Synthetic Studies toward SNF4435 C and SNF4435 D
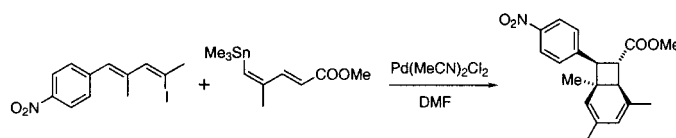
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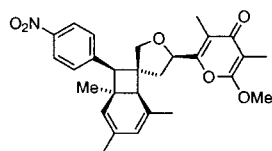
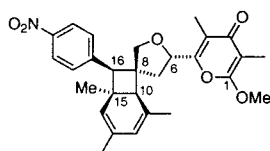*trauner@cchem.berkeley.edu*

ABSTRACT

A synthetic approach toward the immunosuppressants SNF3345 C and SNF4435 D featuring a tandem Stille coupling/electrocyclization cascade is described.

SNF4435 C and SNF4435 D are two natural products recently isolated from a culture broth of *Streptomyces spectabilis*.[1] Both compounds have been shown to selectively block induced B-cell proliferation versus induced T-cell proliferation and show potent immunosuppressive activity in vitro.[2] Hence, they are expected to exhibit a pharmacological profile different from established immunosuppressant drugs such as cyclosporin A or FK-506 and represent important new lead compounds for drug development. In a separate study, the compounds were shown to reverse multidrug resistance in tumor cells, rendering them potentially useful in anticancer therapy.[3]

Their novel skeleton contains a bicyclo[4.2.0]octadiene nucleus linked to a spiro-fused tetrahydrofuran ring. This tricyclic core is substituted with an unusual nitrophenyl ring and a γ-pyrone moiety and contains five stereocenters, two of which are quaternary.

Biosynthetic considerations further add to the attractiveness of the SNF4435 compounds as synthetic targets. We propose that the molecules can be traced back to a common precursor **1** (Scheme 1). Interestingly, compound **1** is a stereoisomer of spectinabilin, another natural product previously isolated from *S. spectabilis*.[4]

SNF4435 C   SNF4435 D

In addition to their interesting biological activity, the natural products display a fascinating molecular architecture.

spectinabilin

According to our biosynthetic hypothesis, conrotatory 8π-electrocyclization of **1** affords the cyclooctatrienes **2a** and **2b** with some induction provided by the stereocenter on the tetrahydrofuran ring (C6). A subsequent stereoselective disrotatory 6π-electrocyclization affords SNF4435 C and D. Presumably, **1** is formed by a polypropionate synthase from six units of propionyl coenzyme A, one acetyl coenzyme A,
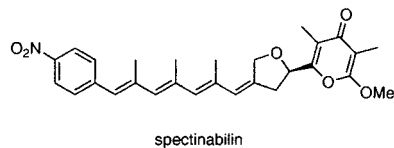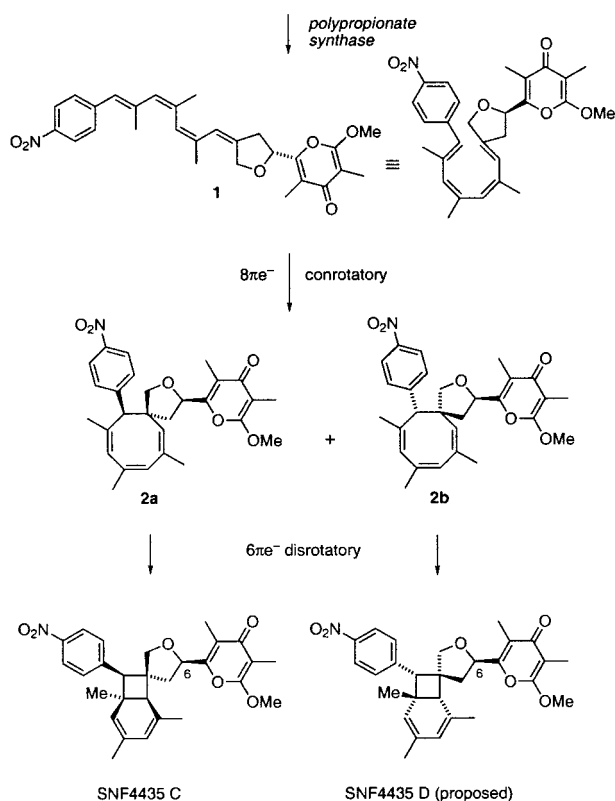
(1) (a) Kurosawa, K.; Takahashi, K.; Tsuda, E. *J. Antibiot.* **2001**, *54*, 541. (b) Takahashi, K.; Tsuda, E.; Kurosawa, K. *J. Antibiot.* **2001**, *54*, 548.
(2) Kurosawa, K.; Takahashi, K.; Fujise, N.; Yamashita, Y.; Washida, N.; Tsuda, E. *J. Antibiot.* **2002**, *55*, 71.
(3) Kurosawa, K.; Takahashi, K.; Tsuda, E.; Tomida, A.; Tsuruo, T. *Jpn. J. Cancer Res.* **2001**, *92*, 1235.

