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FEATURE ARTICLE

Assembly of the antifungal agent FR-900848 and the CETP inhibitor U-106305: studies on remarkable multicyclopropane natural products†

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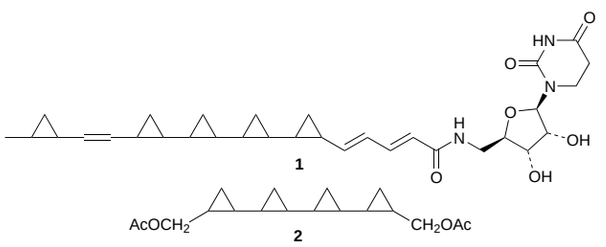
The full structural elucidation of FR-900848, an antifungal pentacyclopropane nucleoside natural product from *Streptoverticillum fervens*, is reported. A series of model compounds are prepared using multiple asymmetric Simmons–Smith cyclopropanation reactions. Comparisons of spectroscopic data of synthetic 1,2-dicyclopropylethene, quatercyclopropane-2,2‴-dimethanol and 2-methylcyclopropanecarbaldehyde derivatives of defined absolute stereochemistry with FR-900848 and its degradation products are used to unequivocally establish the absolute stereochemistry of the natural product.

A C_2-symmetric quatercyclopropane-2,2‴-dimethanol is converted by a sequence of desymmetrisation, selective monocyclopropanation of a 5-(quatercyclopropyl)penta-2,4-dien-1-ol derivative, deoxygenation and Horner–Emmons homologation into the fatty acid side chain of FR-900848. Coupling of this carboxylic acid with 5′-amino-5′-deoxy-5,6-dihydrouridine gives synthetic FR-900848. The unusual helical structure of FR-900848 is discussed and compared with U-106305, a cholesteryl ester transfer protein inhibitor from the fermentation broth of *Streptomyces* sp. UC 11136. The full structure and stereochemistry of U-106305 is established by total synthesis using a bi-directional strategy closely following the route to FR-900848.

Introduction

There is very considerable alarm amongst the medical profession regarding fungal disease. Dermatophyte infections such as tinea pedis and candidiasis, although rarely fatal, are common and widespread throughout the world.[1] 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 immunocompromised patients. Current therapies for the treatment of serious systemic fungal infection are deficient. There is need for novel therapies for serious fungal disease and for the management of the legions of topical fungal infections. In consequence several pharmaceutical companies world-wide are seeking to develop superior fungicidal agents. Owing to evolutionary pressures of microbial antagonism, fermentation broths are rich sources of novel anti-infective agents, and natural product chemistry continues to play a major role in antibiotic discovery.

In 1990 Yoshida *et al*. in the Fujisawa laboratories in Tsukuba reported the partial structural elucidation of a remarkable natural product.[2]‡ 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′-deoxy-5,6-dihydrouridine derivative was unusual but not especially exciting. However, the fact that FR-900848 **1**,



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,[2] 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[3] that the central quatercyclopropane unit **2**, obtained by ozonolysis with a sodium borohydride work-up and acetylation, was C_2-symmetric. This partial structural assignment followed from the simplicity of the ^{1}H NMR spectrum and the presence of only seven lines in the ^{13}C NMR spectrum. In addition, the $[\alpha]_D$ for diester **2** was consistent with a C_2-structure rather than *meso* stereochemistry.

FR-900848 **1** shows potent, selective activity against filamentous fungi such as *Aspergillus niger*, *Mucor rouxianus*, *Aureobasidium pullulans*, 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.[2,4] Thus FR-900848 **1** 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 **1** is considerably conformationally restricted. The influence of this fact on bioactivity and mode of antifungal action is as yet undefined. The biosynthetic origin of FR-900848 **1** is not yet clear nor is it obvious as to what evolutionary advantage there is in endowing a fatty acid with five cyclopropane ring systems with the attendant strain energy of about 130 kcal mol^{-1}. Finally, FR-900848 **1** provides an intriguing model upon which to design a new class of materials: stereoregular poly(cyclopropene). Such compounds may well have unique and useful physical properties. All these factors underscore the potential importance of synthetic chemistry on FR-900848 **1** and related multicyclopropane arrays.

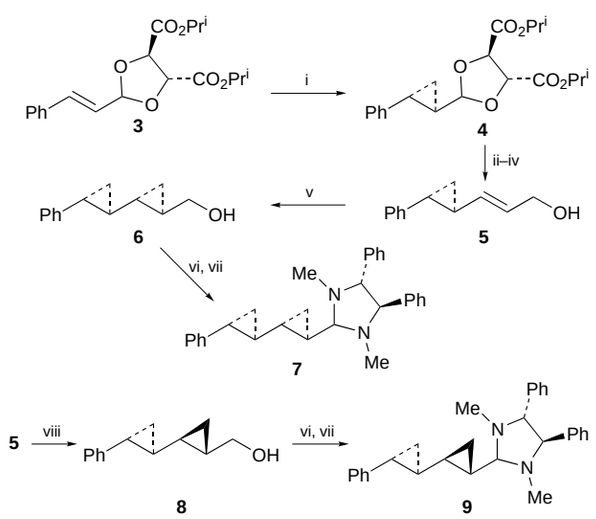
Stereoselective synthesis of bicyclopropanes

There is an extensive literature on the synthesis and reactions of bicyclopropane arrays. For example, Buchert and Reissig[5] have reported the synthesis of highly substituted bicyclopropanes. In addition, Nijveldt and Vos have carried out an X-ray crystallographic study of bicyclopropane.[6] Prior to the discovery of FR-900848 **1**, little attention was paid to issues of stereochemistry in bicyclopropane chemistry. Recently, ourselves[7–9] and the Zercher[10,11] and Armstrong[12] groups have independently reported stereoselective methods for the preparation of bicyclopropane systems relevant to the total synthesis of FR-900848 **1**. All of these approaches have applied known asymmetric Simmons–Smith reactions to control all four stereocentres in the assembly of 2,2′-disubstituted bicyclopropanes.

