Conversion of Marcfortine A to Paraherquamides *via* a Novel Platinum−Oxygen-Mediated Ring Contracting Reaction

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The paraherquamides and marcfortines represent a novel class of anthelmintics. The sole structural difference between marcfortine A (**1**) and paraherquamide A (**5**) occurs in ring G. By employing a ring contracting reaction utilizing platinum and oxygen (Pt/O_2) at a key point in the synthesis, we were able to directly convert marcfortine A to the intermediate 16-oxoparherquamide B (**2**), thereby eliminating six steps in our earlier synthesis. Paraherquamide A was also prepared from 14α-hydroxymarcfortine A (**3**) and 14α-hydroxy-14*β*-methylmarcfortine A (**6**) using Pt/O_2 chemistry. Additionally, parahequamide derivative **20** was synthesized from marcfortine A derivative **16**.

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 (**1**), paraherquamide A (**5**), 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 (**5**) were described by Williams et al.[5] We have utilized paraherquamide B for the first formal synthesis of paraherquamide A.[6] 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.[7a] Marcfortine A, reported by Polonsky et al.,[7b] 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.

Our earlier conversion of marcfortine A (**1**) to paraherquamide A (**5**) required 13 steps.[6] By employing a ring contracting reaction utilizing platinum and oxygen (Pt/O_2) at a key point in the synthesis, we were able to directly convert marcfortine A to the intermediate 16-oxoparaherquamide B (**2**), thereby eliminating six steps in our earlier synthesis. Paraherquamide A was also prepared from **3** and **6** using Pt/O_2 (Scheme 1).

Although the Pt/O_2 reaction has been used for oxidation of primary and secondary alcohols,[8] hydroxylation of 12a-deoxytetracyclines,[9] oxygenation of cholesterol,[10] and oxidation of tertiary amines,[3e] this reaction has not been used extensively compared to singlet oxygen reactions.[11]

When marcfortine A was treated with Pt on carbon (10%) in dioxane/water under an oxygen atmosphere (balloon pressure, room temperature, 2−4 days), four products (**2**, **8**−**10**) were isolated (Scheme 2). The reaction was not accelerated by heating. Performing the reaction under oxygen at 1000 psi resulted in acceleration with very little effect on the product ratios. Yields varied depending on the activity of the platinum.

Dioxo compound **8** was converted to **2** in 80% yield by treatment with *m*-chloroperbenzoic acid (*m*-CPBA). According to the literature, six-membered rings containing a 1,2-dicarbonyl moiety are converted to five-membered ring hydroxy acids only in the presence of a strong base.[12] By contrast, our method is performed under neutral conditions and is more efficient. A plausible mechanism, possibly operative in Pt/O_2 chemistry (*vide infra*), is shown in Scheme 3.

Subsequently, we examined several marcfortine A derivatives as substrates for the Pt/O_2 reaction. When

