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Total synthesis of the potent androgen receptor antagonist, (–)-arabilin. A strategic, biomimetic [1,7]-hydrogen shift

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Abstract

The first total synthesis of (–)-arabilin, a *Streptomyces* metabolite that inhibits hormone activation of the androgen receptor (AR), was completed. The key step, a [1,7]-hydrogen shift, establishes the enol ether-containing skipped tetraene substructure. This non-enzymatic, 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 of SNF4435 C (**3a**),⁴ both of which were isolated from the same organism.

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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>

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

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, non-enzymatic 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

A thermal, [1,7]-hydrogen shift is, in principle, 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 a [1,7]-antarafacial hydrogen shift⁸ 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 the *E*, *E*-iododiene **6** and the known chiral vinyl stannane **7**.¹⁰

Before investing in the preparation of the proposed biosynthetic intermediate **5**, we tested the facility of the [1,7]-hydrogen shift in a closely related model system. Thus the iodotriene **8** (for the preparation, see Supporting Information) and vinyl stannane **9**¹¹ were exposed to the Pd (0)/CuTC catalytic system¹² at room temperature. Monitoring the coupling reaction by TLC revealed the formation of a yellow product after approximately 2 hours and its subsequent disappearance concurrent with the formation of a new colorless product. The 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 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 as 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 was unstable.^{5a}

Having established that the anticipated [1,7]-hydrogen shift was 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 the (*E,E*)-iododiene **6**.

The desired **6** was obtained by defunctionalization of the iodo ester **14**, itself prepared by a Still-Gennari reaction with the iodo reagent **13**^{15,16} (Scheme 4). This 4-step scheme¹⁷

utilizes one chromatographic separation (of **15** from small amounts of its *E*, *Z* isomer) and affords 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°) whereas the value reported for the natural product was -166.2° (c 0.13, CHCl_3 , 25°). The calculated enantiomeric excess of our synthetic material is 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 it supports the premise that this rearrangement is a non-enzymatic step in the biosynthesis of this interesting natural product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

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

Scheme 2.

The Postulated Key Step for the Total Synthesis, Tandem Coupling and [1,7]-Hydrogen Shift

Scheme 3.
Tandem Reaction in Model System

Scheme 4.
Synthesis of the Iododiene 6

Scheme 5.
Convergent Synthesis of (–)-Arabilin