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Total Synthesis of the Potent Androgen Receptor Antagonist (−)-Arabilin: A Strategic, Biomimetic [1,7]-Hydrogen Shift

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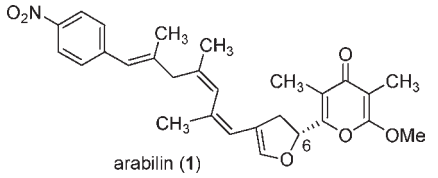
Supporting Information

ABSTRACT: The first total synthesis of (−)-arabilin, a *Streptomyces* metabolite that inhibits hormone activation of the androgen receptor, has been completed. The key step, a [1,7]-hydrogen shift, establishes the enol ether-containing skipped-tetraene substructure. This nonenzymatic pericyclic reaction is considered to be biomimetic.

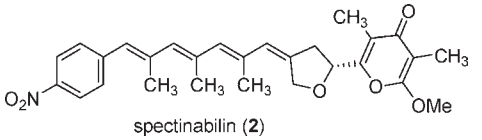
Arabilin (**1**) is a natural product that was isolated by the Imoto group from *Streptomyces* sp. MK756-CF1 during a screen for androgen receptor (AR) antagonists.[1] Arabilin competitively blocks binding of dihydrotestosterone (DHT) to the AR with an IC_{50} of 11 μM and inhibits DHT-induced expression of prostate-specific antigen mRNA in LNCaP cells. New structural classes of AR antagonists, especially those that retain activity against hormone refractory prostate cancer, are important leads for drug development.[2]



arabilin (**1**)

The structure of arabilin was determined by a combination of spectroscopic techniques, including HMQC, HMBC, and NOE NMR methods. Although the configuration at C-6 was not determined, we initially assumed this to be (*R*) by analogy to that of its congeners.

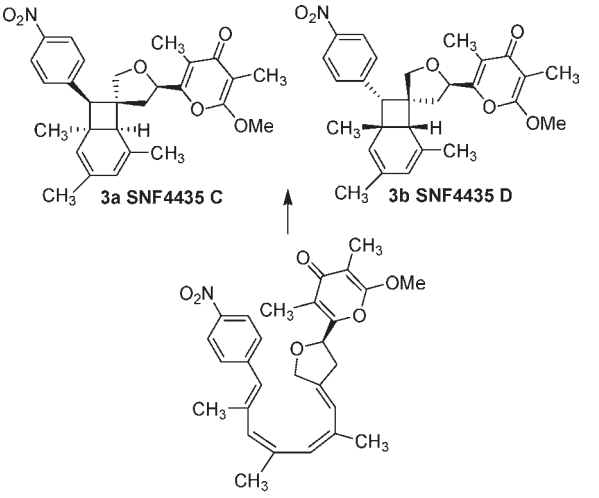
The structure of arabilin is as intriguing as its potential role in mechanistic and pharmacological studies. It is a biogenetic relative of spectinabilin (**2**) [the fully conjugated (*E*,*E*,*E*,*Z*)-tetraene][3] and SNF4435 C (**3a**),[4] both of which were isolated from the same organism.



spectinabilin (**2**)

The SNF compounds (**3a** and **3b**) are presumably derived biogenetically from the fully conjugated (*E*,*Z*,*Z*,*Z*)-tetraene **4** (or possibly from the *Z*,*Z*,*Z*,*E* isomer) by a nonenzymatic, thermal 8π,6π tandem electrocyclization reaction (Scheme 1).[5] Spectinabilin and the SNF compounds have the *R* configuration at C-6.

Scheme 1. Nonenzymatic 8π,6π Electrocyclization of (*E*,*Z*,*Z*,*Z*)-Tetraene 4



We were intrigued by the possibility that, in nature, the enol ether-containing skipped-polyene system of arabilin is formed from a conjugated tetraene system by another thermally allowed, nonenzymatic rearrangement, in this case, a [1,7]-hydrogen shift.[6] *The thermal [1,7]-hydrogen shift is well-known as a step in the series of sigmatropic rearrangements that leads to the biosynthesis and biomimetic chemical synthesis of vitamin D compounds. However, aside from its role in the vitamin D system, it is unknown as a component of a rationally designed total synthesis.* Furthermore, in geometrically disposed trienes, it is reversible, in some cases leading to mixtures of isomers.[7]

