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C24 AND C25 SUBSTITUTED MARCFORTINE A DERIVATIVES

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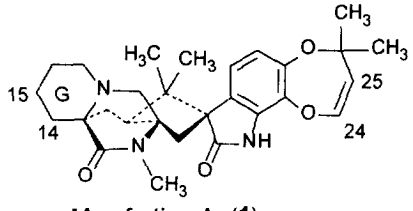
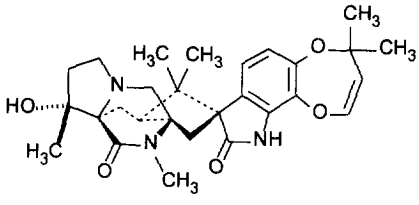
Abstract: The dioxepinoindole ring found in marcfortine A (**1**) is unique among natural products. In order to determine the importance of the substitution pattern of the C24-C25 olefin, we synthesized a variety of analogs at these positions. With the exception of compound **5**, none of these compounds exhibited any anthelmintic activity.

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 (**2**)

The potent antiparasitic activity of marcfortine A (**1**), paraherquamide A (**2**), and their analogs has been described by scientists at Merck.[3] Because the marcfortines and paraherquamides are unique both structurally and in their mode of action, they represent a promising new class of anthelmintics. Marcfortine A (**1**), a fungal metabolite of *Penicillium roqueforti*, reported by Polonsky et al.,[4] is structurally related to paraherquamide A (**2**) which was originally isolated from *penicillium paraherquei.*[5] Paraherquamide A (**2**) contains a five-membered G-ring possessing a hydroxyl group and a methyl group, whereas the G-ring of marcfortine A (**1**) is six-membered and unsubstituted. To investigate the effect on anthelmintic activity by changing the substitution pattern at C24/C25, we synthesized a number of analogs.

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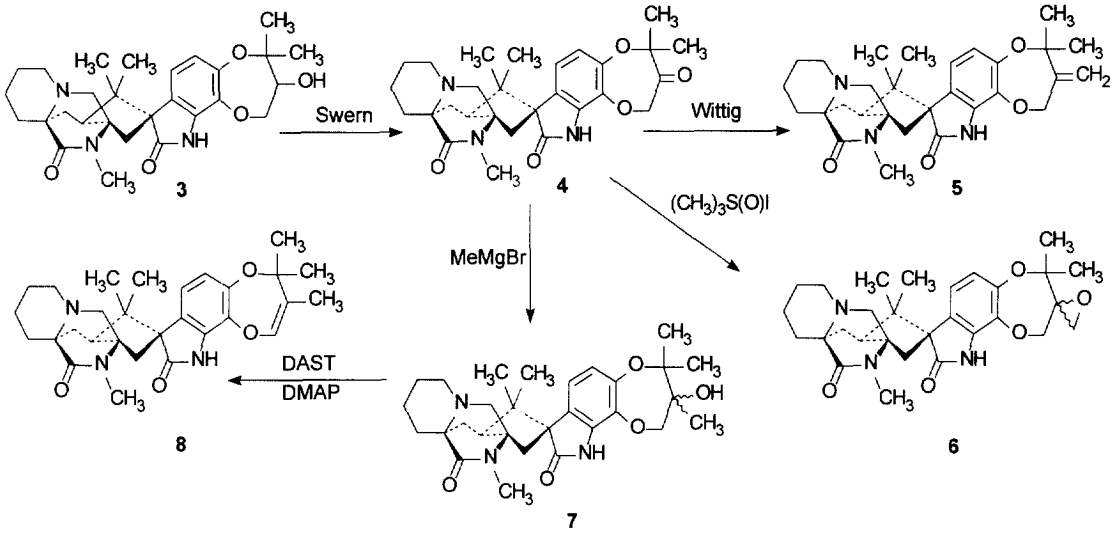
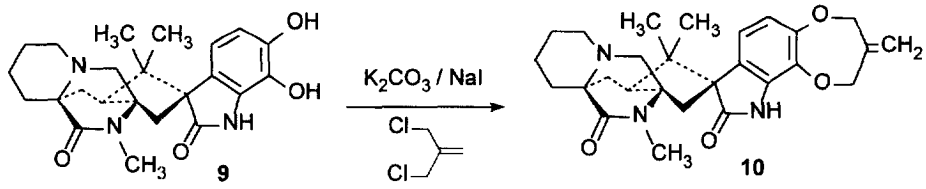