(4) Kakinuma, K.; Hanson, C. A.; Rinehart, K. L., Jr. *Tetrahedron* **1976**, *32*, 217. To the best of our knowledge, this interesting antibiotic has not yet been synthesized.

Scheme 1. Proposed Biosynthesis of the SNF Compounds

attempting a synthesis of **1** directly, however, we decided to probe the proposed electrocyclization cascade with simplified compounds. Those would incorporate all of the essential features of the polyene portion and the nitrophenyl substituent of **1** but lack the γ-pyrone moiety and possibly the tetrahydrofuran ring. We now report the results of our studies, which were guided by the biosynthetic hypothesis presented above and led to an advanced synthetic precursor of the SNF4435 compounds.

Our initial attempts centered on the use of the Still−Gennari reaction as a method for the installment of (Z)-configured double bonds (Scheme 2).[8]

Scheme 2[a]
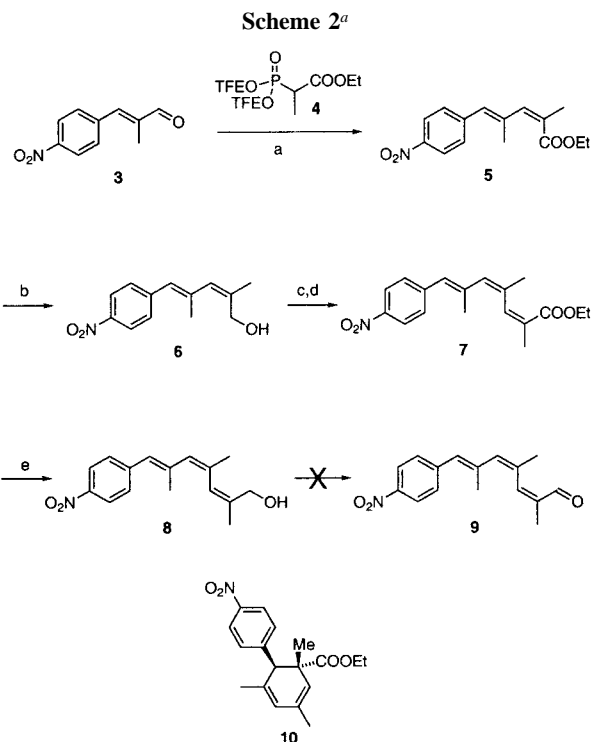
[a] Reagents and conditions: (a) **4**, KHMDS, 18-C-6, THF, −78 °C (78%). (b) DIBAH, CH_2Cl_2, −78 °C (89%). (c) Dess−Martin periodinane, CH_2Cl_2, rt. (d) **4**, KHMDS, 18-C-6, THF, −78 °C (96% from **6**). (e) DIBAH, CH_2Cl_2, −78 °C (> 80% by NMR).

and *p*-aminobenzoic acid as the source of the nitrophenyl ring.[4,5]

The electrocyclization cascade bears resemblance to the one found in the biosynthesis of the endiandric acids initially proposed by Black[6] and synthetically verified by Nicolaou et al.[7] It would be interesting to determine whether the cyclizations proceed spontaneously at room temperature or require enzyme catalysis. The two SNF4435 compounds were isolated in a 2.3:1 ratio, which is roughly the degree of 1,3-diastereoselection that can be expected in a non-enzymatic electrocyclization event. Note that according to our biosynthetic scheme, the minor component SNF4435 D is not the C6 epimer of SNF4435 C, as originally proposed, but is instead diastereomeric with respect to all other stereocenters. The absolute configuration of the natural products and their relative stereochemistry with respect to each other remains to be determined.

