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"Endo" and "Exo" Bicyclo[4.2.0]-octadiene Isomers from the Electrocyclization of Fully Substituted Tetraene Models for SNF 4435C and D. Control of Stereochemistry by Choice of a Functionalized Substituent

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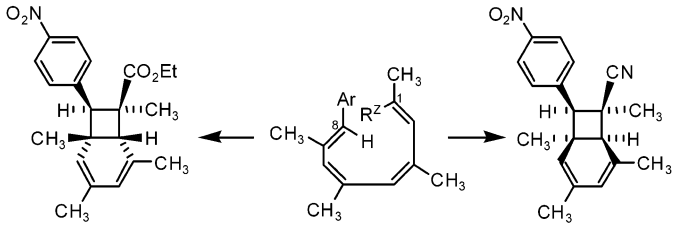
ABSTRACT



A tandem electrocyclic closure, perceived as the key step in a biomimetic approach to SNF 4435C and D, was tested with 1,1,8-trisubstituted tetraene substrates. The ratio of endo:exo products could be controlled by the choice of the R^z substituent at C-1. On the basis of these results, a short stereoselective route to an advanced SNF 4435 intermediate was devised.

SNF4435C and D are natural products reported in 2001[1] as isolates from *Streptomyces spectabilis*, a soil organism from Okinawa. Their reported biological activities are significant, and their novel structures present interesting questions of biosynthetic origins and biomimetic synthetic approaches.

The SNF compounds originally attracted attention in a screen for immunosuppressants, exhibiting activity at submicromolar concentrations. Subsequently, they were shown to act by suppression of B-cell proliferation induced by lipopolysaccharide (LPS) versus T-cell proliferation induced by Con A.[2] This mechanism of action is distinct from that of FK-506. Additional interest in the SNF compounds arose from the discovery that they demonstrated reversal of multidrug resistance (MDR) in vitro in several cell lines at nanomolar concentrations. Furthermore, SNF 4435C showed positive effects in vincristine-treated mice that bore VCR-resistant P388 leukemia.[3] On the basis of these results, Kurosawa and co-workers suggested that these drugs act in the MDR test by modulating cellular P-glycoprotein via direct binding.

Structure elucidation showed SNF 4435C and D to be substituted bicyclo[4.2.0]octadienes, spiro-fused to a pyrone-

(1) Kurosawa, K.; Takahashi, K.; Tsuda, E. *J. Antibiot.* **2001**, *54*, 541.
(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.

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substituted tetrahydrofuran substituent.[4] Relative stereochemistry was established on the basis of NOE experiments. The two compounds are stereoisomers in which four of the five chiral centers have the same stereochemistry relative to each other and fifth chiral center is epimeric (C-6).

As these two isomers may be derived from a single biosynthetic precursor (see below), it seems likely that they are diastereomeric at all centers except C-6. On the basis of this supposition, Beaudry and Trauner proposed that the structures of SNF 4435C and D should be drawn as **1a** and **1b**, respectively, isomeric at carbons 8, 10, 15, and 16 (Figure 1).[5] We have adopted this convention in this paper. Acceptance of this premise leads to a further postulate. Because SNF 4435C and D are congeners of spectinabilin **2**,[6] a structural isomer for which the stereocenter at C-6 has been assigned as *R*,[7] it is reasonable to believe that structures of SNF 4435C and D have the absolute stereochemistry shown with the 6*R*-configuration.

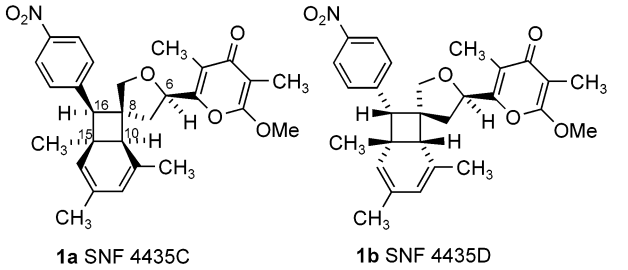


Figure 1. Structures of SNF 4435C and SNF 4435D. Absolute stereochemistry as predicted in this communication.