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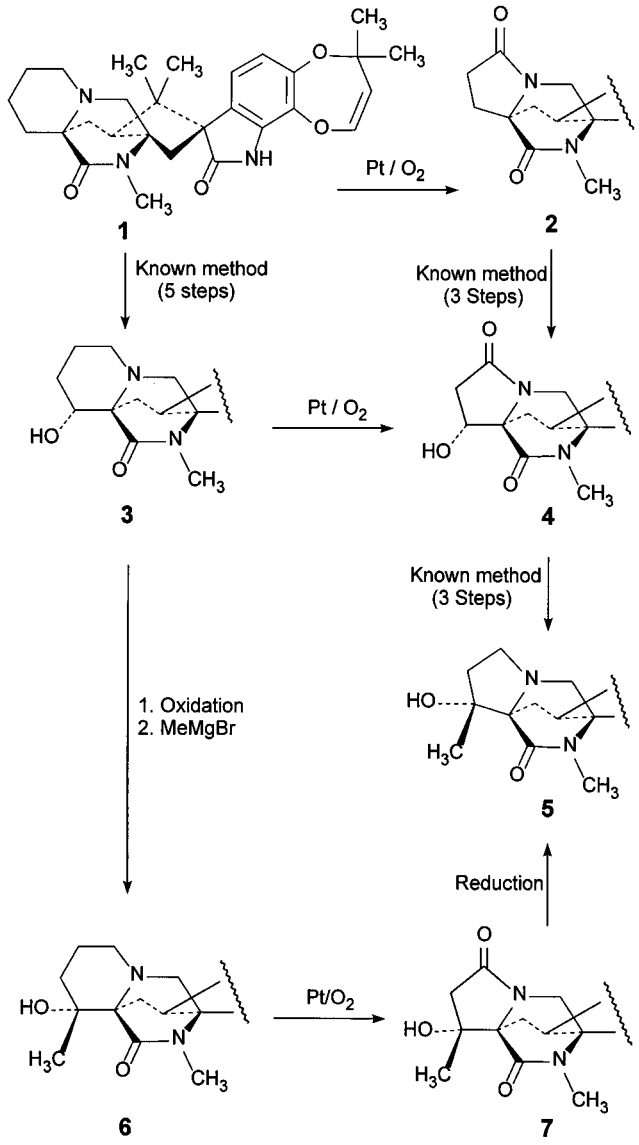
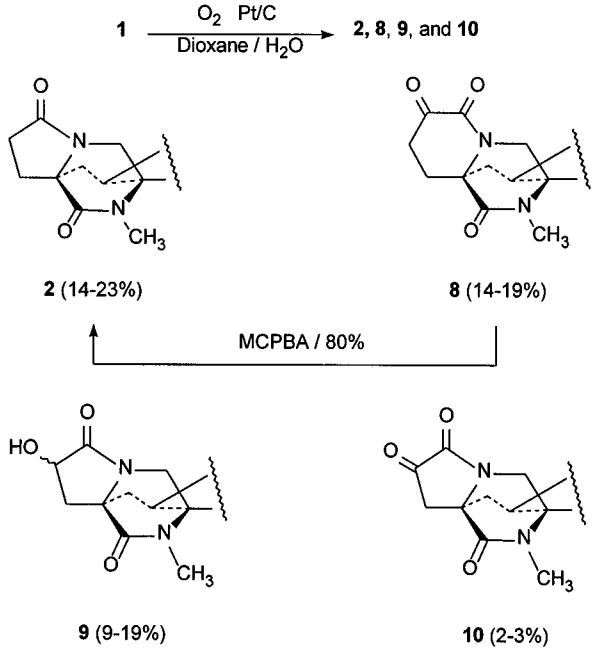
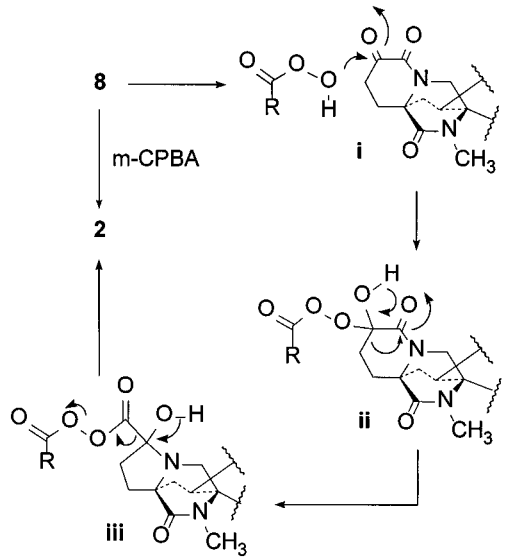
Scheme 1



Scheme 2



Scheme 3



6 was subjected to Pt/O_2 chemistry, three products (**7**, **12**, and **13**) were isolated in poor yield (Scheme 4). In the case of **3**, the Pt/O_2 reaction mixture was treated straightaway with *m*-CPBA without isolation of any intermediate products, giving the desired compound **4** (43% yield). Compound **4** can be converted to paraherquamide A (**5**) in three steps.[6] Compound **7** was converted to paraherquamide A (**5**) by treatment with alane−dimethylethyl amine complex in THF (30% yield).

The conjugate addition of lithium dimethylcopper to **14**[13] gave **15** in 60% yield (Scheme 5). The metal ion may coordinate with the hydroxyl group[14] so that addition of the methyl group takes place on the face of the ring where the hydroxyl group resides. Subsequent treatment of **15** with borane−dimethyl sulfide complex in THF gave **16** (50% yield). When **16** was subjected to Pt/O_2 chemistry, four products (**15**, **17**−**19**) were isolated.

