14,15-DISUBSTITUED MARCFORTINE A DERIVATIVES

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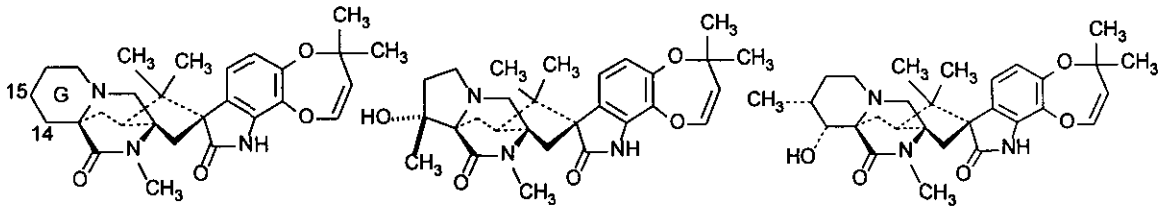
Abstract- The novel 14,15-disubstituted marcfortine A derivatives (**4** and **14**) were synthesized starting with the known derivatives (**5** and **10**). Assay of their anthelmintic activity disclosed some novel aspects of the structure-activity relationships for marcfortine A (**1**).

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.

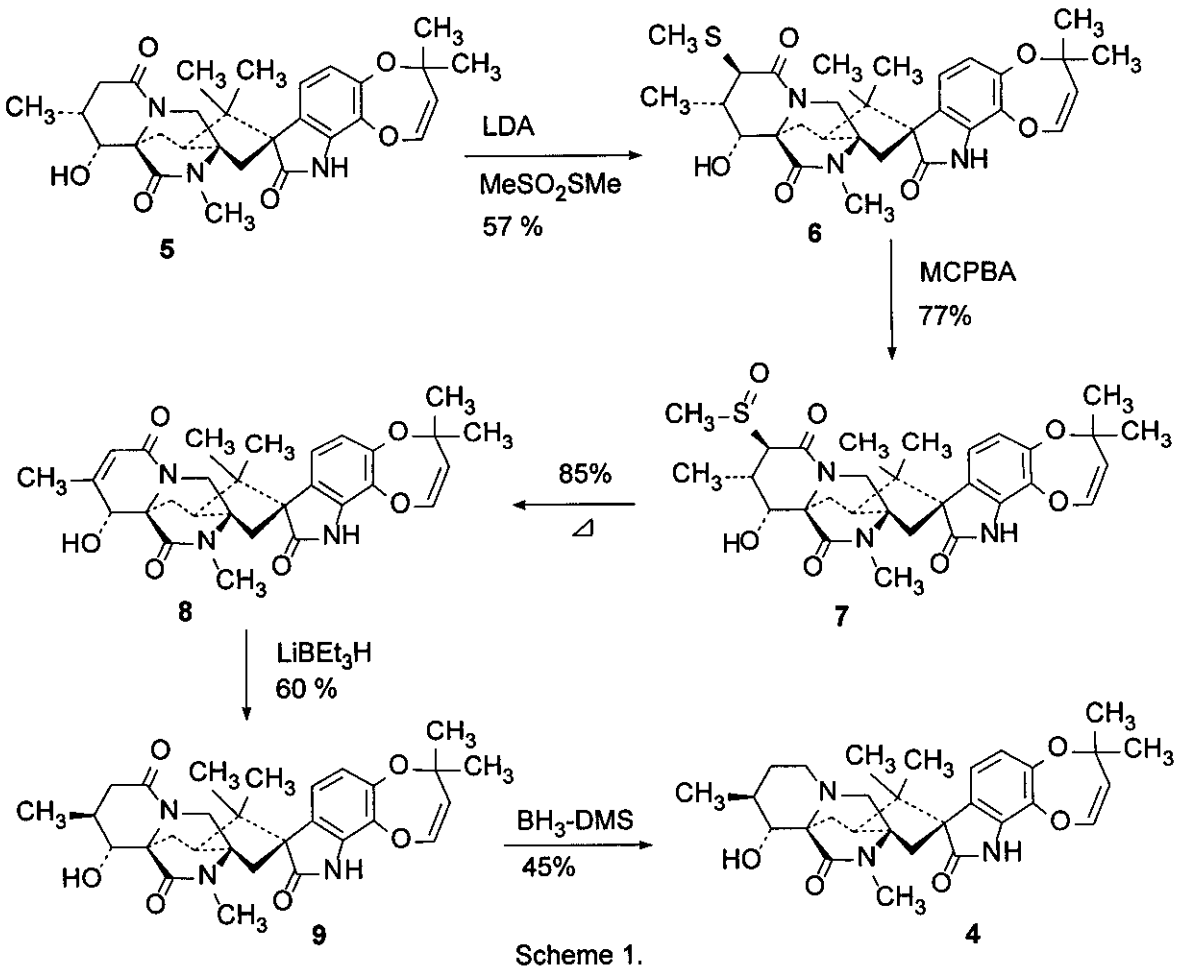


Marcfortine A (**1**) Paraherquamide A (**2**) **3**

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.