With its four trisubstituted double bonds, three of which are (Z)-configured, the hypothetical biosynthetic intermediate **1** is in itself a formidable synthetic challenge. Instead of

Condensation of the known aldehyde **3**[9] with trifluoroethyl phosphonate **4** afforded dienoate **5** with excellent diastereoselection (Z:E > 20:1).[10] Exhaustive reduction of the ester function gave allylic alcohol **6**. Dess−Martin oxidation[11] of **6** then set the stage for a second application of reagent **4**,

(5) (a) Kawai, S.; Kobayashi, K.; Oshima, T.; Egami, F. *Arch. Biochem. Biophys.* **1965**, *112*, 537. (b) Yamazaki, M.; Katoh, F.; Ohishi, J. I.; Koyama, Y. *Tetrahedron Lett.* **1972**, *26*, 2701.

(6) Banfield, J. E.; Black, D. St. C.; Johns, S. R.: Willing, R. I. *Aust. J. Chem.* **1982**, *35*, 2247 and references therein.

(7) (a) Nicolaou, K. C.; Sorensen, E. J. In *Classics in Total Synthesis*; VCH: Weinheim, 1996; p 265 and references therein. For a similar electrocyclization cascade, see: (b) Vogt, P.; Schlageter, M.; Widmer, E. *Tetrahedron Lett.* **1991**, *32*, 4115.

(8) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(9) Obtained in one step from *p*-nitrobenzaldehyde and propionaldehyde: Hirata, Y.; Nakata, H.; Yamada, K.; Okuhara, K.; Naito, T. *Tetrahedron* **1961**, *14*, 252.

(10) The stereochemistry of the major isomers **5**, **7**, **16**, and **20** was elucidated by NOESY experiments and in some cases indirectly confirmed by X-ray structure analysis of compounds **10** and **13** (see Supporting Information). Similarly, the *syn* stereochemistry of aldol **12** was validated by the structure of **13**.

(11) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Boeckman, R. K. Jr.; Pengcheng, S.; Mullins, J. J. *Org. Synth.* **1999**, *77*, 141.

affording triene ester **7**. Again, very high diastereoselectivity (Z:E > 20:1) was observed.[10] However, despite many attempts, we were unable to convert **7** into the aldehyde **9** as a precursor for the final olefination. This was mostly due to the instability of the intermediary allylic alcohol **8** toward aqueous workup. Furthermore, **7** readily underwent disrotatory electrocyclization at room temperature to afford cyclohexadiene carboxylate **10**. Unfortunately, this reaction proved to be essentially irreversible, rendering **10** useless as an intermediate in our synthesis.

In an attempt to avoid the unwanted 6π-electrocyclization and to circumvent sensitive triene intermediates, we decided to install the third double bond at a later stage of the synthesis via stereospecific *syn* elimination of a secondary hydroxy group (Scheme 3). This strategy was again inspired by

Scheme 3[a]
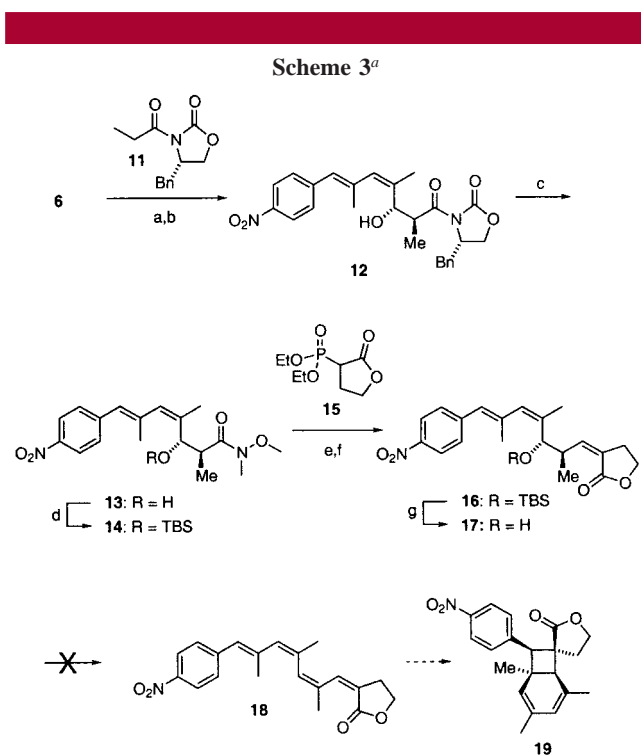
[a] Reagents and conditions: (a) Dess−Martin periodinane, CH₂Cl₂, rt. (b) **11**, Bu₂BOTf, Et₃N, THF, −78 → 0 °C (90% from **6**). (c) MeHNOMe·HCl, AlMe₃, PhMe, rt (78%). (d) TBSCl, Im, DMF, DMAP, rt (99%). (e) DIBAH, CH₂Cl₂, −78 °C. (f) **15**, KHMDS, 18-C-6, THF, −78 → 0 °C (63% from **14**). (g) HF−Py, Py, MeOH, rt (76%).

