Conversion of Marcfortine A to Paraherquamide A *via* Paraherquamide B. The First Formal Synthesis of Paraherquamide A

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The paraherquamides and marcfortines represent a novel class of anthelmintics. The sole structural difference between paraherquamide A and marcfortine A occurs in ring G. We synthesized paraherquamide B from marcfortine A in six steps. Paraherquamide A was then prepared from paraherquamide B in seven steps. This represents the first formal synthesis of paraherquamide A.

Helminths, especially parasitic nematodes, cause substantial health problems in humans and domestic animals. Currently, three distinct chemical classes are used for broad spectrum control of gastrointestinal nematodes in veterinary medicine: benzimidazoles, imidazothiazoles, and macrocyclic lactones.[1] None of these drugs is ideally suited for all therapeutic situations, and each class has been challenged by the development of drug-resistant nematode strains.[2] Expansion of the anthelmintic arsenal is thus an urgent goal. Marcfortine A, paraherquamide A, and their analogs have potent antiparasitic activity.[3] Because the marcfortines and paraherquamides are unique both structurally and in their mode of action, they represent a promising new class of anthelmintics.

The paraherquamides were isolated from *Penicillium* sp.[4] A total synthesis of the enantiomer of paraherquamide B, which is the simplest member of the paraherquamide family, and synthetic studies of paraherquamide A were described by Williams et al.[5] We have utilized paraherquamide B for the first formal synthesis of paraherquamide A. A ready supply of paraherquamide B was generated by conversion of the more easily obtained marcfortine A which has the same absolute configuration as the paraherquamides.[6a] Marcfortine A, reported by Polonsky et al.,[6b] is a fungal metabolite of *Penicillium roqueforti* and is structurally related to paraherquamide B, the sole difference occurring in ring G: paraherquamide B contains a five-membered G-ring whereas the G-ring of marcfortine A is six-membered. Opening the G-ring of marcfortine A, oxidatively removing one carbon atom, and reclosing was expected to give paraherquamide B. This we accomplished in six steps (Scheme 1). Treatment of marcfortine A with cyanogen bromide[7] opened the G-ring and gave bromo derivative **1**. We were unable to form the terminal methylene **3** in a single step from **1** through base-catalyzed elimination of HBr using either DBU/CH_3CN, KOH/MeOH, or ^{t}BuOK/DMSO. We overcame this resistance to elimination by first converting **1** to selenide **2** which was accomplished by treating **1** with diphenyl diselenide in the presence of sodium borohydride. Oxidation of **2** with $NaIO_4$ followed by elimination of the resulting selenol in refluxing benzene gave terminal alkene **3** in 80% yield. Hydrolysis of the cyano group with NaOH in ethylene glycol[8] produced **4** (50% yield) which under standard osmylating conditions gave diol **5** (70%). Cleavage of the diol with $NaIO_4$ to an intermediate aldehyde followed by an intramolecular reductive amination with sodium borohydride formed the five-membered ring of paraherquamide B (50%) whose 300-MHz ^{1}H NMR and HRMS spectra were identical with those reported for the natural material.[4c]

We converted paraherquamide B to paraherquamide A in seven steps (Scheme 2). Oxidation of paraherquamide B with I_2/$NaHCO_3$[9] in THF/H_2O gave lactam **6** (40%) and 12-oxoparaherquamide B (25%). Treatment of **6** with LDA and phenylselenenyl chloride followed by oxidation of the resulting selenide with H_2O_2 gave the α,β-unsaturated lactam **7** (58%). Our initial attempts to epoxidize **7** were unsuccessful: H_2O_2/NaOH, *m*-CPBA, isovaleraldehyde/VO(acac)$_2$, and *n*-BuLi/H_2O_2 all failed to give the epoxide **8**. However, treatment of **7** in THF with triton B[10a] and *tert*-butyl hydroperoxide[10b] gave epoxide **8** (58%), the ^{1}H NMR spectrum of which showed a single stereoisomer. The stereochemistry was assigned to **8** based on the stereochemistry of alcohol **10** (*vide*

