J|A|C|S
COMMUNICATIONS

Published on Web 04/02/2002

A Synthesis of (+)-FR182877, Featuring Tandem Transannular Diels−Alder Reactions Inspired by a Postulated Biogenesis

David A. Vosburg, Christopher D. Vanderwal, and Erik J. Sorensen*

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

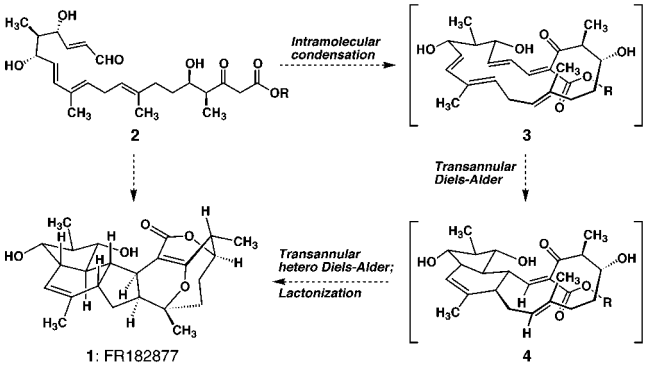
Received February 9, 2002

In the course of designing a synthesis for a complex natural product, it can be profitable to consider how its structure may have arisen in nature.[1] "Biogenetic-type" syntheses are those that imitate established or presumed biosynthetic pathways[1a] and can uncover distinctly direct pathways for creating complex molecular architectures. The application of potentially natural reaction channels to the chemical synthesis of structurally complex, bioactive natural products has been a theme of previous studies from our laboratory,[2] and we contemplated the structural origin of the cytotoxic, bacterial-derived natural product FR182877 (**1**) (Scheme 1). The unique, hexacyclic architecture of this natural product, a substance formerly known as WS9885B, was described by scientists from the Fujisawa Pharmaceutical Company.[3] FR182877 (**1**) is a member of a growing family of secondary metabolites that bind and stabilize cellular microtubules and exhibits a potency comparable to that of the anticancer drug Taxol.[4] While the biosynthesis of **1** has not yet been reported, this natural product is a close structural relative of the polyketide hexacyclinic acid[5] and can be reduced to the same alternating sequence of six acetate and four propionate units.[6]

With a complex hexacyclic ring system comprising 12 stereocenters and a strained bridgehead alkene, FR182877 (**1**) is an intimidating objective for research in organic synthesis. In prior publications, we proposed that the structure of compound **1** could arise from a significantly less complex polyunsaturated compound of type **2** (Scheme 1) by a cascade of intramolecular reactions.[6,7] In evaluating the potential of FR182877 (**1**) for a constitutional self-assembly, we found that a variant of our original biogenetic postulate in which the structure of **1** would form from a polyunsaturated macrocycle of type **3** by successive transannular Diels−Alder reactions is chemically feasible (see **3** → **4** → **1**).[8] The first synthesis of the published structure for FR182877 (**1**) based on this concept is the subject of this communication.

When compound **6**, the trimethylsilyl ether of the recently described alcohol **5**, was reacted with known dienylstannane **7** under previously reported conditions,[6] a smooth union occurred, and compound **8** was isolated in 85% yield (Scheme 2). The efficiency of this Stille coupling,[9] which occurs via a π-allyl palladium(II) intermediate, prompted us to consider the feasibility of achieving a bond formation between carbons 1 and 19 of **9** by a charge-driven, intramolecular attack of a deprotonated β-keto ester on an electrophilic π-allyl Pd(II) intermediate.[10,11] Toward this end, *C*-acylation of lithium *tert*-butyl acetate by the Weinreb amide moiety of **8**[12,13] afforded the expected β-keto ester, which was smoothly converted to the key macrocyclization substrate **9** by the following sequence: (1) selective cleavage of the C-1 and C-16 silyl ethers with *n*-Bu_4NF, (2) conversion of the primary hydroxyl group to the corresponding mixed carbonate with methyl chloroformate, and (3) resilylation of the C-16 secondary hydroxyl group. To our delight, the critical C1−C19 ring closure was achieved in 80% yield by exposure of a dilute (5 mM) solution of **9** in THF to Pd_2dba_3 (10 mol %) at 40 °C.[10,11] The efficient formation of carbocycle **10** by this method stands in sharp contrast to unsuccessful early efforts to achieve ring-forming Knoevenagel condensations of compounds related to **2** (Scheme 1).