Although the Pt/O_2 chemistry performed on **16** does give **19** (the desired product) in trace amounts, it can be more readily prepared by oxidation of **18** with *m*-CPBA (80% yield). Subsequently, **19** was reduced with LAH/$AlCl_3$ in THF to give **20** (40% yield).

A plausible mechanism for the Pt/O_2-mediated ring contracting reaction is shown in Scheme 6. In this mechanism, **A** exists in equilibrium with **B** (one can speculate about the formation of **A**). Intermediate **B** undergoes molecular oxidation accompanied by partial allylic hydroxylation to give intermediates **C** and **D**. Each of these is further oxidized to give putative intermediate **E** and product **8**. A final oxidative step, probably involving hydrogen peroxide generated *in situ* and proceeding by a mechanism paralleling that described for the *m*-CPBA reaction (Scheme 3), leads to products **2**, **9**, and **10**.

In conclusion, we have demonstrated the utility of a novel Pt/O_2-mediated ring contracting reaction in the conversion of marcfortines to paraherquamides.

Experimental Section

General Information. ^1H NMR spectra were recorded on either a 300 or 400 MHz and ^{13}C NMR spectra were recorded on either a 75 or 100 MHz NMR spectrometer. Column

(13) Lee, B. H.; Clothier, M. F. *J. Org. Chem.* **1997**, *62*, 1863.
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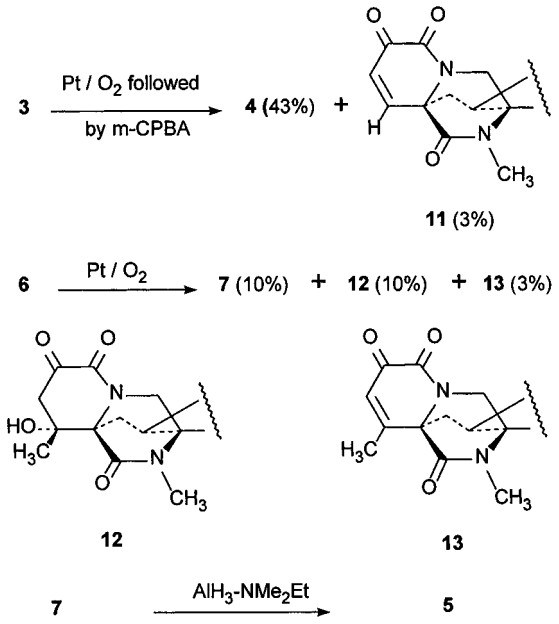
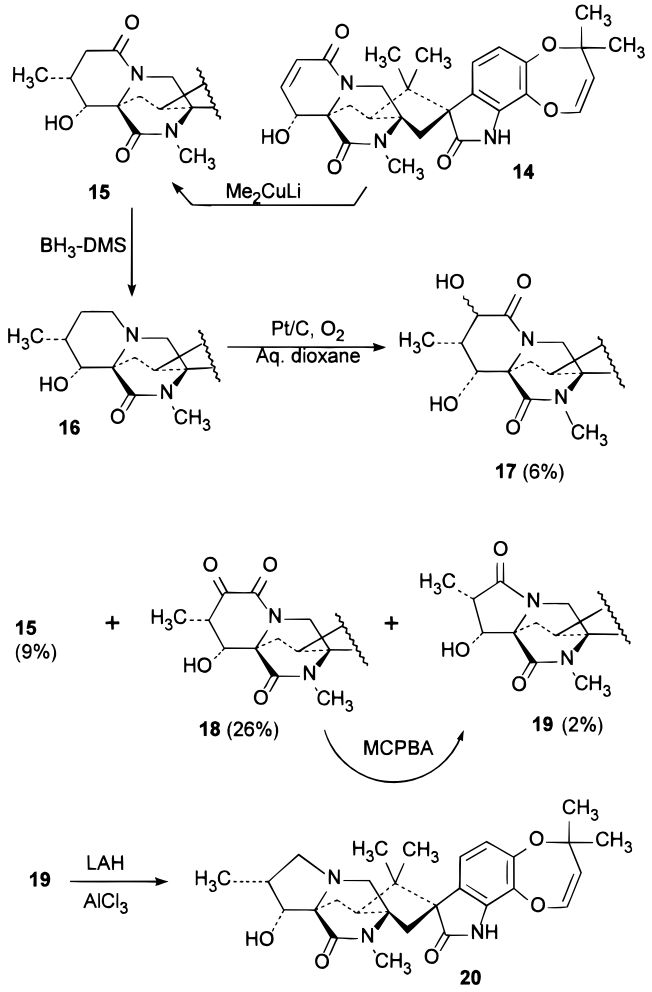
Scheme 4

