Communication

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

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SNF4435 C (**1a**) and SNF4435 D (**1b**) are immunosuppressant and multidrug resistance (MDR) reversal agents isolated from the culture broth of an Okinawan strain of *Streptomyces spectabilis* in 2001.[1] On the basis of biosynthetic considerations including the known 6*R* configuration of spectinabilin (**2**), a *S. spectabilis* co-metabolite, the absolute stereochemistry of SNF4435 C and that of SNF4435 D have been assigned as shown[2] (Figure 1).
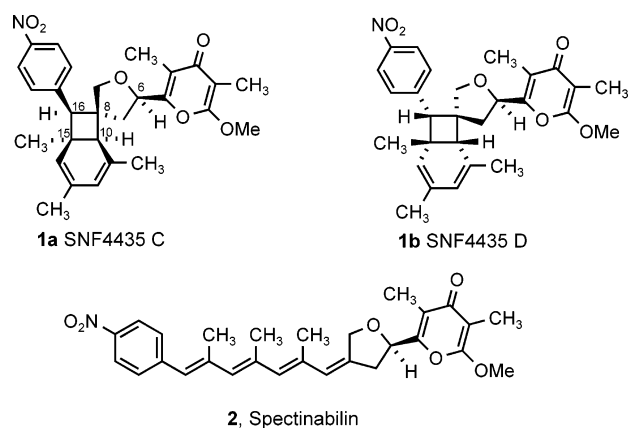
Figure 1. Structures of SNF4435 C and D and their co-metabolite, spectinabilin

The SNF compounds have small, compact structures that are based on a unique, rigid tricyclic core. This nucleus bears five chiral centers, four of which are adjacent on the periphery of the cyclobutane ring.

The synthesis of targets with a high level of local complexity is generally best accomplished by strategies that assemble the stereochemically dense moiety by concerted reactions or cascades. In fact, the double thermal electrocyclization of substituted tetraenes[3] has been recognized as a possible biosynthetic event in the construction of the bicyclo[4.2.0]octadiene substructure of the SNF compounds.[2,4,5]

Studies of a biomimetic approach (Scheme 1, Table 1) in which model tetraenes **6** serve as unstable key intermediates have demonstrated that the tandem process is stereoselective, providing the endo bicyclo[4.2.0]octadiene system **8** when R^Z is a hydrogen[4,5] or a cyano substituent,[2] i.e., when R^Z is small in the lateral direction (Table 1, entries a and b). An interaction of the *p*-nitrophenyl group with the adjacent methyl group is thought to disfavor a transition state resembling conformer **7′** relative to one resembling conformer **7** for the disrotatory 6π closure. On the other hand, model substrates in which R^Z is an alkyl group or an ester group (entries c−e) give significant amounts of exo product **9**;[2] for these substrates, transition states **7** and **7′** are competitive.

In this communication, we report the surprising endo selective closure of substrates in which the R^Z and R^E substituents are tied back in a five-membered ring and the application of this steric effect in the efficient total synthesis of (−)-SNF4435 C and (+)-SNF4435 D.

Scheme 1. Endo and Exo Products from the Tandem Thermal Electrocyclization of Substituted Tetraenes^a
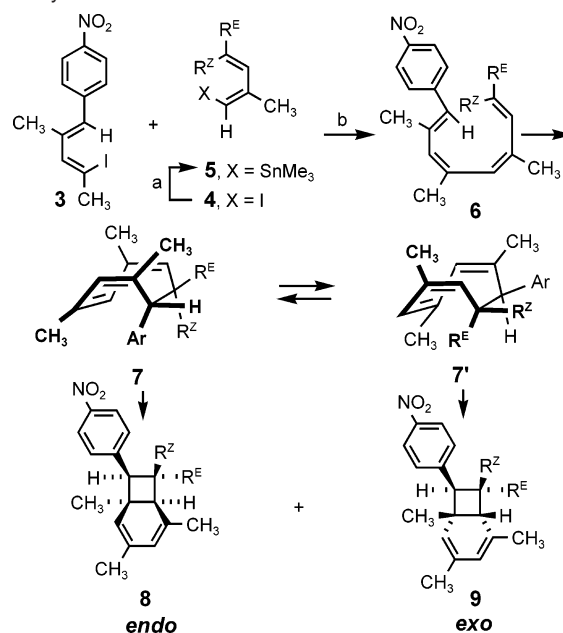
^{a} Reagents and conditions: (a) Sn$_2$Me$_6$, Pd(PPh$_3$)$_4$, PhH, reflux (b) Pd(CH$_3$CN)Cl$_2$, DMF, rt.