Since 14α-hydroxy-15α-methylmarcfortine A (**3**) showed good activity in our jird model,[6] 14,15-disubstituted derivatives of marcfortine A were synthesized. To investigate the significance of the chirality of the C-15 position on anthelmintic activity, we prepared 14α-hydroxy-15β-methylmarcfortine A (**4**, scheme 1). Sulfenylation of 14α-hydroxy-15α-methyl-17-oxomarcfortine A (**5**)[7] with methyl methanethiol sulfonate and LDA gave 14α-hydroxy-15α-methyl-16β-methylsulfenylmarcfortine A (**6**) in 57% yield. (Both

phenyl disulfide and phenylselenyl chloride failed to react with **5**.) Oxidation with *m*-CPBA in methylene chloride at -78 °C gave 14α-hydroxy-15α-methyl-16β-methylsulfinylmarcfortine A (**7**) in 77 % yield which



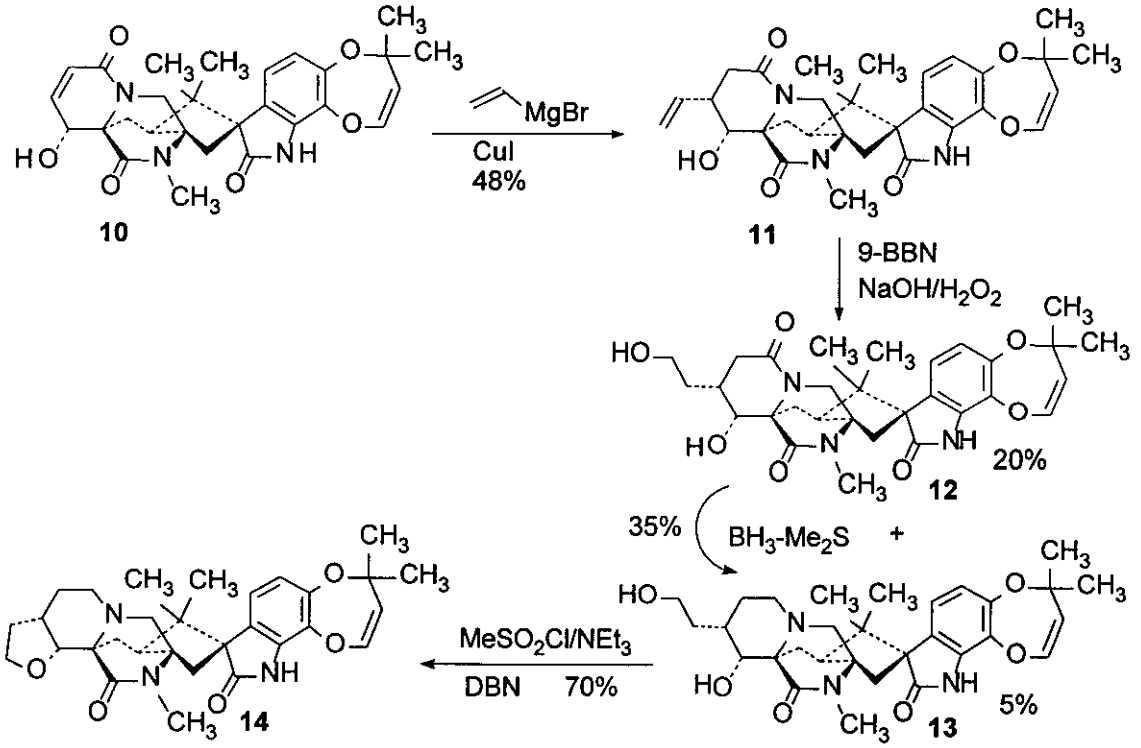
Scheme 1.

