

Total Synthesis of (–)-SNF4435 C and
(+)-SNF4435 D

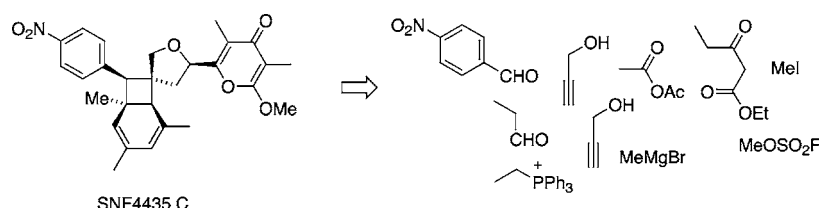
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ABSTRACT



A convergent, biomimetic total synthesis of the immunosuppressant polyketides SNF4435 C and D is described. The synthetic pathway features a stereo- and regioselective [3,3]-sigmatropic rearrangement as well as a high-yielding Stille coupling/ 8π – 6π electrocyclization cascade.

The highly unsaturated polyketides SNF4435 C and D have attracted considerable attention due to their immunosuppressive and anticancer activity.¹ The compounds were found to inhibit B-cell proliferation in an IL2-independent way and revert multidrug resistance in certain cancer cell lines. In addition, their unusual structure and interesting biosynthesis has made them attractive targets for total synthesis.²

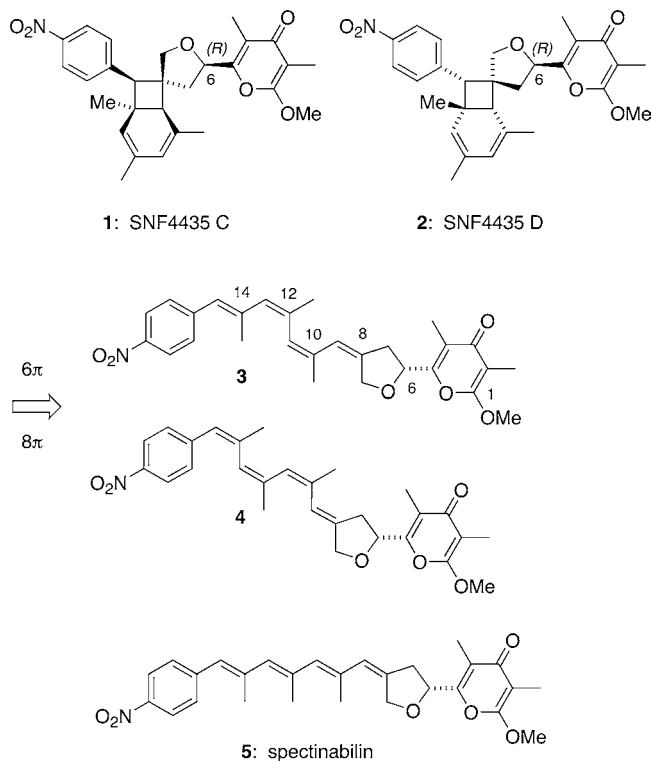
Biosynthetically, the bicylo[4.2.0]octadiene core of the natural products presumably arises through a thermal 8π – 6π electrocyclization cascade from a highly substituted conjugated polyene (Scheme 1).^{2a,d,3} In compliance with the conrotatory nature of thermal 8π electrocyclizations, this would require a (Z,Z,Z,E)-configured precursor **3** or its (E,Z,Z,Z)-configured counterpart **4**. These tetraenes are geometrical isomers of the previously isolated antibiotic spectinabilin (**5**),⁴ whose spontaneous or enzyme-catalyzed isomerization could account for the formation of the SNF compounds.^{2d,e}

(1) (a) Kurosawa, K.; Takahashi, K.; Tsuda, E. *J. Antibiot.* **2001**, *54*, 541. (b) Takahashi, K.; Tsuda, E.; Kurosawa, K. *J. Antibiot.* **2001**, *54*, 548. (c) Kurosawa, K.; Takahashi, K.; Fujise, N.; Yamashita, Y.; Washida, N.; Tsuda, E. *J. Antibiot.* **2002**, *55*, 71. (d) Kurosawa, K.; Takahashi, K.; Tsuda, E.; Tomida, A.; Tsuruo, T. *Jpn. J. Cancer Res.* **2001**, *92*, 1235.

