Approaches to the Assembly of the Antifungal Agent FR-900848: Studies on the Asymmetric Synthesis of Bicyclopropanes and an X-Ray Crystallographic Analysis of (4*R*,5*R*)-2-[(1*R*,3*S*,4*S*,6*R*)-6-Phenyl-1-bicyclopropyl]-1,3-dimethyl-4,5-diphenylimidazolidine

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Both *syn*- and *anti*-bicyclopropane derivatives are efficiently prepared with good relative and absolute stereocontrol; structures are unequivocally determined by an X-ray crystallographic study of the title imidazolidine derivative.

FR-900848 **1** is an antibiotic extracted from the fermentation broth of *Streptoverticullum fervens* HP-891.[1] It shows selective activity against filamentous fungi but not against yeasts or Gram-negative or -positive bacteria.[1] Structurally FR-900848 is remarkable: it is a nucleoside antibiotic endowed with a rich array of cyclopropanes.† We are intrigued both by the structure of the tetracyclopropane entity and the legion of structural ambiguities. Consequently, we have started synthetic studies in this area. Enantioselective Simmons–Smith reactions to provide simple monocyclopropanes are now well established procedures.[2–4] Herein we report our studies on the preparation and characterisation of both *syn*- and *anti*-bicyclopropanes.

trans-Cinnamaldehyde **2** was converted, *via* the chiral acetal **3**[3]‡ and Yamamoto asymmetric Simmons–Smith cyclopropanation,[3] into the phenylsubstituted cyclopropyl acetal[3] **4** in good diastereoisomeric excess (*ca.* 85%). Separation of the diastereoisomers by column chromatography (SiO_2) and acid hydrolysis of pure acetal **4** afforded the enantiomerically pure (1*R*, 2*R*)-2-phenylcyclopropylcarboxaldehyde **5**. Horner–Emmons homologation of aldehyde **5** gave the corresponding (*E*)-α,β-unsaturated ester and subsequent reduction generated the enantiomerically pure alcohol **6**.§ Reaction of allylic alcohol **6** with diethylzinc and diiodomethane in the presence of L-(+)-diethyl tartrate according to the Fujisawa protocol[5] afforded both the bicyclopropyl derivatives **7** and **9** (6:1)¶ (Scheme 1) as an inseparable mixture of isomers. Alternatively, reaction of allylic alcohol **6** with diethylzinc and diiodomethane in the presence of D-(−)-diethyl tartrate gave both bicyclopropanes **7** and **9** (1:6).¶ Again, the mixture of *syn*-**7** and *anti*-**9** isomers could not be separated. Treatment of allylic alcohol **6** with diethylzinc and diiodomethane with the absence of tartrate esters generated compounds **7** and **9** (≈1:1) in 82% yield. It is clear that from these observations the pre-existing cyclopropane ring in alkene **6** has little or no influence on the stereochemical outcome of the second cyclopropanation reaction. Thus, *syn*- or *anti*-bicyclopropanes can be prepared *via* reagent control of stereochemistry.

The structural assignments of the *syn*- and *anti*-bicyclopropanes **7** and **9** require substantiation. Thus, PCC oxidation of the mixture of alcohols **7** and **9** (6:1) and subsequent condensation with (4*R*,5*R*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine[6,7] led to the formation of the imidazolidines **8** and **10** (6:1).¶ The major isomer **8** was isolated by fractional recrystallisation from acetone and water and this gave material suitable for single-crystal X-Ray analysis. The crystal structure‖ of imidazolidine **8** enabled us to determine the relative and absolute stereochemistry of all cyclopropane stereocentres since (4*R*,5*R*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine was used to prepare adduct **8**. Knowledge of the imidazolidine stereochemistry allows, by analogy, the deduction and definition of the stereochemistries of both the imidazolidine **8** and all other isomers in Scheme 1. Thus both cyclopropanation reactions to respectively generate cyclopropanes **4** and **7** proceed with tartrate directed attack on the alkenes **3** and **6**,[4,5] thereby generating the *syn*-bicyclopropane **7**. Alternatively, reagent control can also be used to prepare the *anti*-bicyclopropane system **9**. Further studies on the chemistry of FR-900848 (**1**) are underway and will be reported in due course.