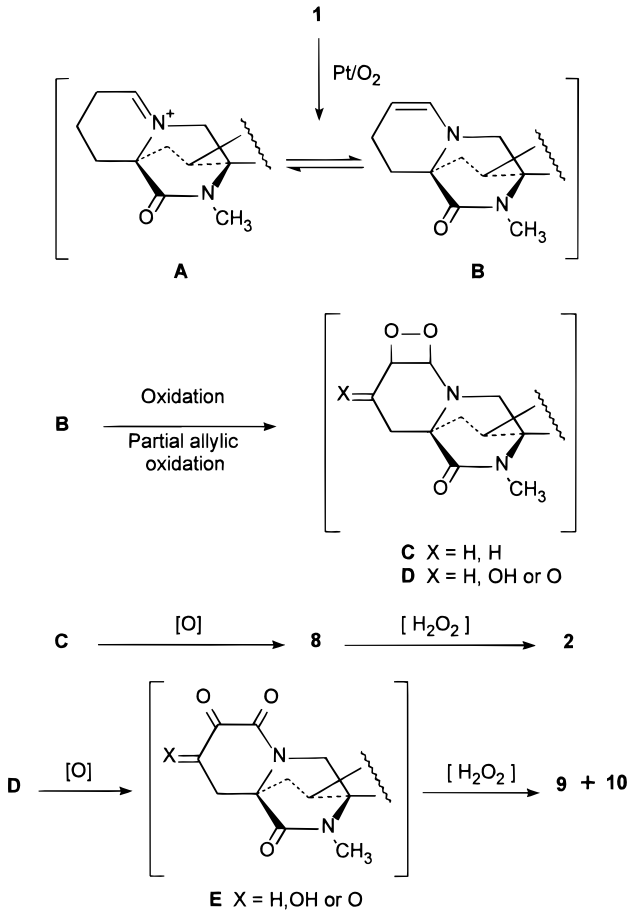


Scheme 5



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 solution of 5−7% phosphomolybdic acid, or staining with I_2. All solvents and reagents were commercial grade and used without further purification.

Scheme 6



The Pt/O_2-Mediated Ring Contracting Reaction with 1. Marcfortine A (**1**, 1.1 g, 2.3 mmol) was dissolved in dioxane/water (3/1, 150 mL) and treated with Pt/C (10%, 10 g). The resulting mixture was stirred under an O_2 atmosphere (oxygen balloon) at 20−25 °C for 48−96 h. The insoluble materials were filtered off, and the resulting mixture was partitioned between CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a residue. The residue was chromatographed (silica gel; acetone/ CH_2Cl_2, 30/70) to give four products as solids.

16,17-Dioxomarcfortine A (8): 160−220 mg, 14−19% yield, as a solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 6.81 and 6.71 (d, J = 8.2 Hz, 2H), 6.34 and 4.92 (d, J = 7.7 Hz, 2H), 3.92 and 3.81 (d, J = 13.5 Hz, 2H), 3.40−3.30 (m, 2H), 3.12 (s, 3H), 3.11−3.00 (m, 1H), 2.98−2.85 (m, 1H), 2.89−2.75 (m, 2H), 2.20−1.60 (m, 3H), 1.45 and 1.44 (s, 6H), 1.11 and 0.88 (s, 6H); HRMS (EI) m/z 505.2235 ($C_{28}H_{31}N_3O_6$ requires 505.2213).

16-Oxoparaherquamide B (2) was identical to the previously synthesized material[6] on the basis of ^{1} H NMR and TLC.