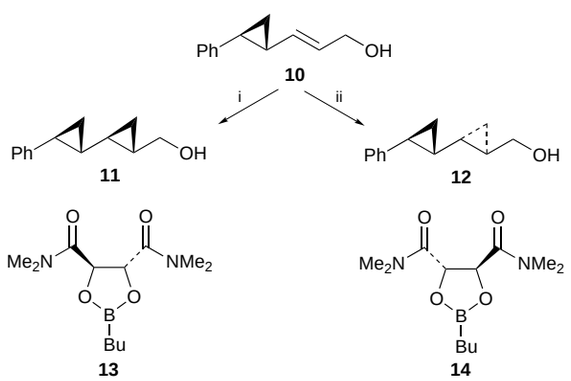
We have prepared both the *syn*- and *anti*-bicyclopropanes **6** and **8** stereoselectively using both Yamamoto[13,14] and Fujisawa[15] asymmetric cyclopropanation chemistry (Scheme 1). Thus Yamamoto cyclopropanation of the chiral acetal **3** gave cyclopropane **4**[13] as a single diastereoisomer following chromatographic purification. Subsequent acid hydrolysis, Horner–Emmons homologation and DIBAL-H reduction gave the enantiomerically pure allylic alcohol **5**. Reaction of alcohol **5** with diethylzinc and diiodomethane in the presence of L-(+)-diethyl tartrate or D-(−)-diethyl tartrate according to the Fujisawa protocol,[15] respectively gave the *syn*- and *anti*-bicyclopropane derivatives **6** (ds 6 : 1) and **8** (ds 6 : 1). Thus, *syn*- or *anti*-bicyclopropanes can be prepared *via* reagent control. In contrast, treatment of alcohol **5** with diethylzinc and diiodomethane with the absence of tartrate esters gave both bicyclopropanes **6** and **8** (*ca.* 1 : 1) in 82% yield. It is clear from these observations that the prexisting cyclopropane ring in alkene **5** has little influence on the stereochemistry of the second cyclopropanation reaction. Zercher has observed similar low stereoselectivity in the cyclopropanation of racemic alkene **5**.[10] The structures of the bicyclopropanes **6** and **8** were unambiguously established by oxidation and conversion[16,17] into the imidazolidines **7** and **9** respectively and an X-ray crystal structure analysis[7] of isomer **7**.

Zercher has utilised the excellent Charette asymmetric cyclopropanation reaction[18,19] for the highly stereoselective preparation of both *syn*- and *anti*-bicyclopropanemethanol derivatives.[10] These studies are exemplified by the chemistry in Scheme 2. Thus the allylic alcohol **10** was respectively converted into the bicyclopropanes **11** (67%) and **12** (72%) using the tartramide additives **13** and **14** to control absolute stereochemistry (ds > 12 : 1). In addition, the Zercher group has used double Charette asymmetric cyclopropanation chemistry and sulfur ylide methodologies to elaborate various bicyclopropanes with the *cis-trans*- and *cis-cis*-ring stereochemistries.[10,11] During these studies this group noted, in some cases, that the prexisting cyclopropane ring dramatically influenced the stereochemistry of the second cyclopropanation reaction. For example, this is underscored by the high *anti*-selectivity in the cyclopropanation of alkene **17** to provide bicyclopropane **18**, in contrast to the lower stereoselectivities observed on the cyclopropanation of alkenes **15** and **19** (Scheme 3). In general in these systems, except when substrate and reagent stereochemical biases are mismatched, Simmons–Smith cyclopropanation in the presence of the Charette additives **13** and **14** proceeds with good to excellent stereoselectivity. It is probable that the diastereoselectivity in the conversion of alkene **17** into the bicyclopropane **18** has its origin in steric approach control and the minimization of allylic 1,3-strain.[20] The use of the Charette chemistry[18,19] will feature repeatedly in this article and there is no doubt that the method represents a significant advance in enantioselective synthesis.

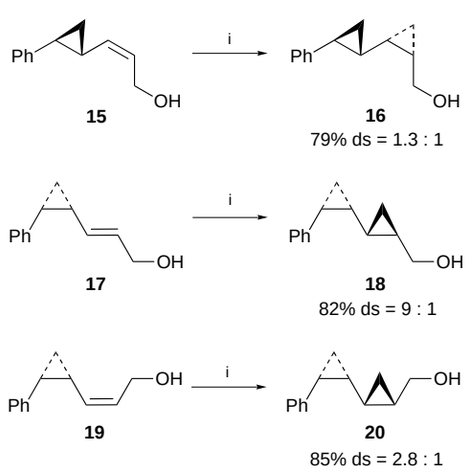
We have shown that 2,4-dienols **21** react with diethylzinc and diiodomethane in 1,2-dichloroethane at −20 °C to generate the corresponding racemic bicyclopropane derivatives **23** and **24** in good yield (68–80%) and with good diastereoselectivity (5 : 1 to > 95 : 5) favouring the *anti*-isomers **23** (Scheme 4).[8] It is reasonable to speculate that the reaction involves the intermediacy of the monocyclopropane **22** and stereoelectronic control of the second cyclopropanation step (see Fig. 1). In this analysis, overlap of the most electron-rich cyclopropane σ-bond



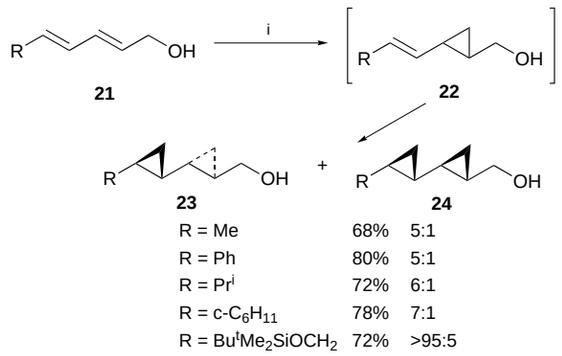
Scheme 1 *Reagents and conditions*: i, Et_2Zn, CH_2I_2, PhMe, −20 °C, 91%; ii, TsOH, H_2O, THF, 60 °C, 93%; (iii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C, 95%; iv, DIBAL-H, CH_2Cl_2, −78 °C, 89%; v, L-(+)-diethyl tartrate, Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, −12 °C, 72%; vi, pyridinium chlorochromate, NaOAc, SiO_2, CH_2Cl_2, 0 °C; vii, (1*R*,2*R*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine, Et_2O, 4 Å molecular sieves, 25 °C; viii, D-(−)-diethyl tartrate, Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, −12 °C, 84%