Modification of the A-ring began with the alcohol **3**,[6] which was synthesized according to the method of Williams.[7] Swern oxidation of **3** provided the ketone **4**, which was subjected to Wittig olefination with methyltriphenylphosphonium bromide and *n*-BuLi to give the exocyclic methylene containing compound **5** in 50% yield. Tebbe reagent failed to provide any desired material **8**. The versatile ketone **4** was also epoxidized with trimethylsulfoxonium iodide and potassium *t*-butoxide in DMSO to give a 35% yield of **6,** whereas Grignard chemistry (MeMgBr) gave a quantitative yield of **7**. Treatment of 7 with DAST afforded a 35% yield of the desired analog **8**. Prior to the successful DAST reaction a variety of reagents failed to dehydrate the hydroxy methyl compound **7** to produce **8**. Unsuccessful reagents included: Burgess' reagent, $(PhO)_3P^+CH_3^-$ (MTPI), pyridine-$SOCl_2$, *p*-TsOH, and $FeCl_3$-SiO_2. We reasoned *apriori* that both compounds **5** and **8** would have anthelmintic activity since they contained the crucial C26 dimethyl moiety[6] and likewise retained the proper geometry of the A ring found in the parent compound marcfortine A based on modeling studies. Furthermore, these structures should be less readily hydrolyzed under acidic conditions.

The biological activity of the compounds described in this report was evaluated in our anthelmintic assay which uses immunosuppressed Mongolian gerbils (jirds) inoculated with *Haemonchus contortus* and *Trichostrongylus colubriformis*.[8] With the exception of compound **5** none of these compounds were active.

Since the exocyclic methylene analog **5** had activity we chose to prepare a simplified analog. Thus, the catechol **9**[6] was reacted with 3-chloro-2-chloromethyl-1-propene, K_2CO_3, and NaI in DMF for 16 h to give the exocyclic methylene compound **10** which lacked the C26 dimethyls. Compound **10** was inactive, which further emphasizes the importance of the C26 dimethyls.



Experimental Section

Compound 4. To oxalyl chloride (0.045 mL, 0.5 mmol) in CH_2Cl_2 (5 mL) was added DMSO slowly dropwise in CH_2Cl_2 (1 mL). Following 0.25 h of stirring at - 78 °C, compound **3** (60 mg, 0.12 mmol) was added dropwise in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 0.25 h, then quenched with NEt_3 (0.25 mL) and stirred at ambient temperature for 0.25 h. The reaction mixture was partitioned between $NaHCO_3$ (sat., 25 mL) and EtOAc (25 mL). The organic extract was dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel (5% MeOH/CH_2Cl_2) to give **4** (30 mg, 50%) as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, NH), 6.77 (d, 1H), 6.64 and 4.89 (d, J = 13.6 Hz, 2H, C_{24}-H), 3.70 (d,1H), 3.11 (s, N-Me), 3.02 (t, 1H), 2.70 and 1.85 (d, J = 15.6 Hz, 2H, C_{10}-H), 2.65 (m, 1H), 2.40 (d, 1H), 2.31 (m, 1H), 2.15 (d, 1H), 1.95–1.85 (m, 1H), 1.80–1.0 (m, 7H), 1.53 and 1.51 (s, 6H), 1.13 (s, 3H), 0.85 (s, 3H). HRMS (FAB) *m/z* [M + H] calcd for $C_{28}H_{35}N_3O_5$+H: 494.2655; measured: 494.2662.

Compound 5. To methyltriphenylphosphonium bromide (dried overnight in the oven, 70 mg, 0.2 mmol) in THF (2 mL) at room temperature was added n-BuLi (1.6 M in hexanes, 0.1 mL, 0.2 mmol) dropwise. Following 5 min of stirring compound **4** (25 mg, 0.05 mmol) was added. The resulting mixture was stirred for 0.5 h at room temperature, quenched with H_2O (10 mL) and extracted into EtOAc (25 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel (40% acetone/hexane) to give **5** (14 mg, 50%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, NH), 6.61 and 6.53 (d, J = 8.1 Hz, 2H), 5.29 and 5.14 (s, 2H), 4.95 and 4.82 (d, J = 11.1, 2H), 3.66 (d, J = 11.3, 2H), 3.10 (s, 3H), 3.01 (t, 1H), 2.65 and 1.82 (d, J = 15.5, 2H), 2.70–2.65 (m, 1H), 2.40 (d, 1H), 2.35–2.20 (m, 1H), 2.10 (d, 1H), 1.75–1.20 (m, 6H), 1.50 and 1.48 (2s, 6H), 1.09 and 0.81 (2s, 6H). HRMS (FAB) *m/z* [M + H] calcd for $C_{29}H_{37}N_3O_4$+H: 492.2862; measured: 492.2858.

