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Functionalization of Marcfortine A at C12 and C17 by Treatment with Metallic Oxidizing Agents

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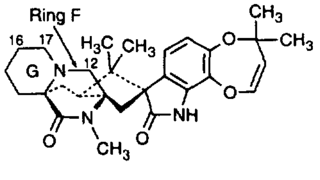
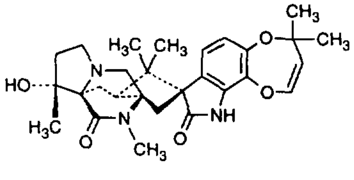
Abstract: Treatment of Marcfortine A with various metallic oxidizing agents has led to functionalization at C12, C16, and C17. The new functional groups provide opportunities for further elaboration of this important new class of anthelmintics. Copyright © 1996 Elsevier Science Ltd

Marcfortine A is a fungal metabolite of *Penicillium roqueforti*, which was reported by Polonsky, et al.[1] It is structurally related to paraherquamide A which was isolated from *Penicillium paraherquei*.[2] Marcfortine A, paraherquamide A and their analogs are potent antiparasitic agents.[3] In our continuing search for new and more effective anthelmintics, we have chemically and biologically modified marcfortine A which has led to compounds with improved biological activity in our anthelmintic screens. This report describes the formation of novel marcfortine A analogs resulting from the introduction of additional functional groups to the F and G rings through the application of various oxidative procedures. These procedures were expected to produce compounds similar to those arising from oxidative biotransformations. In addition to providing us with the opportunity to investigate the significance of oxygen functionalization on anthelmintic activity, the resulting increased functionality has enabled still further modification of this important new class of anthelmintics.



Marcfortine A

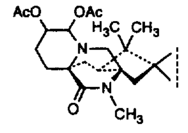
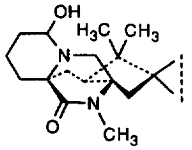
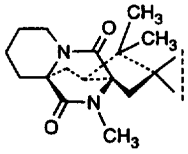
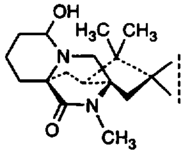
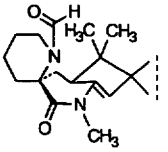
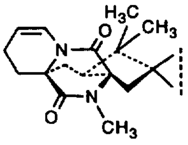
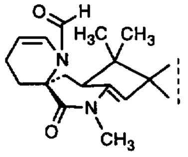
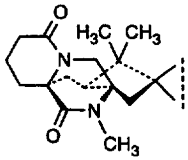
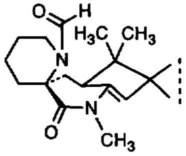


Paraherquamide A

We have found that oxidizing agents such as $Pb(OAc)_4$, $Mn(OAc)_3$, $Tl(OAc)_3$, SeO_2, and $FeCl_3$[4] oxidize marcfortine A at a carbon atom alpha to the tertiary nitrogen atom, exclusively, thereby functionalizing positions C12 and/or C17 to produce analogs of type I (intact F ring) and/or type II (ruptured F ring). Compounds of type I can be prepared from $Pb(OAc)_4$ and SeO_2 while $FeCl_3$ produces compounds of type II through oxidation at C12 followed by beta-elimination of a formamide moiety. Manganese triacetate and $Tl(OAc)_3$ give both types of products. Of the oxidizing agents examined, only $Mn(OAc)_3$ performed an oxidative dehydration in ring G to give enamide compounds of types I and II.