(2) (a) Beaudry, C. M.; Trauner, D. *Org. Lett.* **2002**, *4*, 2221. (b) Parker, K. A.; Lim, Y.-H. *Org. Lett.* **2004**, *6*, 161. (c) Parker, K. A.; Lim, Y.-H. *J. Am. Chem. Soc.* **2004**, *126*, 15968. (d) Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Cowley, A. R. *Org. Lett.* **2002**, *4*, 3731. (e) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 2473.

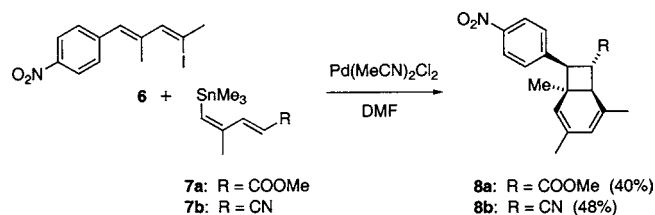
(3) This biosynthetic pathway was first found in the endiandric acids. (a) Bandaranayake, W. M.; Banfield, J. E.; Black, D. S. C. *J. Chem. Soc., Chem. Commun.* **1980**, 902. (b) Nicolaou, K. C.; Sorensen, E. J. In *Classics in Total Synthesis*; VCH: Weinheim, 1996.

Scheme 1



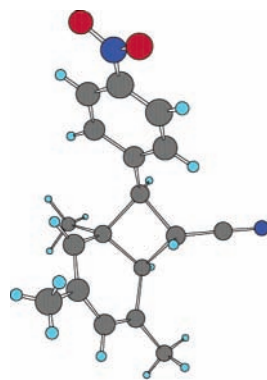
In 2002, we outlined a cross-coupling/electrocyclization strategy for the synthesis of SNF4435 C and D and their

Scheme 2



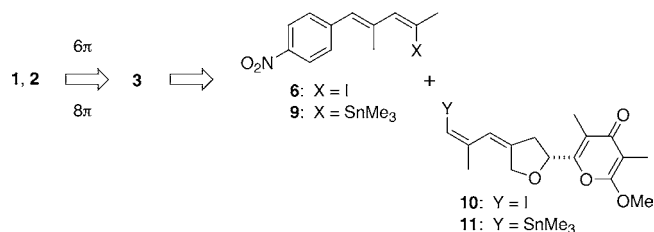
congeners (Scheme 2).^{2a} Stille coupling of vinyl iodide **6** with vinyl stannane **7a** triggered a stereoselective $8\pi-6\pi$ electrocyclization cascade to afford bicyclo[4.2.0]octadiene **8a**. Nitrile **8b** was prepared from **7b** using an analogous reaction cascade. A similar strategy was adopted in Parker's total synthesis, which confirmed our prediction about the relative stereochemistry of the SNF compounds and established their absolute configuration as (6*R*).^{2c}

Although **8a,b** were formed as racemates, the enantiomeric nature of the bicyclo[4.2.0]octadiene core of SNF4435 C and D would allow for a stereodivergent asymmetric synthesis from these intermediates. Our assumption, however, that the carbomethoxy or nitrile group in **8a/b** would provide a functional handle for the installation of the spiro tetrahydrofuran ring proved to be overly optimistic. Despite numerous attempts, we were unable to deprotonate and alkylate either **8a** or **8b**. As is evident from the X-ray structure of nitrile **8b** depicted in Figure 1, the proton resides on the concave side of the bicyclo[4.2.0]octadiene system and is further shielded from attack of a base by the *endo*-*p*-nitrophenyl substituent.

Figure 1. X-ray structure of nitrile **8b**.

We therefore decided to focus on the preparation of the fully substituted (*Z,Z,Z,E*)-tetraene **3** via transition-metal-mediated cross-coupling. To achieve maximum convergency, **3** is best disconnected along C10–C11 bond to yield two diene building blocks (Scheme 3). Whereas the left part was

