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

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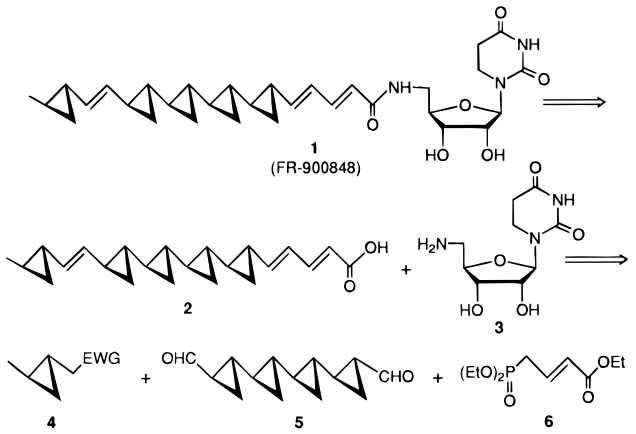
Streptoverticillium fervens elaborates a unique nucleoside antibiotic, FR-900848 (**1**), whose structure was published without assignment of relative or absolute configurations.[1] It displays potent and highly specific inhibitory activity against filamentous fungi including several pathogens responsible 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 LD_{50} > 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 attention[3] 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 principle[6] 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 considerations[7] 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 ^{13}C NMR spectrum

Scheme 1



of the serial tetracyclopropane fragment revealed seven resonances only and was most consistent with a *meso* or C_2-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−Juteau[12] asymmetric cyclopropanation of *trans*-allylic alcohol **7**.[13] Silylation of the derived cyclopropylmethanol[14] under standard conditions furnished stannane **8** which was *trans*metalated with *sec*-BuLi. The newly generated lithium anion was added to $[ICuPBu_3]_4$[15] and then subjected to an O_2-induced[16] dimerization[17] at low temperature to give *syn-trans,trans*-bicyclopropane **9** (98% ee[18]), $[\alpha]_D^{23}$ −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 $RuCl_3$-catalyzed oxidation of the liberated alcohol. The one-

(1) Yoshida, M.; Ezaki, M.; Hashimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. *J. Antibiotics* **1990**, *43*, 748−754.

(2) Sternberg, S. *Science* **1994**, *266*, 1632−1634. Georgopapadakou, N. H.; Walsh, T. J. *Ibid.* **1994**, *264*, 371−373.

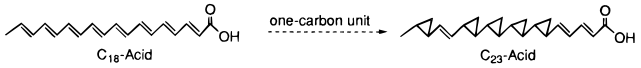
(3) Theberge, C. R.; Zercher, C. K. *Tetrahedron Lett.* **1994**, *35*, 9181−9184. Armstrong, R. W.; Maurer, K. W. *Ibid.* **1995**, *36*, 357−360. Barrett, A. G. M.; Kasdorf, K.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1781−1782. Barrett, A. G. M.; Doubleday, W. W.; Tustin, G. J.; White, 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.; Borrmann, 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 C_{23}-acid **2** is derived biogenetically from an even-numbered C_{18}-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 (2^n 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 $^1H/^{13}C$ 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.

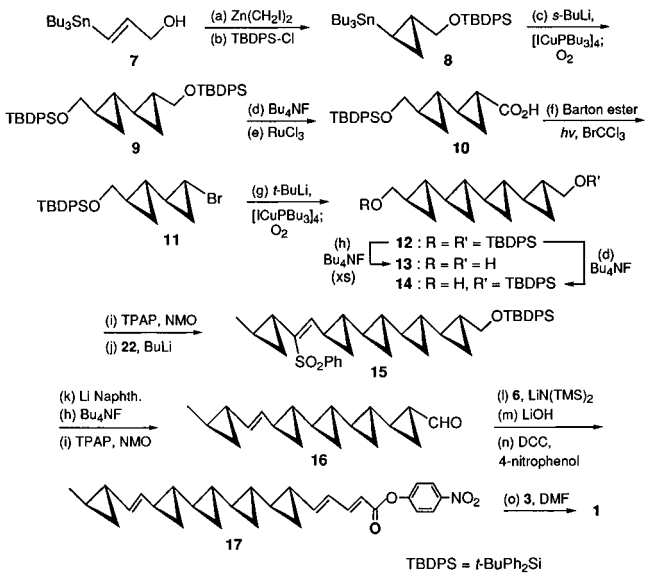
(16) Lipshutz, B. H.; Kayser, F.; Maullin, N. *Tetrahedron Lett.* **1994**, *35*, 815−818.

