Approaches to the Assembly of the Antifungal Agent FR-900848: Determination of the Geometry of the Dicyclopropylethene Unit and an X-Ray Crystallographic Study of (1*R*,2*S*)-1,2-Bis[(1*S*,2*S*)-2-methylcyclopropyl]-1,2-ethanediyl 3,5-Dinitrobenzoate

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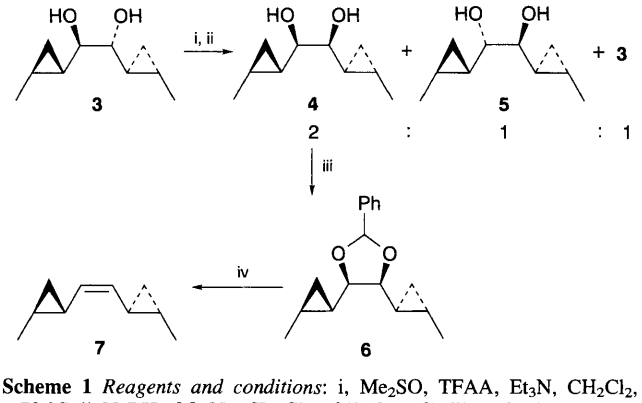
Whitham elimination is used to prepare (*Z*)-1,2-bis[(1*S*,2*S*)-2-methylcyclopropyl]ethene, which along with the corresponding *E*-alkene, is used as a structural model to determine that the geometry of the dicyclopropylethene unit of FR-900848 is *trans*.

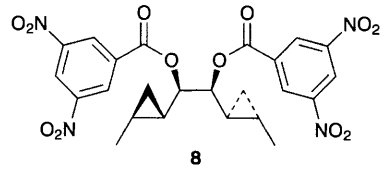
FR-900848 **1** is a natural product which shows potent activity against filamentous fungi.[1] There are eleven elements of ambiguity in the structure: the geometry of Δ^{18}, the stereochemistry of the isolated cyclopropane and the stereochemistry of the tetracyclopropane unit. Herein we report on the synthesis and characterization of (*Z*)-1,2-bis[(1*S*,2*S*)-2-methylcyclopropyl]ethene **7** as a structural model of the dicyclopropylethene unit. Comparison of the spectroscopic data of *cis*-alkene **7** and the corresponding *trans*-alkene[2] **2** with that of the side chain of FR-900848 **1** has led to the determination of the geometry of Δ^{18} as *trans*.

Recently we described a stereospecific synthesis of diol **3** from D-mannitol using a double asymmetric Simmons–Smith cyclopropanation reaction.[2] Oxidation of *syn*-diol **3** (Scheme 1) using a variation of the Swern reaction[3] followed by sodium borohydride reduction provided a 2 : 1 : 1 mixture of *anti*-diol **4**† (36% from **3**) and the two possible *syn*-diols (36% from **3**). Much to our delight, *anti*-diol **4** was readily isolable by column chromatography, and the mixture of *syn*-diols **3** and **5** could be recycled to provide additional *anti*-diol **4** (33%). Diol **4** was converted (3,5-dinitrobenzoyl chloride, Et_3N, PhH; 95%) into the corresponding 3,5-dinitrobenzoate **8**. A single-crystal X-ray structure determination of diester **8** established the relative stereochemistry of all chiral centres present in the molecule (Fig. 1).‡ The absolute stereochemistry of the cyclopropane centres of diol **3** were determined from a previous X-ray crystallographic study of (1*R*,2*R*)-1,2-bis[(1*S*,2*S*)-2-methylcyclopropyl]-1,2-ethanediyl 3,5-dinitrobenzoate,[2] which allowed for the identification of the absolute stereochemistry of dicyclopropanes **4**, **6** and **8**.

Condensation of the diol **4** with benzaldehyde gave a mixture of the two isomers of the benzylidene derivative **6** (96%). Subsequent elimination[4] using butyllithium provided geometrically pure (*Z*)-1,2-bis[(1*S*,2*S*)-2-methylcyclopropyl]ethene **7** (71%).§ Our assignment of *cis*-geometry for alkene **7** is consistent with the spectroscopic assignments made by Nishida and coworkers from their non-selective synthesis of both (*E*)- and (*Z*)-1,2-di(cyclopropyl)ethene.[5]



Scheme 1 *Reagents and conditions*: i, Me_2SO, TFAA, Et_3N, CH_2Cl_2, −78 °C; ii, $NaBH_4$, MeOH, CH_2Cl_2, 72% (from **3**); iii, PhCHO, camphorsulfonic acid, 96%; iv, BuLi, pentane, 71%