underwent elimination of methanesulfenic acid in refluxing toluene/ethylene chloride to give 14α-hydroxy-15β-methyl-15,16-dehydromarcfortine A (**8**) in 85% yield. Reduction with lithium triethylborohydride gave 14α-hydroxy-15β-methyl-17-oxomarcfortine A (**9**) in 60% yield, recovered starting material (**8**, 30%) and (**5**) in 4% yield. Compound (**9**) was reduced with BH_3-Me_2S complex to give **4** in 45% yield.

Surprisingly, compound (**4**) did not show any activity at a dose which compound (**3**) demonstrates 100 % clearance. Perhaps, overall shape of the G-ring relative to the hydroxy group may be more important than the chirality of the C-15 methyl group.

To investigate the significance of the hydrogen bonding on the C-14 hydroxyl position on anthelmintic activity, we prepared a 14,15-fused ring analog of marcfortine A (**14**, Scheme 2). This analog should have similar geometry in the G-ring with respect to compound (**3**), especially at the crucial C-15 methyl and C-14

oxygen functionalities. Thus, it will help clarify the importance of hydrogen bonding of the C-14 hydroxy. The previously described material (**10**)[7] reacted with vinylmagnesium bromide and copper iodide in tetrahydrofuran at 0 °C to give the 1,4 addition product (**11**) in 48% yield as well as 22% recovered starting material (**10**). Hydroboration with 9-BBN followed by NaOH and H_2O_2 workup provided the desired alcohol (**12**), albeit in low yield (20%), recovered staring material (**11**) (20%) and a small amount (5%) of the C-17 reduced alcohol (**13**). Reduction of the C-17 carbonyl of (**12**) with BH_3-Me_2S complex gave (**13**) in 35% yield. The two sources of compound (**13**) were combined, mesylated with methanesulfonyl chloride and triethylamine, then treated with excess DBN to give the furan containing marcfortine A analog (**14**) in 70% yield. Compound (**14**) shows no antiparasitic activity suggesting that hydrogen bonding of the C-14 alcohol group is indeed important for anthelmintic activity.



10 **11** **12** **13** **14**

Scheme 2.

EXPERIMENTAL

^1H NMR spectra were recorded on a 400 MHz and ^{13}C NMR spectra were recorded on a 100 MHz NMR spectrometer. Column chromatography was 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 done with UV light, or I_2 staining. All solvents and reagents were commercial grade and used without further purification.

