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The Total Synthesis of Spectinabilin and Its Biomimetic Conversion to SNF4435C and SNF4435D

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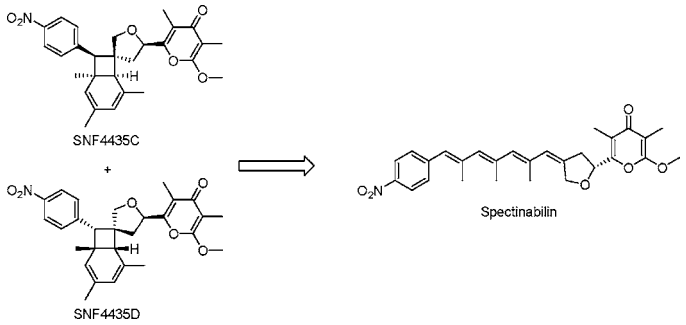
ABSTRACT



A short synthesis of (±)-spectinabilin via a *trans*-selective Suzuki coupling and subsequent Negishi-type methylation, and its biomimetic conversion to (±)-SNF4435C and (±)-SNF4435D is described.

The creation of a biogenetic hypothesis for the formation of complex natural products based on cycloadditions and/or electrocyclizations, and supported with experimental demonstration through biomimetic synthesis, has proven to be a powerful combination in organic synthesis that is of continued interest to us.[1] In this respect, the recently reported isolation of two novel polypropionate derived metabolites from *Streptomyces spectabilis*, SNF4435C (**1**) and SNF4435D (**2**), caught our attention (Scheme 1).[2,3] Biologically, both homochiral compounds have been shown to selectively suppress induced B-cell proliferation versus induced T-cell proliferation and show potent immunosuppressive activity in vitro. This activity indicates a different mode of action from that of known immunosuppressants cyclosporine A (CsA) and FK-506, thus opening up the possibility of developing new immunosuppressants based on these novel structures.[4,5] These compact molecules feature five stereogenic centers, four of which reside on the cyclobutane ring of the rare bicyclo[4.2.0]octadiene nucleus, that hitherto has only been encountered in a few natural products, among them the endiandric acids.[6] Interestingly, another metabolite spectinabilin (**3**) has been isolated from the same actinomycete.[7,8] Although **3** possesses insignificant biological activities, its complex polypropionate−acetate structure alone featuring a

(1) (a) Tchabanenko, K.; Adlington, R. M.; Cowley, A. R.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 585. (b) Rodriguez, R.; Adlington, R. M.; Moses, J. E.; Cowley, A.; Baldwin, J. E. *Org. Lett.* **2004**, *6*, 3617. (c) Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Claridge, T. D. W.; Odell, B. *Org. Lett.* **2003**, *5*, 661. (d) Moses, J. E.; Commeiras, L.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2003**, *5*, 2987. (e) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C. *Chem. Eur. J.* **1999**, *5*, 3154.

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

(3) Takahashi, K.; Tsuda, E.; Kurosawa, K. *J. Antibiot.* **2001**, *54*, 548.

(4) Kurosawa, K.; Takahashi, K.; Fujise, N.; Yamashita, Y.; Washida, N.; Tsuda, E. *J. Antibiot.* **2002**, *55*, 71.

(5) Kurosawa, K.; Takahashi, K.; Tsuda, E.; Tomida, A.; Tsuro, T. *Jpn. J. Cancer Res.* **2001**, *92*, 1235.

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

(7) Kakinuma, K.; Hanson, C. A.; Rinehart, K. L. *Tetrahedron* **1976**, *32*, 217.

(8) Isaka, M.; Jaturapat, A.; Kramyu, J.; Tanticharoen, M.; Thebtaranonth, Y. *Antimicrob. Agents Chemother.* **2002**, *46*, 1112.