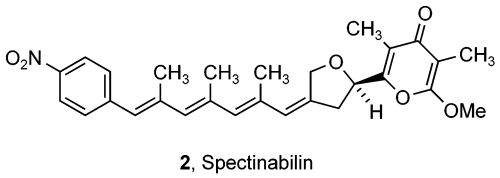
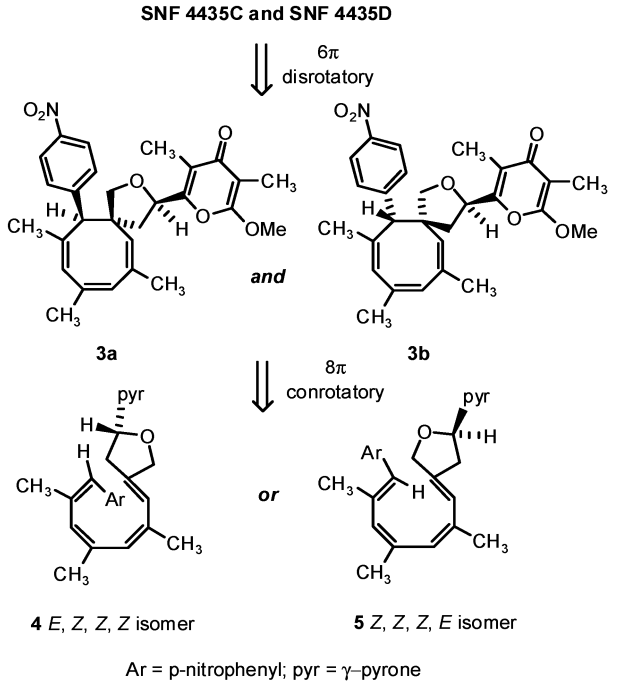


Figure 2. Spectinabilin, (*E*,*E*,*E*,*Z*)-tetraene isomer.

Seeking a biomimetic synthetic approach, we considered the possible biosynthetic origin of the SNF compounds. This led us to the premise that the 6,4-ring system is the product of a 6π electrocyclization within a cyclooctatriene (i.e., **1a** and **1b** ⟹ **3a** and **3b**), that the cyclooctatriene is, itself, an electrocyclic ring-closure product and that the linear precursor is the polypropionate-derived tetraene or its geometric isomer (**3a** and **3b** ⟹ **4** and/or **5**). Indeed, a similar 8π, 6π closure has been postulated as the key ring-forming process in the biosynthesis of the endiandric acids,[8] an insight that led to the biomimetic synthesis of these polyacetates.[9] An analysis similar to ours was made by Trauner, who was the first to describe the key features of the biosynthetic scheme in the literature.[5] Both Trauner and, more recently, Baldwin[10] have now reported model studies for the double-electrocyclization sequence with 1,8-disubstituted tetraenes.

Scheme 1. Suggested Biosynthesis of SNF 4435C and D (relative stereochemistry only)



Our own approach has been to explore the electrocyclization requirements of 1,1,8-trisubstituted tetraenes, substrates with substitution patterns more pertinent to the apparent biosynthetic pathway. Although synthetic equivalents of either tetraene **4** or **5** might be expected to undergo the symmetry-allowed double cyclization, there are significant differences between the closure of these substrates and those that have been studied previously.[11] The literature does not describe the 8π electrocyclization of a 1,1,8-trisubstituted tetraene. Examination of the putative helical transition state[12] for either of the proposed 8π cyclizations places the C-1 substituents squarely above the distal double bond, introducing what may be substantial steric interactions (Figure 3). On the other hand, because the vinyl methyl groups at positions 11, 13, and 15 should favor the reactive conformation (syn, syn, syn) of the substrate, the desired closure

