

Synthesis of the Polycyclopropane Antibiotic FR-900848 via the Horeau Gambit

J. R. Falck,* Belew Mekonnen, Jurong Yu, and Jing-Yu Lai

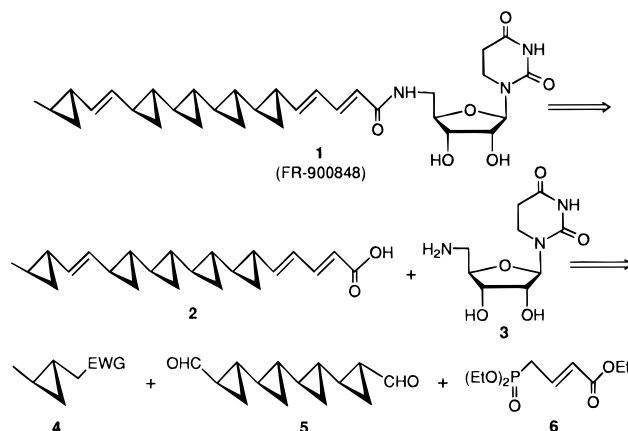
Departments of Molecular Genetics and Pharmacology
University of Texas Southwestern Medical Center
Dallas, Texas 75235

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Streptovorticillium fervens elaborates a unique nucleoside antibiotic, FR-900848 (**1**), whose structure was published without assignment of relative or absolute configurations.¹ It displays potent and highly specific inhibitory activity against filamentous fungi including several pathogens responsible for significant human morbidity/mortality but is almost inactive against Gram-positive and Gram-negative bacteria. In light of its low toxicity in mammals (murine LD₅₀ > 1g/kg), **1** represents a promising new lead to counter the alarming increase in the incidence of systemic fungal infections as well as the concomitant appearance of drug resistant strains.² The most distinctive structural feature of **1** is its lipidic proboscis endowed with five cyclopropane rings. Such unprecedented functionality poses a daunting synthetic challenge and accordingly has engendered considerable attention³ that has culminated in a recent total synthesis.⁴ Herein, we describe a conceptually distinct approach to **1** that (a) independently confirms the complete architecture of FR-900848, (b) validates methodology for the stereocontrolled assembly of polycyclopropanes,⁵ and (c) illustrates a variant of the Horeau principle⁶ leading to material of high enantiomeric enrichment.

A retrosynthetic analysis, outlined in Scheme 1, bisected **1** into fatty acid **2** and dihydrouridine **3**. The former was provisionally assigned an *all-trans* stereochemistry based on biogenetic considerations⁷ and the latter was presumed to have the configuration typical of nucleosides. Moiety **2** was simplified further by dismantling into monocyclopropane **4**, tetracyclopropane **5**, and the Horner–Emmons reagent **6**.⁸ Additional insight into the configuration of **1** came from its ozonolytic degradation by Fujisawa scientists.⁹ The ¹³C NMR spectrum

Scheme 1



of the serial tetracyclopropane fragment revealed seven resonances only and was most consistent with a *meso* or *C₂*-symmetric product. Combined with extensive NMR comparisons with the *syn/anti*-bicyclopropanes generated from 2,4-hexadiene-1,6-diol (mucondiol) via nonselective cyclopropanation, an *all-trans, all-syn* geometry for **2** was targeted. The absolute configuration was selected arbitrarily and would be confirmed *en route* by comparison with a suitable degradation fragment from natural material.

A reiterative dimerization strategy^{10,11} (Scheme 2) was embraced for the preparation of the tetracyclopropane core of **2** and commenced with a moderately stereospecific (88–90% ee) Charette–Juteau¹² asymmetric cyclopropanation of *trans*-allylic alcohol **7**.¹³ Silylation of the derived cyclopropylmethanol¹⁴ under standard conditions furnished stannane **8** which was *transmetalated* with *sec*-BuLi. The newly generated lithium anion was added to [ICuPBu₃]₄¹⁵ and then subjected to an O₂-induced¹⁶ dimerization¹⁷ at low temperature to give *syn-trans,trans*-bicyclopropane **9** (98% ee¹⁸), [α]_D²³ –41.5° (c 0.23, absolute EtOH). The enrichment in enantiomeric composition is a manifestation of the statistical distribution of products and represents a variant of the Horeau amplification principle.⁶ Classical resolution techniques are obviated and greater latitude regarding optical purity of precursors is possible.