14α-Hydroxy-15α-methyl-16β-methylsulfenyl-17-oxomarcfortine A (6). 14α-Hydroxy-15α-methyl-17-oxomarcfortine A (**5**, 0.18 g, 0.35 mmol) was added dropwise in THF (2 mL) at - 78 °C to an LDA solution which was prepared by adding a solution of BuLi (1.6 M, 0.8 mL, 1.3 mmol) dropwise to diisopropylamine (0.19 mL, 1.4 mmol) at 0 °C in THF (4 mL). The reaction mixture was allowed to slowly warm to -20 °C over 1 h. The resulting mixture was then treated with methyl methanethiolsulfonate (0.04 mL, 0.39 mmol) at -20 °C. The reaction was immediately quenched with saturated sodium bicarbonate solution (20 mL) and extracted with methylene chloride (25 mL). The organic layer was dried ($MgSO_4$), concentrated and the residue purified on a Chromatotron (2 mm, 60% ethyl acetate in hexane) to yield **6** as a white solid (0.12 g, 57%). Analytical sample was obtained by recrystallization from CH_2Cl_2/hexane. mp 242-245 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 3H), 1.09 (s, 3H), 1.30 (d, J = 6.8 Hz, 3H, C_{15}-*Me*), 1.41 and 1.43 (2s, 6H), 1.9-2.4 (m, 3H), 2.12 (s, 3H, S-Me), 2.2-2.35 (m, 1H, C_{15}-H), 2.75 (d, J = 15.8 Hz, 1H, C_{10}-H), 3.04 (s, 3H, N-Me), 3.14 (t, J = 10.6 Hz, 1H, C_{20}-H), 3.28 (d, J = 11.2 Hz, 1H, C_{16}-H), 3.65 and 3.79 (d, J = 12.9 Hz, 2H, C_{12}-H), 4.38 (d, J = 1.8 Hz, 1H, C_{14}-H), 4.88 and 6.31 (d, J = 7.7 Hz, 2H, C_{24}-H and C_{25}H), 6.68 and 6.82 (d, J = 8.2 Hz, 2H, C_4-H and C_5-H), 8.52 (s, 1H, NH); MS (FAB) *m/z* 568 [M+H]; *Anal.* Calcd for $C_{30}H_{37}N_3O_6S$: C, 63.47; H, 6.57; N, 7.40. Found: C, 63.13; H, 6.55; N, 7.26.

14α-Hydroxy-15α-methyl-16β-methylsulfinyl-17-oxomarcfortine A (7). To 14α-hydroxy-15α-methyl-16β-methylsulfenyl-17-oxomarcfortine A (**6**, 0.12 g, 0.2 mmol) in methylene chloride (5 mL) at -78 °C was added dropwise a solution of *m*-CPBA (64% pure, 66 mg, 0.23 mmol) in CH_2Cl_2 (2 mL). The reaction was quenched with aqueous saturated sodium thiosulfate (10 mL) and sodium bicarbonate (10 mL) solutions. The mixture was diluted with methylene chloride (25 mL), and the organic layer separated, dried ($MgSO_4$) and concentrated. The residue was purified on silica gel (Chromatotron, 1 mm plate, 8% MeOH in CH_2Cl_2) to yield **7** as a white solid (80 mg, 77%). Analytical sample was obtained by recrystallization from Et_2O. mp 200-205 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.11 (s, 3H), 1.40 (d, J = 7.0 Hz, 3H, C_{15}-Me), 1.39 and 1.41 (2s, 6H), 1.98 and 2.11 (m, 2H, C_{19}-H), 2.08 and 2.81 (d, J = 15.8 Hz, 2H, C_{10}-H), 2.85 - 3.0 (m, 1H, C_{15}-H), 2.91 (s, 3H, OS-Me), 3.10 (s, 3H, N-Me), 3.23 (t, J = 10.6 Hz, 1H, C_{20}-H), 3.49 (d, J = 11.2 Hz, 1H, C_{16}-H), 3.59 and 3.87 (d, J = 12.9 Hz, 2H, C_{12}-H), 4.64 (d, J = 1.8 Hz, 1H, C_{14}-H), 4.91 and 6.32 (d, J = 7.7 Hz, 2H, C_{24}-H and C_{25}H), 6.71 and 6.82 (d, J = 8.2 Hz, 2H, C_4-H and C_5-H), 7.59 (s, 1H, NH). MS (FAB) *m/z* 584 [M+H]; *Anal.* Calcd for $C_{30}H_{37}N_3O_7S$: C, 61.73; H, 6.39; N, 7.20. Found: C, 61.45; H, 6.71; N, 7.03.

