Approaches to the Assembly of the Antifungal Agent FR-900848: Studies on Double Asymmetric Cyclopropanation and an X-Ray Crystallographic Study of (1*R*,2*R*)-1,2-Bis-[(1*S*,2*S*)-2-methylcyclopropyl]-1,2-ethanediyl 3,5-Dinitrobenzoate

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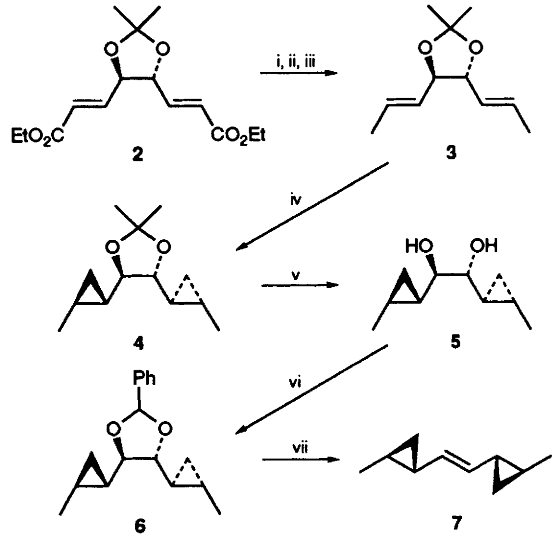
Double asymmetric Simmons–Smith cyclopropanation and Whitham elimination were used to prepare (*E*)-1,2-bis-[(1*S*,2*S*)-2-methylcyclopropyl]ethene, the dicyclopropylethene unit of FR-900848.

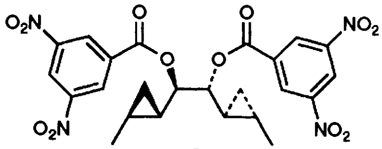
FR-900848 **1** is a natural product isolated from the fermentation broth of *Streptoverticillium fervens*.[1] It shows potent, selective activity against filamentous fungi such as *Aspergillus niger* but is essentially inactive against non-filamentous fungi such as *Candida albicans* and Gram-positive and -negative bacteria. Structurally the molecule is remarkable since it is endowed with five cyclopropanes, four of which are contiguous. However, 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 are all unknown. Herein, we report model studies on the synthesis and characterisation of (*E*)-1,2-bis-[(1*S*,2*S*)-2-methylcyclopropyl]ethene **7**. The reactions are relevant to the complete structural assignment of FR-900848 **1** and, ultimately, its total synthesis.

Reduction of the known diester **2**[2]† *via* the corresponding diol and allylic chloride gave the (*E*,*E*)-diene **3**‡ (56%). Double Simmons–Smith reaction proceeded with excellent diastereoselectivity to provide only a single dicyclopropane (89%). Examination of the ^{1}H NMR and ^{13}C NMR spectra of the product was consistent with its structural assignment as the C_2 symmetric isomer **4** and this conclusion was verified by a single crystal X-ray structural determination. It is clear that the sense of asymmetry in the double cyclopropanation reaction was the result of coordination of the zinc carbenoid reagent by the Lewis basic dioxolane ring oxygen prior to each cyclopropanation event. Related high diastereoselectivity in the mono-cyclopropanation of 1,3-dioxolanyl-alkenes has precedent for example in the recent studies by Taguchi *et al.*[3] Additionally other groups have successfully used oxygen ligand coordination to direct the stereochemistry of the Simmons–Smith reaction.[4]

Acid mediated deprotection of the dicyclopropane **4** gave the vicinal diol **5** (63%) which was converted [3,5-dinitrobenzoyl chloride, Et_3N, PhH; 84%] 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).§ Since diester **2** was originally prepared from 3,4-*O*-isopropylidene-D-mannitol, the crystal structure also allows for the unambiguous identification of the absolute stereochemistry of dicyclopropanes **4**, **5**, **6** and **8**. Condensation of the diol **5** with benzaldehyde gave the benzylidene derivative **6** (64%). Subsequent butyllithium mediated metallation resulted in C-2 lithiation (1,3-dioxolane numbering) and elimination[5] to provide geometrically pure (*E*)-1,2-bis-[(1*S*,2*S*)-2-methylcyclopropyl]ethene **7** (60%).¶ Nishida and coworkers have previously reported geometrically non-selective syntheses of both (*E*)- and (*Z*)-1,2-di(cyclopropyl)ethene[6] and the spectro-