Scheme 2 *Reagents and conditions*: i, Et_2Zn, CH_2I_2, **13**, 67%; ii, Et_2Zn, CH_2I_2, **14**, 72%



Scheme 3 *Reagents and conditions*: i, Et_2Zn, CH_2I_2, 0 °C



Scheme 4 *Reagents and conditions*: i, Et_2Zn, CH_2I_2, $(CH_2Cl)_2$, −20 °C

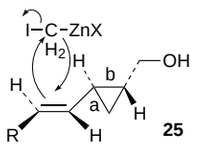
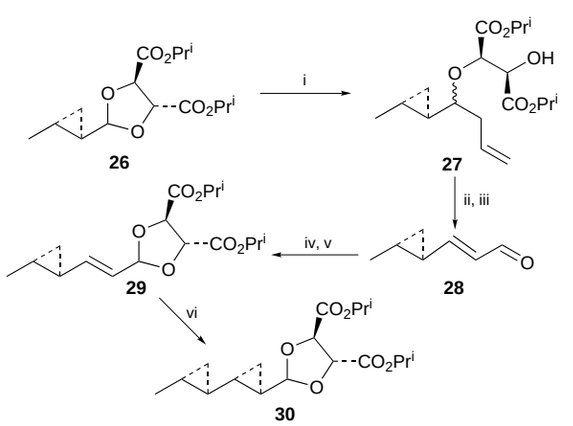


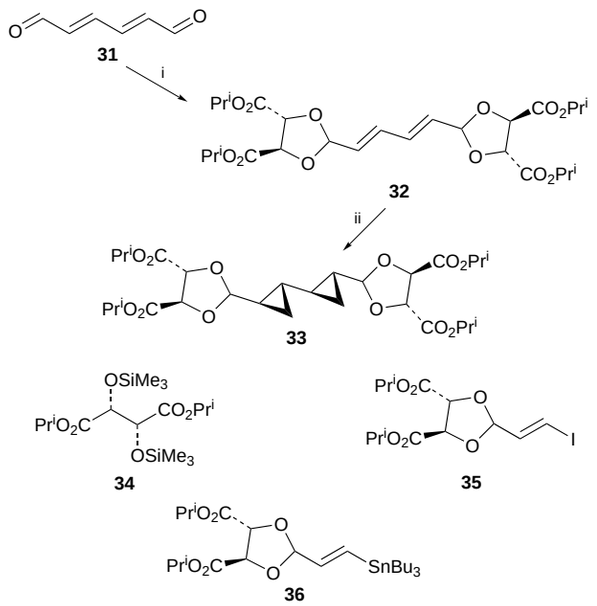
Fig. 1

(bond a, not bond b) with the alkene π-system should enhance its nucleophilicity and favour *anti*-delivery of the zinc carbenoid electrophile.

Armstrong has used both Yamamoto cyclopropanation[13] and allylsilane chemistry in the elaboration of a *syn*-bicyclopropane **30** (Scheme 5).[12] Thus sequential reaction of the acetal **26** with allylsilane in the presence of titanium(IV) chloride, ozone and triethylamine gave the enal **28**. Condensation with L-(+)-diisopropyl tartrate gave the corresponding acetal **29** and this was further cyclopropanated to produce the bicyclopropane **30** (65%, > 90% de). We have also used a double Yamamoto cyclopropanation strategy to produce a *syn*-bicyclopropane (Scheme 6).[9,21] Noyori acetalisation[22] of muconaldehyde[23] **31** or, alternatively, the Stille coupling[24] of vinyl iodide **35** with the vinyl stannane **36** gave the dienyl diacetal **32**. In turn, both alkenes **35** and **36** were prepared[21] from prop-2-ynyl alcohol *via* radical hydrostannylation, PCC oxidation and Noyori acetalisation.[22] Cyclopropanation of diene **32** according to the Yamamoto adaptation of the Simmons–Smith reaction[13] provided dicyclopropane **33** in good overall yield (56% from dial **31**) and essentially as a single diastereoisomer. A single crystal X-ray structure determination of bicyclopropane **33** was used to establish the relative and absolute stereochemistry of the four new chiral centres present in the molecule.[9] It is clear from this result that diene double cyclopropanation provides a simple



Scheme 5 *Reagents and conditions*: i, $Me_3SiCH_2CH{=}CH_2$, $TiCl_4$, CH_2Cl_2, −78 °C, 59%; ii, O_3, then Ph_3P work-up, 90%; iii, Et_3N, heat, 90%; iv, EtOH, pyridinium toluene-*p*-sulfonate, $HC(OEt)_3$; v, L-(+)-diisopropyl tartrate, EtOH, 35%; vi, CH_2I_2, Et_2Zn, 65%



Scheme 6 *Reagents and conditions*: i, **34**, $Me_3SiOSO_2CF_3$ (cat), $MeC(OSiMe_3){=}NSiMe_3$, CH_2Cl_2, −78 to 25 °C, 73%; ii, Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, −20 °C, 78%

entry to *syn*-bicyclopropane systems. Clearly, following the Yamamoto mechanistic model, each Lewis basic acetal oxygen should independently direct the Simmons–Smith zinc carbenoid to one face of the adjacent alkene.

Stereoselective syntheses of quatercyclopropanes and the stereochemical elucidation of FR-900848 1

We have explored three strategies for the stereoselective construction of quatercyclopropane arrays: (i) a double Yamamoto cyclopropanation followed by a double Charette cyclopropanation,[9,25] (ii) a double Charette cyclopropanation followed by a second double Charette cyclopropanation,[26] and (iii) a tetraene tetracyclopropanation reaction.[21] In the first approach (Scheme 7), acid catalysed hydrolysis of the diacetal **33** gave the corresponding dialdehyde, which was directly homologated using a double Wittig reaction to provide a mixture of the *E*,*E*-diester **37** and the *E*,*Z*-diester **38** (3.7 : 1). DIBAL-H reduction of pure diester **37** gave the corresponding diol **39** in high yield (91%). Pre-mixing of diol **39** with dioxaborolane **14** followed by treatment with preformed bis(iodomethyl)zinc gave quatercyclopropane **40** (94%), essentially as a single diastereoisomer. Likewise, use of dioxaborolane **13** gave the quatercyclopropane **41** (100%). It was apparent from ^1H and ^{13}C NMR data that the quatercyclopropanes **40** and **41** were two different C_2-symmetric isomers, and we rigourously established structures by an X-ray crystallographic study[25] of the bis(4-bromobenzoate) ester derived from **40** (Fig. 2). Interestingly, the four cyclopropyl units that form the backbone of the molecule are arranged helically.