14α-Hydroxy-15-methyl-15,16-dehydro-17-oxomarcfortine A (8). 14α-Hydroxy-15α-methyl-16β-methylsulfinyl-17-oxomarcfortine A (**7**, 80 mg, 0.14 mmol) was heated to reflux in ethylene dichloride/toluene (1:1, 20 mL) for 48 h. The reaction mixture was cooled to rt, quenched with a saturated aqueous sodium bicarbonate (10 mL) solution. The mixture was extracted with EtOAc (25 mL) and the organic layer was dried ($MgSO_4$), and concentrated. The residue was purified on a silica plate (Chromatotron, 1 mm, 30% acetone in CH_2Cl_2) to yield **8** as a white solid (60 mg, 85%). Analytical sample was obtained by recrystallization from CH_2Cl_2/hexane. mp 210-213 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.07 (s, 3H), 1.45 and 1.47 (2s, 6H), 1.88 and 2.15 (m, 2H, C_{19}-H), 2.08 (br s, 3H, C_{15}-Me), 2.06 and 2.80 (d, J = 15.6 Hz, 2H, C_{10}-H), 3.12 (s, 3H, N-Me), 3.20 (t, J = 10.6 Hz, 1H, C_{20}-H), 3.62 and 4.20 (d, J = 12.6 Hz, 2H, C_{12}-H), 4.95 (m, 1H, C_{14}-H), 4.91 and 6.31 (d, J = 7.7 Hz, 2H, C_{24}-H and C_{25}H), 5.79 (br s, 1H, C_{16}-H), 6.72 and 6.85 (d, J = 8.2 Hz, 2H, C_4-H and C_5-H), 7.41 (s, 1H, NH); HRMS (FAB) *m/z* 520.2449 ($C_{29}H_{33}N_3O_6$ + H requires 520.2447); *Anal.* Calcd for $C_{29}H_{33}N_3O_6$: C, 67.04; H, 6.40; N, 8.09. Found: C, 66.67; H, 6.71; N, 7.83.

14α-Hydroxy-15β-methyl-17-oxomarcfortine A (9). 14α-Hydroxy-15-methyl-15,16-dehydro-17-oxomarcfortine A (**8**, 30 mg, 0.058 mmol) was dissolved in THF (5 mL) and treated with a solution of lithium triethylborohydride in THF (1 M, 0.6 mL, 0.6 mmol) at 0 °C. The mixture was stirred for 1.5 h at 0 °C, then quenched by adding MeOH (1 mL), and concentrated. The resulting solid was purified on silica gel (Chromatotron, 1 mm plate, 4 % MeOH/CH_2Cl_2) to yield **9** as a white solid (18 mg, 60%). Analytical sample was obtained by recrystallization from Et_2O/hexane. mp 219-222 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ 0.88 (s, 3H), 1.07 (s, 3H), 1.14 (d, J = 5.6 Hz, 1H), 1.44 and 1.46 (2s, 6H), 1.66 (dd, J = 10.1, 12.8 Hz, 1H, C_{19}-H), 2.0-2.15 (m, 3H, C_{15}-H and C_{10}-H and C_{19} -H), 2.3-2.6 (m, 2H, C_{16}-H), 2.79 (d, J = 15.6 Hz, 1H, C_{10}-H), 3.12 (s, 3H, N-Me), 3.28 (t, J = 9.7 Hz, 1H, C_{20}-H), 3.50 and 4.08 (d, J = 12.7 Hz, 2H, C_{12}-H), 4.10 (d, 1H, J = 9.5 Hz, C_{14}-H), 4.91 and 6.31 (d, J = 7.7 Hz, 2H, C_{24}-H and C_{25}-H), 6.71 and 6.83 (d, J = 8.2 Hz, 2H, C_4-H and C_5-H). HRMS (FAB) *m/z* 522.2610 ($C_{29}H_{35}N_3O_6$ + H requires 522.2604); *Anal.* Calcd for $C_{29}H_{35}N_3O_6$: C, 66.78; H, 6.76; N, 8.06. Found: C, 66.39; H, 7.04; N, 7.71.