(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 $R_t \approx 16.7$ min and the bis-(*S*)-Mosher ester of its enantiomer had a $R_t \approx 29$ min.

S0002-7863(96)01093-1 CCC: $12.00

Scheme 2

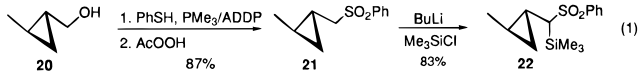


[a]Reaction conditions: (a) (*S,S*)-Dioxaborolane, $ZnEt_2$, CH_2I_2, CH_2Cl_2, 23°C, 14 h (98%). (b) *t*-$BuPh_2SiCl$, ImH, DMF, 23°C, 24 h (88%). (c) *s*-BuLi, THF, -40°C, 1 h; $[ICuPBu_3]_4$ (0.125 equiv), -78°C,1 h; O_2, -78°C, 6h (73%). (d) *n*-Bu_4NF (0.95 equiv), THF, 23°C, 2 h (72%). (e) $RuCl_3/NaIO_4$, $CCl_4/CH_3CN/H_2O$ (1:1:1.5), 23°C, 1.5 h (91%). (f) 2-Mercaptopyridine N-oxide, DCC, DMAP, $BrCCl_3$, 23°C, 4 h; *hv*, 0°C, 1.5 h (77%). (g) *t*-BuLi , THF, -78°C, 1 h; $[ICuPBu_3]_4$ (0.125 equiv), -78°C,1 h; O_2, -78°C, 3h (75%). (h) *n*-Bu_4NF (excess), THF, 23°C, 2 h (95%). (i) TPAP (5%), NMO, 4Å molecular sieves, CH_2Cl_2, 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, $MeOH/H_2O$ (4:1), 23°C, 48 h (>90%). (n) DCC, DMAP, 4-nitrophenol, CH_2Cl_2, 23°C, 24 h (73%). (o) **3**, DMF, 23°C, 3 h (76%).

pot preparation and photolytic decarboxylation of the corresponding Barton thiohydroxamic ester[19] in $BrCCl_3$ 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, stereospecifically[20] transformed **11** into the isotactic tetracyclopropane **12** (>99.9% ee[21]) in good yield. bis-Desilylation led to diol **13**, $[\alpha]_D^{23}$ −151.8° (*c* 1.37, absolute EtOH), whose spectral ($^1H/^{13}C$/CIMS) characteristics were indistinguishable from those of a sample obtained by degradation of natural material ($O_3/NaBH_4$). Following derivatization to the bis-(*S*)-Mosher ester, **13** and the diol from degraded natural material had identical retention times upon chiral phase HPLC analysis[21] and could be clearly resolved from enantiomer **18**

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

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 condensation[22] with thiophenol and peracid oxidation (eq 1), to yield **19** (R = H) as



a mixture of diastereomers. However, Julia elimination[23] (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 ($^1H/^{13}C$ 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.

JA961093G

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

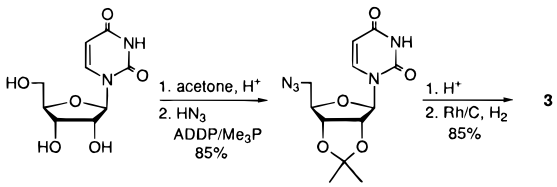
(20) A better indication of the stereospecificity is seen in the dimerization of the *cis*-analog of **11**. The *all-syn-trans,cis,cis,trans*-tetracyclopropane dimer was isolated in 80% yield, and no other stereoisomers were observed.

(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 $R_t \approx 14.4$ min; the bis-(*S*)-Mosher ester of **18** had a $R_t \approx 17.6$ min.

(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 $[\alpha]_D^{23}$ −158° (*c* 0.3, DMSO), whereas the originally reported[1] value was $[\alpha]_D^{20}$ −36.22° (*c* 0.5, DMSO). Unfortunately, a sample of natural material suitable for verification of this measurement could not be obtained. However, the $[\alpha]_D$ −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).