In addition, the quatercyclopropane **40** was prepared from mucondiol using two sequential double Charette cyclopropanation reactions.[26] Since this strategy was crucial in our total synthesis of FR-900848 **1**,[26] discussion of this approach is

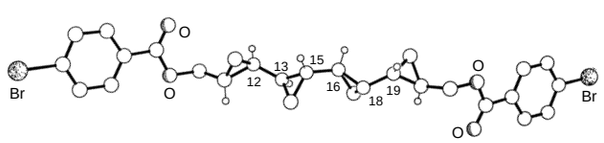
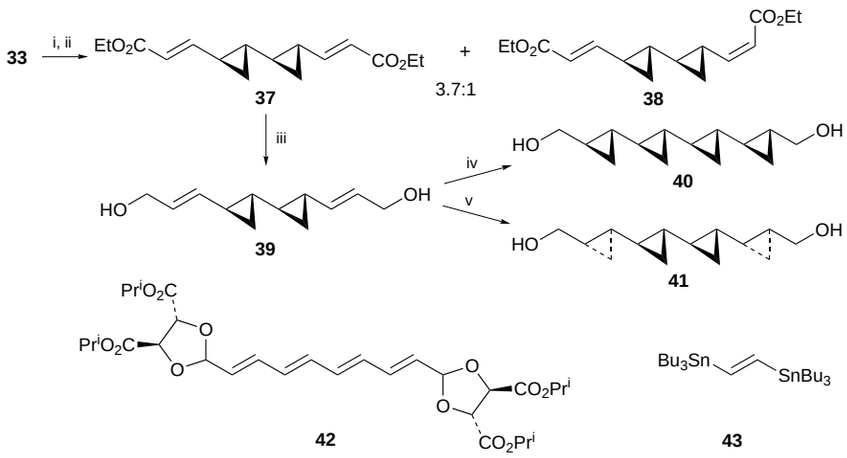


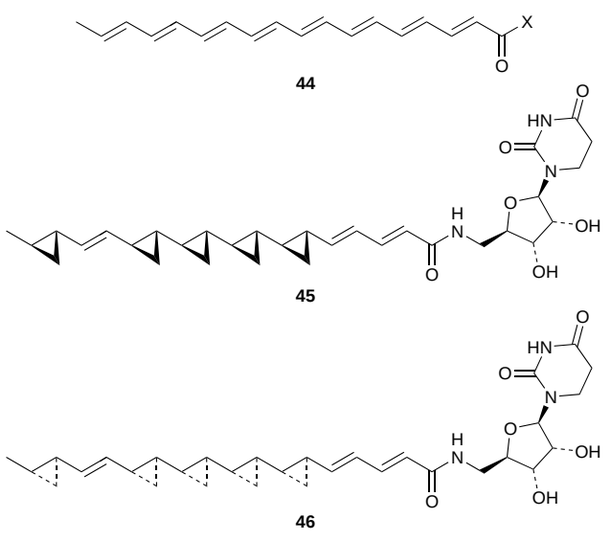
Fig. 2 The molecular structure of the bis(4-bromobenzoate) ester of diol **40** showing the absolute stereochemistry



Scheme 7 *Reagents and conditions*: i, TsOH, THF–H_2O, 55 °C; ii, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 61% from **33**; iii, DIBAL-H, CH_2Cl_2, −78 °C, 91%; iv, **14**, $Zn(CH_2I)_2$, CH_2Cl_2, 0 °C to room temp. 94%; v, **13**, $Zn(CH_2I)_2$, CH_2Cl_2, 0 °C to room temp., 100%

delayed until the next section. Finally, we have briefly examined the preparation of a quatercyclopropane using the direct tetracyclopropanation of a tetraene. Thus tetraene **42** was prepared from the iodoalkene **35** and alkene **43** using a sequence of Stille coupling,[24] iododestannylation and a second Stille coupling. Although reaction of tetraene **42** with diiodomethane and diethylzinc gave a quatercyclopropane, the stereochemical identity of this substance has yet to be established.

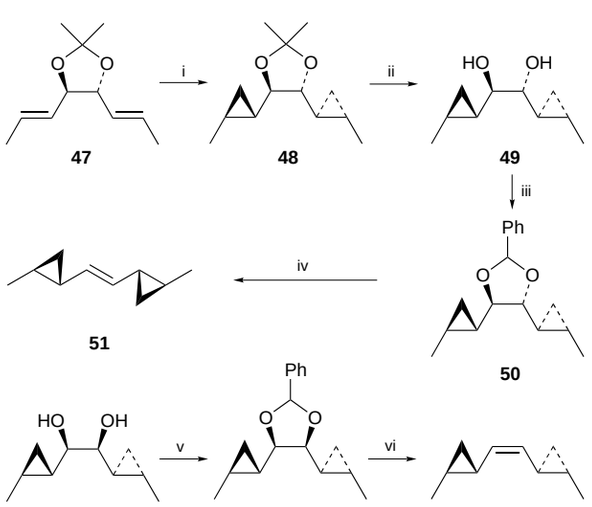
In our structural elucidation of FR-900848 **1** our planning was driven by speculation as to the biosynthetic origin of the natural product.[27] We considered that since the carbon count of **1** is odd at C_{23}, it is likely that all the cyclopropanes are introduced late from a polyenoic acid precusor. This precusor may be derived *via* a mixed acetate/propanoate biosynthetic origin and be already C_{23} or, more likely, the precusor may be the C_{18}-polyene **44** in which the five cyclopropanes are



introduced from a C_1 source such as *S*-adenosyl methionine. If the C_{18}-polyene **44** is indeed a key biosynthetic intermediate then the geometry is most likely to be all *trans* since $\Delta^{2,4}$ are unequivocally *trans*. If these suppositions are true, FR-900848 **1** should be represented by either **45** or **46** since each enzymatic cyclopropanation should retain the alkene geometry and show the same absolute stereochemical bias. In addition, the geometry of Δ^{18} should be *trans* following the same biosynthetic speculation. In consequence of these considerations we sought to prepare model cyclopropane systems including quatercyclopropanes **40** and **41** to establish the sterochemistry of FR-900848 by correlation with key fragments from degradation. Falck[28] has also speculated as to the biosynthetic origin of the natural product and undertaken the synthesis of polycyclopropanated compounds as precursors to FR-900848 **1**.