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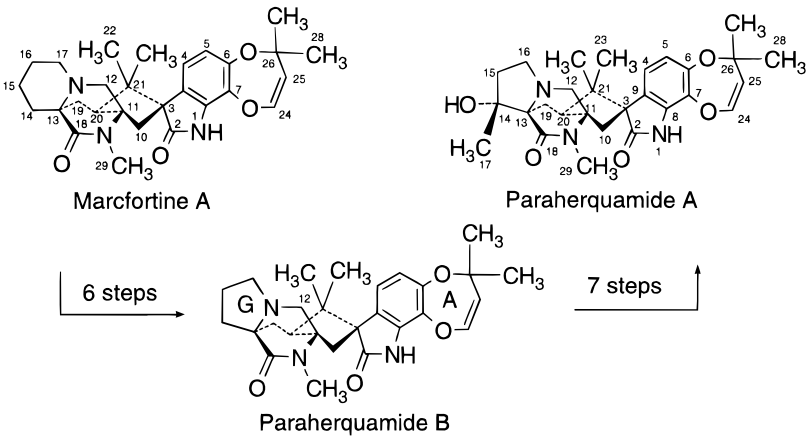
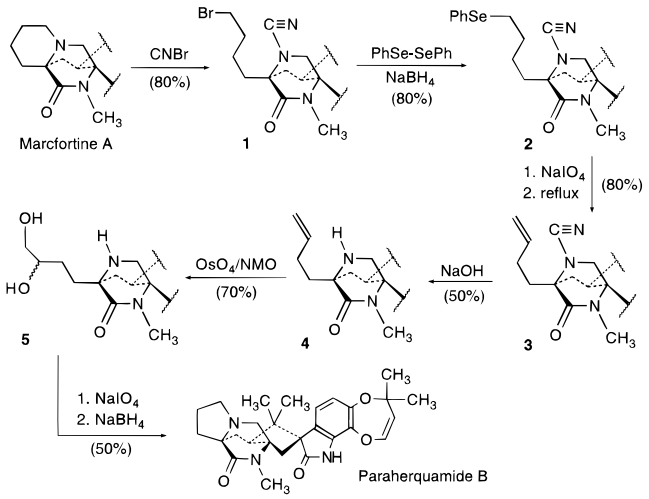
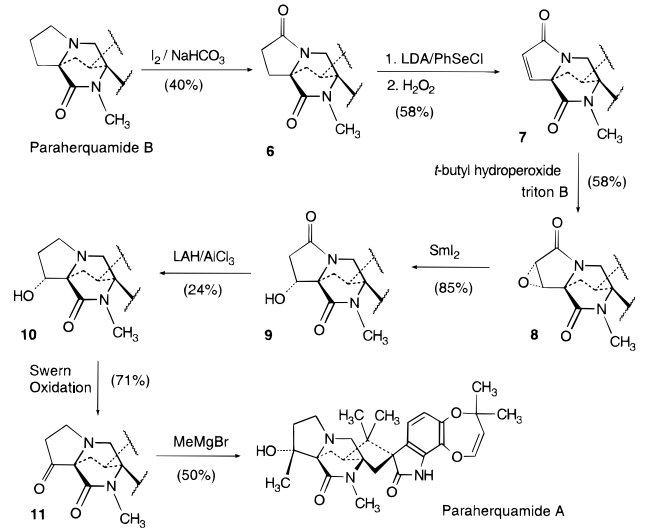


Figure 1.