15-Hydroxy-16-oxoparaherquamide B (9): 100−216 mg, 9−19% yield, as a solid; ^{1}H NMR is complicated by the diastereomers; HRMS (FAB) m/z 494.2292 ($C_{27}H_{31}N_3O_6$ + H requires 494.2291).

15,16-Dioxoparaherquamide B (10): 23−34 mg, 9−19% yield, as a solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.82 and 6.74 (d, J = 8.2 Hz, 2H), 6.33 and 4.92 (d, J = 7.7 Hz, 2H), 4.11 (d, 1H), 3.81 (d, 1H), 3.78 and 2.50 (d, J = 20.1 Hz, 2H), 3.45 (t, 1H), 3.15 (s, 3H), 2.89 and 1.91 (d, J = 15.8 Hz, 2H), 2.50 (d, 2H), 2.18 (dd, 1H), 1.93 (dd, 1H), 1.47 and 1.45 (s, 6H), 1.11 and 0.90 (s, 6H); HRMS (FAB) m/z 492.2141 ($C_{27}H_{29}N_3O_6$ + H requires 492.2134).

Reaction of 8 with *m*-CPBA. Compound **8** (25 mg, 0.05 m mol) was dissolved in CH_2Cl_2 (5 mL) and treated with *m*-CPBA (65% pure, 30 mg). The resulting mixture was stirred at 20−25 °C for 1.5 h. The mixture was partitioned between

CH_2Cl_2 (20 mL) and K_2CO_3 (10%, aqueous solution, 20 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel eluting with methanol/CH_2Cl_2 (5/95) to give **2** as a solid (20 mg, 80%). This material was identical to the previously synthesized material[6] on the basis of TLC and ^{1}H NMR.

The Pt/O_2-Mediated Ring Contracting Reaction with 3. 14α-Hydroxymarcfortine A (**3**, 100 mg, 0.2 mmol) was dissolved in dioxane/water (3/1, 20 mL) and treated with Pt/C (10%, 1 g). The resulting mixture was placed under oxygen (using a balloon) and stirred for 48−96 h at 20−25 °C. The insoluble materials were removed by filtration, and the filtrate was partitioned between $NaHCO_3$ (10% aqueous solution, 20 mL) and CH_2Cl_2 (20 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was redissolved in CH_2Cl_2 (5 mL) and treated with *m*-CPBA (65% pure, 30 mg). The resulting mixture was stirred at 20−25 °C for 1.5 h. The mixture was partitioned between CH_2Cl_2 (20 mL) and KCO_3 (10% aqueous solution, 20 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel eluting with methanol/CH_2Cl_2 (5/95) to give two products.

14α-Hydroxy-16-oxoparaherquamide B (4): 45 mg, 43% yield, as a solid. This material was identical to the previously synthesized material[6] on the basis of TLC and ^{1}H NMR.

14,15-Dehydro-16,17-dioxomarcfortine A (11): 4 mg, 3% yield, as a solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, NH), 7.47 and 6.64 (d, J = 10.5 Hz, 2H), 6.84 and 6.73 (d, J = 8.2 Hz, 2H), 6.32 and 4.91 (d, J = 7.7 Hz, 2H), 4.10 and 3.91 (d, J = 13.8 Hz, 2H), 3.49 (t, 1H), 3.13 (s, 3H), 2.86 and 2.18 (d, J =15.8 Hz, 2H), 2.40 and 1.87 (dd, 2H), 1.47 and 1.46 (2s, 6H), 1.10 (s, 3H), 0.90 (s, 3H); MS (FAB) m/z 504 (M^+ + H).