biogenetic considerations. The biosynthesis of the hypothetical precursor **1** presumably involves several reduction and dehydration steps mediated by a polypropionate synthase complex.

Dess−Martin oxidation of allylic alcohol **6**, followed by reaction of the crude product with the boron enolate of oxazolidinone **11**[12] afforded aldol **12** with the expected high *syn* diastereoselectivity.[10,13] Conversion of **12** into the Weinreb amide **13**,[14] followed by protection of the hindered

secondary alcohol as the TBS ether gave **14**. Reduction of **14** afforded a sensitive aldehyde that was subjected to a Horner−Wadsworth−Emmons olefination with the known phosphono γ-butyrolactone **15**.[15] This afforded (Z)-configured alkylidene lactone **16** as the major diastereomer.[10] The deprotection of **16** proved surprisingly difficult, presumably as a result of steric hindrance of the silyl ether. Nevertheless, it could be achieved by treating **16** with HF−pyridine in methanol to afford secondary alcohol **17**.[16]

Unfortunately, all attempts to effect dehydration of **17** via *syn* elimination leading to tetraene **18** and ultimately **19** were unsuccessful. Exposure of **17** to Burgess' reagent,[17] DCC/CuCl,[18] or other dehydrating conditions, as well as attempts to prepare the corresponding xanthates, only led to complex, intractable product mixtures.

At this point we decided to resort to transition metal catalyzed cross-couplings along the central σ bond of the desired tetraene system (Scheme 4).[19] This highly convergent strategy was initially set aside because of anticipated difficulties in procuring the corresponding (Z)-substituted vinyl halide and vinylmetalloid building blocks.

Eventually, however, it was found that aldehyde **3** underwent a clean Stork−Zhao olefination[20] to afford trisubstituted vinyl iodide **20** as the sole isolable diastereomer.[10] Furthermore, the known (Z)-substituted vinyl iodide **22** could be obtained in one step from propargyl alcohol (**21**) through a stereoselective carbocupration/iodination sequence.[21] Oxidation of the allylic alcohol function with concomitant olefination of the unstable intermediary aldehyde following Barrett's protocol[22] afforded iodo dienoate **23**.[23] Conversion of this material into the sensitive vinyl stannane **24** set the stage for the key cross coupling of the two fragments.[24]

In the event, reaction of **20** and **24** in the presence of catalytic amounts of Pd(MeCN)₂Cl₂[25] afforded bicyclo[4.2.0]-octadiene **27** in 40% overall yield (not optimized). This tandem transformation presumably proceeds through the intermediacy of tetraene ester **25**, which undergoes a rapid

(13) Heathcock, C. H. In *Modern Synthetic Methods*; Scheffold, R., Ed.; VCH: Weinheim, 1992; pp 1−102 and references therein.

(14) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.

(15) (a) Lee, K.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 5967. (b) Snider, B. B.; Lu, Q. *Synth. Commun.* **1997**, *27*, 1583.

(16) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685.

(17) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(18) (a) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776. (b) Alexandre, D.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1971**, 1837.

(19) For a review, see: *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.

