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Studies on the Biomimetic Synthesis of SNF4435 C and D

John E. Moses, Jack E. Baldwin,* Rodolfo Marquez, and Robert M. Adlington

Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, U.K.

Andrew R. Cowley

Chemical Crystallography, Oxford University, South Parks Road, Oxford OX1 3QR, U.K.

jack.baldwin@chem.ox.ac.uk.

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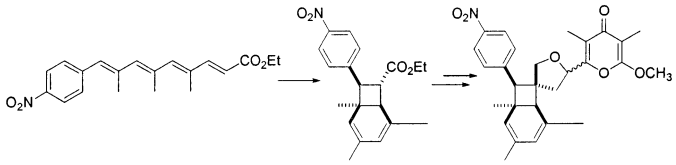
ABSTRACT



The biomimetic synthesis of the bicyclic core of the novel immunosuppresants SNF4435C and SNF4435D is reported. The core framework was efficiently generated from the all-*trans* tetraene precursor in one step and in good yield.

SNF4435C **1** and SNF4435D **2** are novel pentacyclic immunosuppresants isolated in 2001 by Takahashi from the culture broth of a strain of *Steptomyces spectabilis*.[1,2] Biologically, both compounds selectively suppress B-cell growth versus T-cell development. This would indicate a different mode of action from that of the known immunosuppresants cyclosporin A (CsA) and FK-506. This mechanistic difference, however, opens up the possibility of developing new immunosuppresants based on these novel compounds (Figure 1).[3,4]

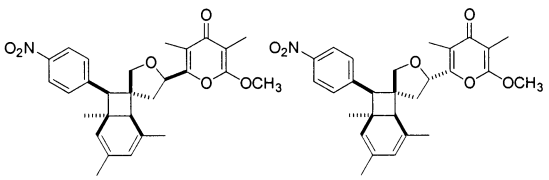


Figure 1. SNF4435C **1** and SNF4435 D **2**.

Structurally, SNF4435C **1** and SNF4435D **2** are pentacyclic structures exhibiting a hexasubstituted bicyclo[4.2.0] core comprising a cyclohexadiene unit in the major ring. This bicyclo[4.2.0]octadiene is connected to a spiro furan unit, which in turn is connected to a γ-pyrone fragment.

The bicyclic core is also linked to a *p*-nitro-phenyl ring like the one present in the *p*-nitro-acyl-(C═C)$_n$-pyrones aureothin **3**, luteothin **4**, neoaureothin **5**, luteoreticulin **6**, and spectinabilin **7** (Figure 2).[5−7]

It is believed that this class of compounds is biosynthesized from *p*-amino benzoate **8** and a combination of propionate

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(2) Takahashi, K.; Tsuda, E.; Kurosawa, K. *J. Antibiotic*. **2001**, *54*, 548.
(3) Kurosawa, K.; Takahashi, K.; Fujise, N.; Yamashita, Y.; Washida, N.; Tsuda, E. *J. Antibiotic*. **2002**, *55*, 71.
(4) Kurosawa, K.; Takahashi, K.; Tsuda, E.; Tomida, A.; Tsuro, T. *Jpn. J. Cancer Res.* **2001**, *92*, 1235.
(5) (a) Maeda, K. *J. Antibiotic*. **1953**, *6*, 137. (b) Washizo, F.; Umezawa, H.; Sugiyama, N. *J. Antibiotic*. **1954**, *7*, 60. (c) Koyama, Y.; Fukakusa, Y.; Kyomura, N.; Yamagishi, S.; Arai, T. *Tetrahedron Lett*. **1969**, 355.
(6) (a) Cassinelli, G.; Grein, A.; Orezzi, P.; Penella, P.; Sanfilippo, A. *Archiv. Microbiol*. **1967**, *55*, 358. (b) Cardani, C.; Ghiringhelli, D.; Silva, A.; Areamone, F.; Camerino, B.; Cassinelli, G. *La Chimica L'Industria* **1970**, *52*, 793.
(7) Kakinuma, K.; Hanson, C. A.; Rinehart, K. L. *Tetrahedron* **1976**, *32*, 217.