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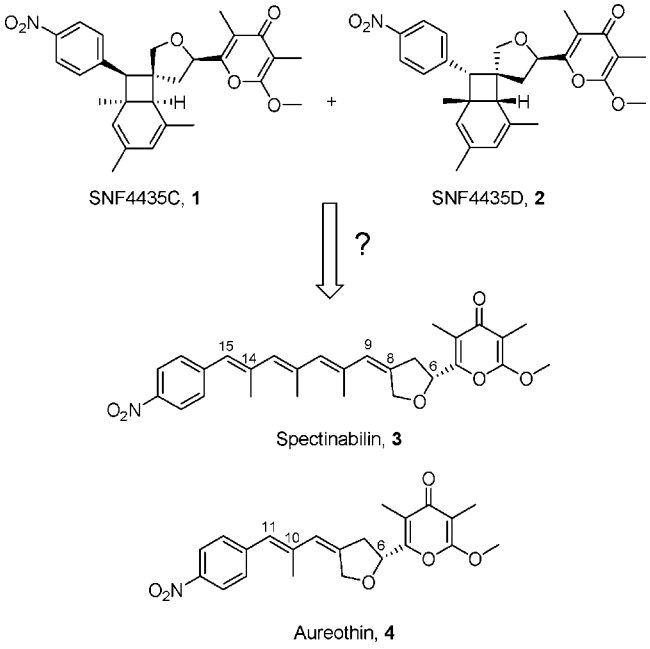
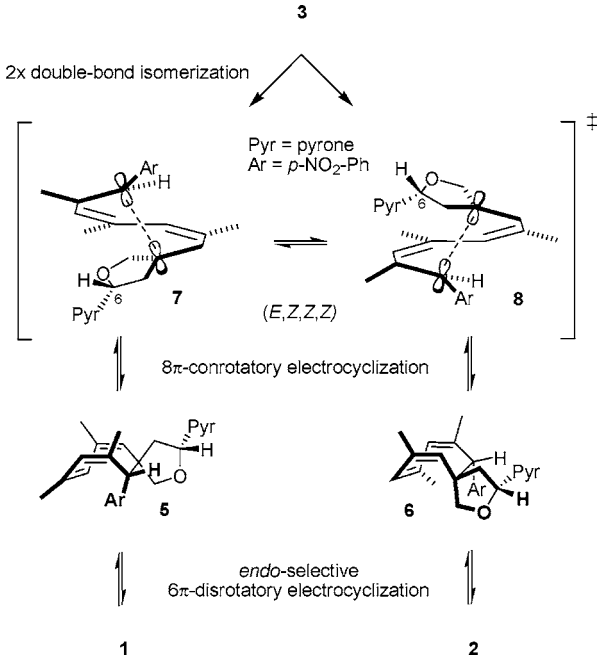
Scheme 1. Metabolites from *Streptomyces spectabilis* (SNF4435C (**1**), SNF4435D (**2**), and Spectinabilin (**3**)) and from *Streptomyces thioluteus* (Aureothin (**4**))



highly substituted tetraene moiety makes it a challenging synthetic target worth pursuing. In addition, it is a constitutional isomer of **1** and **2**. To this end, we[9] and others[10,11] have recently proposed a biogenetic hypothesis for the formation of **1** and **2** from **3** that bears resemblance to the hypothesis proposed by Black for the formation of the endiandric acids,[6] which was subsequently experimentally supported by the work of Nicolaou.[12] We now report the first total synthesis of (±)-**3** and its subsequent biomimetic conversion to (±)-**1** and (±)-**2** through a cascade of *E*/*Z*-isomerizations and electrocyclizations.

Although **3** and the related simpler polypropionate−acetate metabolite aureothin (**4**) are usually isolated as single enantiomers in Nature, it has been reported that **3**[13] and **4**[14] are prone to racemization due to the labile C6-proton. Therefore, we simplified the task of demonstrating our biogenetic hypothesis by developing a short and efficient synthesis of racemic **3** based on our strategy previously developed for the synthesis of (±)-aureothin (**4**).[15] In our proposed biosynthesis of **1** and **2** from **3**, we envisaged that (*E*,*E*,*E*,*Z*)-**3** would undergo *E*/*Z*-isomerizations to form the (*E*,*Z*,*Z*,*Z*)-isomer,[16] which would subsequently be transformed via a thermally allowed conrotatory 8π-electrocyclization to cyclooctatrienes **5** and **6** with possible bias toward **5** via 1,3-asymmetric induction from the C6-stereocenter (Scheme 2).

Scheme 2. Proposed Biosynthesis of SNF4435C, SNF4435D, **1**, and **2** from Spectinabilin (**3**)



The transition structures **7** and **8** may possess a helical geometry in accord with studies of conrotatory 8π-electrocyclizations via ab initio molecular orbital theory.[17] The cyclooctatrienes **5** and **6** could last undergo an *endo*-selective disrotatory 6π-electrocyclization to form **1** and **2**, respectively.

