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 bicyclo[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

In 2002, we outlined a cross-coupling/electrocyclization strategy for the synthesis of SNF4435 C and D and their
congeners (Scheme 2). Stille coupling of vinyl iodide 6 with vinyl stannane 7a triggered a stereoselective 8π–6π 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 (6R).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 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 135 to iodomethacrolein 12c readily available in the form of vinyl iodide 6 or its stannane counterpart 9,c 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.

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

![Figure 1. X-ray structure of nitrile 8b.](image)

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![Scheme 2](image)

![Scheme 3. Retrosynthetic Analysis](image)

![Scheme 4](image)

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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 Sx2 transesterification. Hydrolysis of the resulting ester 19 gave carboxylic acid 20, which was activated as the acyl imidazole 21. 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. 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 → 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 1112 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.

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


(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 (αD = −159° (c = 1, CH2Cl2)) with Parker’s [αD = −37.9° (c = 1.06, CH2Cl2)] suggests that the material used in the previous total synthesis2c had indeed undergone partial racemization.