Scheme 1 *Reagents and conditions*: i, DiBAl-H, CH_2Cl_2, −78–0 °C, 87%; ii, CCl_4, Ph_3P, THF, 67 °C, 80%; iii, LAH, Et_2O, 35 °C, 80%; iv, Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, −20 °C, 89%; v, TsOH (cat), THF–H_2O (5/1), 70 °C, 63%; vi, PhCHO, H_2SO_4 (cat), $PhCH_3$, 111 °C, 64%; vii, BuLi, pentane, 60%



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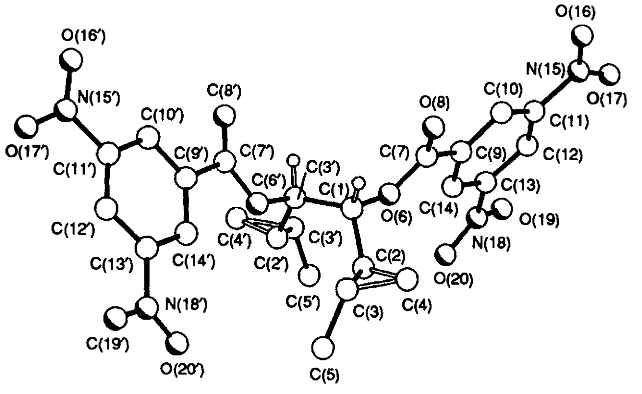
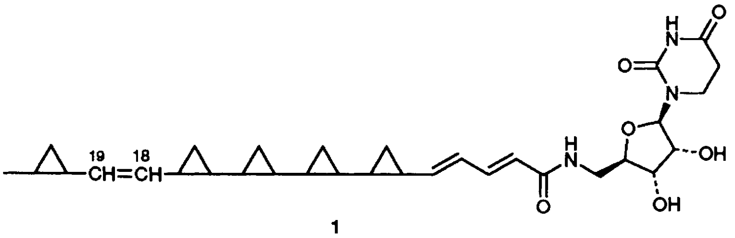


Fig. 1 The molecular structure of ester **8** showing the absolute stereochemistry



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scopic data observed for alkene **7** are fully consistent with our assignment of *trans*-geometry.

These studies clearly illustrate a highly stereoselective method for the preparation of a key unit of FR-900848 **1**. Additionally, they underscore the excellence of the Whitham protocol[5] for the geometrically specific synthesis of delicate alkenes. Further studies on the chemistry of FR-900848 **1** will be reported in due course.

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Footnotes

† (*E,E*)-Diester **2** was synthesised *via* the oxidative cleavage of 3,4-*O*-isopropylidene-D-mannitol [$Pb(OAc)_4$, CH_2Cl_2], treatment of the solution of the resultant crude dialdehyde with $Ph_3P{=}CHCO_2Et$ in CH_2Cl_2, and isomerisation of the product diester [I_2 (cat), *hv*, $CHCl_3$] to convert the undesired (*E,Z*)-isomer to **2**.

‡ Compounds **2**, **3**, **4**, **5**, **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, orthorhombic, a = 9.443(2), b = 21.991(8), c = 6.370(2) Å, V = 1323 Å^3, space group $P2_12_12$, Z = 2 (the molecule has crystallographic C_2 symmetry), D_c = 1.40 g cm^{-3}, μ(Cu-Kα) = 9.9 cm^{-1}, $F(000)$ = 580. A clear prism of dimensions 0.20 × 0.23 × 0.37 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 = 0.44, R_w = 0.049 for 1180 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 130°$]. 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. Subsequent isolation, on a small scale, was accompanied by significant mass losses.

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