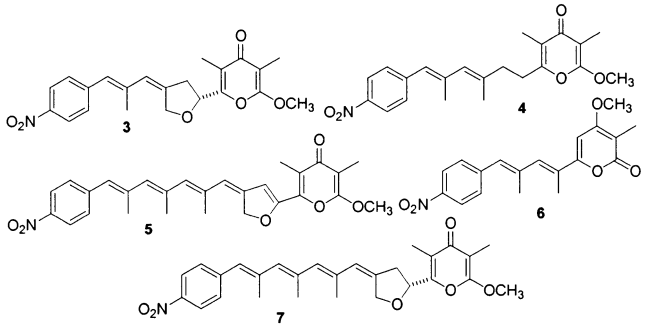
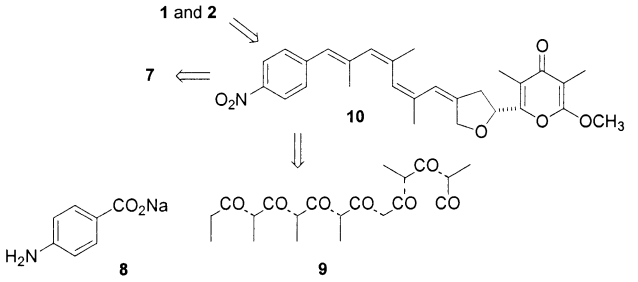


Figure 2. *p*-Nitro-acyl-(C═C)$_n$-pyrones aureothin **3**, luteoreticulin **4**, luteothin **5**, neoaureothin **6**, and spectinabilin **7**.

and acetate units, as demonstrated in the biosynthesis of aureothin **3**.[8]

In the case of spectinabilin **7**, it is expected that a para-amino benzoate unit **8** will combine with an equimolar amount of acetate and six propionate units **9**, the same ratio found in the SNF compounds **1** and **2**. Hence, a clear link between these metabolites and tetraene **10** can be proposed (Scheme 1).

Scheme 1. Proposed Biosynthesis of **1** and **2**

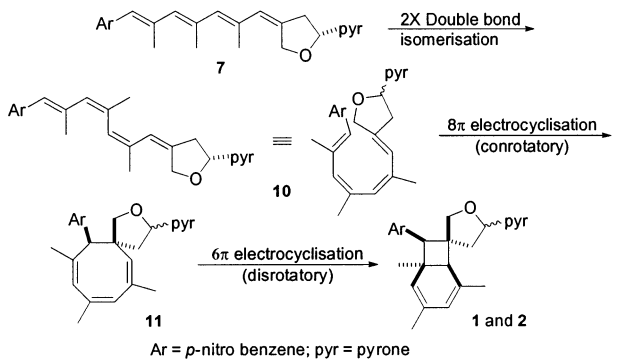


The combination of this biosynthetic information, together with the inherent instability of spectinabilin **7** over a period of time, prompted us to consider the possibility that spectinabilin is a direct precursor of SNF4435C **1** and SNF4435D **2** via either an in vitro or in vivo double-bond isomerization.[7]

In our proposed biosynthesis, we envisaged SNF4435C **1** and SNF4435D **2** as having originated from the (*E*,*Z*,*Z*,*Z*)-tetraene **10**, an isomer of spectinabilin **7** that is able to undergo a thermal 8π conrotatory electrocyclization to generate the cyclooctatetraene **11**. This cyclooctatetraene **11** can then undergo a further thermal 6π electron disrotatory cyclization to generate the desired bicyclic [4.2.0] core (Scheme 2).

A comparable approach has been recently reported by Trauner.[9] A similar double-electrocyclization hypothesis for

Scheme 2. Proposed Conversion of Spectinabilin **7** into **1** and **2**

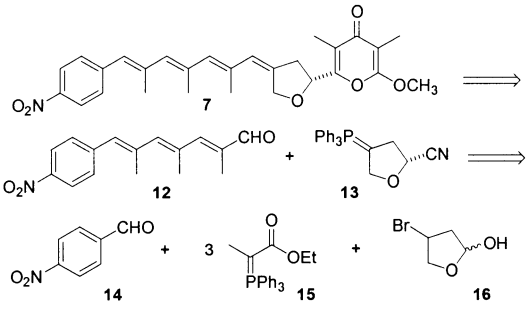


Ar = *p*-nitro benzene; pyr = pyrone

the biosynthesis of the bicyclic[4.2.0] core of the endiandric acids proposed by Black[10] has been experimentally demonstrated by the work of Nicolaou.[11] Likewise, Widmer[12] has employed this type of approach in his studies on vitamin A.

As far as our approach to spectinabilin **7** is concerned, we decided to use a stabilized ylide Wittig approach as to ensure the correct geometry at each of the first three double bonds starting from nitrobenzaldehyde **14**.[13] The final trisubstituted olefin would be installed through a normal Wittig approach starting from the *bis*-functionalized ylide **13**. The ylide itself could be generated from lactol **16**, which would provide us with an easily accessible handle for the introduction of the pyrone unit (Scheme 3).

