Approaches to the Assembly of the Antifungal Agent FR-900848: Studies on the Synthesis of C_2 Symmetric Tetracyclopropane Derivatives and an X-Ray Crystallographic Study of (1*R*,3*S*,4*S*,6*R*)-Bicyclopropyl-1,6-di-{2-[(4*R*,5*R*)-di-(isopropyloxycarbonyl)-1,3-dioxolane]}

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Two sequential asymmetric bicyclopropanation reactions were used to prepare (1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-quatercyclopropyl-1,12-dimethanol and (1*S*,3*R*,4*R*,6*S*, 7*S*,9*R*,10*R*,12*S*)-quatercyclopropyl-1,12-dimethanol.

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 (1*R*,3*S*,4*R*,6*S*,7*S*,9*R*,10*S*,12*R*)-quatercyclopropyl-1,12-dimethanol **7** and (1*S*,3*R*,4*R*,6*S*,7*S*,9*R*,10*R*,12*S*)-quatercyclopropyl-1,12-dimethanol **8**. The reactions are relevant to the complete structural assignment of FR-900848 **1** and, ultimately, to its total synthesis.

Noyori acetalisation[2] of muconaldehyde[3] **2** followed by cyclopropanation according to the Yamamoto adaptation of the Simmons–Smith reaction[4] provided dicyclopropane **3**† in good yield (56% from dial **2**). A single crystal X-ray structure determination of dicyclopropane **3** established the relative stereochemistry of all four chiral centres present in the molecule (Fig. 1).‡ Since the dioxolane units of the dicyclopropane **3** were derived from (*R*,*R*)-diisopropyl tartrate, the crystal structure also allows for the unambiguous identification of the absolute stereochemistry of dicyclopropane **3** and derivatives **4**, **5** and **6**. Subsequent acid catalysed deprotection of the diacetal **3** gave the corresponding dialdehyde which was directly homologated using a double Wittig reaction to provide a mixture of the (*E*,*E*)-diester **4** and the (*E*,*Z*)-diester **5** (3.7 : 1). Chromatography gave the pure (*E*,*E*)-isomer **4** (47% from diacetal **3**). All attempts at isomerization of the (*E*,*Z*)-diester **5** to provide the desired (*E*,*E*)-diester **4** failed. DIBAL-H reduction of diester **4** gave the corresponding diol **6** in high yield (91%).

Initially we examined the double Fujisawa asymmetric cyclopropanation[5] of the diene **6** to provide the corresponding tetracyclopropanedimethanol derivatives. Although such a process proved successful, we have found the recently published Charette protocol[6] to be far superior. Pre-mixing of diol **6** with dioxaborolane **10** followed by treatment with preformed bis(iodomethyl)zinc gave tetracyclopropane **7** (94%), with only an insignificant amount of minor isomer observed by ^{13}C NMR. Likewise, use of dioxaborolane **11** gave the tetracyclopropane **8**

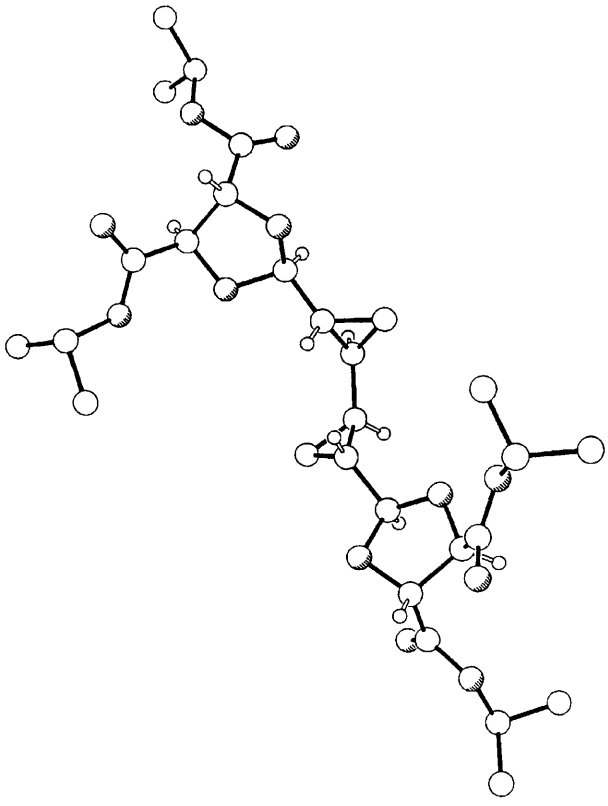
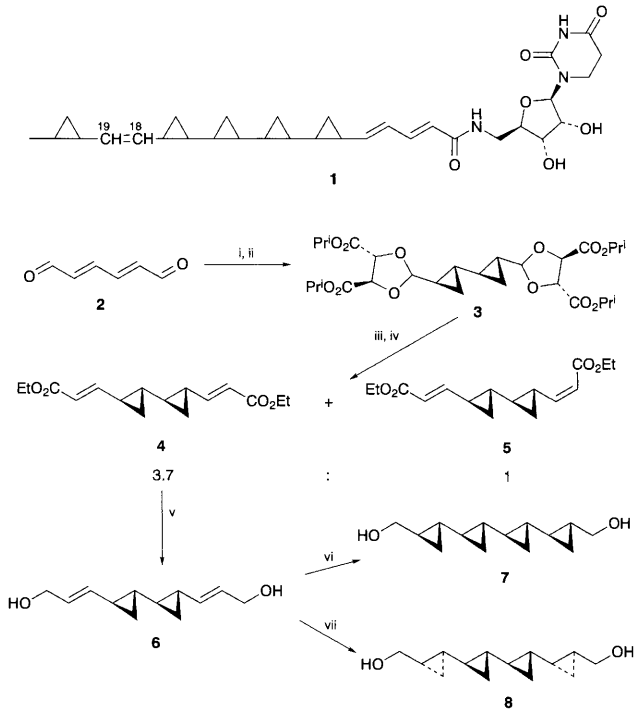
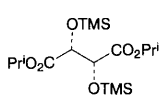