Our short synthesis of (±)-**3** starts from boronic ester **9**, which was easily synthesized from known pyrone **10** (Scheme 3).[15] Suzuki coupling of **9** with dibromide **11**, using TlOEt as base, proceeded with complete *trans*-selectivity with respect to **11** affording the light-sensitive **12** as a separable *E*/*Z* mixture (*E*/*Z*, 1:1.2). The required dibromide **11** was synthesized from the known aldehyde **13**,[18] which can be obtained in three steps from *p*-nitrobenzaldehyde. The Negishi-type coupling of (*Z*)-**12** with Me_2Zn proceeded with full retention of stereochemistry and efficiently afforded pure (±)-**3**.[19] The same procedure was applied to the synthesis of the (*E*,*E*,*E*,*E*)-isomer, isospectinabilin (**3a**), from (*E*)-**12**. The spectral data for (±)-**3** (IR, ^{1}H NMR, ^{13}C NMR) were in excellent agreement to that of an authentic sample of (−)-

(9) Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Cowley, A. R. *Org. Lett.* **2002**, *4*, 3731.

(10) Trauner and co-workers were the first to propose that **2** is diastereomeric to **1** with respect to all stereocenters except C6, which was later confirmed by Parker and co-workers (ref 11), see: Beaudry, C. M.; Trauner, D. *Org. Lett.* **2002**, *4*, 2221.

(11) (a) Parker, K. A.; Lim,Y.-H. *J. Am. Chem. Soc.* **2004**, *126*, 15968. (b) Parker, K. A.; Lim, Y.-H. *Org. Lett.* **2004**, *6*, 161.

(12) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5560 and references therein.

(13) In fact, the isolation of partially racemized **3** has been reported, see: Nair, M. G.; Chandra, A.; Thorogod, D. L. *Pestic. Sci.* **1995**, *43*, 361.

(14) Ishibashi, Y.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3643.

(15) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 641.

(16) Parker and co-workers synthesized (−)-**1** and (+)-**2** by forming the (*E*,*Z*,*Z*,*Z*)-isomer in situ via a Stille coupling; see ref 11.

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

(18) Moses, J. E.; Baldwin, J. E.; Brückner, S.; Eade, S. J.; Adlington, R. M. *Org. Biomol. Chem.* **2003**, *1*, 3670.

(19) Shi, J.-C.; Zeng, X.; Negishi, E.-I. *Org. Lett.* **2003**, *5*, 1825.

3,[20] and to the previously reported data.[7] In addition, the previously tentative assignmemt[7] of the (*E*,*E*,*E*,*Z*)-geometry of **3** was confirmed by 1D nOe experiments.[21]

Scheme 3. Synthesis of (±)-**3** and Its (*E*,*E*,*E*,*E*)-Isomer **3a** from Boronic Ester **9**

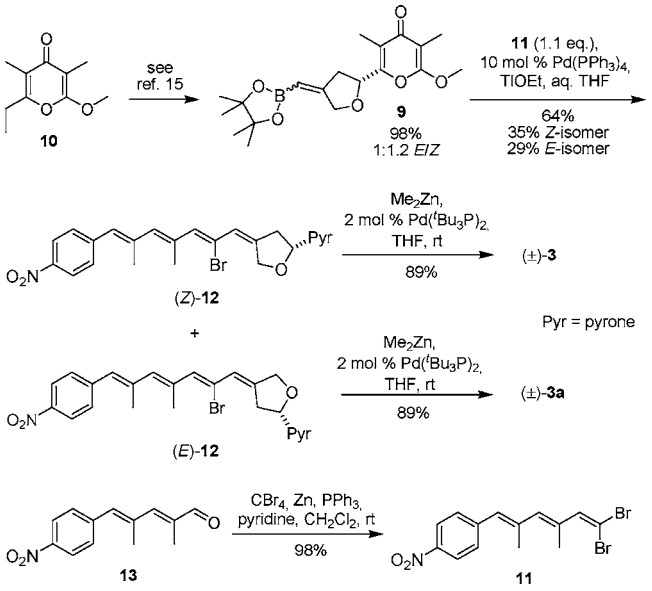
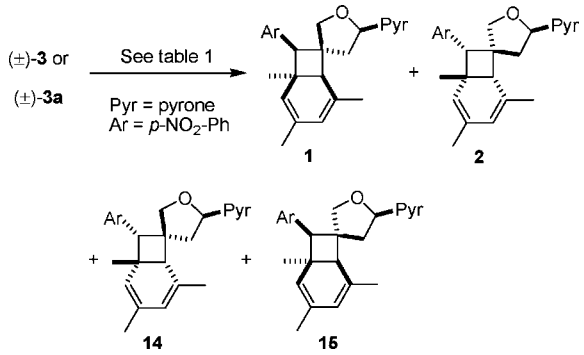