Scheme 3. Retrosynthetic Analysis of Spectinabilin



Our synthesis began with *p*-nitro-benzaldehyde **14**, which was treated under Wittig conditions to generate the desired conjugated ester **17**, which was efficiently reduced to the allylic alcohol **18** in good yield. Swern oxidation of alcohol

(8) (a) Yamakazi, M.; Maebayashi, Y.; Katoh, H.; Ohishi, J. I.; Koyama, Y. *Chem. Phar. Bull*. **1975**, *23*, 569. (b) Yamazaki, M.; Katoh, F.; Ohishi, J. I.; Koyama, Y. *Tetrahedron Lett*. **1972**, 2701.

(9) Beaudry, C. M.; Trauner, D. *Org. Lett*. **2002**, *4*, 2221.

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

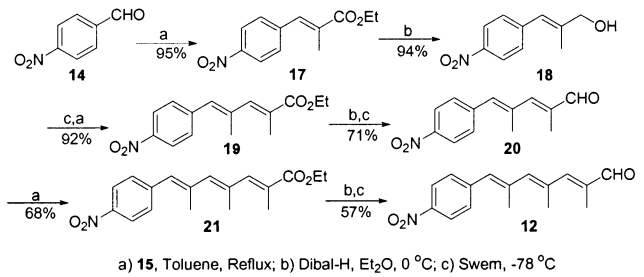
(11) (a) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc*. **1982**, *104*, 5555. (b) Nicolaou, K. C.; Petasis, N. A.; Uenishi, J.; Zipkin, R. E. *J. Am. Chem. Soc*. **1982**, *104*, 5557. (c) Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc*. **1982**, *104*, 5558. (d) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc*. **1982**, *104*, 5560.

(12) Vogt, P.; Schlageter, M.; Widmer, E. *Tetrahedron Lett*. **1991**, *32*, 4115.

(13) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev*. **1989**, *89*, 863.

18, afforded the desired aldehyde intermediate, which was promptly olefinated under Wittig conditions to the conjugated ester **19** in excellent yield for both steps (Scheme 4).

Scheme 4

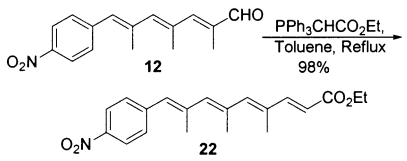


a) **15**, Toluene, Reflux; b) Dibal-H, Et_2O, 0 °C; c) Swem, -78 °C

Enoate **19** was then subjected to a further reduction/oxidation cycle to efficiently generate dienaldehyde **20**, which was then subjected under the same Wittig conditions as before to afford the expected trienoate as a single isomer **21**. Finally, treatment of trienoate **21** to reduction and oxidation afforded the crucial trienaldehyde **12** in good overall yield.

At this point, however, it was decided to generate a simpler, readily accessible model of spectinabilin **7** on which the validity of our biomimetic isomerization hypothesis could be readily assessed. Thus, treatment of trienaldehyde **12** with ethyl triphenyl phosphonoacetate generated the desired tetraene ester **22** in good yield and as a single double-bond isomer (Scheme 5).

Scheme 5



The (*E*,*E*,*E*,*E*)-double-bond stereochemistry was corroborated by X-ray analysis, which interestingly revealed a significant lack of planarity in the tetraene ester **22** due to the strong steric interactions between the alkene methyl substituents (Figure 3).[14]

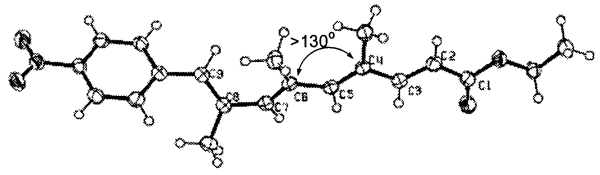


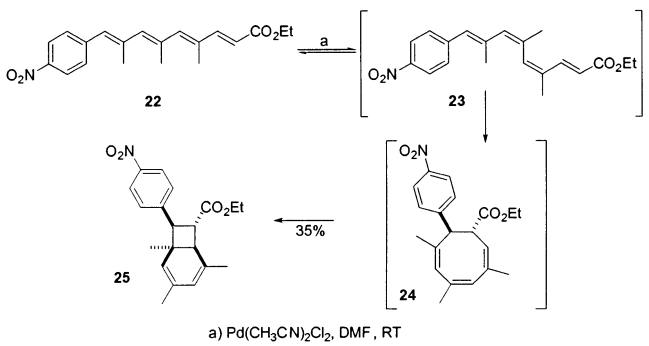
Figure 3. X-ray structure of tetraene **22**.