Scheme 1. A Variant of Our Original Biogenetic Model



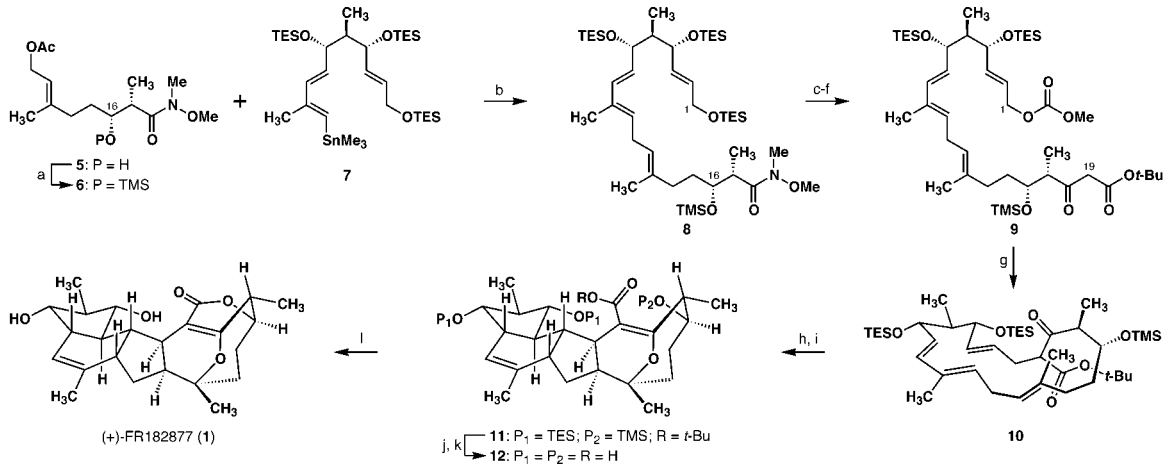
To evaluate the hypothesis outlined in Scheme 1, we needed only to introduce unsaturation between the two carbonyl functions. Reaction of the stabilized enolate derived from **10** with phenylselenenyl bromide afforded a ca. 3:1 mixture of inseparable diastereomers. When this mixture of organoselenides was treated with *m*CPBA in CH_2Cl_2 at −78 °C, a protected version of compound **3** (Scheme 1) and its geometrical isomer were efficiently formed.[14] Remarkably, when a solution of these geometrically isomeric macrocycles in chloroform was warmed to 40 °C, compound **11** was produced in an isolated yield of 40%;[15] these tandem transannular Diels−Alder reactions[16] transformed a 19-membered ring carbocycle to a complex pentacycle with seven new contiguous stereocenters. Moreover, this process is diastereoselective and yields a pentacyclic compound with relative stereochemical relationships that are reflected in FR182877 (**1**). To the best of our knowledge, this is the first example of a double transannular Diels−Alder reaction.

From compound **11**, the final ascent to **1** was straightforward. Solvolysis of the three silyl ethers and cleavage of the *tert*-butyl ester function in **11** were best achieved with PPTS/MeOH and trifluoroacetic acid, respectively. Finally, an EDC-mediated lactonization of triol carboxylic acid **12** afforded (+)-FR182877 [(+)-**1**].[17] The spectroscopic data that was accumulated for this substance matched the published spectra for FR182877[3] in every detail; however, the sign of the $[\alpha]_D$ for our synthetic sample indicates that the compound shown as **1** in Schemes 1 and 2 is the

* To whom correspondence should be addressed. E-mail: sorensen@scripps.edu.

10.1021/ja025885o CCC: $22.00

Scheme 2 [a]



[a] Key: (a) TMSCl, imidazole, CH_2Cl_2, 96%; (b) Pd_2dba_3 (0.1 equiv), LiCl, *i*-Pr_2NEt, NMP, 40 °C, 80 min, 85%; (c) LDA, *t*-BuOAc, Et_2O, −78 °C → rt, 81%; (d) TBAF (2 equiv), THF, −40 → 0 °C, 86%; (e) MeOCOCl, pyridine, CH_2Cl_2, 93%; (f) TMSCl, imidazole, CH_2Cl_2, 95%; (g) Pd_2dba_3 (0.1 equiv), THF, 40 °C, 12 h, 80%; (h) KHMDS, PhSeBr, THF, −10 °C, 91%; (i) *m*CPBA, CH_2Cl_2, −78 °C; then $CHCl_3$, 40 °C, 4 h, 40%; (j) PPTS, MeOH; (k) TFA/CH_2Cl_2 (1:9), 0 °C → rt; (l) EDC, DMAP, CH_2Cl_2, 62% from **11**.

enantiomer of naturally occurring FR182877.[18] This finding is of much interest from a biosynthetic perspective because it suggests that FR182877 and hexacyclinic acid are closely related with respect to constitution and absolute stereochemistry.[5,6]

The asymmetric synthesis of (+)-FR182877 described herein issued from the following question: Can the unique architecture of **1** arise spontaneously from a polyunsaturated precursor by a cascade of cyclizations? In our effort to address this question experimentally, we found that two π-allyl Pd(II)-mediated bond forming reactions facilitated a synthesis of a polyunsaturated macrocycle that can indeed undergo a remarkable sequence of complexity-generating reactions with minimal instigation. The diastereoselectivity observed for this polycyclization process is apparently intrinsic to structures of type **3** and does not result from the influence of an external asymmetric catalyst. This synthesis of FR182877 validates our biogenetic proposal and provides a chemical rationalization of its structure.