Scheme 1



Scheme 2



infra). Presumably, the double bond of **7** was attacked by peroxide from behind giving the α-epoxide, since the back side is less hindered. In any case, the stereochemistry of these chiral centers is of little consequence since they are removed at a later stage of the synthesis. While standard methods utilizing $NaBH_4$, BH_3−THF, and super hydride (Et_3BHLi) failed to open the epoxide ring, samarium iodide[11] provided the required 14α-hydroxy compound **9** in good yield (85%). Although this single electron transfer reagent has been shown to cleave epoxyketones, to our knowledge this is the first instance of its application to amides. Reduction of **9** with LAH/$AlCl_3$ gave **10** in only modest yield (24%), because the A-ring was partially cleaved by the reducing agent. The stereochemistry of **10** was established by comparison of its ^{1}H NMR spectrum with that reported by Blizzard et al. in their synthesis of **10** by an alternate synthetic route.[3a] This also confirmed the stereochemical assignment of its precursor, epoxide **8**. Swern oxidation of **10** produced ketone **11** (71%). Reaction of **11** with methyl magnesium bromide in tetrahydrofuran gave paraherquamide A in 50% yield (based on recovered starting material) with formation of only a trace of the related α-methyl epimer. A similar transformation was reported by Blizzard et al.,[3a] in which 5-bromo-14-oxo-17-norparaherquamide A was treated with methyl magnesium iodide in predominantly methylene chloride giving rise to a 2:1 ratio of the α-methyl to *β*-methyl epimers. The reason for the differing facial selectivities is unclear. We suspect that in our case the higher polarity of tetrahydrofuran produces less aggregation of the Grignard reagent, permitting the magnesium ion to coordinate with both the target carbonyl of **11** and the adjacent amide carbonyl thereby directing attack to the *β*-face. The lower solvent polarity of methylene chloride used by Blizzard favors a higher degree of aggregation of the methyl magnesium bromide and lower reactivity which in turn favors attack from the less sterically hindered α-face. As the Grignard reagent becomes bulkier, the degree of aggregation falls off which may explain in part the mixed results Blizzard obtained with ethyl- and vinylmagnesium bromide. The product distribution observed by Blizzard in the case of very bulky benzylmagnesium chloride is consistent with this hypothesis. Semisynthetic paraherquamide A proved to be identical to the natural product obtained from Professor Yamazaki by comparison of the ^{1}H NMR, mobility on TLC, and HRMS spectra.

Experimental Section

General Information. ^{1}H and ^{13}C NMR spectra were recorded on either a 300 MHz or a 400 MHz NMR spectrometer. Column chromatography and flash column chromatography were performed with silica gel grade 60 (230−400 mesh). Preparatory thin layer chromatography (PTLC) was carried out with Kieselgel 60 F_{254} precoated glass plates; visualization was carried out with ultraviolet light and/or heating with a

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solution of 5−7% phosphomolybdic acid; or staining with I_2. All solvents were commercial grade and were distilled and dried as follows: tertrahydrofuran (THF) from potassium benzophenone ketyl; acetonitrile from P_2O_5. All other reagents were commercial grade and used without further purification.

12a-Cyano-17-bromo-17,*N*-seco-marcfortine A (1). Marcfortine A (477 mg, 1 mmol) was dissolved in chloroform (15 mL) and treated with CNBr (1.5 g, 14 mmol) at room temperature. The mixture was heated to reflux for 24 h. It was cooled, diluted with methylene chloride (50 mL), and washed with 10% aqueous K_2CO_3 solution (2 × 30 mL). After the mixture was dried ($MgSO_4$) and concentrated, the residue was purified by silica gel chromatography (15% acetone in methylene chloride) to give **1** as a white solid (467 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1.06 (s, 3H), 1.37 and 1.40 (2s, 6H), 1.4−2.0 (m, 9H), 2.71 (d, J = 15.8 Hz, 1H), 3.05 (s, 3H), 3.14 (t, 1H), 3.32 and 3.85 (d, J = 10.5 Hz, 2H), 3.41 (t, 2H, J = 6.7 Hz), 4.84 and 6.25 (d, J = 7.7 Hz, 2H), 6.64 and 6.75 (d, J = 8.2 Hz, 2H), 7.67 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 21.7, 23.3, 26.9, 27.3, 29.7, 29.8, 30.8, 32.6, 33.4, 36.2, 46.4, 52.6, 55.8, 62.1, 62.7, 62.8, 79.8, 114.5, 117.5, 120.1, 138.4, 146.3, 171.6, 183.2. MS (FAB): m/e 583 and 585 (M + H$^+$).

12a-Cyano-17-(phenylselenyl)-17,*N*-seco-marcfortine A (2). Diphenyl diselenide (225 mg, 0.72 mmol, 1.5 equiv) was suspended in methanol (15 mL) and solid sodium borohydride added in small amounts until the yellow color disappeared. Compound **1** (280 mg, 0.48 mmol) was added to the mixture at room temperature, and the mixture was stirred for 0.5 h. After the volatile components were removed, the residue was taken up in methylene chloride (50 mL) and washed with 10% aqueous K_2CO_3 solution (2 × 30 mL). The organic layer was dried ($MgSO_4$) and concentrated and the residue purified by silica gel chromatography (4% methanol in methylene chloride) to give **2** as a yellow solid (254 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 3H), 1.11 (s, 3H), 1.44 and 1.47 (2s, 6H), 1.5−2.0 (m, 9H), 2.76 (d, J = 15.8 Hz, 1H), 2.97 (t, 2H, J = 6.7 Hz), 3.10 (s, 3H), 3.18 (t, 1H), 3.42 and 3.90 (d, J = 10.54 Hz, 2H) , 4.91 and 6.32 (d, J = 7.7 Hz, 2H), 6.71 and 6.80 (d, J = 8.2 Hz, 2H), 7.1−7.5 (m, 5H), 7.59 (s, 1H).

