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Semi-Synthesis of 2-Deoxo- and 3-Epi-paraherquamide A

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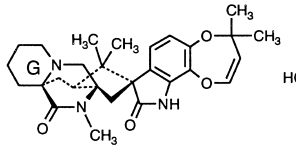
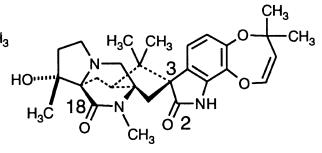
Abstract—2-Deoxo- and 3-epi-paraherquamide A were synthesized from paraherquamide A. 2-Deoxoparaherquamide A has good activity against HC and TC in our jird model comparable to the parent compound, while 3-epi-paraherquamide A showed no activity.

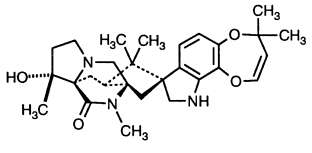
Helminths, especially parasitic nematodes, cause substantial health problems in humans and domestic animals. Currently, three distinct chemical classes are used for broad spectrum control of gastrointestinal nematodes in veterinary medicine: benzimidazoles, imidazothiazoles, and macrocyclic lactones.[1] 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.



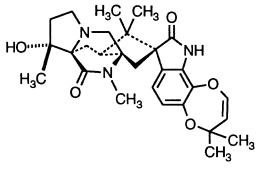
Marcfortine A (**1**)



Paraherquamide A (**2**)



2-Deoxoparaherquamide A (**3**)



3-Epi-Paraherquamide A (**4**)

The potent antiparasitic activity of marcfortine A (**1**), paraherquamide A (**2**) and their analogues 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.

To investigate the significance of the two carbonyl groups (the possible hydrogen bonding to the receptor) on anthelmintic activity, we prepared **3**. 18-Thiomarcfortine A[6] exhibited reduced anthelmintic activity suggesting that the C-18 carbonyl is important for activity. When we treated **1** with lithium aluminum hydride (LAH), 2,18-dideoxomarcfortine A was obtained, which is substantially less active than the parent **1**. Having earlier developed methodology[7] for the selective reduction of secondary amides to amines in the presence of tertiary amides, we applied this methodology to the preparation of **3** (Scheme 1).

A wide variety of reducing agents was tried in order to improve this one-step conversion: alane-*N*,*N*-dimethylethylamine complex, LAH, LAH/$AlCl_3$, $NaBH_4$/acetic acid, $NaBH_4$/CF_3COOH, Red-Al, Super-hydride, Li-9-BBN-hydride, BH_3–THF, Li-tri-*t*-butoxyaluminohydride and $NaBH_4$. The best yield (10–20%) was obtained with $LiBH_4$, but was insufficient for our purposes. Because of a limited amount of parent compound we developed a four-step sequence that provided **3** in 60–70% yield. Thus, compound **1** was reacted with 9-fluorenylmethyl chloroformate (Fmoc-Cl, 1.5 equiv) in the presence of NaH (3 equiv) at 0 °C to give a quantitative yield of **5**. Reduction of **5** with $NaBH_4$ in MeOH at 0 °C gave **6**, which was deprotected with piperidine in THF to give the imine intermediate **7**. This was further reduced with

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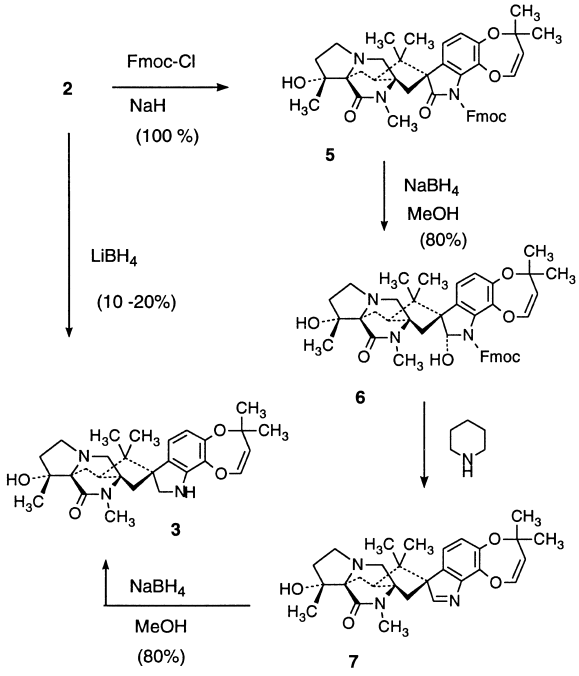
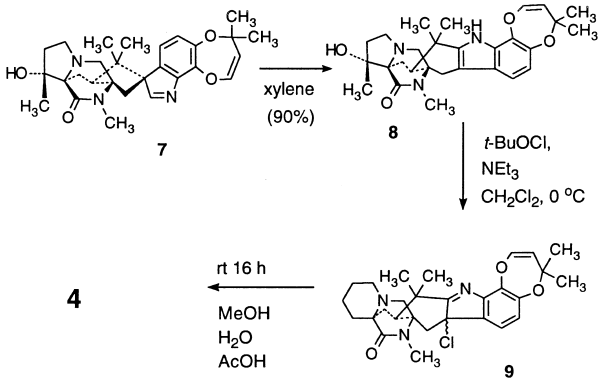


Scheme 1.



Scheme 2.

