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Recent advances in the synthesis of antifungal agents

A.G.M. Barrett,[a] W.W. Doubleday,[b] D. Hamprecht,[a] K. Kasdorf,[a] and G.J. Tustin[a]

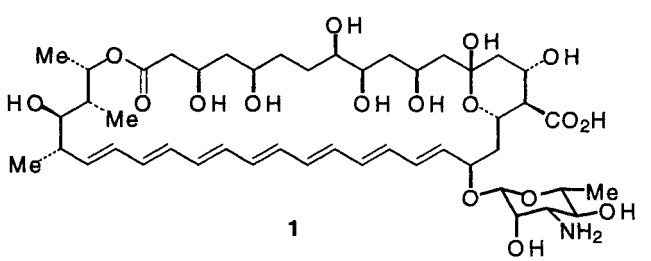
[a]*Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, England*
[b]*Department of Chemistry, Colorado State University, Fort Collins, Colorado, 80523, USA.*

Abstract: FR-900848 is a pentacyclopropane nucleoside antifungal agent isolated from the fermentation broth of *Streptoverticillium fervens*. The full structure with relative and absolute stereochemistry of this unusual natural product were established by a combination of partial synthesis and degradation. This assignment was confirmed by total synthesis from (*E,E*)-2,4-hexadiene-1,6-diol using three sequential asymmetric cyclopropanation reactions, Horner Emmons homologation and selective deoxygenation.

INTRODUCTION

Fungal disease: an overview

There is very considerable alarm amongst the medical profession regarding fungal disease.[1] Dermatophyte infections such as tinea pedis and candidiasis, although rarely fatal, are common and widespread throughout the world. There are other fungal diseases that are far darker in reputation and significance. Pathogens such as *Candida albicans, Cryptococcus neoformans, Pneumocystis carinii* and *Aspergillus fumigatus* are the cause of considerable morbidity and mortality in immuno-compromised patients. Populations at risk from these opportunistic fungal infections include AIDS patients, recipients of cancer chemotherapy and persons with genetically impaired immune function. The majority of AIDS patients die from fungal pneumonia induced by *Pneumocystis carinii.* Invasive pulmonary aspergillosis is the scourge of patients subject to cancer chemotherapeutic regimes. Indeed a significant proportion of patients with this disease are diagnosed only *post-mortem.* Current therapies for the treatment of serious systemic fungal infection are deficient. The gold standard amphotericin (**1**) is acutely toxic and there are resistance problems with azole fungistatic agents such as miconazole (**2**). There is a need for novel therapies for serious fungal disease and for the management of the legions of topical fungal infections. The Barrett group at Imperial College has carried out extensive synthetic studies on natural products such as nikkomycin B (**3**),[2] papuamine (**4**)[3] and papulacandin D (**5**)[4] in the search for superior antifungal agents.



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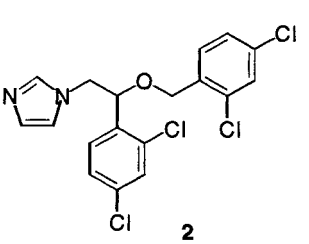

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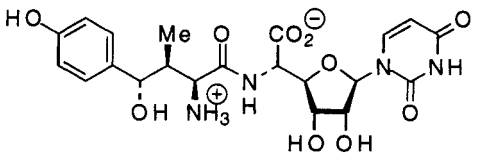

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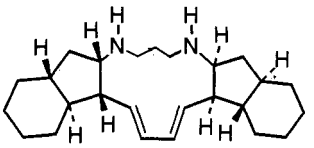

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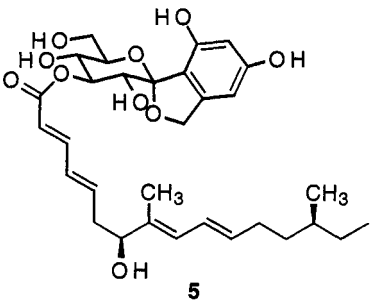

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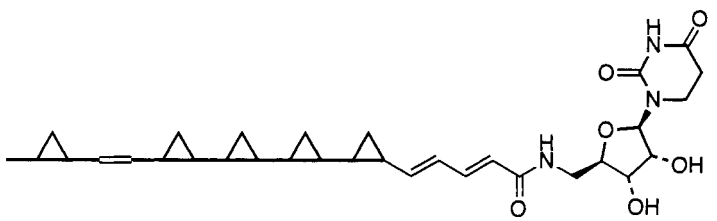
Novel antifungal natural products: FR-900848