12a-Cyano-16,17-anhydro-17,*N*-seco-marcfortine A (3). Compound **2** (1.6 g, 2.42 mmol) was dissolved in ethanol/methylene chloride (30 mL/5 mL). The solution was treated with an aqueous solution of sodium periodate (1.2 g in 10 mL of water) at room temperature and stirred for 0.5 h. The mixture was diluted with methylene chloride (50 mL) and washed with 10% aqueous K_2CO_3 solution (2 × 30 mL). The organic layer was dried ($MgSO_4$) and concentrated and the residue redissolved in benzene (50 mL). After the solution had been heated to reflux for 15 min, the mixture was diluted with ether (50 mL) and washed with 10% aqueous K_2CO_3 solution (2 × 30 mL). The organic layer was dried ($MgSO_4$) and concentrated and the residue purified by silica gel chromatography (0−30% acetone in methylene chloride) to give **3** as a white solid (973 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.13 (s, 3H), 1.44 (s, 6H), 1.7−2.4 (m, 9H), 2.77 (d, J = 15.8 Hz, 1H), 3.13 (s, 3H), 3.22 (t, J = 10.5 Hz, 1H), 3.42 and 3.92 (d, J = 10.6 Hz, 2H), 4.94 and 6.39 (d, J = 7.7 Hz, 2H), 5.10−5.20 and 5.7−5.9 (m, 3H), 6.71 and 6.82 (d, J = 8.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 23.3, 27.0, 27.1, 27.3, 29.7, 29.8, 31.0, 36.1, 46.4, 52.7, 55.8, 62.1, 62.8, 79.8, 114.8, 114.9, 115.2, 117.5, 120.1, 123.6, 132.6, 135.1, 137.4, 138.9, 146.3, 170.8, 182.5. MS (FAB): m/e 503 (M + H$^+$).

16,17-Anhydro-17,*N*-seco-marcfortine A (4). Compound **3** (120 mg, 0.24 mmol) was suspended in ethylene glycol (1 mL). The mixture was treated with NaOH (38 mg, 0.95 mmol, 4 equiv) and heated to 130 °C for 15 min. It was diluted with methylene chloride (50 mL) and washed with 10% aqueous K_2CO_3 solution (2 × 30 mL). The organic layer was dried ($MgSO_4$) and concentrated and the residue purified by silica gel chromatography (5% methanol in methylene chloride) to give **4** as a solid (57 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.13 (s, 3H), 1.44 and 1.45 (2s, 6H), 1.6−2.4 (m, 9H), 2.72 (d, J = 15.6 Hz, 1H), 2.94 and 3.44 (d, J = 11.6 Hz, 2H), 3.08 (t, 1H), 3.11 (s, 3H), 4.91 and 6.35 (d, J = 7.7 Hz, 2H), 4.9−5.2 and 5.8−6.0 (m, 3H), 6.68 and 6.82 (d, J = 8.2 Hz, 2H), 8.27 (s, 1H). MS (FAB): m/e 478 (M + H$^+$).

16,17-Dihydroxy-17,*N*-seco-marcfortine A (5). Compound **4** (24 mg, 0.05 mmol) and 4-methylmorpholine *N*-oxide (20 mg, 0.17 mmol) were dissolved in acetone/water (9:1, 6 mL). The mixture was treated with OsO_4 (24 μL, 2.5% wt in *tert*-butyl alcohol, obtained from Aldrich) and stirred at room temperature for 16 h. It was diluted with in methylene chloride (50 mL) and washed with 10% aqueous K_2CO_3 solution (2 × 30 mL). The organic layer was dried ($MgSO_4$) and concentrated and the residue purified by preparative layer chromatography (10% methanol in methylene chloride) to give **5** (mixture of diastereomer) as a solid (17 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.12 (s, 3H), 1.44 and 1.45 (2s, 6H), 1.6−3.9 (m, 20H), 4.91 and 6.35 (d, J = 7.7 Hz, 2H), 6.68 and 6.82 (d, J = 8.2 Hz, 2H), 8.36 and 8.39 (2s, 1H). MS (FAB): m/e 512 (M + H$^+$).