Later fractions gave **5** (1 mg) and **8** (9 mg, 30%). The ^{1}H NMR (400 MHz) spectra of **5** and **8** (starting material) were identical with the spectra of earlier preparations of these compounds.

14α-Hydroxy-15β-methylmarcfortine A (4). 14α-Hydroxy-15β-methyl-17-oxomarcfortine A (**9**, 17 mg, 0.034 mmol) in THF (3 mL) at 0 °C was treated dropwise with a solution of borane-methyl sulfide complex (10 M, 0.02 mL, 0.2 mmol). The mixture was stirred for 0.5 h at 0 °C, and again treated dropwise with borane dimethyl sulfide complex (10 M, 0.02 mL, 0.2 mmol). The mixture was stirred for an additional 0.5 h

at 0 °C, then quenched with MeOH (4 drops), and concentrated. Preparative thin layer chromatography of the residue on silica gel (0.25 mm, 40 % acetone in hexane) gave **4** (6 mg, 45%) as a white solid. Analytical sample was obtained by recrystallization from acetonitrile. mp 196-199 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.08 (d, J = 6.1 Hz, 3H, C_{15}-Me), 1.16 (s, 3H), 1.2 - 2.8 (m, 9H), 1.44 and 1.46 (s, 6H, C_{27} and C_{28}-H), 3.09 (s, 3H, N-Me), 3.12 (t, J = 10.6 Hz, 1H, C_{20}-H), 3.33 and 3.71 (m, 2H, C_{12}-H), 3.49 (s, 1H, OH), 3.57 (d, J = 3.0 Hz, 1H, C_{14}-H), 4.90 and 6.33 (d, J = 7.7 Hz, 2H, C_{24}-H and C_{25}-H), 6.67 and 6.79 (d, J = 8.2 Hz, 2H, C_4-H and C_5-H), 7.94 (s, 1H, NH); HRMS (FAB) *m/z* 508.2835 ($C_{29}H_{37}N_3O_5$+H requires 508.2811); *Anal.* Calcd for $C_{29}H_{37}N_3O_5$: C, 68.62; H, 7.35; N, 8.28. Found: C, 68.32; H, 7.28; N, 8.12.

14α-Hydroxy-15α-vinyl-17-oxomarcfortine A (11). To CuI (3.75 g, 0.02 mol) in THF (25 mL) at 0 °C was added vinylmagnesium bromide (1 M in THF, 39.5 mL, 0.04 mol) dropwise. Following 0.25 h of stirring , the dark reaction mixture was treated dropwise with **10** (5 g, 0.01 mol) in THF (25 mL). The mixture was stirred at ambient temperature for 0.5 h, quenched with 10% NH_4Cl (100 mL) and extracted into EtOAc (2 x 100 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and purified by flash chromatography to give **11** (2.5 g, 48%) as a white solid. Analytical sample was obtained by recrystallization from EtOAc/hexane. mp 249-252 °C (decomp). Selected ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 and 1.05 (s, 6H), 1.44 and 1.47 (s, 6H), 1.9 - 2.1 (m, 1H), 2.66 (m, 1H), 2.64 (d, 1H), 3.08 (s, 3H), 3.21 (t, J = 10.6 Hz, 1H), 4.50 (s, 1H), 4.91 and 6.34 (d, J = 7.8 Hz, 2H), 5.2 - 5.3 (m, 1H), 6.0 - 6.05 (m, 2H), 6.70 and 6.81 (d, J = 8.1 Hz, 2H), 7.93 (s, NH); MS (ES+) *m/z* 534 $[M + H]^+$; *Anal.* Calcd for $C_{30}H_{35}N_3O_6$: C, 67.52; H, 6.61; N, 7.87. Found: C, 67.17; H, 6.92; N, 7.52. Starting material (**10**, 1.1 g, 22%) was also recovered.