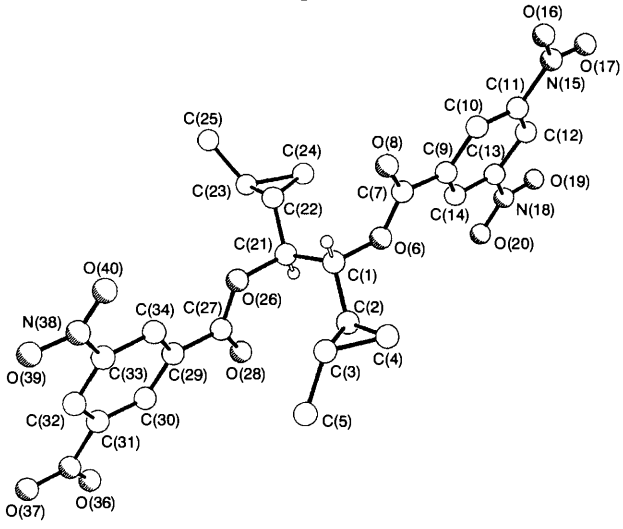
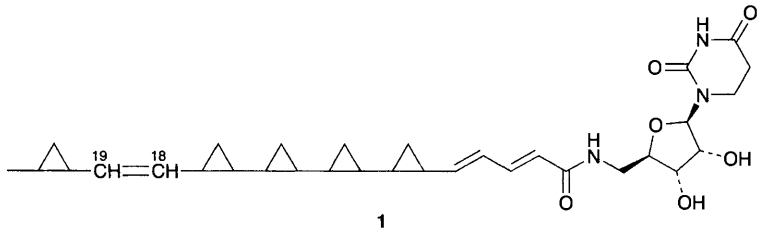


Fig. 1 The molecular structure of diester **8** showing the absolute stereochemistry



Comparison of the spectroscopic data of the *cis*-alkene **7**, the *trans*-alkene **2**, *cis*-1,2-dicyclopropylethene[5] and *trans*-1,2-dicyclopropylethene[5] with those of both the side chain carboxylic acid of FR-900848 **1** and FR-900848 **1** itself allows for the determination of the geometry of the dicyclopropylethene unit of FR-900848 **1** as *trans*.¶ Of particular note in this analysis are the δ values for the vinyl protons in the ^{1}H NMR spectra. The *cis*-alkenes showed δ values of 4.68 and 4.62 whereas the *trans*-alkenes showed δ values of 4.97 and 5.04. FR-900848 **1** and the corresponding free fatty acid‖ showed values of δ 4.95 and 5.02. Further synthetic studies on FR-900848 **1** and related antifungal agents will be reported in due course.

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Footnotes

† Compounds **4**, **6**, **7** and **8** were fully characterised by spectroscopic data and microanalysis or HRMS.

‡ *Crystal data* for **8**: $C_{24}H_{22}N_4O_{12}$, M = 558.5, monoclinic, a = 7.303(6), b = 17.373(9), c = 10.167(8) Å, β = 104.31(2)°, V = 1250 Å^3, space group $P2_1$, Z = 2, D_c = 1.48 g cm^{-3}, μ(Cu-Kα) = 10 cm^{-1}, F(000) = 580. A clear rhombohedron of dimensions 0.10 × 0.13 × 0.17 mm was used. Data were measured on a Siemens P4/PC diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically to give R = 0.051, R_w = 0.056 for 1772 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leqslant 128°$]. 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.

§ The yield of volatile alkene **7** is based upon the ^{1}H NMR spectrum of the product in pentane solution relative to an internal dioxane reference, and upon recovered starting material. Subsequent isolation of alkene **7** on a 12 mg scale was accompanied by significant mass losses.

¶ *Spectroscopic data* for olefinic protons and carbons: *cis*-alkene **7**: ^{1}H NMR ($CDCl_3$, Bruker 500 MHz) δ 4.68 (dd, J = 6.6, 2.2 Hz), ^{13}C NMR ($CDCl_3$, Bruker 125 MHz) δ 131.5; *cis*-1,2-dicyclopropylethene: ^{1}H NMR (CCl_4, JEOL 100 MHz) δ 4.62 (m);[5] *trans*-alkene **2**: ^{1}H NMR ($CDCl_3$, Bruker 500 MHz) δ 5.04 (dd, J = 5.3, 2.6 Hz), ^{13}C NMR ($CDCl_3$, Bruker 125 MHz) δ 130.9; *trans*-1,2-dicyclopropylethene: ^{1}H NMR (CCl_4, JEOL 100 MHz) δ 4.97 (m);[5] side chain carboxylic acid of FR-900848 **1**: ^{1}H NMR ($CDCl_3$, Bruker 400 MHz) δ 5.02 (dd, J = 5.0, 2.5 Hz), ^{13}C NMR ($CDCl_3$, Bruker 100 MHz) δ 131.1, 130.4; FR-900848 **1**: ^{1}H NMR [$(CD_3)_2SO$, Bruker 500 MHz] δ 4.95 (dd, J = 5.2, 2.6 Hz), ^{13}C NMR ($CDCl_3$, Bruker 100 MHz) δ 130.6, 130.3.

‖ Samples and spectra of FR-900848 **1** and the fatty acid side chain of FR-900848 **1** were kindly provided by Dr H. Tanaka, Fujisawa Co. Ltd.

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