In 1990 Yoshida *et al* and co-workers in the Fujisawa laboratories in Tsukuba, Japan reported the partial structural elucidation of a structurally remarkable natural product.[5] Fractionation of the fermentation broth from *Streptoverticillium fervens* and extensive chromatography led to the isolation of a structurally unique nucleoside. The structure of the new isolate was established by extensive NMR spectroscopy and partial degradation. That the compound was a 5'-amino-5'-deoxydihydro-uridine derivative was unusual but not especially exciting. However, the fact that FR-900848 (**6**), the unassuming Fujisawa file number for the new natural product, possessed an unusual fatty acid side chain was most noteworthy. This C_{23} fatty acid residue is endowed with five cyclopropanes, four of which are contiguous. Although the initial degradation studies at Fujisawa determined the constitution of the molecule,[5] there remained eleven elements of ambiguity in the structure: the geometry of Δ^{18}, the stereochemistry of the isolated cyclopropane and the stereochemistry of the quatercyclopropane unit. Tanaka and co-workers, however, did establish[6] that the central quatercyclopropane unit **7**, obtained by ozonolysis with a sodium borohydride work-up and acetylation, was C_2-symmetric.



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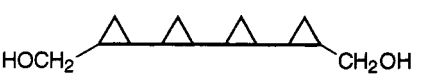

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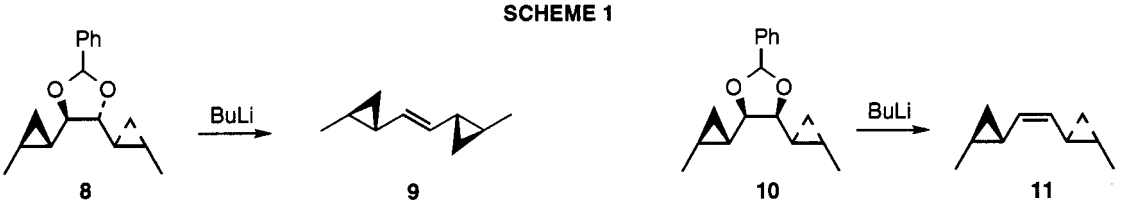
FR-900848 (**6**) shows potent, selective activity against filamentous fungi such as *Aspergillus niger*, *Mucor rouxianus, Aureobasidium pullulans,* and various *Trichophyton* sp. etc. In contrast it is essentially inactive against non-filamentous fungi such as *Candida albicans* and Gram -positive and -negative bacteria. It shows activity *in-vivo* and is not appreciably toxic.[7] Thus FR-900848 (**6**) represents a significant new lead for the design of nucleoside antifungal agents active against the major human pathogen *Aspergillus fumigatus.* It is certain that the fatty acid side chain of FR-900848 (**6**) is considerably conformationally restricted. The influence of this fact on bio-activity and mode of antifungal action is as yet undefined. The biosynthetic origin of FR-900848 (**6**) is not yet clear nor is it obvious as to what evolutionary advantage there is in endowing a fatty acid with 5 cyclopropane ring systems with the attendant strain energy of about 130 kcal.mol^{-1}. All these factors underscore the potential importance of synthetic chemistry on FR-900848 (**6**) and related multicyclopropane arrays.

RESULTS AND DISCUSSION

Structural elucidation of FR-900848

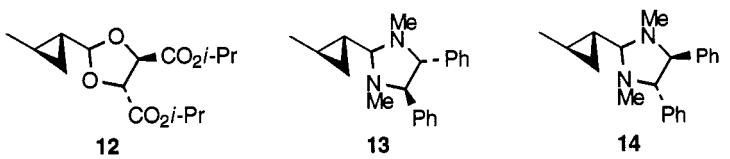
The full structure and stereochemistry of FR-900848 was determined by a combination of synthesis and degradation.[8-14] The isolated alkene unit of FR-900848 (**6**) was established to be *trans* by the synthesis of two model dicyclopropylethene derivatives **9** and **11** (Scheme 1). The dicyclopropane derivatives **8** and **10** were prepared stereospecifically from D-mannitol using a double Simmons-Smith cyclopropanation reaction as the key step. C-2 Lithiation of acetals **8** and **10** resulted in Whitham elimination[15] to respectively provide the geometrically pure *E*-alkene **9** and the geometrically pure *Z*-alkene **11**. Comparisons of the ^{1}H NMR spectra of alkenes **9** and **11** with FR-900848 (**6**) were consistent with the assignment of the natural Δ^{18} geometry as *trans*.