Finally, Upjohn scientists have very recently reported on the isolation and biosynthesis of U-106305, a natural product related to FR-900848 **1**.[29] This substance has been shown to be biosynthetically derived from both acetate and methionine, but more of this later.

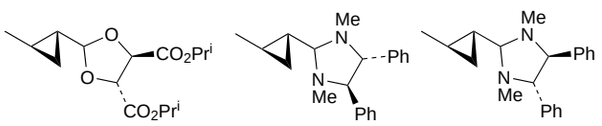
The isolated alkene unit of FR-900848 **1** was established to be *trans* by the following experiments (Scheme 8).[30–32] Double Simmons–Smith cyclopropanation of alkene **47** proceeded with excellent diastereoselectivity to provide only a single C_2-symmetric dicyclopropane **48** (89%). Sequential acid-mediated deprotection (63%) and condensation with benzaldehyde (64%) gave the benzylidene derivative **50**. Subsequent C-2 lithiation (1,3-dioxolane numbering) resulted in Whitham elimination[33] to provide the geometrically pure *E*-alkene **51** (60%). Alternatively, diol **52** was prepared from diol **49** *via* Swern oxidation[34] and sodium borohydride reduction. Whitham elimination of the derived acetal **53** gave the corresponding geometrically pure *Z*-alkene **54**. Comparison of the ^1H NMR



Scheme 8 *Reagents and conditions*: i, Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, −20 °C, 89%; ii, TsOH (cat), THF–H_2O (5 : 1), 70 °C, 63%; iii, PhCHO, H_2SO_4 (cat), PhMe, 111 °C, 64%; iv, BuLi, pentane, 60%; v, PhCHO, camphorsulfonic acid, 96%; vi, BuLi, pentane

spectra of alkenes **51** and **54** with FR-900848 **1** was consistent with the assignment of the natural Δ^{18} geometry as *trans*. Clearly this stereochemical assignment is fragile unless the structures of the acetals **50** and **53** are secure. This insurance was underwritten by single crystal X-ray crystal structures[30,31] for both 3,5-dinitrobenzoate diesters derived from diols **49** and **52**.

The stereochemistry of the quatercyclopropane unit of FR-900848 **1** was determined[25,32] by comparison of the acetates prepared from the model diols **40** and **41** with the corresponding degradation product **2**[3] derived from the natural product. We were delighted to observe that quatercyclopropane **2** was identical in all respects, including the absolute stereochemistry, with the diacetate from diol **40**. Finally, two imidazolidine derivatives **56** and **57** were prepared from crotonaldehyde *via* acetal **55** using Yamamoto asymmetric cyclopropanation,[13,14]

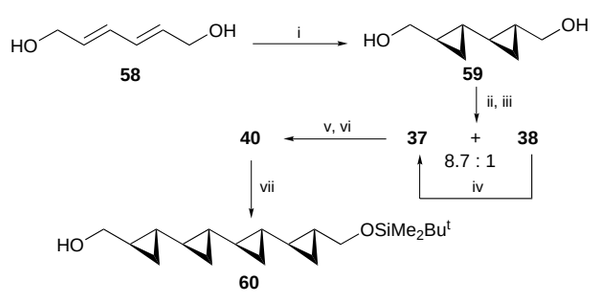


55 **56** **57**

acid catalysed hydrolysis and condensation with the corresponding chiral diamines.[17] Ozonolysis of an authentic sample of FR-900848 **1** and subsequent reaction with (1*R*,2*R*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine gave an imidazolidene derivative which was identical with the synthetic adduct **56**. All these facts are consistent with the assignment of structure **45** to FR-900848.

Total synthesis of FR-900848 45

We have recently reported the total synthesis of FR-900848 **45** using a sequence of Charette cyclopropanation reactions (Schemes 9, 10 and 11).[26] Mucondiol **58** was bicyclopropanated in the presence of the chiral auxillary **14**[18] to provide bicyclopropane **59** (89%) predominately as a single enantiomer (Scheme 9). PCC oxidation and subsequent direct homologation without purification of the intermediate dialdehyde provided a separable mixture of *E*,*E*-diester **37** and the *E*,*Z*-isomer **38** (8.7 : 1, 67% from **59**). The unwanted diester **38** was smoothly converted into diester **37** using $LiTi(OPr^i)_4(SPh)$, a reagent introduced by Hunter[35] for the *Z* to *E* isomerisation of α,β-unsaturated esters. DIBAL-H reduction of diester **37** (94%) and bicyclopropanation of the resultant diol under Charette conditions[18] provided diol **40** (93%), predominately as a single diastereoisomer. Subsequent mono-*tert*-butyldimethylsilylation, oxidation and Horner–Emmons homologation gave esters **61** and **62** (Scheme 10). Again, Hunter isomerisation[35] was crucial in converting the undesired isomer **62** into additional *E*,*E*-ester **61**. Finally, DIBAL-H reduction of *E*,*E*-ester **61** (91%) followed by a third Charette asymmetric cyclopropanation[19] gave the pentacyclopropane alcohol **63** in high yield (90%). Very recently, Charette has reported related monocyclopropanation reactions on related dienols.[36]



