Total synthesis of the antifungal agent FR-900848

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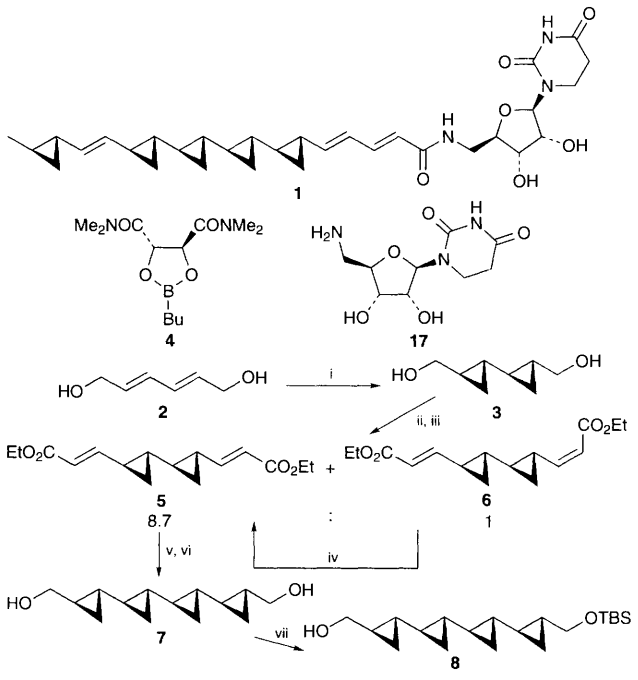
The total synthesis of the antifungal agent FR-900848 is accomplished using Charette asymmetric cyclopropanation to control ten stereocentres.

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 since it is graced with five cyclopropane units, four of which are contiguous. Recently, we reported on degradation and synthetic studies of FR-900848 **1** which allowed us to establish its full structure and absolute stereochemistry.[2,3] Here we report the total synthesis of FR-900848 **1**.

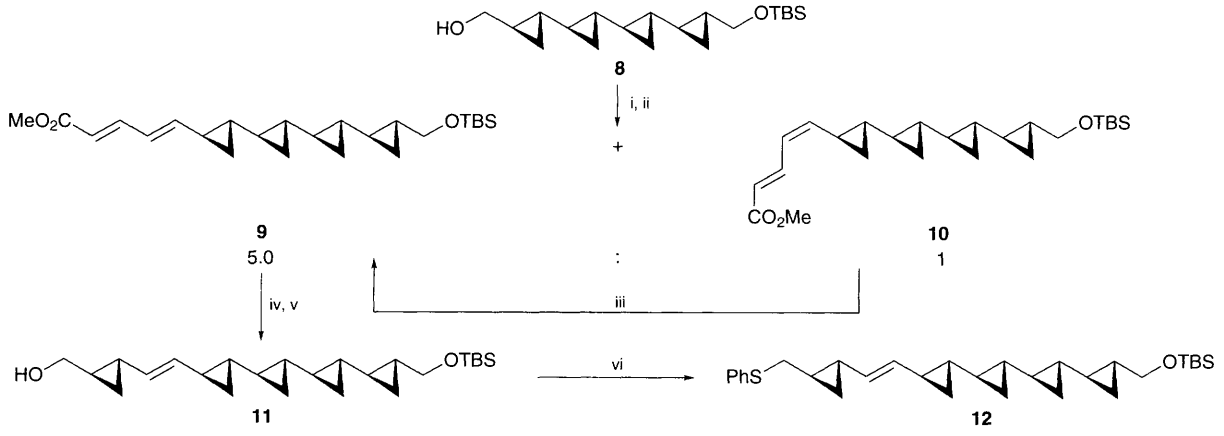
In an improvement of our previous synthesis[3] and following the elegent new cyclopropanation methodology recently reported by Charette,[4] mucondiol **2**[5] was bicyclopropanated (Scheme 1) in the presence of the chiral auxillary **4** to provide diol **3**† in high yield (89%). PCC oxidation and subsequent homologation provided a separable mixture of (*E,E*)-diester **5** and the (*E,Z*)-isomer **6** (8.7 : 1, 67% from **3**). The unwanted diester **6** was smoothly converted into diester **5** using Li-Ti(OiPr)$_4$(SPh), a reagent introduced by Hunter[7] for the (*Z*) to (*E*)-isomerisation of α, β-unsaturated esters. This reaction gave additional diester **5** (50%) and recovered (*E,Z*)-isomer **6** (40%) which was further isomerised.

DIBAL-H reduction of diester **5** (94%) and bicyclopropanation of the resultant diol, under Charette conditions[6] using the chiral auxillary **4**, provided diol **7** (93%) as a single diastereoisomer. Subsequent *tert*-butyldimethylsilylation gave the desired alcohol **8** (44%), recovered diol **7** (44%), and di-protected material (10%). Both starting material **7** and the corresponding diether were recycled. Oxidation of alcohol **8** (Scheme 2) and Wadsworth–Emmons homologation gave esters **9** and **10** (5.0 : 1, 71% from **8**). Again, Hunter isomerisation[7] was crucial in converting the undesired isomer **10** into additional (*E,E*)-ester **9** (63%). Finally, DIBAL-H reduction of (*E,E*)-ester **9** (91%) followed by a third Charette asymmetric cyclopropanation[6] gave the pentacyclopropane alcohol **11** in high yield (90%).