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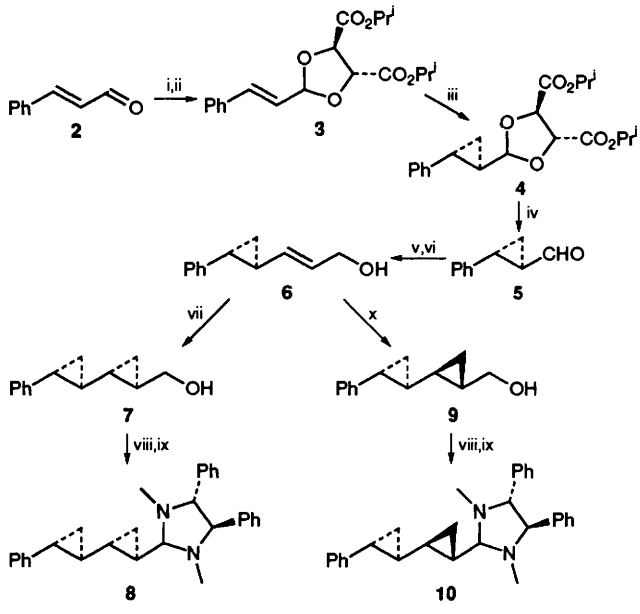

Scheme 1 i, $(EtO)_3CH$, NH_4NO_3, EtOH, 25 °C; ii, L-(+)-diisopropyl tartrate, TsOH, C_6H_6, 80 °C, 70%; iii, Et_2Zn, CH_2I_2, PhMe, −20 °C, 91%; iv, TsOH, H_2O, THF, 60 °C, 93%; v, $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C, 95%; vi, DIBALH, CH_2Cl_2, −78 °C, 89%; vii, L-(+)-diethyl tartrate, Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, −12 °C, 72%; viii, PCC, NaOAc, SiO_2, CH_2Cl_2, 0 °C, 97%; ix, (4*R*,5*R*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine, Et_2O, 4 Å seives, 25 °C; x, D-(−)-diethyl tartrate, Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, −12 °C, 84%

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Footnotes

† There are 2^{11} possible stereoisomers for antibiotic **1** since the absolute stereochemistry of all ten cyclopropane asymmetric centres and the geometry of the isolated alkene unit are unknown.

‡ The full synthetic sequence was repeated for the antipodal series of compounds in the scheme. Diastereoselectivities in all these reactions were consistant with the results reported for the series of enantiomers in the text.

§ All new compounds **6–10** in the scheme (and all their respective antipodes) were fully characterised by spectroscopic data and microanalysis or high resolution mass spectrometry data.

¶ The ratio of diastereoisomers observed in the formation of compounds **7** and **9** were determined by ^{13}C NMR spectroscopy, HPLC analysis and derivatisation with (4*R*,5*R*)-*N*,*N*′-dimethyl-1,2-diphenylethanediamine to form adducts **8** and **10**. The ratios were then obtained by ^{1}H NMR spectroscopy (500 MHz) and integration of the signals for the *N*-methyl substituents. Separation of the mixture of compounds **7** and **9** and their derivatives *via* preparative HPLC, distillation and flash chromatography was not possible.

‖ *Crystal data*: $C_{29}H_{32}N_2$, M = 408.6, space group *I*2 (body-centred cell chosen because *C*-face centred cell has β = 131.90°), monoclinic, a = 21.317(8), b = 5.401(2), c = 20.891(8) Å, β = 94.94(2), V = 2396 Å^3, Z = 4, D_c = 1.13 g cm^{-3}, μ(Cu-Kα) = 5.0 cm^{-1}, F(000) = 880. A clear needle of dimensions 0.09 × 0.17 × 0.63 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 = 0.058, R_w = 0.062 for 1732 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 128°$]. 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.

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