Determination of the Full Structure and Absolute Stereochemistry of the Antifungal Agent FR-900848: an X-Ray Crystallographic Study of (1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-Quatercyclopropyl-1,12-dimethanediyl Di-4-bromobenzoate

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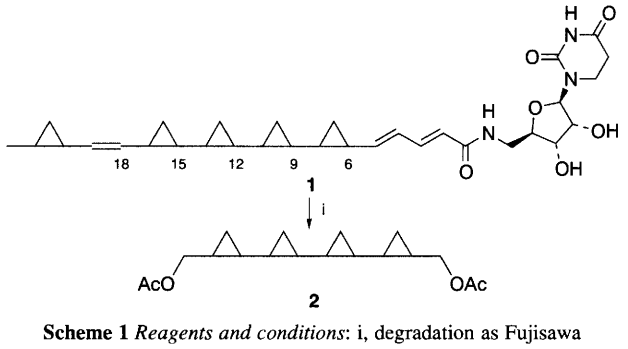
Degradation studies and partial synthesis are used to establish the full structure and absolute stereochemistry of the nucleoside antifungal agent FR-900848.

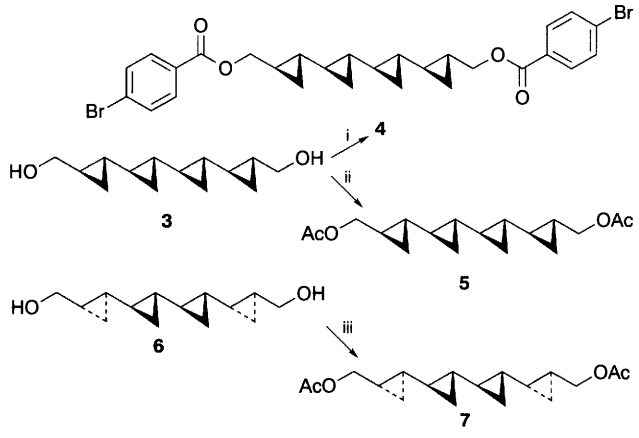
FR-900848 **1** is a nucleoside isolated from the fermentation broth of *Streptoverticillium fervens*.[1] It shows potent, selective activity against filamentous fungi such as *Aspergillus niger* but is essentially inactive against non-filamentous fungi such as *Candida albicans* and Gram-positive and -negative bacteria. Structurally this natural product is quite remarkable being graced with five cyclopropane units, four of which are contiguous. There are eleven elements of ambiguity in the structure: the geometry of Δ^{18}, the stereochemistry of the isolated cyclopropane and the stereochemistry of the tetracyclopropane unit. Fujisawa scientists have carried out limited degradation studies to further clarify the structure.[2] Thus ozonolysis of FR-900848 **1** with a reductive work-up and acetylation gave a C_2 symmetric quatercyclopropyl-1,12-dimethanediyl diacetate **2** (Scheme 1) although the exact structure was not defined at that time. Recently, we determined the geometry of Δ^{18} as *trans* by the synthesis of model 1,2-dicyclopropylethene derivatives and analysis of ^{1}H NMR spectra.[3] Herein we report additional degradation and synthetic studies on FR-900848 **1** and the establishment of its full structure and absolute stereochemistry.

In a previous communication[4] we described stereospecific syntheses of the diols **3** and **6**. However, our structural assignment of these substances was tentative and based only on an analogy with the elegant asymmetric monocyclopropanation chemistry reported by Charette and Juteau.[5]† Since we planned to use both quatercyclopropanes **3** and **6** to reveal the structure of FR-900848 **1**, we sought to unambiguously verify that our structural assignments were indeed correct. Thus diol **3** was converted (4-bromobenzoyl chloride, Et_3N, PhH; 87%) (Scheme 2) into the corresponding diester **4**.‡ A single-crystal X-ray structure determination of diester **4** unambiguously established the relative and absolute stereochemistry of all chiral centres present in the molecule (Fig. 1).§ The four cyclopropyl units that form the backbone of the molecule are arranged helically with the methine protons attached to C(12)C(13), C(15)C(16) and C(18)C(19) in psuedo-*gauche* relationships [the HCCH torsion angles about the C(12)–C(13), C(15)–C(16) and C(18)–C(19) bonds are −44, −51 and −45° respectively]. In addition, this assignment allowed us to identify the second C_2 symmetric quatercyclopropane **6** as the *anti-syn-anti* isomer. Reaction of diol **3** with acetic anhydride in pyridine provided diacetate **5** in high yield (96%). Likewise, acetylation of diol **6** gave diacetate **7** (99%). Comparison of the optical rotation and selected spectroscopic data¶ for the synthetic diacetates **5** and **7** with an authentic sample of the degradation product **2** was most revealing. Much to our delight the samples of diacetates **2** and **5** were identical. Thus the central quatercyclopropane unit of FR-900848 **1** has the (6*R*,8*S*,9*R*,11*S*,12*S*,14*R*,15*S*,17*R*)-stereochemistry (FR-900848 numbering).