Fig. 1 The molecular structure of diacetal **3** showing the absolute stereochemistry



Scheme 1 *Reagents and conditions*: i, **9**, TMSOTf (cat), MeC(OTMS)=NTMS, CH_2Cl_2, −78–25 °C, 73%; ii, Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, −20 °C, 78%; iii, TsOH, THF/H_2O, 55 °C; iv, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 61% from **3**; v, DIBAL-H, CH_2Cl_2, −78 °C, 91%; vi, **10**, $Zn(CH_2I)_2$, CH_2Cl_2, 0–25 °C, 94%; vii, **11**, $Zn(CH_2I)_2$, CH_2Cl_2, 0–25 °C, 100%



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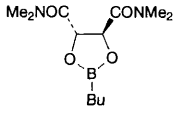

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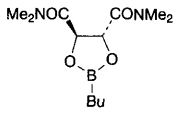

11

(100%). It was apparent from ^{1}H and ^{13}C NMR data that the tetracyclopropanes **7** and **8** were two different C_2 symmetric isomers,§ and we have assigned their stereochemistry by analogy with the absolute stereochemistry of monocyclopropanations observed by Charette.[6]

These studies clearly illustrate that sequential double cyclopropanation provides a highly stereoselective method for the preparation of a key unit of FR-900848 **1**. Additionally, they underscore the excellence of the Charette protocol[6] for the asymmetric cyclopropanation of allylic alcohols.

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Footnotes

† Compounds **3**, **4**, **5**, **6**, **7** and **8** were fully characterised by spectroscopic data and microanalysis and/or HRMS.

‡ *Crystal data* for $C_{28}H_{42}O_{12}$, M = 570.6, orthorhombic, a = 9.323(4), b = 32.862(11), c = 5.173(2) Å, V = 1585(1) Å^3, space group $P2_12_12$, Z = 2 (the molecule has crystallographic C_2 symmetry), D_c = 1.20 g cm^{-3}, μ(Cu-Kα) = 7.8 cm^{-1}, F(000) = 612. A clear needle of dimensions 0.60 x 0.07 x 0.07 mm was used. Data were measured on a Siemens P4/RA 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 = 0.070, R_w = 0.083 for 1229 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 130°$]. The somewhat high final value for R is a consequence of high thermal vibration/disorder in the isopropyl groups. 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.

§ *Spectroscopic data* for tetracyclopropane **7**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.16 (m, 4H), 0.33 (m, 4H), 0.62 (m, 4H), 0.77 (m, 2H), 0.89 (m, 2H), 1.50 (bs, 2H), 3.47 (dd, 4H, J = 6.9, 2.7 Hz), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.2 (2C), 18.1, 18.4, 18.5, 19.8, 66.9; for tetracyclopropane **8**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.11 (m, 4H), 0.29 (m, 4H), 0.54 (m, 4H), 0.68 (m, 2H), 0.83 (m, 2H), 1.25 (m, 2H), 3.40 (dd, 4H, J = 6.9, 1.5 Hz), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.5, 8.6, 18.2, 18.3, 18.5, 19.6, 66.9.

References

1 M. Yoshida, M. Ezaki, M. Hashimoto, M. Yamashita, N. Shigematsu, M. Okuhara, M. Kohsaka and K. Horikoshi, *J. Antibiot.*, 1990, **43**, 748.
2 T. Tsunoda, M. Suzuki and R. Noyori, *Tetrahedron Lett.*, 1980, **21**, 1357.
3 S. G. Davies and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1346.
4 A. Mori, I. Arai and H. Yamamoto, *Tetrahedron*, 1986, **42**, 6447.
5 Y. Ukaji, M. Nishimura and T. Fujisawa, *Chem. Lett.*, 1992, 61.
6 A. B. Charette and H. Juteau, *J. Am. Chem. Soc.*, 1994, **116**, 2651.