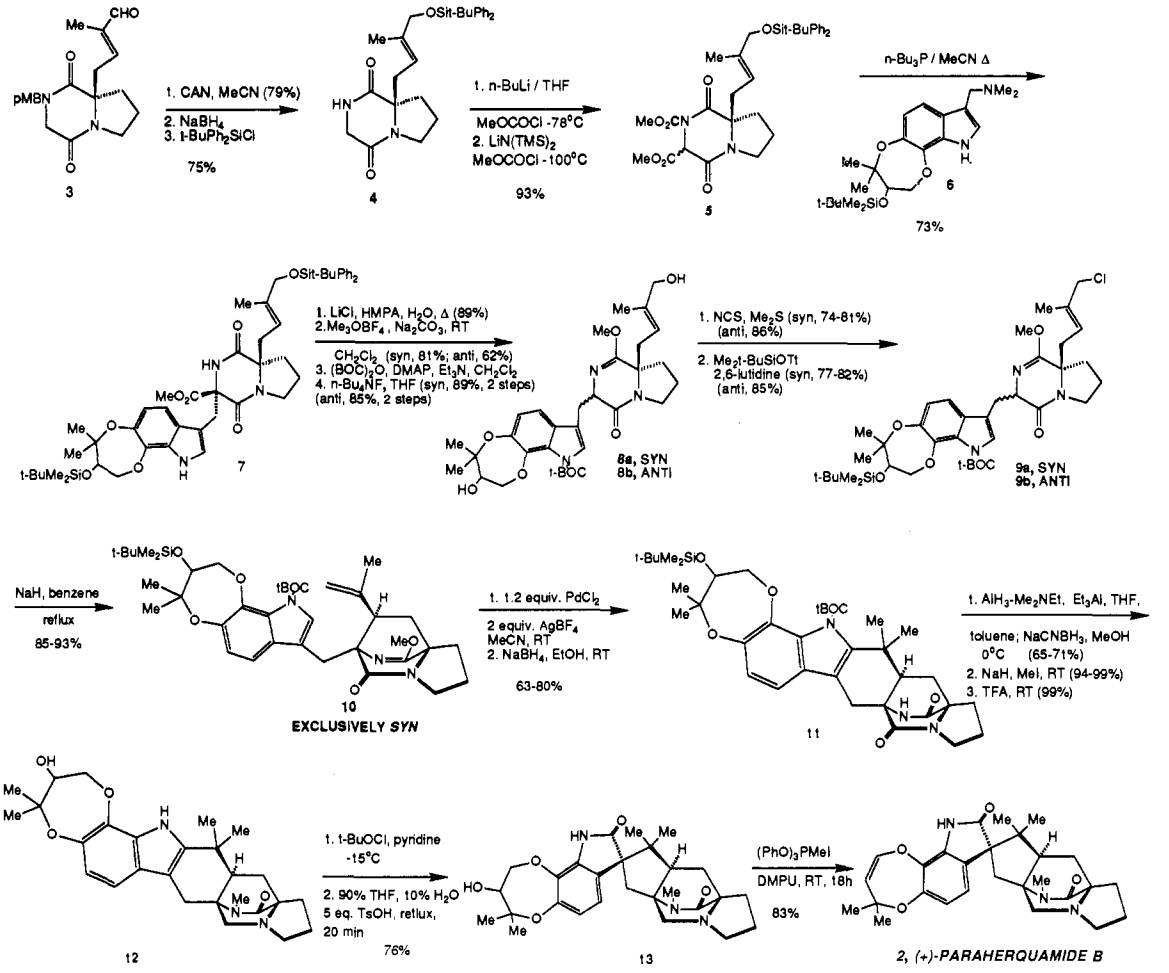
Scheme I



11 in 80% yield. A fortuitous side reaction under these conditions was the cleavage of the lactim ether. Regioselective reduction[18] of the tertiary amide of **11** proceeded cleanly with AlH_3–Me_2-NEt complex and Et_3Al, followed by a $NaCNBH_3$ workup, to give the tertiary amine in 64–71% yield. N-Methylation of the secondary amide (NaH/MeI in DMF, 94–98%), followed by deblocking of both protecting groups (80 equiv of TFA in CH_2-Cl_2), gave the indole **12** in 59% overall yield from **11**. The final oxidative spirooxidation was at first problematic but was eventually solved in a stereocontrolled manner by a two-step oxidation/rearrangement. Although a single chloroindolenine was easily obtained from **12** with *t*-BuOCl and pyridine, affording the desired epimer, the final pinacol-type rearrangement was more difficult. Standard treatment[19] with $MeOH/H_2O/AcOH$ at reflux for 1 h gave only decomposition products, as did treatment with $AgClO_4$ and $HClO_4$.[18] Products resulting from rearrangement/capture of a highly stabilized benzylic carbocation were observed; however, hydration of the chloroindolenine in a less polar solvent system (90% THF/10% H_2O) with 5 equiv of TsOH effected the desired rearrangement to the oxindole (**13**, 76% plus 4% of the unnatural spiroepimer). Finally, dehydration was effected with MTPI in DMPU[20] to give (+)-paraherquamide B (the enantiomer of the natural product) in 83% yield. This material proved to be identical[21] to the natural sample by ^1H NMR, MS, IR, UV, and mobility on HPLC. Use of this synthesis[22] to probe the biogenesis of the paraherquamides and to expand their antiparasitic activities is currently in progress and will reported on in due course.

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Supplementary Material Available: Complete tabulation of spectroscopic and analytical data for all new compounds reported in this paper (20 pages). Ordering information is given on any current masthead page.

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(21) The CD spectra of natural **1** (paraherquamide A) and synthetic **2** (paraherquamide B) were essentially mirror images, confirming the absolute stereochemistry of natural **2** as being the same as **1**, which has been previously documented by single-crystal X-ray analysis of a heavy-atom (bromine) derivative (ref 2).

(22) All new compounds exhibited satisfactory ^1H NMR, IR, combustion analyses, and/or high-resolution mass spectral data consistent with the assigned structures.