Acknowledgment. This paper is dedicated with respect and affection to Professor Roger C. Hahn on the occasion of his 70th birthday. Our work was supported by The Skaggs Institute for Chemical Biology at TSRI, NIH/NCI Grant CA85526, the Beckman Foundation, a Camille-Dreyfus Teacher-Scholar Award, Astra-Zeneca, Eli Lilly, Merck, and predoctoral fellowships from the NSERC of Canada (C.D.V.), Hoffmann-La Roche (C.D.V.), the Skaggs Institute (C.D.V.), NSF (D.A.V.), and ACS/AstraZeneca (D.A.V.). We thank Dr. Sven Weiler (now at Novartis) for early contributions to this project.

Supporting Information Available: Characterization data for **8**, **10**, **11**, and **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For selected discussions and reviews, see: (a) van Tamelen, E. E. *Fortschr. Chem. Org. Naturst.* **1961**, *19*, 242. (b) Woodward, R. B. *Nature* **1948**, *162*, 155. (c) Robinson, R. *The Structural Relations of Natural Products*; Clarendon Press: Oxford, 1955. (d) Barton, D. H. R.; Cohen, T. *Festschrift Arthur Stoll* **1957**, 117. (e) Woodward, R. B. *Pure Appl. Chem.* **1961**, *2*, 383. (f) van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152. (g) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9. (h) Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 5. (i) Eschenmoser, A. B_{12}: Reminiscences and Afterthoughts. In *The Biosynthesis of the Tetrapyrrole Pigments*; Ciba Foundation Symposium 180, Wiley: Chichester, 1994; p 309. (j) Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 14323.

(2) (a) (−)-Hispidospermidin: Tamiya, J.; Sorensen, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9556. (b) FR901483: Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593.

(3) (a) Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123. (b) Sato, B.; Nakajima, H.; Hori, Y.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 204. (c) Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 615.

(4) (a) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15. (b) Kingston, D. G. I. *Chem. Commun.* **2001**, 867.

(5) Höfs, R.; Walker, M.; Zeeck, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3258.

(6) Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett.* **2001**, *3*, 4307.

(7) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Org. Lett.* **1999**, *1*, 645.

(8) The transformations shown in Scheme 1 are generalized and are not meant to preclude other possible orderings of events.

(9) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.

(10) (a) For an example of a palladium-mediated macrocyclization, see: Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 568. (b) For a review, see: Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173.

(11) (a) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809. (b) For a review, see: Tsuji, J. *Tetrahedron* **1986**, *42*, 4361.

(12) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.

(13) Turner, J. A.; Jacks, W. S. *J. Org. Chem.* **1989**, *54*, 4229.

(14) (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697. (b) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813. (c) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*; CIS, Inc.: Philadelphia, 1984. The oxidative deselenylation gives a ca. 1:1 *E*/*Z* ratio of inseparable pentaenes of type **3**, isomeric at the newly formed C1−C19 olefin. Studies to form this olefin with greater *E*-selectivity are in progress.

(15) Pentacycle **11** constitutes ≥50% of the product mass balance and represents ca. 80% yield based on the unisolable *E*-pentaene. The minor reaction products include a diastereomer of **11** and two diastereomeric derivatives of **4**. At room temperature the tandem cycloadditions require *ca.* 24 h. Further studies of this process will be reported in due course.

(16) (a) For an excellent review by the pioneer in the development of the transannular Diels−Alder strategy in organic synthesis, see: Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243. (b) For a recent and elegant biomimetic natural product synthesis featuring intermolecular and transannular Diels−Alder reactions, see: Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773.

(17) The longest linear sequence of 20 steps proceeds in 5% overall yield (86% yield/step) from (*E*)-4-*tert*-butyldimethylsilyloxy-but-2-enal (see ref 6).

(18) Our finding is corroborated in a recent revision of the absolute stereochemistry of FR182877 by Fujisawa scientists (see: *J. Antibiot.* **2002**, *55*, C1). We thank Dr. Seiji Yoshimura from Fujisawa Pharmaceutical Co. for providing us with this information.

JA025885O