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# Total Synthesis of (−)-SNF4435 C and (+)-SNF4435 D

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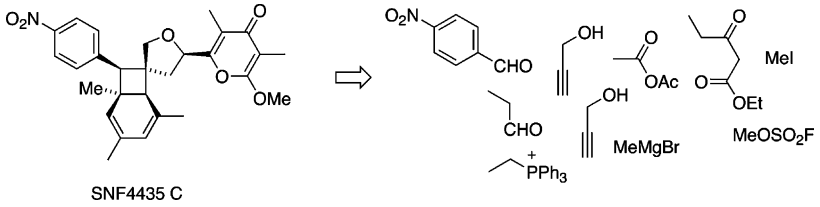
## ABSTRACT

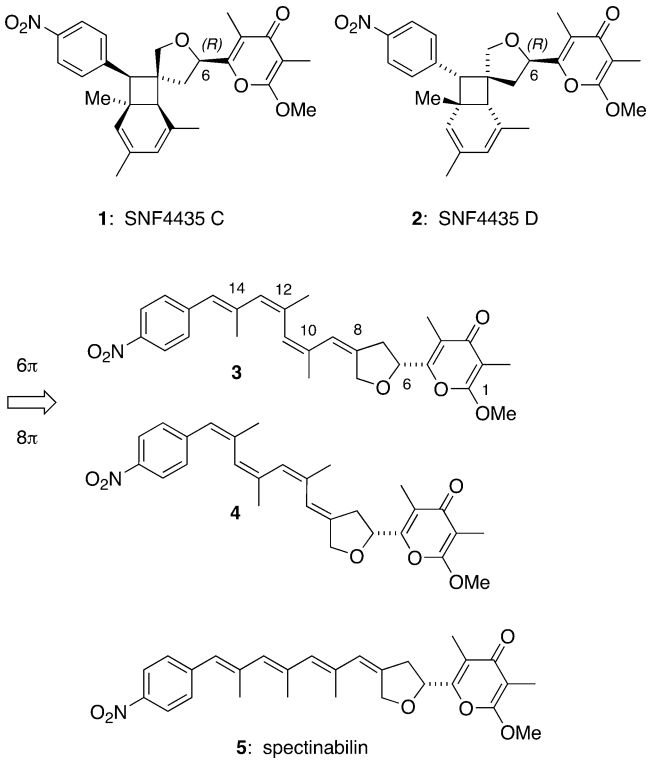



**A convergent, biomimetic total synthesis of the immunosuppressant polyketides SNF4435 C and D is described. The synthetic pathway features a stereo- and regioselective [3,3]-sigmatropic rearrangement as well as a high-yielding Stille coupling/8π–6π electrocyclization cascade.**

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]

**Scheme 1**




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

(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.

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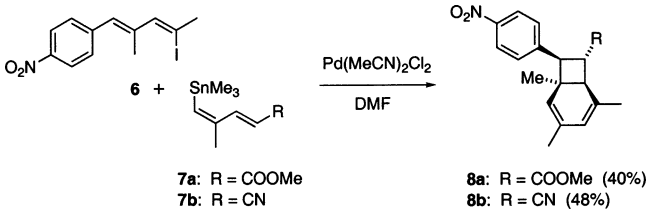
**Scheme 2**




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.

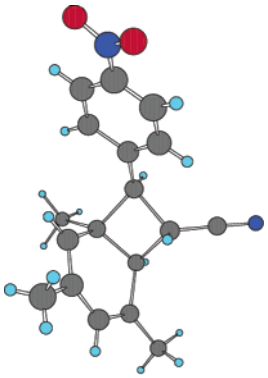
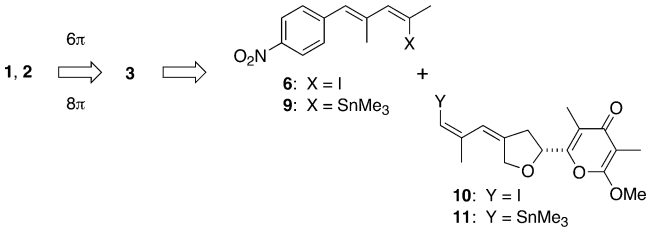