SCHEME 1



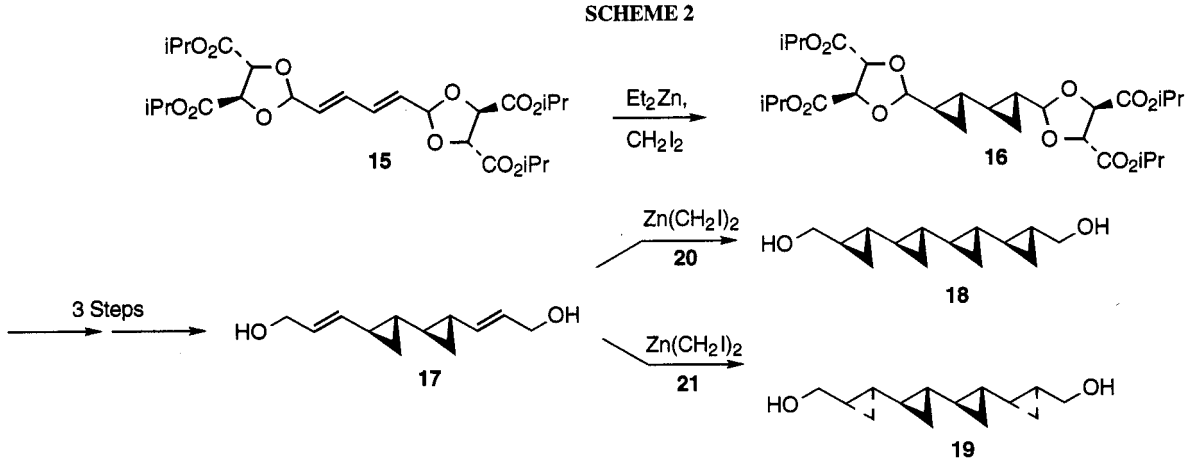
8 **9** **10** **11**

Two imidazolidine derivatives **13** and **14** were prepared from crotonaldehyde *via* acetal **12** using Yamamoto asymmetric cyclopropanation,[16] acid catalysed hydrolysis and condensation with the corresponding chiral diamines.[17] Ozonolysis of an authentic sample of FR-900848 (**6**) and subsequent reaction with (1*R*, 2*R*)-*N*,*N*'-dimethyl-1,2-diphenylethanediamine gave an imidazolidine derivative which was identical with the synthetic adduct **13**.



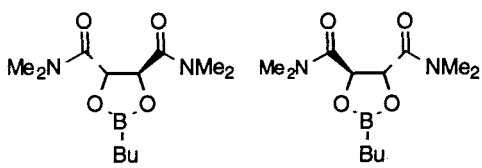
12 **13** **14**

SCHEME 2

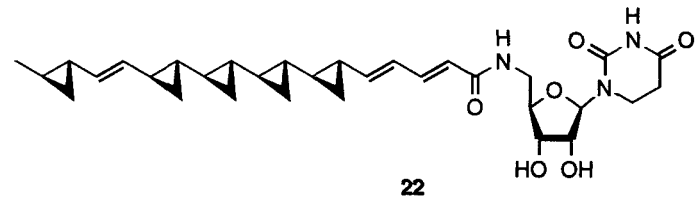


15 **16** **18** **17** **19**

Several strategies have been explored for the stereoselective construction of the quatercyclopropane core of FR-900848 (**6**) and the initial approach is illustrated in Scheme 2. Double Yamamoto cyclopropanation[16] of diene **15** followed by a double Charette cyclopropanation[18,19] of diene **17**, gave either the all-*syn*-quatercyclopropane **18** or the *anti-syn-anti*-quatercyclopropane **19** depending on the absolute stereochemistry of the tartramide additives **20** or **21**. The stereochemistry of the quatercyclopropane unit of FR-900848 (**6**) was determined by comparisons of the acetates prepared from the model diols **18** and **19** with that prepared from the corresponding degradation product diol **2**. From this analysis it was clear that the quatercyclopropane **7** was identical in all respects including the absolute stereochemistry with diol **18**. In each case the structural assignments of synthetic materials were established by X-ray crystallography. All these facts are consistent with the assignment of structure **22** to FR-900848.