14α-Hydroxy-15α-hydroxyethyl-17-oxomarcfortine A (12) and 14α-Hydroxy-15α-hydroxyethyl-marcfortine A (13). To **11** (0.2 g, 0.37 mmol) in THF (10 mL) at rt was added 9-BBN (0.5 M in THF, 1.1 mL, 0.56 mmol) dropwise. Excess reagent (1 mL) was added 1 h later. Following 0.5 h of stirring the reaction was treated successively with NaOH (3 M, 1.2 mL), and H_2O_2 (30%, 0.8 mL). The exothermic reaction mixture was cooled to rt, quenched with a saturated aqueous sodium bicarbonate (10 mL) solution. The mixture was extracted with EtOAc (2 x 25 mL) and the organic layer was dried ($MgSO_4$), and concentrated. The residue was purified on a silica plate (Chromatotron, 1 mm, 10% MeOH/CH_2Cl_2) to yield **12** as a white solid (40 mg, 20%). Analytical sample was obtained by recrystallization from CH_2Cl_2/hexane. mp 268-271 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 and 1.15 (s, 6H), 1.42 and 1.44 (s, 6H), 1.65 - 2.2 (m, 5H), 2.55 (m, 1H), 2.76 (d, J = 15.8 Hz, 1H), 3.05 (s, 3H), 3.17 (t, J = 10.6 Hz, 1H), 3.7 - 3.8 (m, 4H), 4.45 (s, 1H), 4.88 and 6.31 (d, J = 7.8 Hz, 2H), 6.69 and 6.80 (d, J = 8.2 Hz, 2H), 8.26 (s, NH).; MS

(FAB) *m/z* 552 $[M + H]^+$; *Anal.* Calcd for $C_{30}H_{37}N_3O_7$: C, 65.32; H, 6.76; N, 7.62. Found: C, 64.98; H, 6.72; N, 7.45.

Compound (**13**) was also isolated as a white solid (10 mg, 5%). Analytical sample was obtained by recrystallization from CH_2Cl_2/hexane. mp 228-231 °C (decomp). ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 and 1.12 (s, 6H), 1.44 (s, 6H), 1.4- 1.85 (m, 7H), 1.87 and 2.69 (d, 2H, J = 15.76 Hz), 2.07 (m, 1H), 2.3 - 2.75 (m, 6H), 3.03 (t, J = 10.7 Hz, 1H), 3.11 (s, 3H), 3.7 - 3.9 (m, 2H), 3.99 (s, 1H), 4.90 and 6.34 (d, J = 7.6 Hz, 2H), 6.68 and 6.79 (d, J = 8.2 Hz, 1H), 8.16 (s, NH). HRMS (FAB) *m/z* 538.2913 ($C_{30}H_{39}N_3O_6$+H requires 538.2917); *Anal.* Calcd for $C_{30}H_{39}N_3O_6$: C, 67.02; H, 7.32; N, 7.82. Found: C, 66.76; H, 7.53; N, 7.58.

14α-Hydroxy-15α-hydroxyethylmarcfortine A (13). BH_3-DMS (10 M, 0.04 mL, 0.4 mmol) was added dropwise to **12** (22 mg, 0.04 mmol) in THF (2 mL) at 0 °C. The mixture was stirred for an additional 0.5 h at 0 °C, then quenched with MeOH (4 drops), and concentrated. Preparative thin layer chromatography of the residue on silica gel (0.25 mm, 40% acetone in hexane) gave **13** (5 mg, 35%) as a white solid (mp 225-228 °C). ^1H NMR (400 MHz, $CDCl_3$) was identical with that previously reported.