(4) Takahashi, K.; Tsuda, E.; Kurosawa, K. *J. Antibiot.* **2001**, *54*, 548.
(5) Beaudry, C. M.; Trauner, D. *Org. Lett.* **2002**, *4*, 2221.
(6) Kakinuma, K.; Hanson, C. A.; Rinehart, K. L., Jr. *Tetrahedron* **1976**, *32*, 217.
(7) Ishibashi, Y.; Nishiyama, S.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1992**, *33*, 521.
(8) (a) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C.; Falon, G. D.; Gatehouse, B. M. *Aust. J. Chem.* **1981**, *34*, 1655. (b) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C. *J. Chem. Soc., Chem. Commun.* **1980**, *19*, 902.
(9) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5560.
(10) Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Cowley, A. R. *Org. Lett.* **2002**, *4*, 3731.

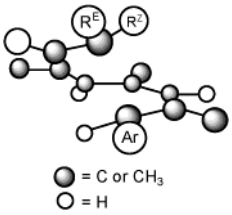


Figure 3. Helical transition state for thermal 8π electrocyclization of tetraene **5** or its equivalent.

should be favored, relative to that of internally unsubstituted tetraenes, by an entropic effect.

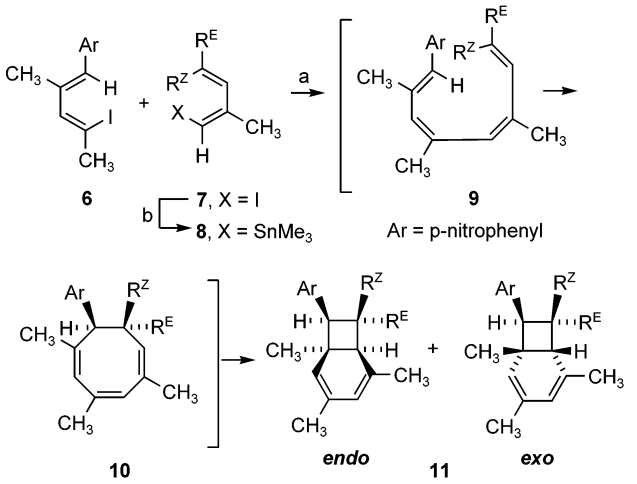
Thus, we addressed the preparation of substrates that would be informative models for the cyclization that might take place in *S. spectabilis* and for cyclizations that we might exploit in total synthesis. We suspected that the electrocyclization of substrates with the geometry of the proposed **5** would be more facile than that of its isomer **4**,[8] and therefore we focused on the preparation and cyclization behavior of (*Z*,*Z*,*Z*,*E*)-1,1,3,5,7,8-substituted 1,3,5,7-tetraenes.

As we suspected that *Z*−*E* isomerization of conjugated polyene intermediates might be facile, we planned a convergent, late-stage coupling to provide the presumably sensitive substrate. We believed that it would be prudent to construct the tetraene directly from two diene precursors rather than from a triene, as trienes themselves are subject to electrocyclization reactions (noted above and observed by Beaudry and Trauner[5] in their studies).

As a model for key conversions in both the biosynthesis and a biomimetic total synthesis, we chose the electrocyclization of the tetraene **9a**, viewed as the Stille coupling product of dienes **6**[5] and **8a**.[13] In fact, palladium-catalyzed coupling was accompanied by double electrocylic closure, providing a mixture of the anticipated endo product and the unprecedented exo product (represented as *endo*- and *exo*-**11a**). The results of this experiment are described in Table 1,[14] entry 1.[15]

In light of the lack of stereospecificity in the double closure of our 1,1,8-trisubstituted tetraene ether **9a** and the specificity

Table 1. Coupling−Tandem Cyclization of Fully Substituted Tetraene Models for SMF 4435C and D[a]



entry	diene	R^Z	R^E	prod[b]	yield	endo	exo
1	**8a**	CH_2OTBS	Me	**11a**	31%[c]	50	50
2	**8b**	H	CO_2Me	**11b**	62%[e]	100	0
3	**8c**	CO_2Et	H	**11c**[d]	38%[e]	100	0
4	**8d**	Me	CO_2Et	**11d**	56%[e]	40	60
5	**8e**	CO_2Et	Me	**11e**	54%[e]	10	90
6	**8f**	CN	Me	**11f**	59%[e]	90	10