Finally, two imidazolidine derivatives **12** and **13** of (1*R*,2*R*)-2-methylcyclopropanecarbaldehyde were prepared from crotonaldehyde (Scheme 3). Yamamoto asymmetric cyclopropanation[6] of the tartrate acetal **9** gave the corresponding cyclopropane **10** with excellent diastereoselectivity (80%; 94% de). Acid-catalysed deprotection of the acetal **10**[6] gave the volatile aldehyde **11** which was not isolated but directly condensed with (1*R*,2*R*)-*N*,*N*′-dimethyl-1,2-diphenylethane-diamine[7] to form the enantiomerically pure imidazolidine **12**. In the same way condensation of the aldehyde **11** with (1*S*,2*S*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine gave the diastereoisomeric imidazolidine **13**. Ozonolysis of an authentic sample of FR-900848 **1**



Scheme 1 *Reagents and conditions*: i, degradation as Fujisawa



Scheme 2 *Reagents and conditions*: i, 4-BrC_6H_4COCl, Et_3N, PhH, 87%; ii, Ac_2O, py, 96%; iii, Ac_2O, py, 99%

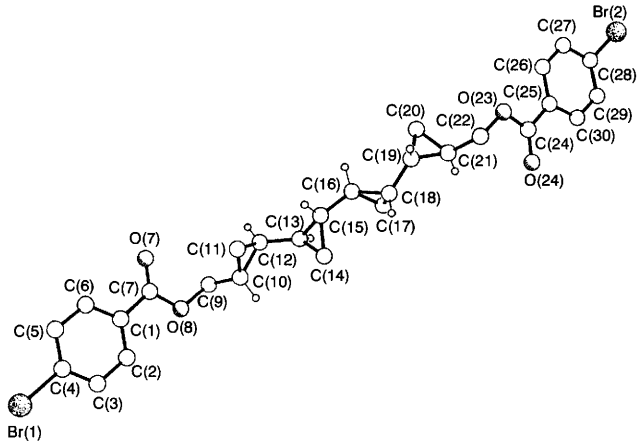
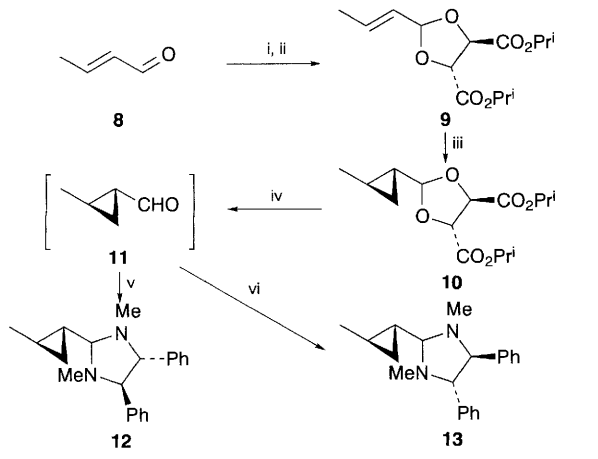
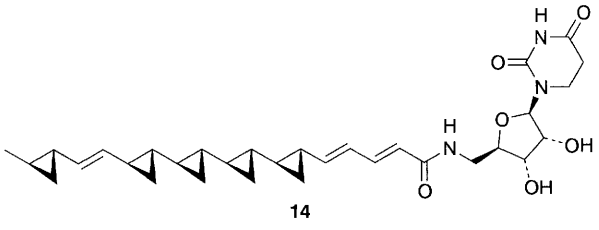


Fig. 1 The molecular structure of diester **4** showing the absolute stereochemistry



Scheme 3 *Reagents and conditions*: i, EtO_3CH, NH_4NO_3, EtOH, 25 °C; ii, L-(+)-diisopropyl tartrate, TsOH, C_6H_6, 80 °C, 60%; iii, Et_2Zn, CH_2I_2, PhMe, −20 °C, 80%; iv, TsOH, H_2O, THF, 60 °C; v, (4*R*,5*R*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine, Et_2O, 4 Å sieves, 25 °C, 37%; vi, (4*S*,5*S*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine, Et_2O, 4 Å sieves, 25 °C, 33%



and subsequent reaction with (1*R*,2*R*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine gave an imidazolidene derivative (94%) which was spectroscopically identical‖ with the synthetic adduct **12**.

It is clear from these results and our prior publication[3] that the structure of FR-900848 **1** is depicted by the formula **14**. Further synthetic studies on FR-900848 **14** and related antifungal agents will be reported in due course.

We thank Fujisawa Pharmaceutical Company Ltd for generous donations of samples of FR-900848 **1** and the diacetate **2** and key spectroscopic data, Glaxo Group Research Ltd for the most generous endowment (to A. G. M. B.), the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College, the Engineering and Physical Science Research Council, Myco Pharmaceutical Inc for support of our research on antifungal agents, G.D. Searle & Company for generous unrestricted support and the Overseas Research Students Program for fellowship support (to K. K.).