Compound 6. To trimethylsulfoxonium iodide (25 mg, 0.12 mmol) in DMSO (3 mL) at room temperature was added the ketone **4** (20 mg, 0.039 mmol) followed by potassium t-butoxide (13 mg, 0.12 mmol). The resulting mixture was stirred for 1 h at room temperature, quenched with H_2O (10 mL) and extracted into EtOAc (25 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel (40% acetone/hexane) to give **6** (7 mg, 35%) as a white solid. ^{1}H NMR was reasonable as a mixture of diastereomers. Selected ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 and 7.65 (s, 1H), 4.62 (d, 1H), 4.37 (d, 1H), 4.30 (d, 1H), 4.11 (d, 1H), 3.61 (d, 1H), 3.02 (s, 3H), 2.31 (d, 1H), 2.07 (d, 1H). HRMS (FAB) *m/z* [M + H] calcd for $C_{29}H_{37}N_3O_5$+H: 508.2811; measured: 508.2821.

Compound 7. To compound **4** (50 mg, 0.1 mmol) in THF (6 mL) at 0 °C was added MeMgBr (3 M in ether, 0.2 mL, 0.6 mmol) dropwise. The reaction mixture was stirred at room temperature for 10 min, quenched with saturated ammonium chloride (15 mL), and extracted into EtOAc (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give **7** (100% yield) as a white solid. ^{1}H NMR was reasonable as a mixture of diastereomers. Selected ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 and 7.62 (s, NH), 3.69 (d, 1H), 3.11 (s, 3H), 3.00 (t, 1H), 2.70 and 1.84 (d, J = 11.4 Hz, 2H), 2.38 and 2.15 (d, J = 11.4 Hz, 2H). HRMS (FAB) *m/z* [M + H] calcd for $C_{29}H_{39}N_3O_5$+H: 510.2968; measured: 510.2959.

Compound 8. To the substrate **7** (20 mg, 0.039 mmol) in CH_2Cl_2 at room temperature was added DMAP (4 mg) followed by DAST (0.02 mL) dropwise. The resulting mixture was stirred for 5 minutes at room temperature, quenched with H_2O (10 mL) and extracted into EtOAc (25 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and chromatographed on silica gel (5% MeOH/CH_2Cl_2) to give **8** (7 mg, 35%) as a white solid. A trace of the exocyclic methylene compound **5** was noticeable by ^1H NMR. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, NH), 6.80 and 6.60 (d, J = 8.2 Hz, 2H), 6.25 (s, 1H), 3.70 (d 1H), 3.11 (s, 3H), 3.02 (t, 1H), 2.75 (d, 1H), 2.76–2.55 (m, 1H), 2.42 (d, 1H), 2.30–2.20 (m, 1H), 2.17 (d, 1H), 1.78–1.30 (m, 8H), 1.65 (s, 3H), 1.46 and 1.45 (2s, 6H), 1.11 and 0.83 (2s, 6H). HRMS (FAB) *m/z* [M + H] calcd for $C_{29}H_{37}N_3O_4$+H:492.2862; measured: 492.2872.

Compound 10. To the diol **9** (35 mg, 0.087 mmol) and 3-chloro-2-chloromethyl-1-propene (0.017 ml, 0.15 mmol) in DMF (4 mL) at room temperature was added K_2CO_3 (66 mg, 0.48 mmol) and NaI (36 mg, 0.24 mmol). The mixture was stirred for 16 h at room temperature, quenched with an aqueous solution of NH_4Cl (0.1 M, 25 mL). The mixture was diluted with ethyl acetate, the organic layer separated, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel chromatography (6% MeOH in methylene chloride) to give **10** as a white solid (8 mg, 18%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3H), 1.14 (s, 3H), 1.4–2.9 (m, 12H), 1.86 and 2.68 (d, J = 15.6 Hz, 2H, C_{10}-H), 3.07 (t, 1H, C_{20}-H), 3.12 (s, 3H, N-Me), 4.75 (AB q, 2H, C_{24}-H & C_{26}-H), 4.81 (s, 2H, C_{24}-H & C_{26}-H), 5.16 (d, J = 12.5 Hz, 2H, C_{25}-methylene), 6.58 and 6.72 (d, J = 8.2 Hz, 2H, C_4-H & C_5-H), 8.01 (s, 1H, NH). MS (FAB) *m/z* [M + H^+] 464.

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