[a] Reaction conditions: (a) Sn_2Me_6, $Pd(PPh_3)_4$, PhH, reflux; (b) $Pd(CH_3CN)_2Cl_2$, DMF, rt. [b] Identified by NOE experiment. [c] Isolated yield; endo and exo products not separated. [d] R^E and R^Z interchanged in the product. [e] Sum of isolated yield of endo and exo products.

reported for the 1,8-disubstituted tetraene ester **9b** in the literature[5] (and confirmed in our own lab, Table 1, entry 2), we next moved to elucidate the requirements for specific closure to *endo*-bicyclo[4.2.0]systems.

The experiment described in entry 3 leads to product **11c** with the same stereochemistry as that obtained in entry 2, indicating isomerization in one of the steps of the cascade. Tetraene **9d**, an alkylated analogue of the endo-selective **9b**, gave a nearly 1:1 mixture of isomers, and tetraene **9e** gave a 1:9 mixture of the desired *endo*-**11e** and the undesired *exo*-**11e**.

In search of guidance for the design of cyclization substrates that would favor endo products, we examined the conformations available to the cyclooctatriene intermediates **10**. Although only qualitative, the picture that emerged allowed us to develop a hypothesis for further work.

In the allowed pericyclic closure that leads to *endo*-**11b**, the cyclooctatriene adopts a conformation that we designate "endo" (Figure 4) in which the nitrophenyl substituent is tucked under the ring (nitrophenyl endo). The alternative, allowed closure would proceed through the conformation labeled "exo", but this is disfavored because of a steric interaction between the nitrophenyl substituent and the adjacent methyl group.

For other substrates in the Table, the situation is more complex. The endo transition state is somewhat disfavored by substrates in which R^Z is a methyl group (compare entries

(11) Although 8π, 6π closures of 1,8-disubstituted 1,3,5,7-(*E*,*Z*,*Z*,*E*)-tetraenes proceed at low temperature (e.g., 2,4,6,8-(*E*,*Z*,*Z*,*E*)-decatetraene closes at −10 °C over 30 h and the subsequent electrocylization occurs at 20 °C over 8 h), closure of (*Z*,*Z*,*Z*,*E*)-tetraenes requires higher temperatures (9 °C for the first step and 40 °C for the second step) and the closure of *Z*,*Z*,*Z*,*Z*-substrates is even slower, affording the [4.2.0] product directly at 65 °C. See: (a) Huisgen, R.; Dahmen, A.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 7130. (b) Huisgen, R.; Dahmen, A.; Huber, H. *Tetrahedron Lett.* **1969**, 1461. (c) For a related example and a literature survey, see: Hayashi, R.; Fernandez, S.; Okamura, W. H. *Org. Lett.* **2002**, *4*, 851.

(12) Thomas, B. E., IV; Evanseck, J. D.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 4165.

(13) Stannane compounds **8** were prepared from the corresponding iododienes **7**; see Supporting Information.

(14) For each of the entries, the linear tetraene **9** underwent the double closure within the time frame of the coupling experiment (i.e., we never saw linear tetraene or cyclooctatriene in any of these experiments). Nuclear Overhauser experiments confirmed the stereochemical assignments of all products in Table 1.

(15) These isomers were not separated. Nevertheless, a NOE experiment on the mixture allowed assignment.

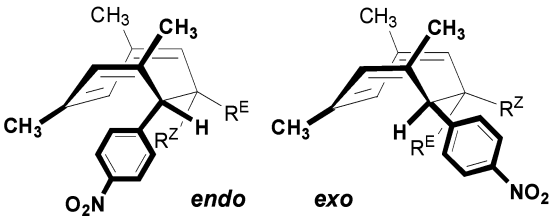


Figure 4. Endo and exo conformations for the cyclization of **10**.

