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An Improved Synthesis of 14α-Hydroxy-15,16-dehydro-17-oxomarcfortine A; A Key Intermediate in the Synthesis of 14α-Hydroxymarcfortine A

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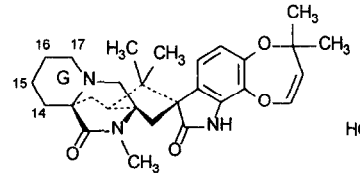
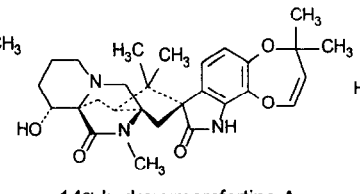
Abstract: An improved synthesis of 14α-hydroxymarcfortine A from marcfortine A was achieved by means of a redesigned synthesis of the key intermediate 14α-hydroxy-15,16-dehydro-17-oxomarcfortine A (**8**).

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.

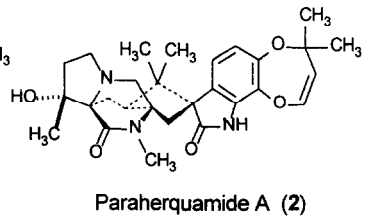
The potent antiparasitic activity of marcfortine A (**1**), paraherquamide A (**2**) and their analogs has been described by scientists at Merck.[3] Because the marcfortines and paraherquamides are unique both structurally and in their mode of action, they represent a promising new class of anthelmintics. 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.



Marcfortine A (**1**)



14α-hydroxymarcfortine A



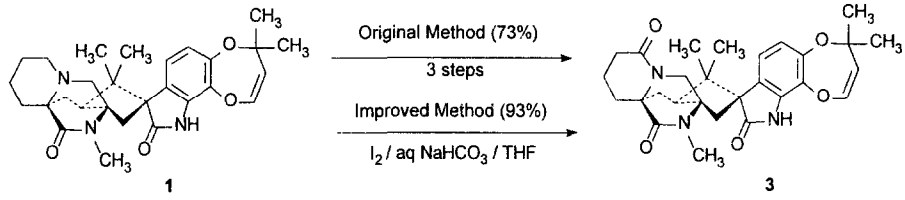
Paraherquamide A (**2**)

To investigate the significance of the hydroxyl group on anthelmintic activity, we prepared 14α-hydroxymarcfortine A. This paper describes a practical synthesis which enabled us to prepare multi-gram

quantities of 14α-hydroxymarcfortine A for biological evaluation.

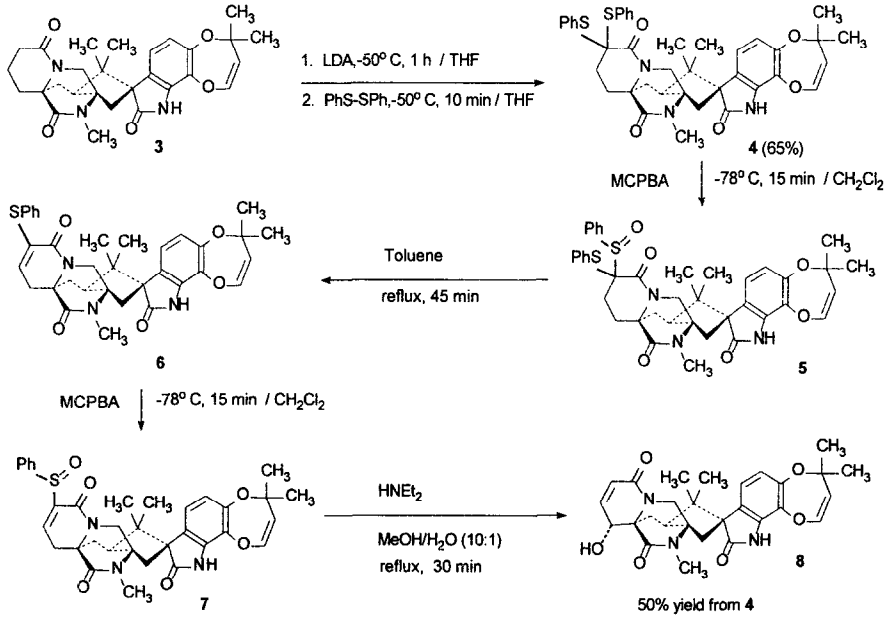
Since the present synthesis is based on our earlier synthesis of 14α-hydroxymarcfortine A,[6] we first needed to prepare 17-oxomarcfortine A (**3**) (Scheme 1). Our original method of C-17 oxidation relied upon a novel reaction of cyanogen iodide. Treatment of marcfortine A with cyanogen iodide produced a mixture (90% yield) of 16α-iodo-17β-cyanomarcfortine A and 16β-iodo-17α-cyanomarcfortine A.

