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Total Synthesis of Jatrophane Diterpenes from *Euphorbia characias*†

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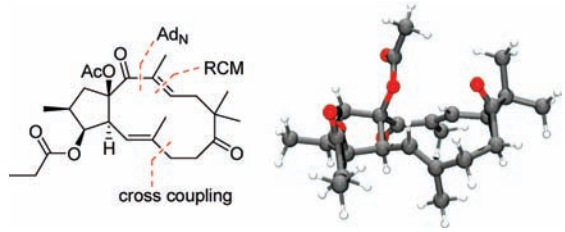
ABSTRACT



The enantioselective total synthesis of the jatrophane diterpene (−)-15-*O*-acetyl-3-*O*-propionylcharaciol is described. Starting from an advanced cyclopentane building block, a *B*-alkyl Suzuki−Miyaura cross-coupling and carbonyl addition were utilized to assemble a fully functionalized triene, and a ring-closing metathesis was then employed to construct the rigid 12-membered ring. Twenty-five years after the original report on the isolation of the natural product, our total synthesis unambiguously corroborates the original tentative structural assignment.

Jatrophane diterpenes have been isolated in great structural diversity from plants of the genus *Euphorbia*.[1] Members of the jatrophane family of diterpenes are characterized by a highly oxygenated *trans*-bicylo[10.3.0]pentadecane scaffold and display a wide range of biological activities[2] such as multidrug resistance modulating properties[3] and cytotoxicity against human cancer cell lines.[4]

Progress toward the total synthesis of jatrophanes from *Euphorbia* plants has been made recently, but to date no total synthesis has been reported.[5,6]

In 1984, Seip and Hecker reported the isolation of the $\Delta^{5,6}\Delta^{12,13}$ jatrophane **2** from *Euphorbia characias* (Figure 1).[7] The structure of **2** was assigned based on ^{1}H NMR (90 MHz) spectroscopy, mass spectrometry, and in analogy to structurally related lathyrane diterpenes from *E. characias*. However, the position of the acyl moieties was only tentatively assigned due to "a lack of material". Herein, we

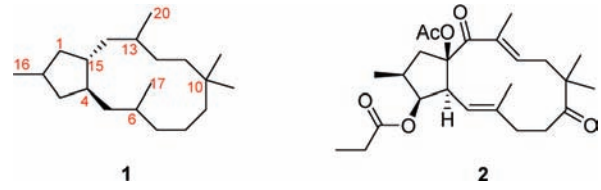


Figure 1. Jatrophane framework (**1**) and the proposed structure of the jatrophane diterpene **2** from *Euphorbia characias*. Jatrophane numbering is used throughout the manuscript.

† Dedicated to Prof. Dr. Hans-Ulrich Rei*β*ig on the occasion of his 60th birthday.

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describe our studies on the total synthesis of 15-*O*-acetyl-3-*O*-propionylcharaciol (**2**) which culminated in the first total synthesis of this natural product and verified the original structural assignment by Seip and Hecker.

From a retrosynthetic perspective, we considered the diol **3**, named characiol by Seip and Hecker, as an obvious intermediate for the synthesis of the diester **2** and planned to disassemble the rigid 12-membered ring of **3** using a ring-closing metathesis (RCM) transform and a cross-coupling transform (Figure 2). This approach considered previous

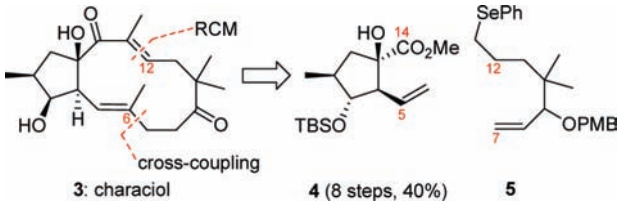
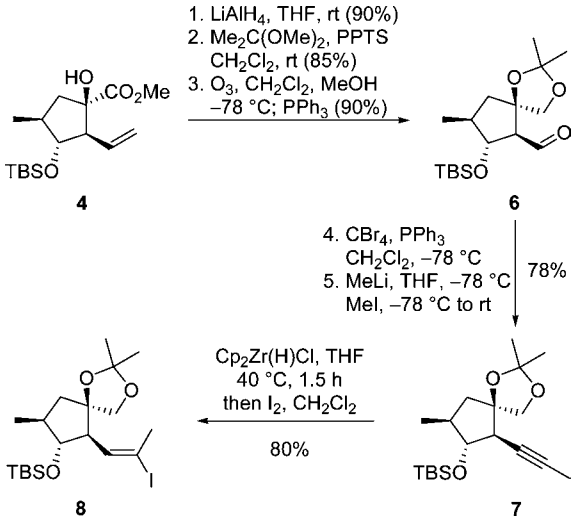