As a prelude to the next level of dimerization (and its attendant Horeau amplification), **9** was converted to carboxylic acid **10** via selective fluoride cleavage of one silyl ether and RuCl₃-catalyzed oxidation of the liberated alcohol. The one-

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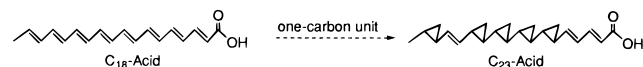
(3) Theberge, C. R.; Zercher, C. K. *Tetrahedron Lett.* **1994**, *35*, 9181–9184. Armstrong, R. W.; Maurer, K. W. *Ibid.* **1995**, *36*, 357–360. Barrett, A. G. M.; Kasdorf, K.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1781–1782. Barrett, A. G. M.; Doubleday, W. W.; Tustin, G. J.; White, A. J. P.; Williams, D. J. *Ibid.* **1994**, 1783–1784. Barrett, A. G. M.; Tustin, G. J. *Ibid.* **1995**, 355–356. Barrett, A. G. M.; Doubleday, W. W.; Kasdorf, K.; Tustin, G. J.; White, A. J. P.; Williams, D. J. *Ibid.* **1995**, 407–408. Barrett, A. G. M.; Kasdorf, K.; White, A. J. P.; Williams, D. J. *Ibid.* **1995**, 649–650. Barrett, A. G. M.; Kasdorf, K.; Tustin, G. J.; Williams, D. J. *Ibid.* **1995**, 1143–1144.

(4) Barrett, A. G. M.; Kasdorf, K. *Chem. Commun.* **1996**, 325–326.

(5) Examples of polycyclopropane syntheses: Conia, J. M.; Denis, J. M. *Tetrahedron Lett.* **1969**, 3545–3546. Ripoll, J. L.; Limasset, J. C.; Conia, J. M. *Tetrahedron* **1971**, *27*, 2431–2452. Kostikov, R. R.; Molchanov, A. P. *Zh. Org. Khim.* **1978**, *14*, 1108–1109. de Meijere, A.; Jaekel, F.; Simon, A.; Bormann, H.; Kohler, J.; Johnels, D.; Scott, L. T. *J. Am. Chem. Soc.* **1991**, *113*, 3935–3941.

(6) For a thorough discussion of the Horeau amplification principle, see: Rautenstrauch, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 515–524.

(7) We speculate that the odd-numbered C₂₃-acid **2** is derived biogenetically from an even-numbered C₁₈-polyunsaturated fatty acid and that the cyclopropanes arise from the addition of one-carbon units donated by S-adenosylmethionine or its equivalent. Since the thermodynamically most stable form of this hypothetical precursor is *all-trans*, then the cyclopropanes and olefins in **2** would also be *trans*.



(8) Available from Aldrich Chem. Co.

(9) Dr. Hirokazu Tanaka (Fujisawa Pharmaceutical Co., Ltd.), personal communication.

(10) Dimerizations of cyclopropane anions have precedence: Slabey, V. A. *J. Am. Chem. Soc.* **1952**, *74*, 4928–4930. Kai, Y.; Knochel, P.; Kwiatkowski, S.; Dunitz, J. D.; Oth, J. F. M.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 137–161. O'Bannon, P. E.; Dailey, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 9244–9245.

(11) The geometric progression (2ⁿ units/dimerization) inherent in this strategy allows one to rapidly accrue repeating functionality. This would be especially important for the preparation of higher homologs of **1** containing, for example, eight serial cyclopropanes.

(12) Review: Charette, A. B.; Marcoux, J.-F. *Synlett* **1995**, 1197–1207.

(13) Imai, N.; Sakamoto, K.; Takahashi, H.; Kobayashi, S. *Tetrahedron Lett.* **1994**, *35*, 7045–7048. Jung, M. E.; Light, L. A. *Ibid.* **1982**, *23*, 3851–3854.

(14) All isolated intermediates were fully characterized by ¹H/¹³C NMR and MS analysis. The elemental composition of an analytical sample was confirmed by combustion analysis or high-resolution mass spectroscopy.