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Footnotes

† Recently, Charette *et al.* have reported the danger of explosions when the asymmetric modification of the Simmons–Smith reaction is scaled up (>8 mmol). An improved less hazardous procedure has just been published.[8]

‡ The new compounds **4**, **5**, **7**, **12** and **13** were fully characterised by spectroscopic data and microanalysis and/or HRMS.

§ *Crystal data* for **4**: $C_{28}H_{28}Br_2O_4$, M = 588.3, monoclinic, a = 5.555(2), b = 18.714(7), c = 12.480(4) Å, β = 96.60(2)°, V = 1288.8(8) Å^3, space group $P2_1$, Z = 2, D_c = 1.52 g cm^{-3}, μ(Cu-Kα) = 42.5 cm^{-1}, F(000) = 596. Data for a clear rhombus of dimensions 0.43 × 0.43 × 0.67 mm were measured on a Siemens P4/PC diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. The data were corrected for Lorentz and polarization factors and for absorption (face-indexed numerical, maximum and minimum transmission factors 0.332 and 0.146). The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically to give R = 0.047, R_w = 0.056 for 2079 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 126°$, $w^{-1} = \sigma^2(F) + 0.0005F^2$]. The absolute stereochemistry was determined by an R-factor test, R_+ = 0.0468, R_- = 0.0512, and by the refinement of a free variable η (that multiplies all f'') which refined to a value of 0.93(9), thus providing a definite assignment for all the chiral centres. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

¶ *Optical rotation and selected spectroscopic data*: diacetate **5**: $[\alpha]_D$ = −144.7 (*c* 1.07, $CHCl_3$,), ^{13}C NMR ($CDCl_3$, Brücker 125 MHz) δ 171.2, 68.4, 21.0, 18.7, 18.4, 17.9, 15.8, 8.6, 8.0; diacetate **7**: $[\alpha]_D$ = −26.0 (*c* 1.01, $CHCl_3$), ^{13}C NMR ($CDCl_3$, Brücker 125 MHz) δ 171.2, 68.4, 21.0, 18.8, 18.2, 18.0, 15.7, 9.0, 8.4; diacetate **2** derived from FR-900848 **1**: $[\alpha]_D$ = −143.8 (*c* 1.04, $CHCl_3$,), ^{13}C NMR ($CDCl_3$, Brücker 125 MHz) δ 171.2, 68.5, 21.0, 18.7, 18.4, 17.9, 15.8, 8.6, 8.0.

‖ *Optical rotation and selected spectroscopic data* (all J in Hz): imidazolidine **12**: $[\alpha]_D$ = −20.2 (*c* 1.00, $CHCl_3$), ^1H NMR ($CDCl_3$, Brücker 500 MHz) δ 7.22–7.10 (10H, m), 3.65 (1H, d, J = 8.5), 3.27 (1H, d, J = 8.5), 3.07 (1H, d, J = 8.3), 2.47 (3H, s), 2.25 (3H, s), 1.17 (3H, d, J = 5.9), 0.85 (2H, m), 0.62 (1H, m), 0.41 (1H, m); ^{13}C NMR ($CDCl_3$, Brücker 125 MHz) δ 140.6, 140.0, 128.2, 128.1, 127.4, 127.3, 90.0, 78.7, 77.2, 39.2, 36.1, 21.3, 18.2, 11.2, 9.4; imidazolidine **13**: $[\alpha]_D$ = −17.6 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, Brücker 500 MHz) δ 7.42–7.24 (10H, m), 3.79 (1H, d, J = 8.5), 3.41 (1H, d, J = 8.5), 3.21 (1H, d, J = 8.3), 2.60 (3H, s), 2.39 (3H, s), 1.30 (3H, d, J = 5.9), 0.92 (2H, m), 0.89 (1H, m), 0.53 (1H, m); ^{13}C NMR ($CDCl_3$, Brücker 125 MHz) δ 140.9, 140.1, 128.2, 128.1, 127.4, 127.2, 89.5, 78.4, 77.6, 38.6, 36.6, 20.6, 18.4, 11.1, 9.9; imidazolidine derived from FR-900848: $[\alpha]_D$ = −20.0 (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$, Brücker 500 MHz) δ 7.22–7.10 (10H, m), 3.65 (1H, d, J = 8.5), 3.27 (1H, d, J = 8.5), 3.07 (1H, d, J = 8.3), 2.47 (3H, s), 2.25 (3H, s), 1.17 (3H, d, J = 5.9), 0.85 (2H, m), 0.62 (1H, m), 0.41 (1H, m); ^{13}C NMR ($CDCl_3$, Brücker 125 MHz) δ 140.5, 139.9, 128.1, 128.0, 127.3, 127.2, 89.9, 78.6, 77.1, 39.1, 36.0, 21.2, 18.1, 11.1, 9.3.

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