Figure 2. Retrosynthetic analysis of characiol (**3**).

futile attempts to employ a RCM for the construction of the C5/C6 double bond.[5d,f] Accordingly, the highly substituted cylopentane segment of **3** would be derived from the building block **4**, for which a scalable access has already been developed.[5d,f] Furthermore, the appropriately functionalized olefin **5**, containing a latent C12/C12′ double bond for the planned RCM, was envisaged as the C7−C12 synthon.

The conversion of the building block **4** to the vinyl iodide **8** that is required for the cross-coupling with the C7−C12 synthon **5** was realized according to Scheme 1. Reduction

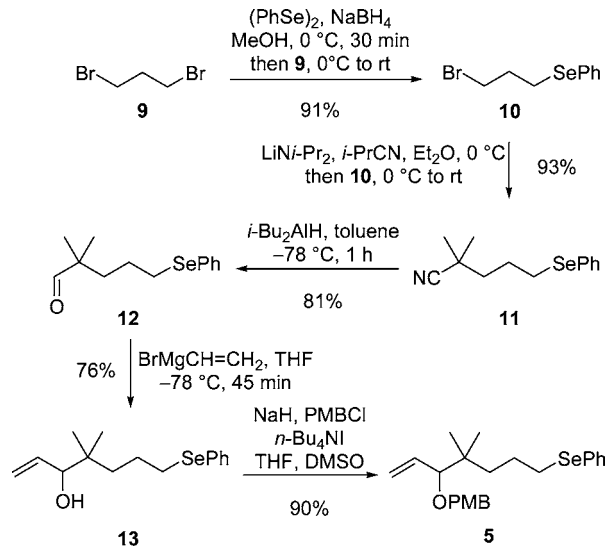
Scheme 1



of the methyl ester **4** and acetalization of the resulting diol were followed by the oxidative cleavage of the double bond to provide the aldehyde **6** which could be purified by chromatography. A two-step procedure was utilized to convert **6** to the alkyne **7**. Thus, olefination[8] of the aldehyde **6** provided a dibromoolefin that was treated with an excess of methyllithium[9] to afford the corresponding lithium acetylide which was in turn reacted in situ with methyliodide to furnish the alkyne **7**. Finally, the targeted vinyl iodide **8** emerged as a single double bond isomer through hydrozirconation[10] of the alkyne **7** and subsequent exposure of the intermediate vinyl zirconium species to iodine.

We next turned our attention to the synthesis of the cross-coupling partner **5** for the vinyl iodide **8** (Scheme 2).

Scheme 2



Dibromide **9**[11] was treated with an in situ generated phenylselenide anion equivalent[12] to provide the bromide **10**[13] which was subsequently used for the alkylation of the enolate of isobutyronitrile to deliver the nitrile **11**. Nitrile **11** was then reduced to the aldehyde **12** which was exposed to vinylmagnesium bromide to furnish the allylic alcohol **13**. In light of the envisioned synthetic sequence ahead of us, we opted for the introduction of a PMB ether as a protecting group[14] for the allylic hydroxyl group in **13**. Overall, the