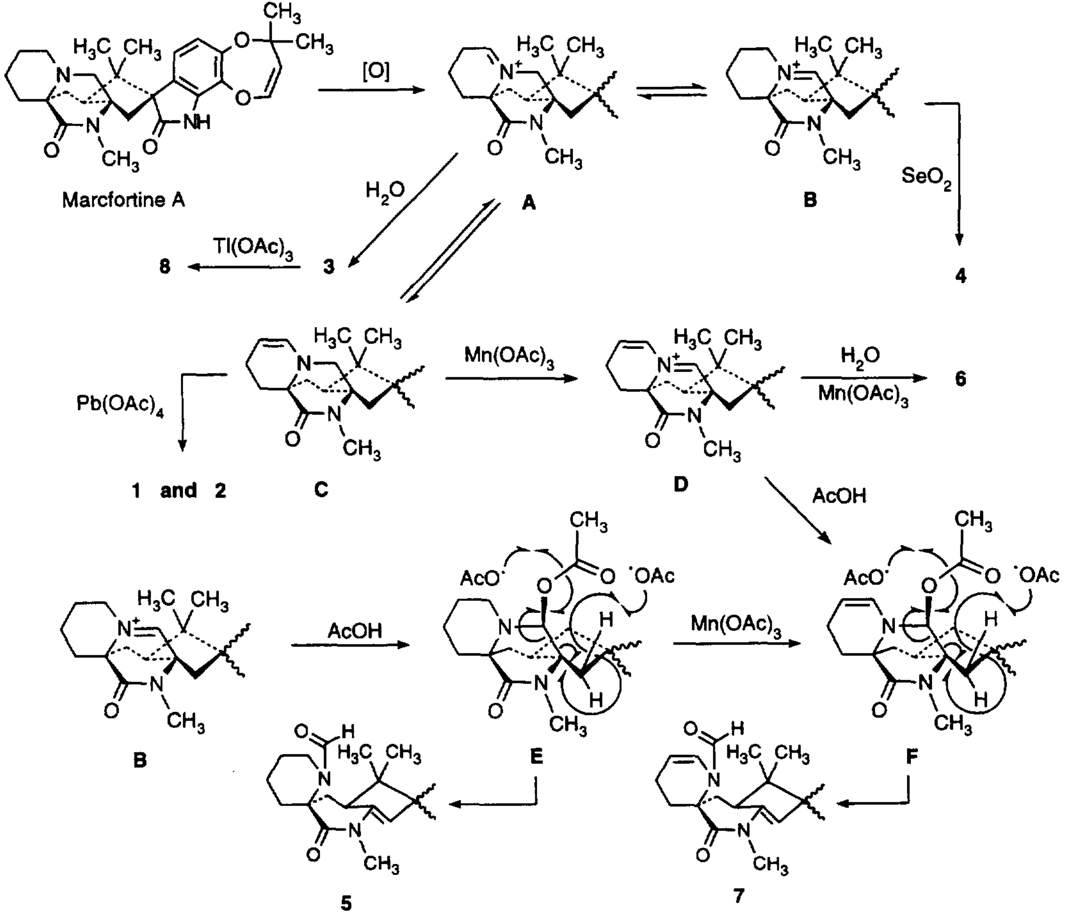
Although marcfortine A is rather resistant to oxidation by these reagents resulting in yields of 20% or less, this deficiency is offset by reasonable recovery rates of marcfortine A (MFA) as shown in Table 1. A plausible mechanism explaining the formation of these products is shown in Scheme 1.

Table 1

Reagent[5,6]	Solvent	Temp/Time	Percent MFA recovered	Product(s)	
$Pb(OAc)_4$ 285 mole%	Benzene	Reflux 3 hrs	30	 (1) 16α, 17α: 6% (2) 16β, 17β: 9%	 (3) 7%
SeO_2 200 mole%	Dioxane (Dry)	Reflux 2 hrs	0	 (4) 20%	 (3) 8.5%
$FeCl_3/H_2O_2$ HOAc/Pyr[4] 85 mole% ($FeCl_3$)	Pyridine	25° 18 hrs	69	 (5) 2.5%	
$Mn(OAc)_3$ 286 mole%	Toluene	Reflux 4 hrs	45	 (6) 3%	 (7) 3%
$Tl(OAc)_3$ 300 mole%	Benzene	Reflux 2 hrs	60	 (8) 1%	 (5) 1%

Although we have not studied the mechanism of these reactions, the products found in Table 1 can be accounted for by invoking iminium ions A and B which are expected to arise from attack of the tertiary nitrogen of marcfortine A on the metal oxide. Intermediate A produces 3 by addition of water present in the undried solvent. Thallium triacetate oxidizes 3 to 8. In the case of SeO_2, water produced during the oxidation reaction adds to B which is then further oxidized to give 4. Equilibration of A to enamine C followed by a second oxidation with $Pb(OAc)_4$ produces diacetates 1 and 2. When $Mn(OAc)_3$ is the oxidizing agent intermediate C undergoes further oxidation to D. Intermediate D adds water which is followed by a third oxidation to produce 6. This intermediate also produces F by adding AcOH. Similarly, addition of AcOH to B forms E which upon further oxidation also gives F. Under radical-induced ring opening, intermediates E and F form 5 and 7, respectively.