Paraherquamide B. Compound **5** (10 mg, 0.02 mmol) was dissolved in ethanol (3 mL) and treated with sodium periodate (0.4 mL of 20 mg/mL aqueous solution) and stirred at 0 °C for 20 min. Sodium borohydride (5 mg) was added to the mixture, which was stirred for an additional 10 min at 0 °C. The mixture was taken up in methylene chloride (20 mL) and washed with 10% aqueous K_2CO_3 solution (2 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated and the residue purified by preparative layer chromatography (7% methanol in methylene chloride) to give paraherquamide B as a solid (5 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.13 (s, 3H), 1.44 and 1.45 (2s, 6H), 1.4−2.8 (m, 10H), 2.65 and 3.65 (d, J = 10.9 Hz, 2H), 3.0−3.2 (m, 4H), 4.89 and 6.32 (d, J = 7.7 Hz, 2H), 6.68 and 6.82 (d, J = 8.2 Hz, 2H), 7.69 (s, 1H). MS (FAB): m/e 464 (M + H$^+$). HRMS (FAB): m/e, 464.2577 ($C_{27}H_{33}N_3O_4$ + H$^+$ requires 464.2549).

16-Oxoparaherquamide B (6). To paraherquamide B (4 mg, 0.0086 mmol) and sodium bicarbonate (10 mg, 0.12 mmol) in tetrahydrofuran (THF, 1.5 mL) and H_2O (0.5 mL) was added I_2 (16 mg, 0.06 mmol) dropwise in THF (1 mL) at ambient temperature. After 1 h of stirring, the reaction was quenched with a saturated aqueous solution of sodium thiosulfate ($Na_2S_2O_3$, 10 mL) and extracted into methylene chloride (CH_2Cl_2, 25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give residue that was purified on silica gel (40% acetone/hexane) to give **6** (1.6 mg, 40%) and 12-oxoparaherquamide B (1 mg, 25%) both as white solids. Compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.10 (s, 3H), 1.43 and 1.46 (2s, 6H), 1.75−2.10 (m, 3H), 2.0 and 2.85 (d, 2H), 2.48−2.55 (m, 1H), 2.88−3.0 (m, 1H), 3.08 (s, 3H), 3.28 (t, 1H), 3.48 and 3.74 (d, 2H), 4.90 and 6.30 (d, J = 7.7 Hz, 2H), 6.60 and 6.80 (d, 2H), 7.27 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 23.5, 23.7, 27.2, 29.8, 29.9, 30.0, 31.1, 36.7, 46.2, 49.0, 53.4, 63.1, 64.9, 65.0, 79.9, 115.2, 117.7, 120.3, 124.3, 132.4, 135.4, 138.9, 146.3, 171.3, 173.4, 182.4. HRMS (FAB): m/e 478.2384 ($C_{27}H_{31}N_3O_5$ + H requires 478.2342).

12-Oxoparaherquamide B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 and 0.83 (s, 6H), 1.46 and 1.44 (s, 6H), 1.95−1.60 (m, 2H), 2.11−1.95 (m, 2H), 2.87 (m, 1H), 3.02 (s, 3H), 3.11 (d, 1H), 3.27 and 2.53 (d, J = 15.2 Hz, 2H), 3.70−3.39 (m, 3H), 4.89 and 6.31 (d, J = 7.7 Hz, 2H), 6.70 and 7.03 (d, J = 8.2 Hz, 2H), 7.35 (s, 1H). HRMS (FAB): m/e 478.2356 (C_{27} $H_{31}N_3O_5$ + H requires 478.2342).