Compound (14). To **13** (10 mg, 0.019 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added triethylamine (0.016 mL, 0.11 mmol) followed by methanesulfonyl chloride (0.004 mL, 0.05 mmol). Excess DBN (2 drops) was then added 15 min later. Following 1 h of stirring the reaction mixture was applied directly on preparative thin layer chromatography plates and eluted with 3% MeOH/CH_2Cl_2 to yield **14** (7 mg, 70%) as a white solid. Analytical sample was obtained by recrystallization from CH_2Cl_2/hexane. mp 210-213 °C (decomp). ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.14 (s, 3H), 1.44 (s, 6H), 1.5-1.75 (m, 3H), 1.8-1.95 (m, 2H), 1.95-2.2 (m, 2H), 2.3-2.45 (m, 2H), 2.5-2.6 (m, 2H), 2.69 (d, J = 15.7 Hz, 1H), 3.12 (s, 3H), 3.7-3.85 (m, 1H), 3.86 (m, 1H), 4.01 (br s, 1H), 4.10 (m, 1H), 4.90 and 6.33 (d, J = 7.7 Hz, 2H), 6.67 and 6.82 (d, J = 8.2 Hz, 2H), 7.79 (s, 1H); HRMS (FAB): *m/z* 520.2801 ($C_{30}H_{37}N_3O_5$ + H requires 520.2811); *Anal.* Calcd for $C_{30}H_{37}N_3O_5$: C, 69.34; H, 7.18; N, 8.09. Found: 68.96; H, 7.38; N, 8.04.

REFERENCES

1. R. C. Lynn, 'Georgis' Parasitology for Veterinarians', W. B. Saunders Co., Philadelphia, 1995, 247.
2. R. Prichard, *Veterinary Parasitology,* 1994, **54**, 259.
3 J. G. Ondeyka, R. T. Goegelman, J. M. Schaeffer, L. Kelemen and L. Zitano, *J. Antibiotics*, 1990, **43**, 1375; J. Leisch and C. Wichmann,. *J. Antibiotics*, 1990, **43**, 1380; W. L. Shoop, J. R. Egerton, C. H. Eary, and D. Suhayda, *J. Parasitology*, 1990, **76**, 349; D. A. Ostlind, W. G. Mickle,

D. V. Ewanciw, F. J. Andriuli, W. C. Campbell, S. Hernandez, S. Mochale and E. Munguira, *Research in Veterinary Science*, 1990, **48**, 260; S. E. Blanchflower, R. M. Banks, J. R. Everett, B. R. Manger and C. Reading, *J. Antibiotics*, 1991, **44**, 492; T. A. Blizzard, G. Marino, P. J. Sinclair and H Mrozik, European Pat. Appl., EP 0 354 615 A1, 1990 (Chem. Abstr., 1990, **113**, P131885s); M. Schaeffer, T. A. Blizzard, J. Ondeyka, R. Goegelman, P. J. Sinclair and H. Mrozik, *Biochemical Pharmacology*, 1992, **43**, 679; H. Mrozik, U.S. Pat. Appl., US 4,866,060, 1989 (Chem. Abstr., 1990, **112**, P48776r); T. A. Blizzard and H. Mrozik, U.S. Pat. Appl., US 4,923,867, 1990 (Chem. Abstr., 1991, **114**, P62467p).

4. J. Polonsky, M. A. Merrien, T. Prange, C. Pascard and S. Moreau, *J. Chem. Soc., Chem. Commun.*, 1980, 601.
5. M. Yamazaki, E. Okuyama, M. Kobayashi and H. Inoue, *Tetrahedron Lett.*, 1981, **22**, 135.
6. G. A. Conder, S. S. Johnson, P. M. Guimond, D. L. Cox and B. L. Lee, *J. Parasitology*, 1991, **77**, 621.
7. B. H. Lee and M. F. Clothier, *J. Org. Chem.*, 1997, **62**, 1863 and 7836; B. H. Lee, PCT Intl. Appl., WO 94/29319, 1994 (Chem. Abstr., 1995, **122**, P314905d).

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