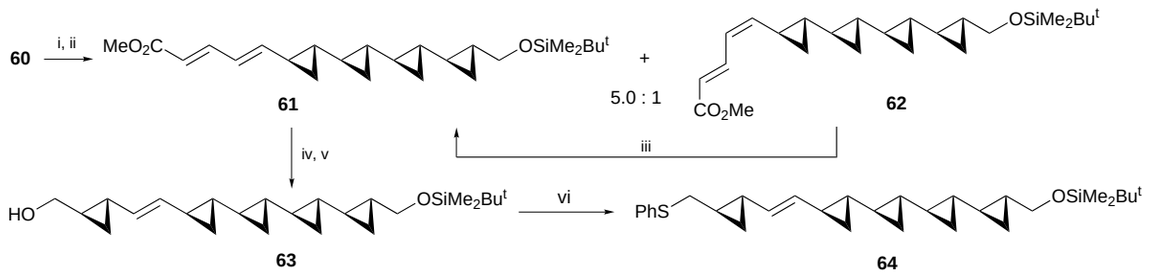
Scheme 9 *Reagents and conditions*: i, **14**, Et_2Zn, CH_2I_2, CH_2Cl_2, 0 to 25 °C, 89%; ii, pyridinium chlorochromate, NaOAc, silica, CH_2Cl_2, 0 to 25 °C; iii, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 67% from **59**; iv, PhSH, BuLi, $Ti(OPr^i)_4$, THF, 0 to 25 °C, 50%; v, DIBAL-H, CH_2Cl_2, −78 °C, 94%; vi, **14**, Et_2Zn, DME, CH_2I_2, CH_2Cl_2, −15 to 25 °C, 93%; vii, NaH, Bu^tMe_2SiCl, THF, 44%

In general we have been significantly frustrated in our attempts to effect substitution reactions on multiple cyclopropanemethanol derivatives *via* hydroxy activation and displacement. Although such approaches usually lead to extensive degradation, reaction of alcohol **63** with *N*-(phenylsulfenyl) succinimide and tributylphosphine[37] cleanly gave the sulfide **64** (89%). Treatment of sulfide **64** with Raney nickel followed by ammonium fluoride gave alcohol **65** without significant alkene hydrogenation or cyclopropane degradation (Scheme 11). Finally, PCC oxidation of alcohol **65**, Horner–Emmons homologation (with Hunter isomerisation[35] of the unwanted *E*,*Z*-ester **67**), potassium trimethylsilanolate[38] mediated hydrolysis and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl)[39] mediated coupling with the nucleoside amine **69**[40] gave FR-900848 **45**. Much to our delight the synthetic material was identical with an authentic sample of the natural product.

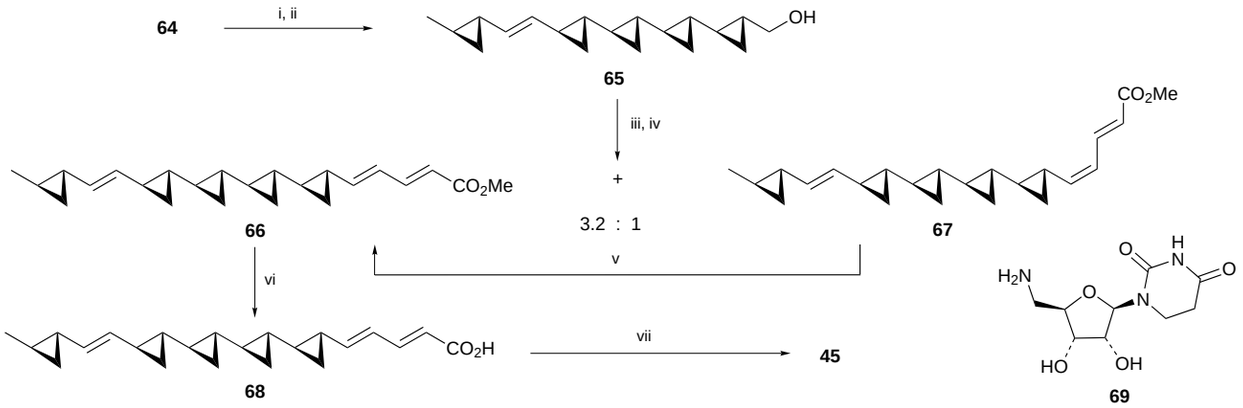
Falck *et al.* have also reported a total synthesis of FR-900848 **45** which elegantly underscores the value of Horeau amplification of absolute stereochemical purity (Scheme 12).[41] The vinylstannane **70** was converted into the corresponding cyclopropane **71** using Charette cyclopropanation[19] and protection. Tin to lithium to copper exchange and oxygenation gave the corresponding bicyclopropane **72**. This in turn was converted *via* the carboxylic acid **73**, Barton bromodecarboxylation[42] and a second dimerization reaction to reveal the quatercyclopropane **75**. These two oxidative dimerization reactions were accompanied by an enhancement in enantiomeric purity from 88–90% ee to > 99% ee in a process that is a variant of the Horeau amplification principle.[43] The diether **75** was converted into FR-900848 **45** using *inter alia* a Julia–Peterson olefination reaction, Horner–Emmons homologation and acylation *via* *p*-nitrophenyl ester activation.

Total synthesis and structural elucidation of U-106305 80

In late 1995 Kuo *et al.* at Upjohn reported the isolation of U-106305 **80** from the fermentation broth of *Streptomyces* sp. UC 11136.[29] The authors determined that all the cyclopropanes are *trans*-disubstituted and that both alkenes are *E*, but the full structure was not determined. Their statement that 'U-106305 represents a structural class of compounds not

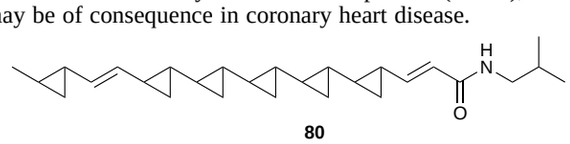


Scheme 10 *Reagents and conditions*: i, pyridinium chlorochromate, NaOAc, silica, CH_2Cl_2, 0 to 25 °C; ii, (*E*)-$MeO_2CCH{=}CHCH_2P(O)(OMe)_2$, NaH, THF, 0 to 25 °C, 71% from **60**; iii, PhSH, BuLi, $Ti(OPr^i)_4$, THF, 0 to 25 °C, 63%; iv, DIBAL-H, CH_2Cl_2, −78 °C, 91%; v, **14**, Et_2Zn, DME, CH_2I_2, CH_2Cl_2, −40 °C, 90%; vi, *N*-(phenylsulfenyl)succinimide, Bu_3P, PhH, 89%