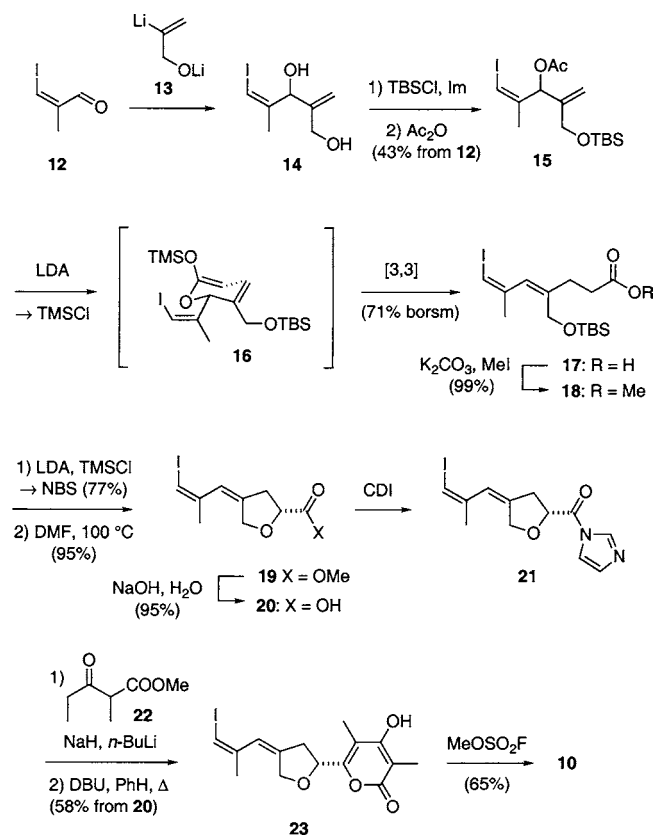
Scheme 3. Retrosynthetic Analysis



readily available in the form of vinyl iodide **6** or its stannane counterpart **9**,^{2a} the right half, featuring an alkylidene tetrahydrofuran moiety and the α -methoxy- γ -pyrone (e.g., **10** or **11**), proved to be much more challenging.

Our ultimately successful strategy hinges on a stereoselective and regioselective [3,3]-sigmatropic rearrangement (Scheme 4). Addition of dianion **13**⁵ to iodomethacrolein **12**⁶

Scheme 4



gave diol **14**, which was selectively protected and acetylated to yield acetate **15**. Ireland–Claisen rearrangement of **15** gave carboxylic acid **17** as a single diastereomer along with recovered starting material.⁷ The stereoselectivity of the rearrangement can be explained by invoking a chair-shaped

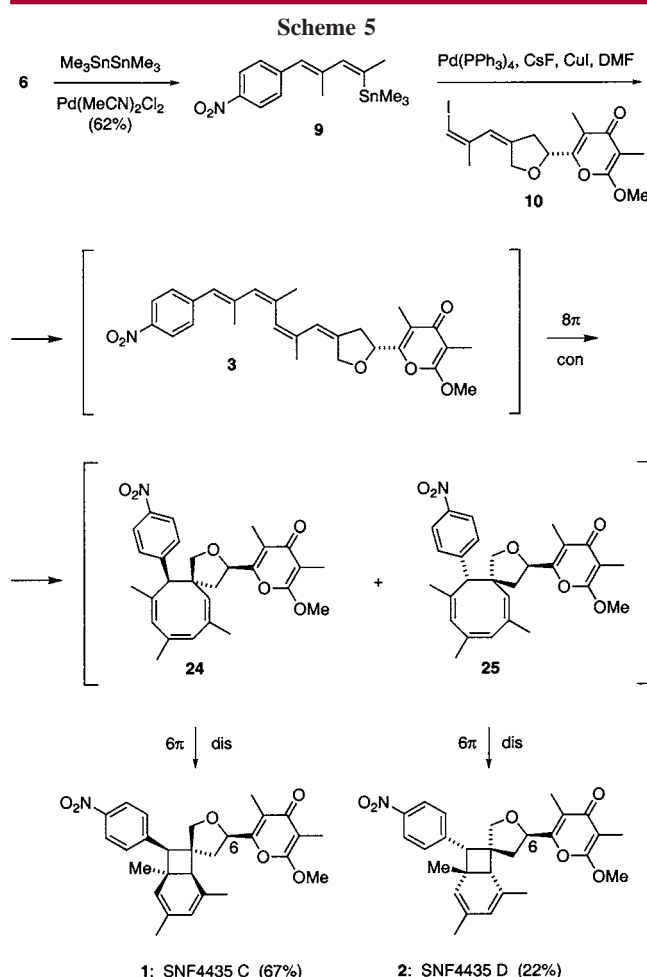
(4) Kakinuma, K.; Hanson, C. A.; Rinehart, K. L., Jr. *Tetrahedron* **1976**, *32*, 217.

(5) (a) Corey, E. J.; Widiger, G. N. *J. Org. Chem.* **1975**, *40*, 2975. (b) Irifune, S.; Kibayashi, T.; Yasutaka, I.; Masaya, O. *Synthesis* **1988**, 366. (6) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.

transition state **16** with the bulky iodo isopropenyl group in a pseudoequatorial position, whereas the regioselectivity presumably arises from the less hindered nature of the methylene group.