In principle, a thermal [1,7]-hydrogen shift is available to conjugated (*E*,*Z*,*Z*,*Z*)-tetraene **4;** however the 8π electrocyclization is facile in this system. Alternatively, arabilin, but not the SNF compounds, could be formed from the *E*,*E*,*Z*,*Z* isomer **5**. The helical transition state required for an antarafacial [1,7]-hydrogen shift[8] is available to isomer **5** (Scheme 2), but that required for the 8π electrocyclization is not.[9] Therefore, we considered tetraene **5** to be a potential biogenetic and synthetic precursor of arabilin. It seemed likely that we could obtain tetraene **5** from the palladium-catalyzed coupling of (*E*,*E*)-iododiene **6** and known chiral vinylstannane **7**.[10]

Before investing in the preparation of the proposed biosynthetic intermediate **5**, we tested the facility of the [1,7]-hydrogen

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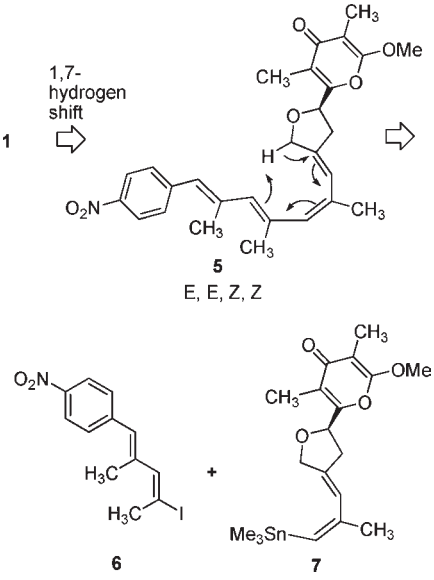
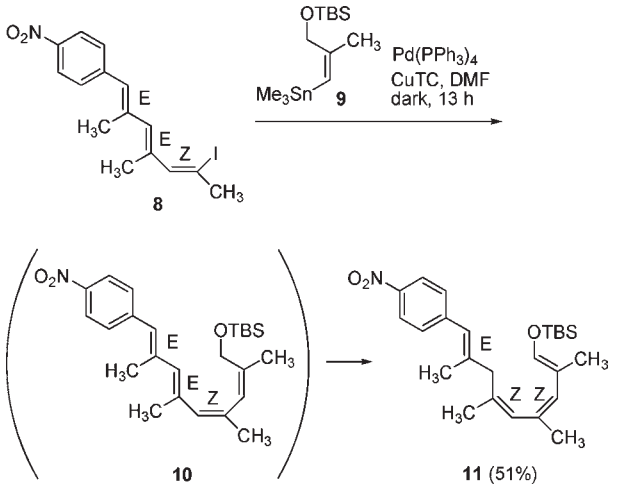
Scheme 2. Postulated Key Step for the Total Synthesis: Tandem Coupling and [1,7]-Hydrogen Shift



Scheme 3. Tandem Reaction in the Model System

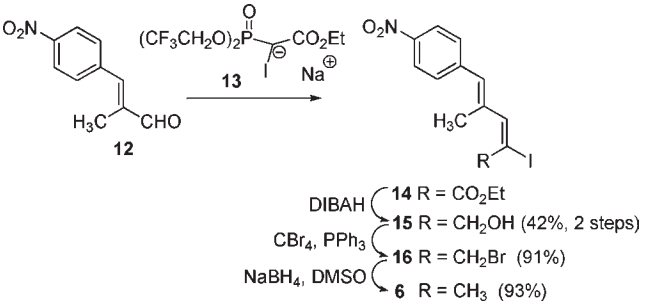


shift in a closely related model system. Thus, iodotriene **8** (prepared as described in the Supporting Information) and vinylstannane **9**[11] were exposed to the Pd(0)/CuTC catalytic system[12] at room temperature. Monitoring of the coupling reaction by TLC revealed the formation of a yellow product after approximately 2 h and its subsequent disappearance concurrent with the formation of a new colorless product. Enol silyl ether **11**, the product of coupling followed by [1,7]-hydrogen migration, was isolated in 51% yield. These results are consistent with the formation of tetraene **10** and its in situ thermal conversion to enol ether **11** (Scheme 3).