We envisaged that such a highly strained tetraene ester (as demonstrated by the >130° angle between C_4, C_5, and C_6 and the 45° dihedral angle of the C_8-C_9 double bond) would be prone to isomerization under the right conditions. Once the desired isomerization had taken place, we would then expect the tetraene **22** to have the necessary (*E*,*Z*,*Z*,*E*)-geometry for the double electrocyclization to take place.

With the required tetraene **22** in hand, the desired isomerizations were attempted under metal(II)-catalyzed conditions. Our choice of conditions stemmed from the well-known ability of palladium(II) salts to interact and isomerize conjugated double-bond systems through either a carbocation or a π-allylic complex.[15]

Thus, treatment of the tetraene ester **22**, with dichlorobis-(acetonitrile)palladium(II) at room temperature, effected the desired cyclization, generating the desired bicyclo[4.2.0] octadiene core **25** of the SNF compounds in reasonable yield and as a single diastereomer. The observed product stereochemistry is consistent with a double isomerization taking place to generate the (*E*,*Z*,*Z*,*E*)-tetraene **23**, which undergoes the expected tandem double electrocyclization to sequentially generate cyclooctatetraene **24** and bicyclo[4.2.0] octadiene **25** (Scheme 6).

Scheme 6



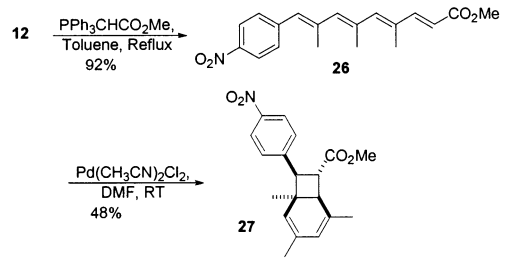
a) $Pd(CH_3CN)_2Cl_2$, DMF, RT

Trauner and co-workers have very recently reported the synthesis of the methyl analogue of ester **25** via the assumed in situ preparation of the methyl analogue of the *E*,*Z*,*Z*,*E*-tetraene **23** via Stille methodology.[9] It was therefore decided to synthesize the tetraene methyl ester analogue **26** for further structural corroboration. Thus, treatment of trienaldehyde **12** with methyl triphenylphosphonoacetate proceeded cleanly and in good yield to afford the desired methyl ester **26**. Methyl ester **26** was then subjected to the same Pd(II)-catalyzed isomerization conditions as before, to afford bicyclic compound **27** in good yield and as a single diastereomer. The one- and two-dimensional ^1H NMR data

(14) Atomic coordinates for **22** are available upon request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (Deposition number CCDC 190072). The crystallographic numbering system differs from that used in the text; therefore, any request should be accompanied by the full literature citation of this paper.

(15) (a) Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627. (b) Sen, A.; Lai, T.-W. *Inorg. Chem.* **1981**, *20*, 4036. (c) Sen, A.; Lai-T.-W. *Inorg. Chem.* **1984**, *23*, 3257.

Scheme 7



obtained for the methyl ester **27** were identical to the literature data.[9]

Finally, preliminary results in the treatment of either tetraene esters **22** or **26** under a variety of both thermal and photochemical conditions failed to generate any of the desired target products **25** or **27**. These results, taken together with those from the related bicyclo[4.2.0] octadiene systems reported by Nicolaou[11] and Widmer[12] in which the electrocyclizations spontaneously take place at or below room temperature, indicate that once the (*E*,*E*,*E*,*E*)-tetraenes **22** or **26** have been isomerized to the corresponding (*E*,*Z*,*Z*,*E*)-isomers by Pd(II) catalysis at room temperature, the double electrocyclization to generate **25** and **27** immediately occurs. The double-electrocyclization steps may possibly benefit from the Pd(II) catalysis.

In conclusion, we have demonstrated a connection between spectinabilin **7** and the SNF family of compounds by efficiently generating the SNF core structures **25** and **27** from the all-*trans* tetraene esters **22** and **26** in a single step and in good yield. It is intriguing to consider that (*E*,*E*,*E*,*E*)-spectinabilin **7** in the presence of an available metal cation could be a possible biological precursor of the SNF family of compounds. An alternative possibility is that both spectinabilin **7** and the SNF compounds **1** and **2** share a common biological pathway that differs at a stage when the double-bond geometries of the tetraene are established.

Acknowledgment. We thank the EPSRC for funding to J.E.M. We thank Dr. B. ODell for NMR assistance.

Supporting Information Available: Experimental procedures for compounds **22** and **25**−**27** and NMR data for compounds **25** and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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