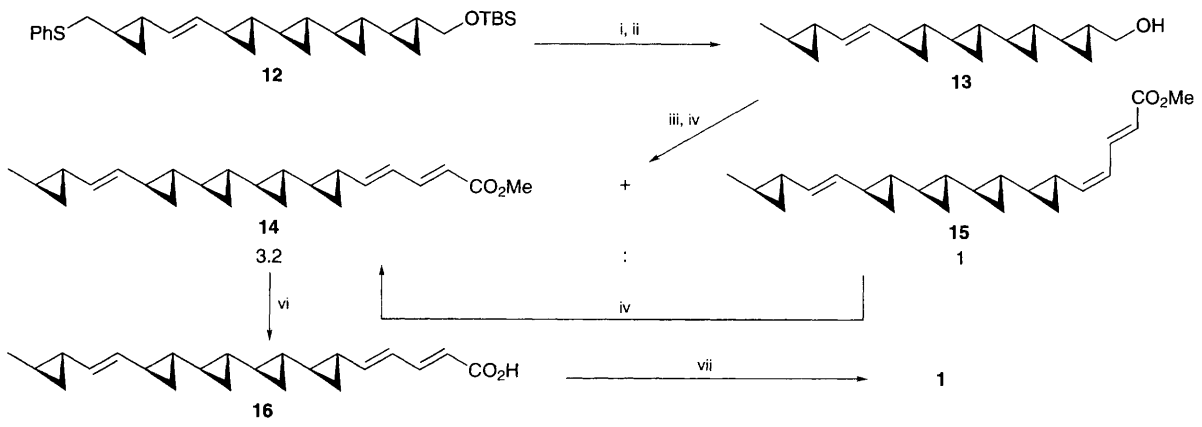
In general we have been significantly frustrated in our attempts to effect substitution reactions on multiple cyclopropanemethanol derivatives *via* hydroxy activation and displace-



Scheme 1 *Reagents and conditions*: i, **4**, Et_2Zn, CH_2I_2, CH_2Cl_2, −15 to 25 °C, 89%; ii, PCC, NaOAc, silica, CH_2Cl_2, 0 to 25 °C; iii, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 67% (from **3**); iv, PhSH, BuLi, Ti(OPr^i)$_4$, THF, 0 to 25 °C, 50%; v, DIBAL-H, CH_2Cl_2, −78 °C, 94%; vi, **4**, Et_2Zn, DME, CH_2I_2, CH_2Cl_2, −15 to 25 °C, 93%; vii, NaH, TBSCl, THF, 44%



Scheme 2 *Reagents and conditions*: i, PCC, NaOAc, silica, CH_2Cl_2, 0 to 25 °C; ii, (*E*)-$MeO_2CCH{=}CHCH_2P(O)(OMe)_2$, NaH, THF, 0 to 25 °C, 71% (from **8**); iii, PhSH, BuLi, Ti(OPr^i)$_4$, THF, 0 to 25 °C, 63%; iv, DIBAL-H, CH_2Cl_2, −78 °C, 91%; v, **4**, Et_2Zn, DME, CH_2I_2, CH_2Cl_2, −40 °C, 90%; vi, *N*-(phenylsulfenyl)succinimide, Bu_3P, PhH, 89%



Scheme 3 *Reagents and conditions*: i, Raney Ni, EtOH, −40 °C; ii, NH_4F, EtOH, 65 °C, 49% (from **12**); iii, PCC, NaOAc, silica, CH_2Cl_2, 0–25 °C; iv, (*E*)-$MeO_2CCH{=}CHCH_2P(O)(OMe)_2$, NaH, THF, 0–25 °C, 63% (from **13**); v, PhSH, BuLi, $Ti(OPr^i)_4$, THF, 0 to 25 °C, 51%; vi, $KOSiMe_3$, CH_2Cl_2, 85%; vii, **17**, bis(2-oxo-3-oxazolidinyl)phosphinic chloride BOP-Cl, Et_3N, *N,N*-dimethylacetamide, 69%

ment. Usually such approaches lead to extensive degradation. In contrast, reaction of alcohol **11** with *N*-(phenylsulfenyl)-succinimide and tributylphosphine[8] cleanly gave the sulfide **12** (89%). Attempted reductive desulfurisation *via* variousmethods at the sulfide or sulfone oxidation levels were all wrecked on the reefs of global rearrangement. However, when sulfide **12** was treated with Raney nickel (Scheme 3) regioselective desulfurisation without skeletal change took place. Subsequent deprotection using ammonium fluoride gave alcohol **13** (49% from **12**).

PCC oxidation of alcohol **13**, Wadsworth–Emmons homologation (with Hunter isomerisation[7] of the unwanted (*E,Z*)-ester **15**), and hydrolysis using potassium trimethylsilanolate[9] gave the FR-900848 side chain carboxylic acid **16** (48% from **13**). Coupling of acid **16** and amine **17**[10] using BOP-Cl[11] and triethylamine gave FR-900848 **1** (69%) and recovered acid **16** (10%). Much to our delight the synthetic material was identical with an authentic sample.‡

It is clear from these results that Charette[4,6] triple asymmetric cyclopropanation is appropriate for the elaboration of FR-900848 **1** with excellent overall stereochemical control. Alternative condensation strategies of monocyclopropane and quatercyclopropane arrays to elaborate Δ^{18} have the disadvantages of low geometric control and/or degradation.

We thank Fujisawa Pharmaceutical Company Ltd. for generous donations of samples of FR-900848 **1** and key spectroscopic data, Dr G. Tustin and Ms A. Daumens for preparing amine **17**,[10] the EPSRC National Chiroptical Spectroscopy Facility for CD spectra, 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.).

Footnotes

† The new compounds **3**, **5**, **6**, **7**, **8**, **9**, **11**, **12**, **13**, **14**, **16** and **1** were fully characterised by spectroscopic data and microanalysis and/or HRMS.
‡ The compounds matched by ^1H NMR, ^{13}C NMR, $[\alpha]_D$, UV, CD and HPLC.

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Received, 30th October 1995; Com. 5/07128C