Synthesis of 6 from 14-Oxomarcfortine A. 14-Oxomarcfortine A[13] (0.87 g, 1.77 mmol) was dissolved in THF (150 mL) and cooled to 0 °C in an ice−water bath. A solution of methylmagnesium bromide (3 M, 8.9 mL, 26.6 mmol) was added in a rapid, dropwise fashion. The cooling bath was removed and the reaction mixture stirred at rt for 40 min. The reaction mixture was cooled to −5 °C and the reaction quenched by adding a saturated NH_4Cl solution (2 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL). The extracts were combined, washed in turn with water and saturated NaCl, and dried over Na_2SO_4. Filtration to remove the solid and concentration of the filtrate gave a yellow glass and solid. This was purified by silica gel chromatography to give **6** (0.417 g, 46%) as a solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (br s, NH), 6.80 and 6.66 (d, 2H), 6.30 and 4.89 (d, 2H), 3.65 (d, 1H), 3.09 (s, NCH_3), 2.95 (t, 1H), 2.69 and 1.85 (d, 2H), 1.47 (s, 3H), 1.45 and 1.44 (s, 6H), 1.08 (s, 3H), 0.85 (s, 3H); HRMS (FAB) m/z 508.2816 ($C_{29}H_{37}N_3O_5$ + H requires 508.2811).

The Pt/O_2-Mediated Ring Contracting Reaction with 6. Compound **6** (100 mg, 0.2 mmol) was dissolved in dioxane/water (3/1, 20 mL) and treated with Pt/C (10%, 1 g). The resulting mixture was placed under oxygen (using a balloon) and stirred for 48−96 h at 20−25 °C. After the insoluble materials were filtered off the filtrate was partitioned between $NaHCO_3$ (10% aqueous solution) and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel eluting with methanol/CH_2Cl_2 (5/95) to give three products.

14α-Hydroxy-16,17-dioxo-14β-methylmarcfortine A (12): 11 mg, 10% yield, as a solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 and 6.67 (d, J = 8.2 Hz, 2H), 6.28 and 4.85 (d, J = 7.7 Hz, 2H), 3.80 and 3.71 (d, J = 13.4 Hz, 2H), 3.54 (d, 1H), 3.36 (d, 1H), 3.19 (t, 1H), 2.76 (s, 3H), 2.22−2.10 (m, 2H), 1.67 (s, 3H), 1.42 and 1.39 (s, 6H), 1.09 and 0.85 (s, 6H); HRMS (FAB) m/z 536.2392 ($C_{29}H_{33}N_3O_7$ + H requires 536.2397).

14α-Hydroxy-16-oxo-14β-methylparaherquamide B (7): 11 mg, 10% yield, as a solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.0 (s, 1H), 6.85 and 6.70 (d, 2H), 6.35 and 4.91 (d, 2H), 3.65 and 3.53 (d, 2H), 3.27 (t, 1H), 3.02 (s, 3H), 2.85−2.70 (m, 2H), 2.55 (d, 1H), 2.30−1.65 (m, 4H), 1.82 (s, 3H), 1.44 and 1.42 (s, 6H), 1.09 and 0.87 (s, 6H); HRMS (FAB) m/z 508.2463 ($C_{28}H_{33}N_3O_6$ + H requires 508.2447).

14-Methyl-14,15-dehydro-17-oxomarcfortine A (13): 4 mg, 3% yield, as a solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 6.82 and 6.74 (d, J = 8.2 Hz, 2H), 6.32 and 4.92 (d, J = 7.7 Hz, 2H), 4.05 and 3.91 (d, J = 13.7 Hz, 2H), 3.55−3.45 (m, 1H), 3.12 (s, 3H), 2.86 and 2.19 (d, J = 15.8 Hz, 2H), 2.60−2.50 (m, 2H), 2.37 (s, 3H), 2.0−1.55 (m, 4H), 1.47 and 1.45 (s, 6H), 1.11 and 0.93 (s, 6H). HRMS (FAB): m/z 518.2277 ($C_{29}H_{31}N_3O_6$ + H requires 518.2281).

Conversion of 7 to Paraherquamide A. Compound **7** (50 mg, 0.1 mmol) was dissolved in THF (6 mL) at 0 °C under N_2 and treated with alane−*N*,*N*-dimethylethylamine complex (Aldrich, 0.8 mL, 0.5 M solution in toluene, 0.4 mmol). The mixture was stirred at 0 °C for 1 h and quenched by the dropwise addition of methanol (1 mL). After 30 min the mixture was concentrated. The residue was 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% methanol/CH_2Cl_2) to give paraherquamide A (**5**, 12 mg, 30% yield based on starting material recovery) as a white solid which was identical to the previously synthesized material[6] based on TLC (R_f 0.23 in 4% methanol/CH_2Cl_2) and ^{1}H NMR. HRMS (FAB): m/z 494.2671 (C_{28} $H_{35}N_3O_5$ + H requires 494.2655).