(20) (a) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173. (b) Chen, J.; Wang, T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827.
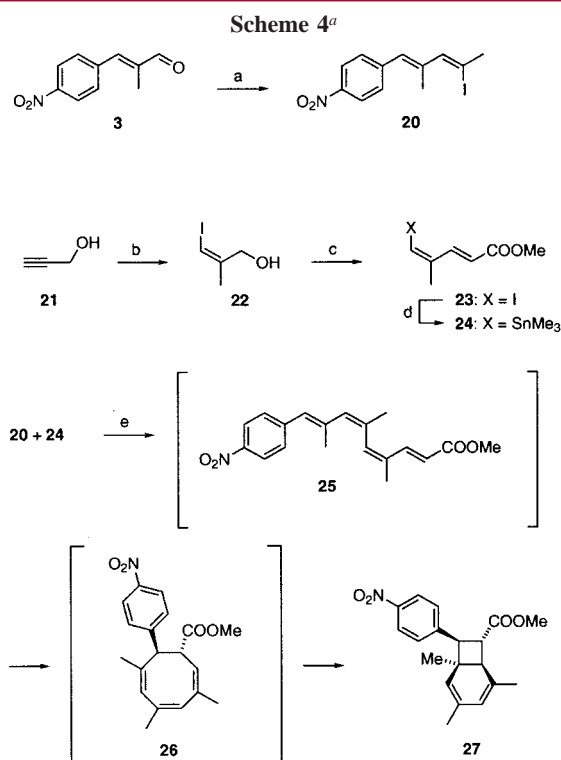
(21) (a) Duboudin, J. G.; Jousseaume, B.; Bonakdar, A. *J. Organomet. Chem.* **1979**, *168*, 227. (b) Han, Q.; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692.

(22) Barrett, A. G. M.; Hamprecht, D.; Ohkubo, M. *J. Org. Chem.* **1997**, *62*, 9376.

(23) Unfortunately, all attempts to effect an analogous condensation with phosphonolactone **15** were unsuccessful because of the instability of (Z)-3-iodomethacrolein under the reaction conditions.

(24) (a) Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett.* **2001**, *3*, 4307. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

(12) Gage, J. R.; Evans, D. A. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, p 339.
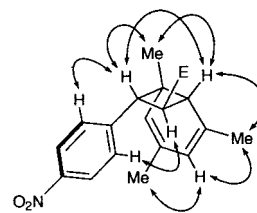
Scheme 4[a]

electrocyclization cascade similar to the one proposed in Scheme 1 (**25** → **26** → **27**). It is interesting to speculate whether the transition metal catalyzes the electrocyclizations, potentially providing an opportunity for asymmetric synthesis.

The high stereoselectivity of the overall reaction can be explained by the concerted nature of the electrocyclizations and the avoidance of torsional strain between the nitrophenyl group and the adjacent methyl group in the step leading to cyclobutane formation (**26** → **27**). The relative stereochemistry of **27** was confirmed by NOESY experiments (Figure 1 and Supporting Information).[26]

Figure 1. Selected NOE signals of compound **27**.

In summary, we have outlined a synthetic strategy toward SNF4435 C and SNF4435 D that is guided by their proposed biosynthesis (Scheme 1). A novel Stille coupling/electrocyclization tandem reaction has been developed. Our most advanced compound (**27**) contains a substantial part of the natural products, featuring three out of five stereocenters and their core bicyclo[4.2.0]octadiene skeleton. Its carbomethoxy substituent provides a functional handle for the installation of the spiro-fused tetrahydrofuran ring. Studies toward the asymmetric synthesis of **27** and related intermediates as well as the total synthesis of the SNF4435 compounds are underway in our laboratories and will be reported in due course.

Supporting Information Available: Spectroscopic and analytical data for compounds **20**, **23**, **24**, and **27** and X-ray structures of compounds **10** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) (a) Paquette, L. A.; Barriault, L.; Pissarnitski, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2000**, *122*, 619. (b) Nicolaou, K. C.; Li, Y.; Weyershausen, B.; Wei, H.-X. *Chem. Commun.* **2000**, 307. For an extensive review of the Stille reaction, see: (c) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1994**, *50*, 1.

(26) The spectral data of **27** resemble the corresponding signals of the SNF compounds. For instance, the vinylic proton at C14 is markedly shifted upfield (δ 5.00 in SNF4435 C, 4.93 in SNF4435 D, and 4.41 in **27**).