Scheme 1



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5. General procedure used for $Pb(OAc)_4$, $Mn(OAc)_3$, $Tl(OAc)_3$ and SeO_2. The solid metal oxide was added to a solution of marcfortine A in solvent (20 mL per mmol) and the resulting mixture refluxed for the time specified in Table 1. Filtration through sintered glass, followed by concentration and silica gel chromatography gave the products of Table 1. Representative spectroscopic data follow: Compound **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.06 (s, 3H), 1.45 & 1.46 (2s, 6H), 1.48-1.55 (m, 1H), 1.60-1.78 (m, 1H), 1.80 (t, 1H), 1.90 & 2.73 (d, J = 15.7 Hz, 2H), 2.0-2.40 (m, 3H), 2.05 & 2.15 (2s, 6H), 3.06 (s, 3H), 3.1-3.4 (m, 4H), 4.91 & 6.37 (d, J = 7.7 Hz, 2H), 6.69 (d, 1H), 6.80-6.90 (m, 2H), 8.55 (bs, 1H). MS (FAB) M/Z [M+H] 594. Compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 & 0.84 (2s, 6H), 1.44 & 1.46 (2s, 6H), 1.7-2.3 (m, 4H), 2.49-2.60 (m, 1H), 2.57 & 3.35 (d, J = 15.2 Hz, 2H), 3.06 (s, 3H), 3.25-3.40 (m, 1H), 3.48 (t, 1H), 4.89 & 6.31 (d, J = 7.7 Hz, 2H), 5.32 (dt, 1H), 6.70 & 7.00 (d, J = 8.1 Hz, 2H), 6.92 (d, J = 7.9 Hz, 1H), 8.18 (bs, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.37, 19.54, 22.96, 26.72, 28.00, 29.68, 29.98, 31.20, 31.58, 46.25, 53.18, 60.57, 62.69, 69.10, 79.71, 110.42, 115.11, 117.58, 121.34, 125.13, 132.32, 136.12, 138.86, 146.02, 168.12, 171.32, 183.05. HRMS (FAB) M/Z [M+H] calculated for $C_{28}H_{31}N_3O_5$+ H_1: 490.2342; measured: 490.2312.
6. Marcfortine A (0.1 g, 0.2 mmol), ferric chloride (2.7 mg, 0.017 mmol), acetic acid (0.05 mL), pyridine (1.3 mL), and H_2O_2 (30%, 0.01 mL) were combined and stirred in an open flask at room temperature. The resulting green reaction mixture was stirred overnight and then partitioned between NaOH (1 M, 25 mL) and methylene chloride (25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to give a residue which upon silica gel chromatography (3% MeOH/CH_2Cl_2) gave **5** (2.5 mg, 2.5%) and unreacted MFA (0.69 g, 69%). Compound **5** exhibited the following spectroscopic data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.12 (s, 3H), 1.43 (s, 3H), 1.46 (s, 3H), 1.5-1.9 (m, 11H), 2.06 (bs, 3H), 2.29-2.38 (m, 2H), 3.12 (d, 1H), 3.19 (s, 3H), 3.21-3.3 (m, 1H), 3.45-3.7 (m, 2H), 4.87 (d, 1H), 4.60 (d, 1H), 6.3 (d, 1H), 6.7 (d, 1H), 6.80 (d, 1H), 7.48 (s, 1H), 7.99 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.01, 21.77, 22.57, 22.66, 26.10, 29.46, 29.72, 30.04, 30.89, 42.20, 43.72, 50.03, 59.61, 66.45, 79.72, 102.38, 115.14, 117.33, 122.03, 124.98, 132.43, 135.26, 138.91, 146.03, 147.24, 162.35, 169.39, 180.43. HRMS (FAB) M/Z [M+H] calculated for $C_{28}H_{33}N_3O_5$ + H_1: 492.2498; measured: 492.2520.

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