Scheme 11 *Reagents and conditions*: i, Raney Ni, EtOH, −40 °C; ii, NH_4F, EtOH, 65 °C, 49% from **64**; iii, pyridinium chlorochromate, NaOAc, silica, CH_2Cl_2, 0 to 25 °C; iv, (*E*)-$MeO_2CCH{=}CHCH_2P(O)(OMe)_2$, NaH, THF, 0 to 25 °C, 63% from **65**; v, PhSH, BuLi, $Ti(OPr^i)_4$, THF, 0 to 25 °C, 51%; vi, $KOSiMe_3$, CH_2Cl_2, 85%; vii, **69**, BOP-Cl, Et_3N, DMA, 69%

previously reported from microbial fermentations' is inaccurate and both FR-900848 **45** and U-106305 **80** are clearly very closely related. It is therefore reasonable to speculate that U-106305 **80** has the same stereochemistry as **81**. It should be noted that U-106305 **80** is also biologically active. It is an inhibitor of cholesteryl ester transfer protein (CETP), which may be of consequence in coronary heart disease.



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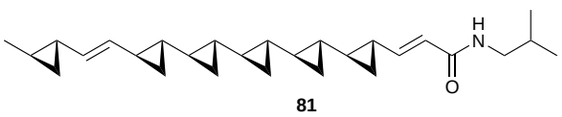
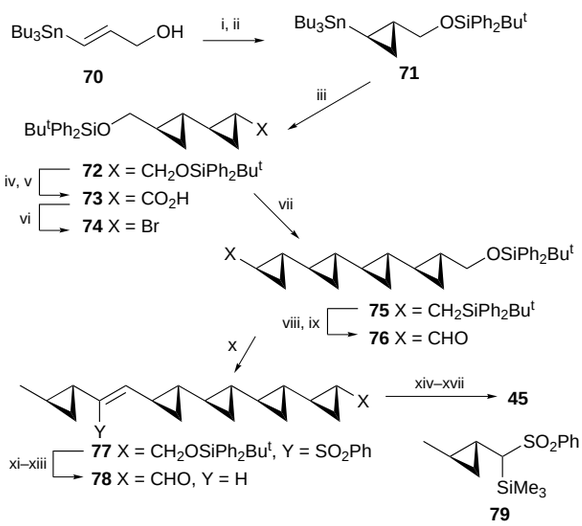


81

We have synthesized U-106305 **81** using a bi-directional approach to assemble the C_2-symmetrical quinquecyclopropane unit **87** using methodology as for FR-900848 **45** (Scheme 13).[44] Charette cyclopropanation[19] of diol **82** gave **83** in 89% ee. Dess–Martin oxidation[45] and Wittig olefination gave the diene diester **84**. Much to our delight, fractional recrystallization of **84** was especially efficient in enriching the material in the required enantiomer. Thus recrystallizaton from Et_2O–hexanes gave first racemic material and subsequently enantiomerically pure *E,E*-diester **84**. The structures for both the enantiomerically pure diester **84** and the corresponding racemic modification were confirmed by X-ray crystallography.[46] Diester **84** was converted onto the corresponding tercyclopropane and subsequently the quinquecyclopropane **87** using two sequential double Charette cyclopropanation reactions.[19] The structure of the near-helical quinquecyclopropane **87** was confirmed by X-ray analysis[44] and is shown in Fig. 3. This substance was



Scheme 12 *Reagents and conditions*: i, **14**, Et_2Zn, CH_2I_2, CH_2Cl_2, 23 °C, 98%; ii, Bu^tPh_2SiCl, imidazole, DMF, 23 °C, 88%; iii, Bu^sLi, THF, −40 °C, then $[ICuPBu_3]_4$, −78 °C, then O_2, −78 °C, 73%; iv, Bu_4NF, THF, 23 °C, 72%; v, $RuCl_3$, $NaIO_4$, CCl_4, MeCN, H_2O, 23 °C, 91%; vi, *N*-hydroxypyridine-2-thione, DCC, DMAP, $BrCCl_3$, 23 °C; hν, 0 °C, 77%; vii, Bu^tLi, THF, −78 °C, then $[ICuPBu_3]_4$, −78 °C, then O_2, −78 °C, 75%; viii, Bu_4NF, THF, 23 °C, 72%; ix, Pr_4NRuO_4, NMO, 4 Å molecular sieves, CH_2Cl_2, 23 °C, 91%; x, **79**, BuLi, THF, −78 °C, 65%; xi, Li, naphthalene, THF, −78 °C, 70%; xii, Bu_4NF, THF, 23 °C, 95%; xiii, Pr_4NRuO_4, NMO, 4 Å molecular sieves, CH_2Cl_2, 23 °C, 91%; xiv, (*E*)-EtO_2C-$CH{=}CHCH_2P(O)(OEt)_2$, $LiN(SiMe_3)_2$, THF, −78 °C, 89%; xv, LiOH, MeOH, H_2O, 23 °C, 90%; xvi, 4-nitrophenol, DCC, DMAP, CH_2Cl_2, 23 °C, 73%; xvii, **69**, DMF, 23 °C, 76%