Table 1. Synthesis of (±)-**1**, (±)-**2**, and Isomers **14** and **15** from (±)-**3** or Its (*E*,*E*,*E*,*E*)-Isomer **3a**[a,b]



entry	substrate	mol % of $PdCl_2(MeCN)_2$	temp, °C	ratio **1**:**2**:**14**:**15**[c]	yield,[d] %
1	**3**	0	70	3.6:1:0:0	23
2	**3**	25	20	4.5:1.0:4.5:1.7	<5
3	**3**	25	70	2.8:1.1:2.1:1.0	40
4	**3**	25	50	3.9:1.0:2.8:1.2	nd
5	**3**	25	110	2.9:1.0:2.0:1.1	nd
6	**3**	100	70	nd	~0
7	**3a**	25	70	2.0:1.0:5.7:3.0	31

[a] Reactions were performed in DMF in the dark. [b] nd = not determined. [c] Ratios determined from analysis of ^{1}H NMR spectra of crude product. [d] Sum of isolated yields of **1**, **2**, **14**, and **15**.

Next, we examined various conditions for the conversion of **3** to **1** and **2**. Neither **1** nor **2** could be detected (^{1}H NMR) by exposure of **3** in solution to sunlight.[22] On the other hand, heating a solution of (±)-**3** in DMF at 70 °C for 3 days resulted in 23% of (±)-**1** and (±)-**2** as a 3.6:1 mixture after extensive purification by preparative TLC (Table 1, entry 1). In an attempt to optimize this conversion, we considered palladium(II) methodology to facilitate the requisite *E* to *Z* isomerization, i.e., (*E*,*E*,*E*,*Z*) to (*E*,*Z*,*Z*,*Z*), as we have previously demonstrated in a model study.[9] However, when **3** was subjected to $PdCl_2(MeCN)_2$ under standard conditions[9] at room temperature only traces of **1** and **2** could be detected, suggesting that the *E*/*Z*-isomerizations were too slow at this temperature (entry 2). By varying both the catalyst loading and temperature we found the best conditions to involve heating a solution of **3** in DMF with 25 mol % of $PdCl_2(MeCN)_2$ at 70 °C for 1 day in the dark (entry 3). This afforded 22% of a separable 2.5:1 mixture of (±)-SNF4435C (**1**) and (±)-SNF4435D (**2**).[23] To our surprise, 18% of two unexpected isomers **14** and **15** could also be isolated in a 2.1:1 ratio from the reaction mixture.[24]

Lower temperatures led to a more complex reaction mixture (entry 4), whereas elevated temperatures or higher catalyst loading led to increased decomposition (entry 5 and 6). Also, the individual ratios **1**:**2** and **14**:**15** decreased with increasing temperature, while the overall ratio of **1** and **2** to **14** and **15** remained nearly constant (entry 2−5). Interestingly, the ratios of **1** and **2** are close throughout to that found in Nature (2.3:1),[3] thus supporting our biogenetic hypothesis for their formation. The 1,3-diastereoselection induced from the C6-stereocenter in the 8π-electrocyclization step is almost of the same magnitude for **14** and **15** compared to **1** and **2**, resulting in roughly equal ratios of **1**:**2** and **14**:**15**.