**Figure 1.** X-ray structure of nitrile **8b**.

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

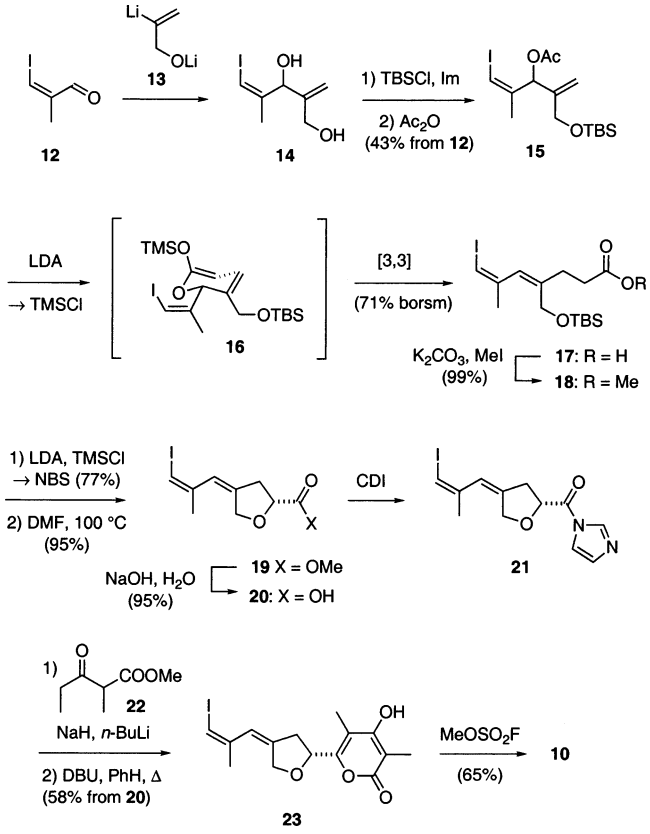
**Scheme 3.** Retrosynthetic Analysis




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-$\gamma$-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.

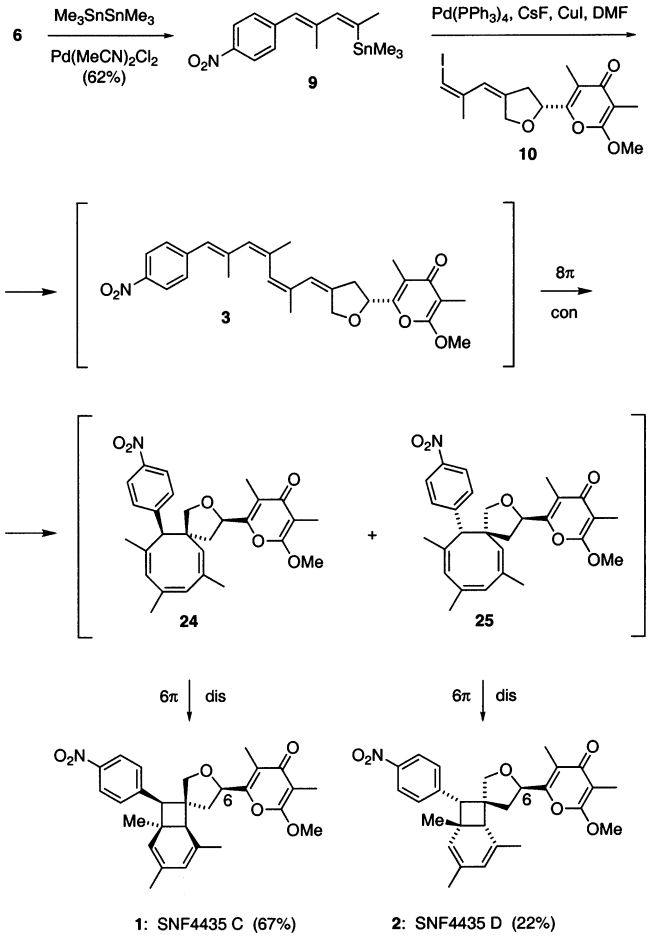
(6) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.

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** → **18**), α-bromination, and a high-yielding $S_N2$ transetherification. 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 conditions[8] 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

**Scheme 5**




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 modification[11] presumably gave tetraene **3**. Under the reaction conditions, this intermediate underwent rapid 8*π*−6*π* 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 8*π* electrocyclization step governed by the α-methoxy-*γ*-pyrone substituent. In contrast to this, the disrotatory 6*π* electrocyclization component of the cascade (**24**/**25** → **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 8*π* 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.

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**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** [$\alpha_D = -159°$ ($c = 1$, $CH_2Cl_2$)] with Parker's [$\alpha_D = -37.9°$ ($c = 1.06$, $CH_2Cl_2$)] 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.