20 **21**



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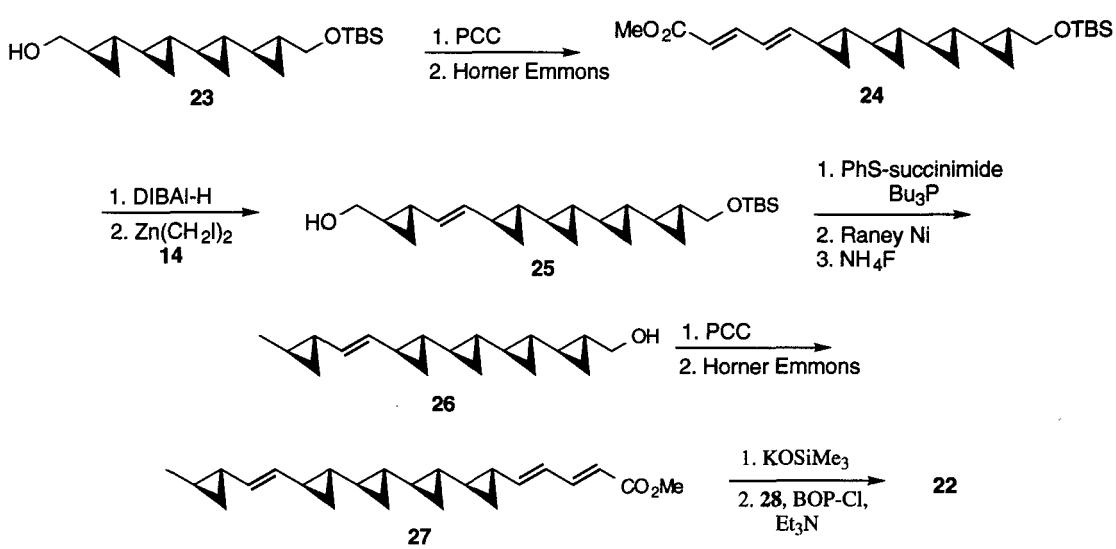
Total synthesis of FR-900848

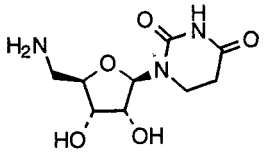
The total synthesis of FR-900848 (**22**) has recently been completed using a sequence of Charette cyclopropanation reactions (Scheme 3).[20] As a more concise alternative to Scheme 2, (*E,E*)-2,4-hexadiene-1,6-diol was bicyclopropanated in the presence of the chiral auxiliary **20** and homologated to provide the bicyclopropane **17** and subsequently the quatercyclopropane **18**. Subsequent mono-*t*-butyldimethylsilylation, oxidation and Horner-Emmons homologation gave ester **24**. DIBAL-H reduction followed by a third Charette asymmetric cyclopropanation gave the pentacyclopropane alcohol **25**. Reaction of alcohol **25** with *N*-

SCHEME 3



23 **24** **25** **26** **27**

(phenylsulfenyl)succinimide and tributylphosphine[21] cleanly gave the corresponding sulfide which was desulfurized using Raney nickel without significant alkene hydrogenation or cyclopropane degradation. Work-up with ammonium fluoride gave alcohol **26**. Finally, PCC oxidation, Horner-Emmons homologation, potassium trimethylsilanolate mediated hydrolysis and BOP-Cl mediated coupling with the nucleoside amine **28**[22] gave FR-900848 (**22**). The synthetic material was identical with an authentic sample of the natural product.



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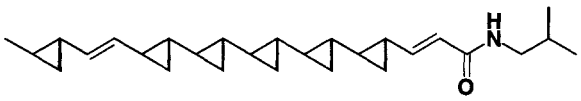
It is clear from these results that triple Charette asymmetric cyclopropanation is appropriate for the elaboration of FR-900848 (**22**) with excellent overall stereochemical control. In our hands, alternative strategies involving the condensation of monocyclopropane and quatercyclopropane derivatives to elaborate Δ^{18} have the disadvantages of low geometric control and/or degradation. Armstrong, Falck and Zercher have recently reported alternative approaches to the total synthesis of FR-900848 (**22**).[23-25] Finally, it is important to mention the recent isolation and partial characterisation of the cholesteryl ester transfer protein inhibitor U-106325 (**29**) from the fermentation broth of UC 11136.[26] Clearly, this hexacyclopropane natural product bears a striking resemblance to FR-900848 (**22**).



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