Synthesis of 14α-Hydroxy-15α-methyl-17-oxomarcfortine A (15). Copper iodide (800 mg, 4 mmol) was suspended in THF (100 mL) and treated with a solution of MeLi (1.4 M, 20 mL, 28 mmol) at 0 °C. The mixture was stirred for 10 min, and then **14**[13] (1 g, 2 mmol) in THF (15 mL) was added to the mixture. The resulting mixture was stirred for an additional 15 min and then quenched with a saturated aqueous NH_4Cl solution (20 mL). It was diluted with CH_2Cl_2 (150 mL) and the organic layer dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (Chromatotron, 4 mm plate, 4% methanol in CH_2Cl_2) to give **15** (0.6 g, 60%) as a solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H, NH), 6.80 and 6.71 (d, J = 8.2 Hz, 2H), 6.32 and 4.91 (d, J = 7.7 Hz, 2H), 4.35 (m, 1H), 3.65 (s, 2H) 3.20 (t, 1H, J = 10.5 Hz), 3.06 (s, 3H), 2.79 and 2.09 (d, J = 15.8 Hz, 2H), 2.5−1.9 (m, 5H), 1.46 and 1.44 (2s, 6H), 1.13 (d, 3H), 1.12 (s, 3H), 0.88 (s, 3H); selected ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.3, 27.4, 34.1, 37.2, 51.0, 53.0, 69.8, 80.2, 115.6, 118.0, 120.8, 124.6, 132.6, 135.7, 139.3, 146.6, 169.7, 171.4, 182.3; MS (FAB) m/z 522 [M + H].

Synthesis of 16. Compound **15** (90 mg, 0.18 mmol) was dissolved in THF (10 mL) and treated with a solution of borane−dimethyl sulfide complex (12 M, 0.15 mL, 1.8 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C and then quenched with methanol (0.4 mL) and stirred for an additional 0.5 h at rt. The solvent was evaporated, and the residue was subjected to silica gel chromatography (30% acetone in CH_2Cl_2) to give **16** (45 mg, 50% yield) as a solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 6.79 and 6.70 (d, J = 8.2 Hz, 2H), 6.40 and 4.91 (d, J = 7.7 Hz, 2H), 3.81 (br s, 1H), 3.68 (d, J = 11.8 Hz, 1H), 3.11 (s, 3H,), 3.03 (t, J = 10.2 Hz, 1H), 2.68 and 1.87 (d, J = 15.6 Hz, 2H), 2.62 (dt, 1H), 2.5−2.3 (m, 3H), 1.99 and 1.71 (dd, J = 10.2, 13.2 Hz, 2H), 1.6−1.2 (m, 2H), 1.44 (s, 6H), 1.11 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.85 (s, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 18.1, 20.9, 24.1, 26.7, 28.2, 28.7, 30.2, 30.3, 31.4, 37.3, 47.0, 53.1, 54.9, 61.0, 63.5, 64.8, 64.8, 72.6, 80.2, 115.4, 117.6, 120.7, 125.1, 132.9, 135.6, 139.4, 146.5, 174.0, 183.9; HRMS (FAB) m/z 508.2840 ($C_{29}H_{37}N_3O_5$ + H requires 508.2811).

The Pt/O_2-Mediated Ring Contracting Reaction with 16. Compound **16** (100 mg, 0.2 mmol) was dissolved in dioxane/water (3/1, 20 mL) and treated with Pt/C (10%, 1 g). The resulting mixture was placed under oxygen (using a balloon) and stirred for 48 h at 20−25 °C. The insoluble materials were filtered off, and the filtrate was partitioned between aqueous $NaHCO_3$ (10%) and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel eluting with methanol/ CH_2Cl_2 (5/95) to give four products.

