

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

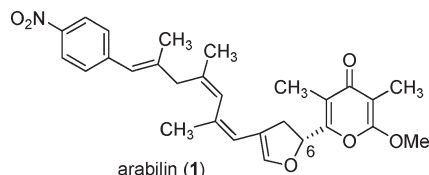
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Supporting Information

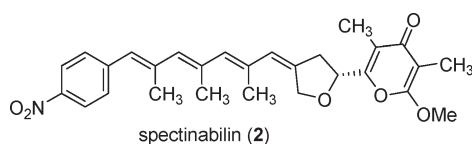
ABSTRACT: The first total synthesis of (–)-arabilin, a *Streptomyces* metabolite that inhibits hormone activation of the androgen receptor, has been completed. The key step, a [1,7]-hydrogen shift, establishes the enol ether-containing skipped-tetraene substructure. This nonenzymatic pericyclic reaction 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 IC₅₀ 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

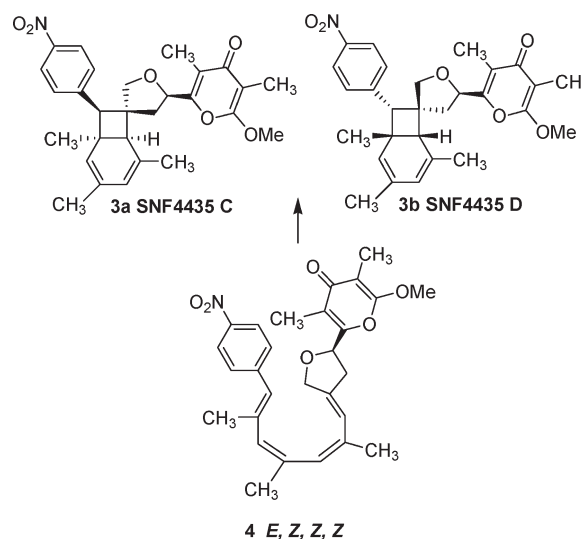


The structure of arabilin was determined by a combination of spectroscopic techniques, including HMQC, HMBC, and NOE NMR methods. Although the configuration at C-6 was not determined, we initially assumed this to be (*R*) by analogy to that of its congeners.

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.



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 8 π ,6 π tandem electrocyclic reaction (Scheme 1).⁵ Spectinabilin and the SNF compounds have the *R* configuration at C-6.

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

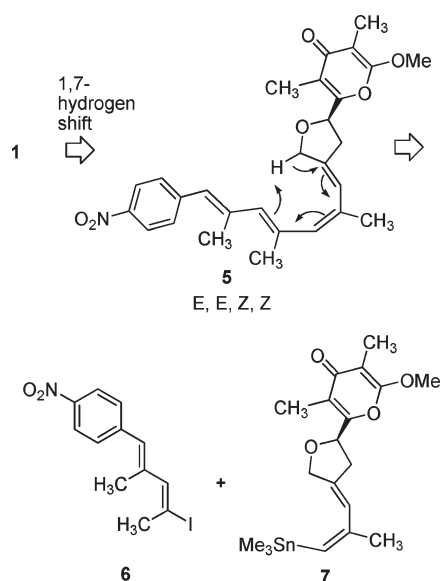
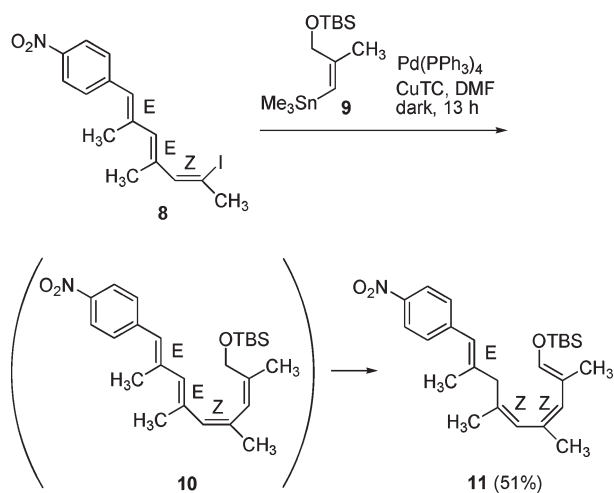
We were intrigued by the possibility that, in nature, the enol ether-containing skipped-polyene system of arabilin is formed from a conjugated tetraene system by another thermally allowed, nonenzymatic rearrangement, in this case, a [1,7]-hydrogen shift.⁶ The thermal [1,7]-hydrogen shift is well-known 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 disordered 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 8 π 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 shift⁸ is available to isomer **5** (Scheme 2), but that required for the 8 π 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

Received: October 12, 2011

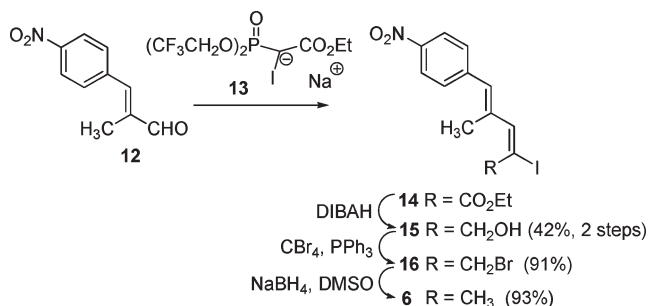
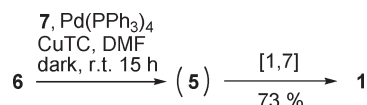
Published: November 16, 2011

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 system¹² 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 scheme¹⁷ 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 $^\circ\text{C}$), whereas the value reported for the natural product was -166.2° (c 0.13, CHCl_3 , 25 $^\circ\text{C}$). 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

S **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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■ ACKNOWLEDGMENT

We are grateful to the National Institutes of Health (GM 74776) and to Stony Brook University for financial support of this work. In addition, we thank the National Science Foundation for a grant to Stony Brook University for the purchase of NMR instrumentation (CHE-0131146).

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