14,15-Dehydro-16-oxoparaherquamide B (7). A solution of lithium diisopropylamide prepared from *n*-butyllithium (1.6 M, 0.6 mL, 0.98 mmol) and diisopropylamine (0.14 mL, 1.0 mmol), in THF (8 mL), was cooled to −78 °C and treated dropwise with **6** (0.12 g, 0.25 mmol) in THF (4 mL). The reaction slowly warmed to −5 °C over a 0.5 h period and was then recooled to −78 °C and treated dropwise with phenylselenyl chloride (0.06 g, 0.3 mmol) in THF (3 mL). This caused the turbid solution to clear. The reaction mixture was quenched 5 min later with saturated $NaHCO_3$ (10 mL) and extracted into CH_2Cl_2 (25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give residue that was diluted with THF (15 mL) and treated with H_2O_2 (30%, 0.1 mL). The reaction mixture was stirred for 0.5 h at ambient temperature and then quenched with NaOH (1 N, 15 mL) and extracted into CH_2Cl_2 (25 mL). The organic layer was dried

($MgSO_4$), filtered, and concentrated to give residue that was subjected to silica gel chromatography to yield **7** (0.07 g, 58%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 and 1.07 (2s, 6H), 1.45 and 1.47 (2s, 6H), 1.56 and 2.36 (dd, 2H), 2.09 and 2.85 (d, J = 15.7 Hz, 2H), 3.09 (s, 3H), 3.36 (t, 1H), 3.60 and 3.95 (d, J = 11.9 Hz, 2H), 4.91 and 6.32 (d, 2H), 6.25 and 7.36 (d, 2H, J = 9.1 Hz), 6.71 and 6.81 (d, 2H), 7.78 (brs, NH). HRMS (FAB): m/e 476.2195 (C_{27} $H_{29}N_3O_5$ + H requires 476.2185).

14α,15α-Epoxy-16-oxoparaherquamide B (8). Triton B (benzyltrimethylammonium hydroxide, 40 wt % in methanol, 0.7 mL, 1.6 mmol) was evaporated to dryness under vacuum to remove all MeOH. It was then diluted with THF (10 mL) and treated with *tert*-butyl hydroperoxide (anhydrous, 5−6 M in decane, 0.4 mL, 2.4 mmol) followed by addition of **7** (0.17 g, 0.3 mmol) in THF (3 mL) 5 min later. The reaction mixture was stirred for 2 h at room temperature and then quenched with water (25 mL) and extracted into EtOAc (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a residue that was subjected to silica gel chromatography to yield **8** (0.1 g, 58%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 and 1.06 (2s, 6H), 1.44 and 1.46 (2s, 6H), 1.91 and 2.18 (dd, 2H), 2.00 and 2.83 (d, J = 15.7 Hz, 2H), 3.08 (s, 3H), 3.34 (t, 1H), 3.52 and 3.66 (d, 2H), 3.70 and 4.41 (d, J = 2.9 Hz, 2H), 4.91 and 6.31 (d, J = 7.7 Hz, 2H), 6.71 and 6.78 (d, J = 8.2 Hz, 2H), 7.52 (s, NH). HRMS (FAB): m/e 492.2145 (C_{27} $H_{29}N_3O_6$ + H requires 492.2134).

14α-Hydroxy-16-oxoparaherquamide B (9). To a solution of **8** (20 mg, 0.04 mmol) in THF (3 mL) and MeOH (0.5 mL) at 0 °C under N_2 was added samarium(II) iodide (0.1 M in THF, 2 mL, 0.24 mmol) dropwise until a green color persisted in the reaction mixture. The reaction was then quenched with saturated K_2CO_3 (15 mL) and extracted into CH_2Cl_2 (25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give **9** (18 mg, 85%) as a white solid without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 and 1.06 (2s, 6H), 1.45 and 1.47 (2s, 6H), 1.90−2.11 (m, 2H), 2.49−2.61 (m, 2H), 2.04 and 2.80 (d, J = 15.7 Hz, 2H), 2.91 (dd, 1H), 3.08 (s, 3H), 3.30 (t, 1H), 3.50 and 3.80 (d, J = 12.0 Hz, 2H), 4.91 and 6.32 (d, J = 7.7 Hz, 2H), 5.10 (m, 1H), 6.72 and 6.81 (d, J = 8.2 Hz, 2H), 7.78 (s, NH).