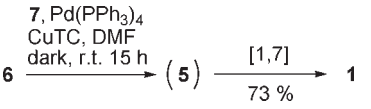
We believe that this report represents only the third account of a [1,7]-hydrogen shift that provides an enol ether product.[13] Furthermore, this reaction is clearly exothermic, suggesting interesting extensions in methodology development.

An analysis of the rearrangement of intermediate **10** in the context of the literature on related compounds is consistent with

Scheme 4. Synthesis of Iododiene 6



Scheme 5. Convergent Synthesis of (−)-Arabilin



a picture in which the [1,7]-hydrogen shift is accelerated by both a substituent-enforced favorable conformation and an oxygen substituent on the developing double bond. Internally unsubstituted 2,4,6-(*Z*,*Z*,*E*)-trien-1-ols and their ethers are known as natural products and synthetic intermediates.[14] [1,7]-Hydrogen shifts have not been reported for these systems, and there is presumably no difficulty in isolating or storing them. On the other hand, attempts to prepare 9-*p*-nitrophenyl-2,4,6-trimethyl-2,4,6-(*Z*,*Z*,*E*)-hexatrien-1-ol led to the conclusion that this alcohol is unstable.[5a]

Having established the anticipated [1,7]-hydrogen shift to be an efficient process, we turned our attention to its application in the total synthesis. At this point, we needed to select a coupling strategy that would lead to the biomimetic intermediate **5**. For the approach outlined in Scheme 2, we needed (*E*,*E*)-iododiene **6**.

The desired iododiene **6** was obtained by defunctionalization of iodo ester **14**, itself prepared by a Still−Gennari reaction with iodo reagent **13**[15,16] (Scheme 4). This four-step scheme[17] utilized one chromatographic separation (of **15** from small amounts of its *E*,*Z* isomer) and afforded the desired iododiene **6** quite cleanly from the reduction of bromide **16**.[18]

Coupling of iododiene **6** with stannane **7** under the conditions that had proven successful in the model system gave arabilin (**1**) directly in 73% yield (Scheme 5). The optical rotation of our synthetic arabilin was −139.4° (*c* 0.33, $CHCl_3$, 20−21 °C), whereas the value reported for the natural product was −166.2° (*c* 0.13, $CHCl_3$, 25 °C). The calculated enantiomeric excess of our synthetic material was 84%.[19] The correlation confirms the assignment of the C-6 asymmetric center in arabilin as *R*.

The first total synthesis of (−)-arabilin requires 15 steps in the longest linear sequence and 19 steps total from commercially available starting materials. It demonstrates the effective use of a [1,7]-hydrogen shift as a key step in total synthesis and supports the premise that this rearrangement is a nonenzymatic step in the biosynthesis of this interesting natural product.

■ ASSOCIATED CONTENT

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

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(6) The [1,7]-hydrogen shift has been proposed as a step in a biosynthetic pericyclic cascade in algae. See: Pohnert, G.; Boland, W. *Tetrahedron* **1994**, *50*, 10235–10244.

(7) In the vitamin D_2 synthesis, thermal equilibrium of the pre-vitamin and vitamin (1:6) is obtained after 6 h of refluxing in methanol and stirring at 35−40 °C overnight. See: Okabe, M. *Org. Synth.* **1999**, *76*, 275–286.

(8) As predicted by Woodward and Hoffman and demonstrated by Okamura. See: (a) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781–853. (b) Hoeger, C. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1985**, *107*, 268–270.

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(13) For examples in the vitamin D series, see: (a) Dmitrenko, O.; Bach, R. D.; Sicinski, R. R.; Reischl, W. *Theor. Chem. Acc.* **2003**, *109*, 170–175 and references therein. For an unanticipated example, see: (b) Ohmori, K.; Mori, K.; Ishikawa, Y.; Tsuruta, H.; Kuwahara, S.; Harada, N.; Suzuki, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 3167–3171. Akerling, Z. R.; Norton, J. E.; Houk, K. N. *Org. Lett.* **2004**, *6*, 4273–4275.

(14) For examples, see the syntheses of phostriecin (fostriecin) and cytostatin in the following leading references: (a) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 3752–3755. (b) Burke, C. P.; Swingle, M. R.; Honkanen, R. E.; Boger, D. L. *J. Org. Chem.* **2010**, *75*, 7505–7513.

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(19) In this asymmetric synthesis, the enantiomeric excess of the final product was similar to that obtained from the same iodopyrone intermediate in our synthesis of SNF4435 C and D (see ref 10).