Table 1. Ratio of Endo:Exo Products for Scheme 1^a

| 5	R^Z	R^E	8 : 9 (endo : exo)	Isolated Yield (%)
a.^{b}	H	CO$_2$Me	100 : 0	62
b.^{c}	CN	CH$_3$	90 : 10	59
c.^{c}	CH$_3$	CO$_2$Et	40 : 60	56
d.	CH$_3$	CH$_3$	50 : 50	55
e.^{c}	CO$_2$Et	CH$_3$	10 : 90	54
f.^{d}			95 : 5	57
g.^{e}			82 : 18	47

^{a} Identified by nOe experiments. ^{b} See refs 2 and 4. ^{c} Reference 2. ^{d} The minor product, *exo*-**9f** had R^Z and R^E interchanged. See the Supporting Information. ^{e} Substrate **4g** was prepared from diol **17**.

Building on observations made during model studies, we subjected vinyl stannane **5f** to Stille coupling with vinyl iodide **3**.[4] As expected, aryl bicyclooctadiene product was isolated directly. Remarkably, the product was almost exclusively the endo compound **8f**. This result should be compared with the coupling/tandem closure experiment with **5c** in which endo **8c** and exo **9c** were formed in almost equal amounts.

A substrate more closely related to intermediates for SNF4435 synthesis was then tested. Coupling of the dienyl tin **5g** with vinyl iodide **3** gave endo products and exo products in a ratio of 4.5:1. Comparison of this result with that derived from an acyclic analogue (entry d, endo:exo, 1:1) confirms a trend for the enhanced production of endo products from substrates in which R^Z and R^E are connected in a five-membered ring.

With this discovery as a basis, we have completed a biomimetic, asymmetric synthesis of SNF 4435C and D (Scheme 2). Reagent

Scheme 2. Total Synthesis of (−)-SNF4435 C and (+)-SNF4435 D[a]
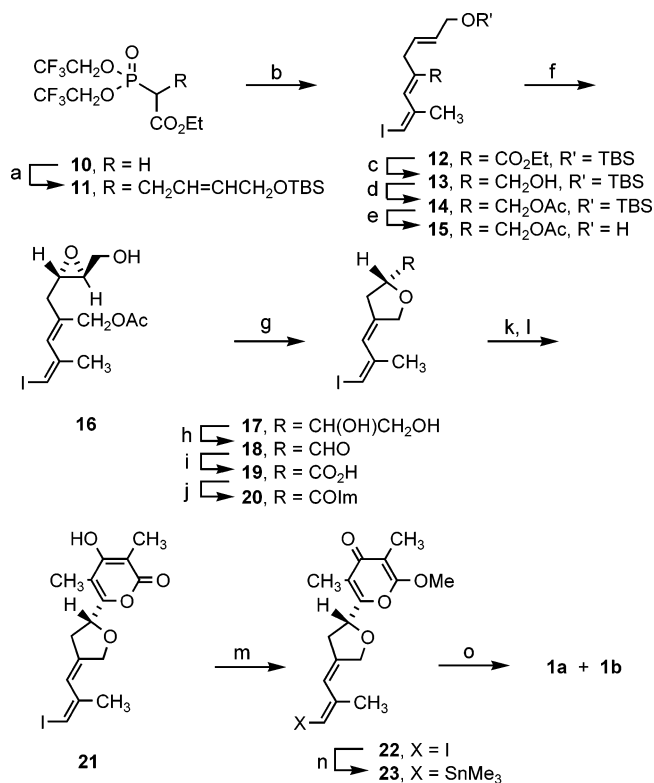
[a] Reagents and conditions: (a) NaH, then *trans*-MsOCH$_2$CH=CHCH$_2$-OTBS, NaI, THF, rt (72%); (b) KHMDS, 18-crown-6, 0 °C, then (Z)-3-iodo-2-methylpropenal, THF, −78 °C (71%); (c) Dibal-H, CH$_2$Cl$_2$, −78 °C (99%); (d) Ac$_2$O, DMAP, py, CH$_2$Cl$_2$ (98%); (e) TBAF, THF, 0 °C (94%); (f) Ti(OPr^i)$_4$, (+)-DET, t-BuOOH, CH$_2$Cl$_2$, −20 °C, 5 h (92%, > 90 ee%); (g) K$_2$CO$_3$, MeOH, rt (quantitative); (h) NaIO$_4$, MeOH−H$_2$O and then (i) AgNO$_3$, KOH, EtOH−H$_2$O, 0 °C to rt (87%); (j) carbodiimidazole (CDI), THF, rt (93%); (k) ethyl 3-methyl-4-oxopentanoate, NaH, n-BuLi, THF, −78 °C; (l) DBU, PhH, reflux (55% for two steps); (m) MeOSO$_2$F, CH$_2$Cl$_2$, rt (74%); (n) Sn$_2$Me$_6$, Pd(PPh$_3$)$_4$, PhH, reflux (86%); (o) **3**, Pd(CH$_3$CN)$_2$Cl$_2$, DMF, rt (53%).