2 and 4), presumably because of steric repulsion between this methyl group and the adjacent aryl substituent. The endo transition state becomes more disfavored in substrates in which R^Z is an ester group (entries 3 and 5); the plane of the ester and the plane of the aryl group must be parallel, a situation that leads to transannular interactions between the ester group and the cyclooctatriene ring.

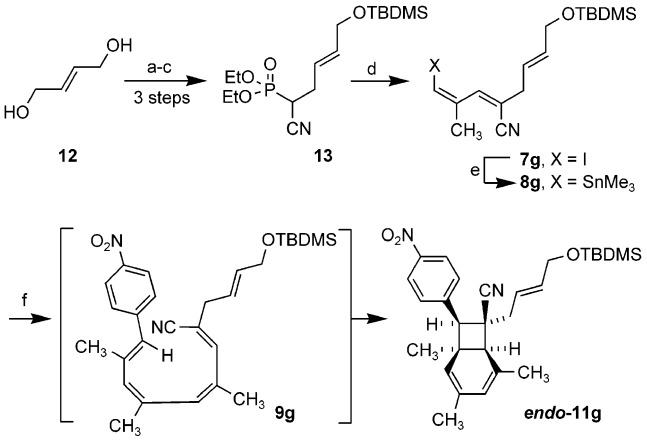
Considering mechanisms for minimizing the steric repulsion between R^Z and the aromatic group and also between R^Z and the cyclooctatriene ring, we imagined that R^Z might be the long but slender nitrile. Indeed, entry 6 shows that tetraene **9f** closed to give *endo*-**11f** as the almost exclusive product.

Thus, a dramatic reversal of product distribution results from the replacement of an ester group (entry 5) with a nitrile group (entry 6). We attribute the lowering of the transition state energy for the endo product to the smaller steric requirement for the R^Z substituent, which must be tucked into the endo cavity as the reaction proceeds.

Viewing the functional group pattern in the target structures **1a** and **1b** and noting the requirements for endo-selective tandem closure, we concluded that tetraene **9g** or a similar cyanotetraene might prove to be a key intermediate in a total synthesis. We have now demonstrated the accessibility of the appropriate precursors and the good behavior of the 1,3,6-triene system under the Stille coupling conditions.

The preparation of the vinyl tin reagent **8g**, required for this approach, proved to be quite straightforward. The commercially available *trans*-2-butene-1,4-diol (**12**) was subjected to a three-step sequence that afforded the Horner−Wadsworth−Emmons reagent **13**. Condensation with (*Z*)-3-iodo-2-methyl-propenal gave the 1,3,6-(*Z*,*Z*,*E*)-triene **7g**,

Scheme 2[a]



[a] Reagent and conditions: (a) TBDMSCl, Et_3N, DMAP, DMF, 40 °C (92%); (b) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C (96%); (c) diethyl(cyanomethyl)phosphonate, NaH, DME, 0 °C (62%); (d) (*Z*)-3-iodo-2-methylpropenal, KHMDS, toluene, −78 °C (89%); (e) Sn_2Me_6, $Pd(PPh_3)_4$, PhH, reflux (84%); (f) **6**, $Pd(CH_3CN)_2Cl_2$, DMF, rt (53%).

and stannylation provided the reagent for the coupling protocol.

The three-step, one-pot transformation of vinyl stannane **8g** to bicyclo **11g** endo provided a 53% yield of crystalline material after chromatography. A small amount (4%) of the exo isomer was recovered from a slow-moving fraction.

With impressive stereoselectivity in these most recent cyclizations established and with appropriately functionalized substrates readily available, we are continuing our pursuit of a biomimetic synthesis of SNF 4435C and D.

Acknowledgment. This work was supported by the National Institutes of Health and by SUNY at Stony Brook. We are grateful to Professor Nancy Goroff for assistance with molecular modeling studies. We also thank Dr. Tun-Li Shen (Brown University) for mass spectroscopic data.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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