The formation of **14** and **15** is consistent with the 8π/6π-electrocyclization cascade of either of the (*Z*,*Z*,*Z*,*Z*)- and (*E*,*Z*,*Z*,*E*)-isomers, **3b** and **3c** (Scheme 4). We have not observed this "over-isomerization" previously with similar tetraenes.[9,18] X-ray structures have indicated a lack of planarity of the polyene backbone of structures similar to **3** presumably due to 1,3-steric interactions between the methyl groups.[9,18] This should lead to a decrease in the conjugation of the C8−C9 double bond with the electron-deficient *p*-nitrophenyl ring. The more electron-rich C8−C9 double bond is expected to be more prone to isomerizations with the cationic palladium moiety versus the C14−C15 double bond.[25] Hence, we favor that **14** and **15** may be formed

(20) We are grateful for an authentic sample of (−)-spectinabilin (**3**) donated by Dr. M. Isaka, National Center for Genetic Engineering and Biotechnology, Klong Luang, Pathumthani 12120, Thailand.

(21) See the Supporting Information.

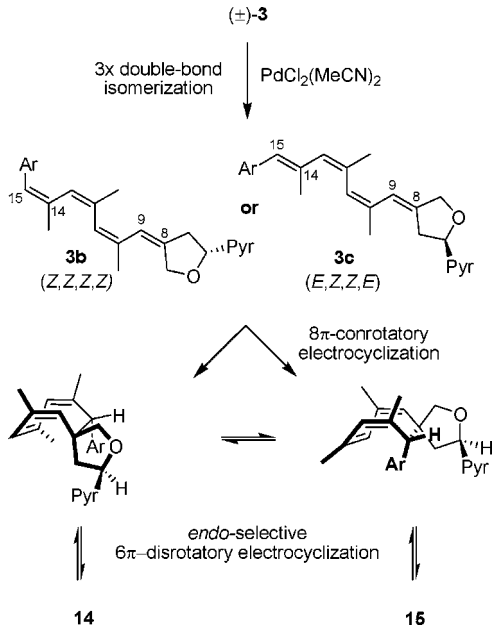
(22) Spectinabilin (**3**) is sensitive to light and will during initial exposure to sunlight in solution undergo *E* to *Z* isomerization of the C14−C15 double bond as observed by ^{1}H NMR. The same is true for the C10−C11 double bond in aureothin (**4**). Prolonged exposure of **3** to light leads to a complex product mixture.

(23) **1** and **2** could be separated by preparative TLC, see the Supporting Information.

(24) Isomers **14** and **15** were only formed in trace amounts (^{1}H NMR) when subjecting **3** to heating in DMF without $PdCl_2(MeCN)_2$. The structure of **14** and **15** was unambiguously confirmed by NMR, IR, and HRMS; see the Supporting Information.

(25) Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627.

Scheme 4. Proposed Cascade for the Formation of **14** and **15**



predominately via the (*E*,*Z*,*Z*,*E*)-isomer **3c**. In support of this was the observation that subjection of the (*E*,*E*,*E*,*E*)-isomer **3a** to similar conditions provided 23% of a 1.9:1 mixture of **14** and **15** and minor amounts of **1** and **2** (8%) (entry 7).

In conclusion, we have developed a short and efficient total synthesis of (±)-spectinabilin (**3**) from boronic ester **9**[15] that demonstrates the usefulness of palladium-mediated reactions in the efficient assembly of congested polyene structures. The successful biomimetic conversion of spectinabilin (**3**) to SNF4435C (**1**) and SNF4435D (**2**) shows that our biogenetic hypothesis connecting these natural products is chemically feasible. If the hypothesis is true, it seems likely that Nature uses efficient enzyme-mediated *E*/*Z*-isomerizations which the subsequent cyclization cascade is likely to benefit from as well.[26]

Acknowledgment. We thank Roche for funding to Mikkel F. Jacobsen and EPSRC for funding to J. E. Moses. We thank Dr. B. Odell for NMR assistance.

Supporting Information Available: Full experimental details, and copies of spectra (^{1}H NMR and ^{13}C NMR) for compounds (±)-**1**, (±)-**2**, (±)-**3**, **3a**, (*E*)-**12**, (*Z*)-**12**, **14**. and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) For an example of enzymatic *E*/*Z*-isomerization in Nature, the conversion of tetraene *all-trans*-retinol to 11-*cis*-retinol in the retinoid cycle, see: Kuksa, V.; Imanishi, Y.; Batten, M.; Palczewski, K.; Moise, A. R. *Vision Res.* **2003**, *43*, 2959.