10[6] was alkylated with the mesylate derived from the trans 4-silyloxybuten-1-ol.[7] Then condensation with (Z)-3-iodo-2-methylpropenal[8] gave triene **12**. Adjustment of oxidation state and protecting groups in three steps gave allylic alcohol **15**. Sharpless asymmetric epoxidation[9] provided epoxy acetate **16**. Potassium carbonate deacylation promoted the 5-exo-trig closure to the key diol **17**.[10] Periodate cleavage and oxidation of the resulting aldehyde **18** to the carboxylic acid **19**[11] was followed by activation (with CDI)[12] and condensation of the acyl imidazole **20** with the dianion of ethyl 3-methyl-4-oxopentanoate.[13] Cyclization gave α-pyrone **21**,[14] and methylation[15] afforded the desired γ-pyrone-bearing vinyl

iodide **22**. Stannylation[16] gave the unstable reagent **23** which was immediately subjected to coupling with vinyl iodide **3**. Tandem electrocyclization of the resulting tetraene took place in the coupling medium to afford 53% of a 4:1 mixture of the two endo products, SNF4435 C and D. Separation by chromatography provided SNF4435 C ([α]^{21}$_D$ (c 0.1, CH$_2$Cl$_2$) = −72.6°) and SNF4435 D ([α]^{21}$_D$ (c 0.09, CH$_2$Cl$_2$) = +56.4°), confirming our previous assignment[2] of the absolute stereochemistry of the natural products.

The ratio of SNF4435 C and SNF4435 D from the biomimetic scheme is close to that found in nature (2.3:1).[1a] This result is consistent with the premise that the biosynthesis of these materials involves the 8π/6π cyclization of the E,Z,Z,Z-isomer of spectinabilin and that an enzyme is not involved in this process.

The substituent effects that control the product ratios in tetraene−cyclooctatriene−bicyclooctadiene transformations are not understood in detail. The parent system was subjected to semiempirical and ab initio calculations up to the MP2/6-31G* level by Houk and co-workers[3a] in 1993. Their results demonstrated that accurate modeling of this energy surface is a significant challenge. The experiments described above provide additional data for testing the computational modeling of pericyclic reactions with more recently developed density functional methods.

The short synthesis (14 steps from the Still−Gennari reagent **10**) of (−)-SNF4435 C and (+)-SNF4435 D illustrates the power of biomimetic strategies and the pedagogical value of examining transformations postulated for biosynthetic steps. In particular, it demonstrates the exploitation of subtle steric effects for the control of the stereochemistry of the 8π/6π tandem closures.

Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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