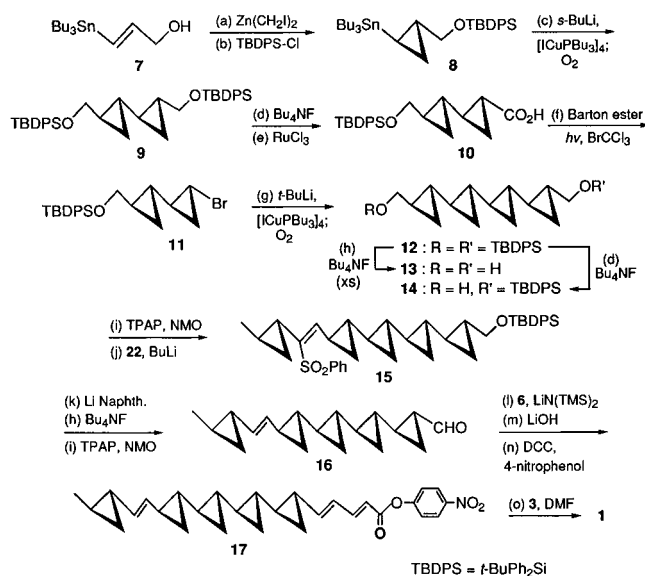
(15) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379–1389.

(16) Lipshutz, B. H.; Kayser, F.; Maullin, N. *Tetrahedron Lett.* **1994**, *35*, 815–818.

(17) cf.: Walborsky, H. M.; Banks, R. B.; Banks, M. L. A.; Duraisamy, M. *Organometallics* **1982**, *1*, 667–674.

(18) Chiral phase HPLC analysis was performed on a Chiralcel OD column (Daicel, 4.6 × 250 mm) using 0.8% *i*-PrOH/hexane at a flow rate of 1 mL/min. The bis-(S)-Mosher ester of **9** had a R_t ≈ 16.7 min and the bis-(S)-Mosher ester of its enantiomer had a R_t ≈ 29 min.

Scheme 2



^aReaction conditions: (a) (S,S)-Dioxaborolane, ZnEt₂, CH₂Cl₂, CH₂Cl₂, 23°C, 14 h (98%). (b) *t*-BuPh₂SiCl, ImH, DMF, 23°C, 24 h (88%). (c) *s*-BuLi, THF, -40°C, 1 h; [ICuPBu₃]₄ (0.125 equiv), -78°C, 1 h; O₂, -78°C, 6 h (73%). (d) *n*-Bu₄NF (0.95 equiv), THF, 23°C, 2 h (72%). (e) RuCl₃/NaO₄, CCl₄/CH₃CN/H₂O (1:1:1.5), 23°C, 1.5 h (91%). (f) 2-Mercaptopyrindine N-oxide, DCC, DMAP, BrCCl₃, 23°C, 4 h; *hν*, 0°C, 1.5 h (77%). (g) *t*-BuLi, THF, -78°C, 1 h; [ICuPBu₃]₄ (0.125 equiv), -78°C, 1 h; O₂, -78°C, 3 h (75%). (h) *n*-Bu₄NF (excess), THF, 23°C, 2 h (95%). (i) TPAP (5%), NMO, 4 Å molecular sieves, CH₂Cl₂, 23°C, 0.3 h (91%). (j) 22, *n*-BuLi, THF, -78°C, 0.5 h (65%). (k) Li, naphthalene, THF, -78°C, 0.1 h (70%). (l) 6, LiN(TMS)₂, THF, -78°C to 23°C, 3 h (89%). (m) LiOH, MeOH/H₂O (4:1), 23°C, 48 h (>90%). (n) DCC, DMAP, 4-nitrophenol, CH₂Cl₂, 23°C, 24 h (73%). (o) 3, DMF, 23°C, 3 h (76%).