$NaBH_4$ in MeOH at 0 °C to give **3**.[8] Compound **3** turned out to have excellent activity in our jird and sheep models. Indeed, in the sheep model, the potency of this compound was 2- to 4-times greater than that of the parent compound (paraherquamide A) against *Haemonchus* and *Trichostrongylus*. While this was a very exciting development, we were concerned about the toxicity of the compound. Merck had reported[9] that paraherquamide A is quite toxic to mice with an estimated LD_{50} of less than 15 mg/kg. In dogs, the toxicity is even greater with death seen at doses as small as 0.5 mg/kg. The scope of this toxicity is interesting as paraherquamide is quite safe for sheep, jirds and even rats. However, such dog and mouse toxicity is unacceptable. Furthermore, we had had several conversations with our colleagues at both Merck and Pfizer who reported that despite extensive analogue programs they were unable to solve the toxicity problem in paraherquamides. We were pleased to discover that mice could be dosed at up to 200 mg/kg of compound **3** without any untoward toxic effects. In dogs, a 25 mg/kg dose produced only mild and reversible mydriasis, the animals being quite contented otherwise. We were surprised that a seemingly minor change in a complex structure, i.e. removal of a single oxygen atom, could result in such a dramatic reduction in toxicity.

To investigate the significance of the chirality of the C-3 position on anthelmintic activity, we prepared 3-epi-paraherquamide A (**4**, Scheme 2). Compound **7** was heated under refluxing in xylene to give the rearranged product **8** in good yield. Compound **8** was subjected to conditions described by Williams[10] to provide **4**[11] in low yield. Compound **4** did not show any anthelmintic activity.

References and Notes

1. Lynn, R. C. *Georgis' Parasitology for Veterinarians*; W. B. Saunders Co.: Philadelphia, 1995; p 247.
2. Prichard, R. *Veterinary Parasitology* **1994**, *54*, 259.
3. (a) Ondeyka, J. G.; Goegelman, R. T.; Schaeffer, J. M.; Kelemen, L.; Zitano, L. *J. Antibiot*. **1990**, *43*, 1375. (b) Liesch, J.; Wichmann, C. *J. Antibiot*. **1990**, *43*, 1380. (c) Shoop, W. L.; Egerton, J. R.; Eary, C. H.; Suhayda, D. *J. Parasitology* **1990**, *76*, 349. (d) Ostlind, D. A.; Mickle, W. G.; Ewanciw, D. V.; Andriuli, F. J.; Campbell, W. C.; Hernandez, S.; Mochale, S.; Munguira, E. *Res. Vet. Sci*. **1990**, *48*, 260. (e) Blanchflower, S. E.; Banks, R. M.; Everett, J. R.; Manger, B. R.; Reading, C. *J. Antibiot*. **1991**, *44*, 492. (f) Blizzard, T. A.; Marino, G.; Sinclair, P. J.; Mrozik, H. European Pat. Appl. EP 0 354 615 A1, 1990; *Chem. Abstr*. **1990**, *113*, P131885s. (g) Schaeffer, J. M.; Blizzard, T. A.; Ondeyka, J.; Goegelman, R.; Sinclair, P. J.; Mrozik, H. *Biochem. Pharmacol*. **1992**, *43*, 679. (h) Mrozik, H. U.S. Pat. Appl. US 4,866,060, 1989; *Chem. Abstr*. **1990**, *112*, P48776r (i) Blizzard, T. A.; Mrozik, H. U.S. Pat. Appl. US 4,923,867, 1990; *Chem. Abstr*. **1991**, *114*, P62427p.
4. Polonsky, J.; Merrien, M. A.; Prange, T.; Pascard, C.; Moreau, S. *J. Chem. Soc., Chem. Commun*. **1980**, 601.
5. Yamazaki, M.; Okuyama, E.; Kobayashi, M.; Inoue, H. *Tetrahedron Lett*. **1981**, *22*, 135.
6. Lee, B. H.; Clothier, M. F. *Tetrahedron Lett*. **1994**, *35*, 1135.
7. Lee, B. H.; Clothier, M. F. *Tetrahedron Lett*. **1999**, *40*, 643.
8. Compound **3**: white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 & 6.41 (d, J=8.1 Hz, 2H), 6.30 & 4.80 (d, J=7.6 Hz, 2H), 3.94 (d, 1H), 3.51 (d, 1H), 3.39 (d, 1H), 3.19 (m, 1H), 2.92 (s, 3H), 2.53 (d, 1H), 2.38–2.12 (m, 3H), 2.08 (t, 1H), 1.95–1.74 (m, 3H), 1.65 (s, 3H), 1.43 (s, 6H), 0.92 & 0.89 (s, 6H); HRMS (FAB): m/z 480.2869 ($C_{28}H_{37}N_3O_4$+H requires 480.2862).
9. Shoop, W. L.; Haines, H. W.; Eary, C. H.; Michael, B. F. *Am. J. Vet. Res*. **1992**, *53*, 2032.
10. Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc*. **1996**, *118*, 557.
11. Compound **4**: white solid; selected ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.80 & 6.69 (d, J=8.1 Hz, 2H), 6.31 & 4.89 (d, J=7.7 Hz, 2H), 3.81 (d, 1H), 3.30–3.20 (m, 1H), 3.01 (s, 3H), 2.50 (d, 1H), 1.45 and 1.44 (2s, 6H), 1.25 (s, 3H), 0.60 (s, 3H); HRMS (FAB): m/z 493.2577 ($C_{28}H_{35}N_3O_5$+H requires 480.2557).