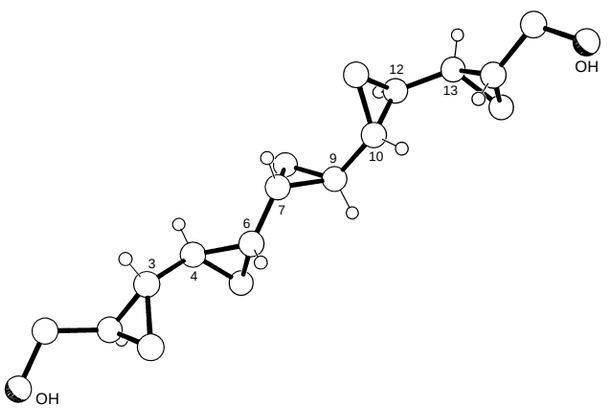
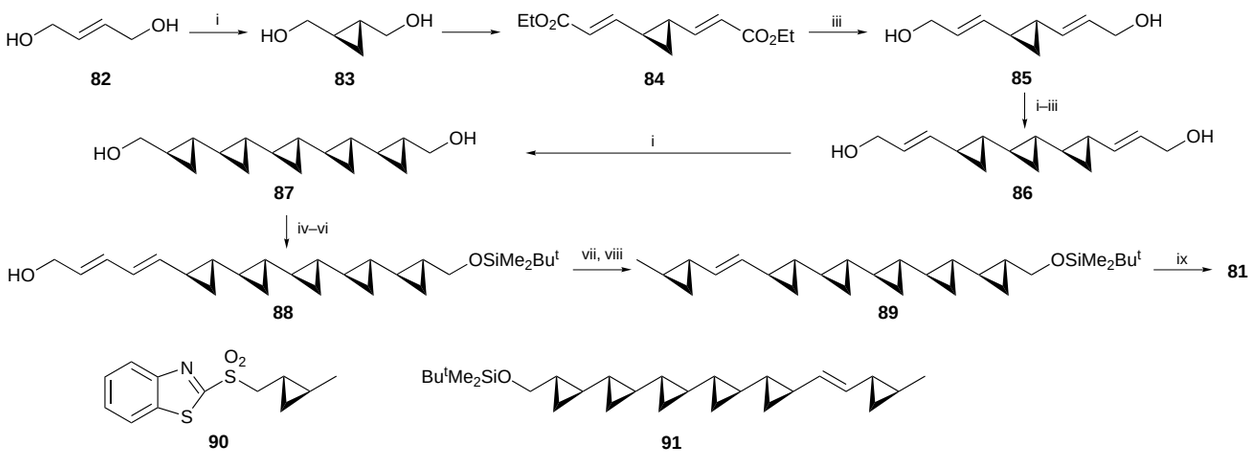


Fig. 3 The molecular structure of the quinquecyclopropanedimethanol **87** showing the absolute stereochemistry

converted into U-106305 **81** using essentially the same strategy as in our synthesis of FR-900848 **45**. The synthetic material was identical in all respects with an authentic sample of U-106305. All these results clearly established the full structure and stereochemistry of U-106305 **81**. Charette and Lebel have also recently reported[47] a total synthesis of the antipode of U-106305 **81** using a bidirectional strategy that is closely related to our work. The synthesis differs in the later stages in the use of a Julia–Lythgo coupling[48] reaction to link the quinquecyclopropane and monocyclopropane units. The use of sulfone **90** provided the corresponding alkene **91** with 4 : 1 *E* : *Z* geometric selectivity.

Future directions

Much remains to be done on the chemistry and biology of multiple cyclopropane arrays. It is clear from the Upjohn work that the biological effects mediated by multiple cyclopropane



Scheme 13 *Reagents and conditions*: i, **14**, 4 Å molecular sieves, $Zn(CH_2I)_2$·DME, CH_2Cl_2, −40 to 25 °C, 83–91%; ii, Dess–Martin periodinane, pyridine, CH_2Cl_2 or DMSO, 25 °C, then PPh_3, *ca*. 10 °C, then $Ph_3P{=}CHCO_2Et$, 75–81%; iii, DIBAL-H, CH_2Cl_2, hexanes, −78 °C, 96–97%; iv, Bu^tMe_2SiCl, imidazole, CH_2Cl_2, 25 °C, 75% (calc.) at 78% conversion; v, Dess–Martin periodinane, pyridine, DMSO, 25 °C, then PPh_3, 25 °C, then (E)-$(MeO)_2P(O)CH_2CH{=}CHCO_2Me$, NaH, DBU, 25 °C, 88%; vi, DIBAL-H, CH_2Cl_2, hexanes, −78 °C, 95%; vii, **14**, 4 Å molecular sieves, $Zn(CH_2I)_2$·DME, CH_2Cl_2, −50 °C → −25 °C, 72%; viii, *N*-(phenylsulfenyl)succinimide, PBu_3, C_6H_6, 25 °C, 91%, then Raney nickel, THF, 25 °C, 44%; ix, Bu_4NF, THF, 25 °C, then DMSO, pyridine, 25 °C, Dess–Martin periodinane, 25 °C; then PPh_3, *ca*. 15 °C; then $Cl^-Ph_3P^+CH_2CONHCH_2Pr^i$, DBU, 25 °C, 91%

fatty amides should be much more general than anti-infective. Further aspects of the synthesis, reactions and properties of cyclopropene oligomers will be reported in due course.

Acknowledgements

Dedicated to Professor Dieter Seebach on the occasion of his 60th Birthday, 31 October 1997.

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Tony Barrett's research interests are concerned with the development of organic and organometallic methodology, the total synthesis of bioactive natural products, asymmetric synthesis and catalysis, polymer supported synthesis, and ligand design and coordination chemistry. He obtained his BSc and PhD degrees at Imperial College and was then appointed as Lecturer in that institute. In 1983 he was appointed a full professor of Chemistry at Northwestern University in Evanston, Illinois, USA and in 1990 he moved to Colorado State University. After nearly ten years research in the USA, he returned to his *alma mater*, Imperial College, as Glaxo Professor of Organic Chemistry, Director of the Wolfson Centre for Organic Chemistry in Medical Science and Head of the Organic Section. Professor Barrett has received several awards for his contributions to research including the 1980 Meldola Medal, the 1982 Harrison Medal, the 1986 Corday–Morgan Medal and the 1994 Tilden Lectureship from the Royal Society of Chemistry, a 1986 Arthur C. Cope Scholar Award from the American Chemical Society, a 1987 Teacher-Scholar Award from the Camille and Henry Dreyfus Foundation and a 1989 Fellowship from the Japan Society for the Promotion of Science.

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Footnotes and References

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† This ChemComm is also available *via* the World Wide Web: http://chemistry.rsc.org/rsc/ccenha.htm

‡ For an earlier report of a natural product that may be identical with FR-900848, see B. C. Das, J. P. Cosson, E. Guittet, M. Hassani, T. Staron and

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