14α-Hydroxy-16,17-dioxo-15α-methylmarcfortine A (18): 28 mg, 26% yield, as a solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.31 (d, J = 7.7 Hz, 1H), 4.90 (d, J = 7.7 Hz, 1H), 4.53 (d, J = 2.1 Hz, 1H), 3.90 (d, J = 12.0 Hz, 1H), 3.75 (d, J = 12.0

Hz, 1H), 3.26 (t, J = 10.2 Hz, 1H), 3.09 (s, 3H), 2.80 (d, J = 15.9 Hz, 1H), 2.3−1.9 (m, 4H), 1.45 and 1.43 (2s, 6H), 1.31 (d, J = 6.6 Hz, 3H), 1.12 (s, 3H), 0.88 (s, 3H); HRMS (FAB) m/z 536.2392 ($C_{29}H_{33}N_3O_7$ + H requires 536.2397).

14α-Hydroxy-16-oxo-15α-methylparaherquamide B (19): 3 mg, 2% yield, as a solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.32 (d, J = 7.7 Hz, 1H), 4.91 (d, J = 7.7 Hz, 1H), 5.0−4.9 (m, 1H), 3.73 (d, J = 12.0 Hz, 1H), 3.52 (d, J = 12.0 Hz 1H), 3.28 (t, J = 9.2 Hz, 1H), 3.06 (s, 3H), 2.9−2.7 (m, 2H), 2.2−1.9 (m, 4H), 1.46 and 1.44 (2s, 6H), 1.26 (d, J = 7.5 Hz, 3H), 1.11 (s, 3H), 0.89 (s, 3H); HRMS (FAB) m/z 508.2453 ($C_{28}H_{33}N_3O_6$ + H requires 508.2447).

14α-Hydroxy-17-oxo-15α-methylmarcfortine A (15): 10 mg, 9% yield, as a solid. This material was identical to the material obtained from the conjugated addition reaction of **14** based on TLC and ^{1}H NMR.

14α-Hydroxy-16-hydroxy-17-oxo-15α-methylmarcfortine A (17): 7 mg, 6% yield, as a solid; ^{1}H NMR was complicated by the diastereomers; HRMS (FAB) m/z 538.2544 ($C_{29}H_{35}N_3O_7$ + H requires 538.2553).

Conversion of 18 to 19. Compound **18** (25 mg, 0.05 mmol) was dissolved in CH_2Cl_2 (5 mL) and treated with *m*-CPBA (65% pure, 30 mg). The resulting mixture was stirred at 20−25 °C for 1.5 h. The mixture was partitioned between CH_2Cl_2 (20 mL) and K_2CO_3 (10%, aqueous solution, 20 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel eluting with methanol/CH_2Cl_2 (5/95) to give **19** as a solid (20 mg, 80%). This material was identical to the material obtained from the Pt/O_2-mediated ring contracting reaction of **16** on the basis of TLC and ^{1}H NMR.

Synthesis of 20. To a solution of LAH (1 M in THF, 0.21 mL, 0.21 mmol) in THF (6 mL) at −60 °C under N_2 was added $AlCl_3$ (18 mg, 0.10 mmol) in three portions. Compound **19** (20 mg, 0.04 mmol) was added dropwise 10 min later at −45 °C in THF (2 mL). The reaction was allowed to warm to −20 °C over a 20 min period and quenched by the dropwise addition of methanol (1 mL). The mixture was stirred at room temperature for 15 min and then treated with $NaCNBH_3$ (50 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 (40% acetone/CH_2Cl_2) to give **20** (5 mg, 40% yield based on the starting material recovered) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.32 (d, J = 7.7 Hz, 1H), 4.90 (d, J = 7.7 Hz, 1H), 4.5−4.4 (m, 1H), 3.65 (d, J =11.0 Hz 1H), 3.08 (s, 3H), 3.04 (t, J = 10.8 Hz, 1H), 2.9−2.7 (m, 3H), 2.62 (d, J = 15.9 Hz, 1H), 2.48 (t, J = 9.1 Hz, 1H), 2.0−1.8 (m, 3H), 1.7−1.5 (m, 1H), 1.46 and 1.45 (2s, 6H), 1.22 (s, 3H), 1.08 (d, J = 7.5 Hz, 3H), 0.86 (s, 3H); HRMS (FAB) m/z 494.2655 (C_{28} $H_{35}N_3O_5$ + H requires 494.2662).

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