pot preparation and photolytic decarboxylation of the corresponding Barton thiohydroxamic ester¹⁹ in BrCCl₃ at 0 °C gave rise to a 14:1 mixture of bromide **11** and its *cis*-isomer, respectively, that was readily separated by chromatography. Repetition of the dimerization sequence, using *tert*-BuLi for anion generation, stereospecifically²⁰ transformed **11** into the isotactic tetracyclopropane **12** (>99.9% ee²¹) in good yield. bis-Desilylation led to diol **13**, [α]_D²³ -151.8° (c 1.37, absolute EtOH), whose spectral (¹H/¹³C/CIMS) characteristics were indistinguishable from those of a sample obtained by degradation of natural material (O₃/NaBH₄). Following derivatization to the bis-(*S*)-Mosher ester, **13** and the diol from degraded natural material had identical retention times upon chiral phase HPLC analysis²¹ and could be clearly resolved from enantiomer **18**



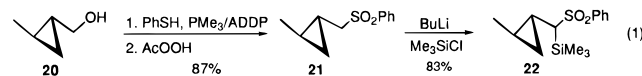
(prepared as described in Scheme 2 using the *R,R*-Charette/Juteau catalyst).

(19) Barton, D. H. R.; Crich, D. C.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, 24, 4979–4982.

(20) A better indication of the stereospecificity is seen in the dimerization of the *cis*-analog of **11**. The *all-syn-trans,cis,cis,trans*-tetracyclopropane dimer was isolated in 80% yield, and no other stereoisomers were observed.

(21) Chiral phase HPLC analysis was performed as described in ref 18. The bis-(*S*)-Mosher ester of **13** and diol from degraded natural material had *R*_t ≈ 14.4 min; the bis-(*S*)-Mosher ester of **18** had a *R*_t ≈ 17.6 min.

Partial deprotection of **12** evolved **14** which was prepared for union with the remaining cyclopropyl unit by catalytic tetrapropylammonium perruthenate (TPAP) oxidation. The resultant aldehyde smoothly accepted the anion of sulfone **21**, made from alcohol **20**^{12,13} via Mitsunobu condensation²² with thiophenol and peracid oxidation (eq 1), to yield **19** (R = H) as



a mixture of diastereomers. However, Julia elimination²³ (R = Ac, Ms) under a variety of conditions resulted in extensive structural collapse and furnished almost none of the desired *trans*-olefin. Alternatively, Peterson-type olefination exploiting **22** secured vinyl sulfone **15** and a variable amount (10–20%) of the *cis*-isomer that was removed chromatographically. The sulfone was stripped away using lithium naphthalenide at -78 °C and aldehyde **16** was isolated after desilylation and oxidation as described above. Horner–Emmons homologation of **16** utilizing the ylide of **6** furnished the *all-trans* adduct as the sole product which was saponified and condensed with 4-nitrophenol using DCC to afford active ester **17**. Acylation of 5'-amino-5'-deoxy-5,6-dihydrouridine (**3**)²⁴ with **17** in DMF at room temperature concluded the synthesis of **1**. Synthetic and natural FR-900848 were identical in all respects (¹H/¹³C NMR, HPLC, FAB-MS).²⁵

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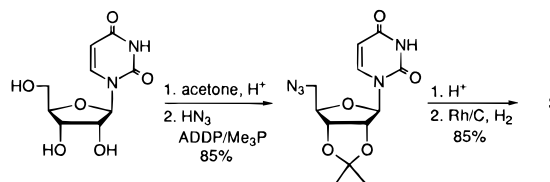
Supporting Information Available: Details of the syntheses and characterization data for new compounds (9 pages). See any current masthead page for ordering and Internet access instructions.

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(22) Hughes, D. L. *Org. React.* **1992**, 42, 335–656.

(23) Kocienski, P. *Phosphorus Sulfur* **1985**, 24, 97–127.

(24) Prepared from commercial uridine by a conventional sequence as summarized below.



(25) The exception was the optical rotation. Synthetic **1** showed [α]_D²³ -158° (c 0.3, DMSO), whereas the originally reported¹ value was [α]_D²⁰ -36.22° (c 0.5, DMSO). Unfortunately, a sample of natural material suitable for verification of this measurement could not be obtained. However, the [α]_D -168.1° (c 0.42, DMSO-*d*₆) of synthetic and natural FR-900848 observed by Dr. Krista Kasdorf, in the laboratories of Professor A. G. M. Barrett, is of a magnitude comparable to ours (Prof. A. G. M. Barrett, personal communication).