Scheme 1



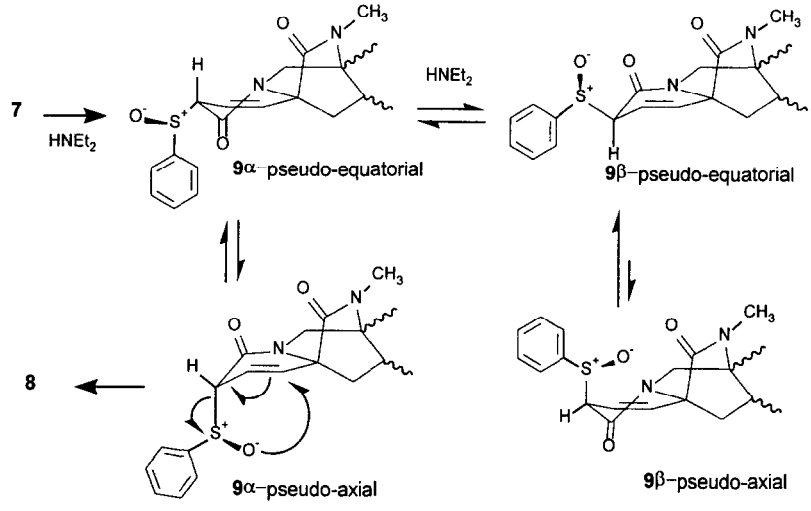
Elimination of HI with potassium hydroxide in methanol gave 16,17-dehydro-17-cyanomarcfortine A which was hydrolyzed by selenium dioxide to give **3** in 51% overall yield. When *p*-toluenesulfonic acid was used in place of selenium dioxide the overall yield improved to 73%. Subsequent to this work, we discovered that treatment of **1** with sodium bicarbonate and iodine in refluxing aqueous tetrahydrofuran also produced **3**, but in a single step and 93% yield.[7] This method not only provided higher yields, but also obviated the use of highly toxic cyanogen iodide and selenium dioxide reagents.

Scheme 2



We reported earlier[6] the preparation of **8** from 17-oxomarcfortine A (**3**). In that synthesis highly toxic selenium reagents were required. In our new synthesis we were able to eliminate these toxic reagents and significantly improve the overall yield (Scheme 2). Thus, **3** was disulfenylated with LDA and phenyl disulfide to give 16,16-bis(phenylsulfenyl)-17-oxomarcfortine A (**4**, 65% yield). Oxidation with 1.1 equivalents of *m*-chloroperoxybenzoic acid provided 16-phenylsulfenyl-16-phenylsulfinyl-17-oxomarcfortine A (**5**). Refluxing in toluene gave 15,16-dehyro-16-phenylsulfenyl-17-oxomarcfortine A (**6**). Subsequent treatment with *m*-chloroperoxybenzoic acid produced 15,16-dehydro-16-phenylsulfinyl-17-oxomarcfortine A (**7**), which underwent rearrangement[8] in the presence of diethylamine in methanol to give 14α-hydroxy-15,16-dehydro-17-oxomarcfortine A[9] (**8**, 50% yield from **4** after silica gel chromatography); 14β-hydroxy-15,16-dehydro-17-oxomarcfortine A was not detected in the reaction mixture.

Scheme 3



We explain the observed α stereoselective introduction of the C14 hydroxy group in Scheme 3. Compound **7** is deconjugated in the presence of diethylamine to give the **9**α and **9**β sulfoxides. The pseudo-axial conformation of the α and β isomers leads to potential rearrangement. However, the β-pseudo-axial conformation is highly disfavored due to repulsive electrostatic interactions between the sulfoxide oxygen and the *N*-methyl lactam oxygen, and thus the rearrangement proceeds *via* the α-pseudo-axial conformation. The preparation of 14α-hydroxymarcfortine A was then completed as previously described.[6] The higher overall yield of this alternative synthesis (33% compared to 21%) coupled with the ability to proceed from **4** to **8** without purifying any of the intermediates and the lower toxicity of the reagents contribute to the superiority of this alternative route.

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9. **14α-hydroxy-15,16-dehydro-17-oxomarcfortine A (8) :** To crude 15,16-dehydro-16-phenylsulfinyl-17-oxomarcfortine A (**7**, 13g) in aqueous MeOH ($MeOH/H_2O$, 10/1, 300 mL) was added diethylamine (15 mL). After 0.5 h of reflux, the reaction was cooled to room temperature, diluted with water (450 mL) and extracted into CH_2Cl_2 (500 mL). Drying ($MgSO_4$), followed by concentration and silica gel chromatography (130 g, 30% acetone/CH_2Cl_2) gave 14α-hydroxy-15,16-dehydro-17-oxomarcfortine A (**8**, 3.6 g, 50% yield from **4**). ^1H NMR and HRMS spectra were identical with the spectra of the previously prepared material.[6]

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