The closure of the alkylidene tetrahydrofuran ring was achieved by esterification (**17** \rightarrow **18**), α -bromination, and a high-yielding S_N2 transesterification. Hydrolysis of the resulting ester **19** gave carboxylic acid **20**, which was activated as the acyl imidazole **21**.^{2c} Condensation of this material with the dianion of β -ketoester **22** followed by base-mediated cyclocondensation gave γ -hydroxy- α -pyrone **23**. Regioselective methylation under Beak's conditions⁸ then afforded key building block **10**.⁹ Since pyrones of type **10** and several intermediates leading to it are prone to racemization under basic conditions,¹⁰ we decided to resolve **10** with preparative chiral chromatography (see the Supporting Information). In addition, this strategy would give us access to both enantiomers of the SNF compounds for biological testing.

With enantiomerically pure (Z,Z)-diene building block **10** in hand, the stage was set to test the cross-coupling electrocyclization cascade again (Scheme 5). In a reversal



of the original polarity pattern, vinyl iodide **6** was converted into vinylstannane **9** by palladium-catalyzed iodine–tin exchange.

Stille coupling of **9** with vinyl iodide **10** using Baldwin's modification¹¹ presumably gave tetraene **3**. Under the reaction conditions, this intermediate underwent rapid 8π – 6π electrocyclization to afford SNF4435 C and D as a 3:1 mixture in 89% combined yield. Other cross-coupling conditions or the use of vinyl iodide **6** and vinylstannane **11** gave consistently lower yields.

Presumably, the ratio of diastereomers reflects the diastereoselectivity of the conrotatory 8π electrocyclization step governed by the α -methoxy- γ -pyrone substituent. In contrast to this, the disrotatory 6π electrocyclization component of the cascade (**24/25** \rightarrow **1/2**) appears to proceed with very high stereoselectivity since no diastereomer with the nitroaryl substituent on the *exo* face of the bicyclo[4.2.0]octadiene skeleton was found. Interestingly, the SNF compounds have been isolated in a 3:1 ratio from natural sources, which reflects the diastereoselectivity of the 8π electrocyclization step.

In conclusion, we have developed a short, stereoselective, and biomimetic synthesis of SNF4435C and D. Future work will focus on the chemoenzymatic synthesis of enantiomerically pure building block **11**¹² and elucidation of the biological mechanism of action of the SNF compounds.

Acknowledgment. We thank Charles M. Blazey and Siamak Dailami (Exelixis, Inc.) for their help with the resolution of compound **10**. This work was supported by National Institutes of Health Grant No.R01 GM067636. D.T. thanks Eli Lilly, Glaxo Smith Kline, Amgen, Merck, and AstraZeneca for Young Investigator Awards. C.M.B. thanks the Bristol-Myers Squibb Corp. and Roche Biosciences for predoctoral fellowships. We also thank Dr. Frederick J. Hollander and Dr. Allen G. Oliver for the crystal structure determination of compound **8b**.

Supporting Information Available: Spectroscopic and analytical data for compounds **7b**, **8b**, **9**, **10**, and **14–23**, as well as an X-ray structure of compound **8b** (ORTEP diagram). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(7) The product of the Ireland–Claisen rearrangement, compound **17** was accompanied by varying amounts of the C-silylated acetate, which could be recycled by hydrolysis and re-acetylation. The corresponding Eschenmoser–Claisen rearrangement proceeds in >80% yield (see the Supporting Information).

(8) Beak, P.; Lee, J. K.; McKinnie, B. G. *J. Org. Chem.* **1978**, *43*, 1367.

(9) Building block **10** had been previously employed after conversion into the corresponding stannane **11** in Parker's synthesis of the SNF compounds. See ref 2c.

(10) (a) Ishibashi, Y.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3643. (b) Comparison of the optical rotation of our compound **10** [$\alpha_D = -159^\circ$ ($c = 1$, CH_2Cl_2)] with Parker's [$\alpha_D = -37.9^\circ$ ($c = 1.06$, CH_2Cl_2)] suggests that the material used in the previous total synthesis^{2c} had indeed undergone partial racemization.

(11) Mee, S. P. H.; Lee, V.; Baldwin J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132.

(12) He, J.; Mueller, M.; Hertweck, C. *J. Am. Chem. Soc.* **2004**, *126*, 16742.