14α-Hydroxyparaherquamide B (10). To a solution of LAH (1 M in THF, 0.36 mL, 0.36 mmol) in THF (6 mL) at −60 °C under N_2 was added $AlCl_3$ (24 mg, 0.18 mmol) in three portions. Compound **9** (30 mg, 0.06 mmol) was added 10 min later at −45 °C dropwise in THF (3 mL). The reaction was allowed to warm to −15 °C over a 20 min period and quenched with dropwise addition of MeOH (1 mL). The mixture was stirred at room temperature for 15 min and then treated with $NaCNBH_3$ (60 mg) and partitioned between water (25 mL) and CH_2Cl_2 (30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a residue that was purified by silica gel chromatography (5% MeOH/CH_2Cl_2) to give **10** (7 mg, 24%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 and 1.13 (2s, 6H), 1.44 and 1.45 (2s, 6H), 1.6−2.3 (m, 7H), 2.48 (m, 1H), 2.64 (d, 1H), 2.70 (d, 1H), 3.09 (s, 3H), 3.21 (t, 1H), 3.65 (d, 1H), 4.75 (brs, 1H), 4.90 and 6.32 (d, J = 7.7 Hz, 2H), 6.68 and 6.82 (d, J = 8.2 Hz, 2H), 7.81 (s, NH). HRMS (FAB): m/e 480.2512 (C_{27} $H_{33}N_3O_5$ + H requires 480.2498).

14-Oxoparaherquamide B (11). To oxalyl chloride (0.006 mL, 0.084 mmol) in CH_2Cl_2 (4 mL) at −78 °C under N_2 was added DMSO (0.25 mL, 3.5 mmol) dropwise in CH_2Cl_2 (4 mL). The reaction was stirred for 10 min and then treated with a solution of **10** (7 mg, 0.014 mmol) dropwise in CH_2Cl_2 (2 mL). Following 10 min of stirring at −78 °C the reaction was quenched with NEt_3 (0.015 mL, 0.1 mmol) and then stirred for 5 min at ambient temperature. The reaction was partitioned between H_2O (15 mL) and CH_2Cl_2 (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a residue that was purified by silica gel chromatography (5% MeOH/CH_2Cl_2) to give **11** (5 mg, 71%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 and 0.89 (2s, 6H), 1.45 and 1.46 (2s, 6H), 1.90 (d, 1H), 2.21 (d, 1H), 2.42−2.75 (m, 5H), 3.09 (s, 3H), 3.18 (t, 1H), 3.38 (t, 1H), 3.75 (d, 1H), 4.90 and 6.32 (d, J = 7.7 Hz, 2H), 6.69 and 6.82 (d, J = 8.2 Hz, 2H), 7.56 (s, NH). HRMS (FAB): m/e 478.2356 (C_{27} $H_{31}N_3O_5$ + H requires 478.2342).

Paraherquamide A. To a solution of **11** (5 mg, 0.01 mmol) in THF (4 mL) at −78 °C under a nitrogen atmosphere was added MeMgBr (3 M in ether, 0.03 mL, 0.09 mmol). The reaction mixture was allowed to slowly warm to −20 °C over a 40 min period. The reaction was quenched with saturated NH_4Cl (15 mL) and extracted into CH_2Cl_2 (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give residue that was purified by silica gel chromatography (4% MeOH/CH_2Cl_2) to give paraherquamide A (2 mg, 50% based on recovery of **11**) as a white solid which was identical to an authentic sample obtained by Professor Yamazaki on TLC (R_f 0.23 in 4% MeOH/CH_2Cl_2, R_f 0.34 in 30% acetone/CH_2Cl_2) and ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 and 1.11 (2s, 6H), 1.45 and 1.46 (2s, 6H), 1.66 (s, 3H), 1.78−1.95 (m, 4H), 2.15−2.41 (m, 2H), 2.57 (d, 1H), 2.70 (d, 1H), 3.00 (d, 1H), 3.06 (s, 3H), 3.21 (m, 1H), 3.61 (d, 1H), 4.89 and 6.31 (d, J = 7.6 Hz, 2H), 6.69 and 6.81 (d, J = 8.2 Hz, 2H), 7.56 (s, NH). HRMS (FAB): m/e 494.2653 (C_{28} $H_{35}N_3O_5$ + H requires 494.2655).

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Supporting Information Available: NMR spectra of new compounds (14 pages). This material is contained in 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.

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