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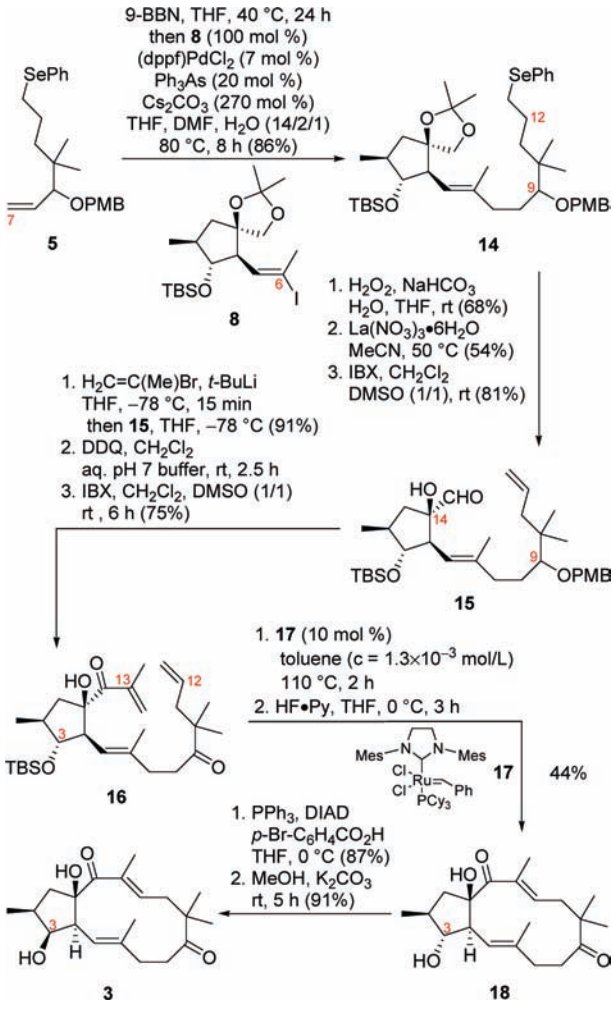
C7−C12 building block (±)-**5** was synthesized in five steps and 47% yield using commercially available substrates and reagents.

Having achieved the synthesis of the vinyl iodide **8** and the olefin **5**, attention was turned toward the fusion of these building blocks (Scheme 3). A *B*-alkyl Suzuki−Miyaura

Scheme 3



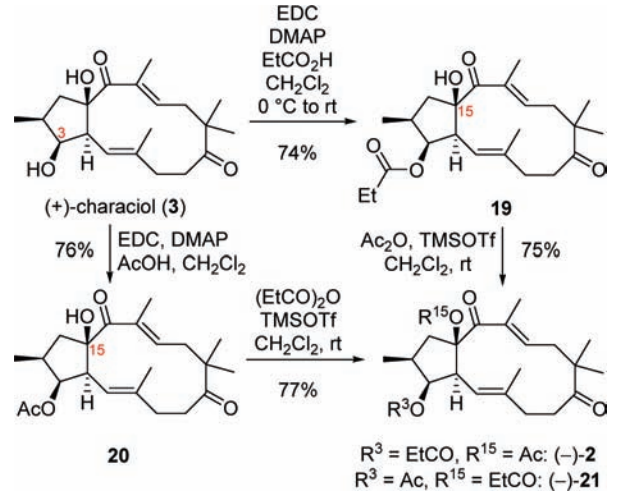
cross-coupling[15] reaction under the conditions originally described by Johnson and Braun[16] delivered the olefin **14** as a mixture of C9 diastereomers. Subsequent oxidation of the selenide to the selenoxide triggered an elimination that furnished the C12/C12′ double bond required for the RCM.[17]

We next faced the challenge of cleaving the isopropylidene acetal in the presence of the TBS and the PMB protecting groups. After substantial experimentation with various Lewis and Brønsted acids, it was determined that the removal of the isopropylidene protecting group was most effectively accomplished using $La(NO_3)_3$ hexahydrate in acetonitrile at elevated temperatures.[18] The resulting diol was subsequently oxidized with IBX to provide the aldehyde **15** as a mixture of C9 diastereomers.[19] The stage was now set for the introduction of the remaining carbon atoms. Nucleophilic addition of isopropenyl lithium, generated in situ by halogen−lithium exchange,[20] to the α-hydroxy aldehyde **15** furnished the corresponding diol. Oxidative removal of the PMB group with DDQ[21] gave the corresponding triol, and subsequent oxidation of the C9 and C14 hydroxyl groups provided the diketone **16**.

With triene **16** in hand, we proceeded to study the key RCM step for the formation of the 12-membered ring. Gratifyingly, exposure of **16** to Grubbs' second-generation metathesis catalyst **17**[22] (0.1 equiv) in refluxing toluene delivered the desired bicyclic product contaminated with inseparable impurities. The byproduct from the RCM could be removed subsequently to the cleavage of the remaining TBS protecting group with HF in pyridine to deliver 3-*epi*-characiol (**18**) in 44% isolated yield from the triene **16**. Finally, a stereospecific Mitsunobu reaction[23] and a subsequent transesterification of the resulting *para*-bromo benzoic acid ester converted 3-*epi*-characiol (**18**) to characiol (**3**).

With the jatrophane core in place, the final task was the regioselective esterification of characiol (**3**) (Scheme 4).

Scheme 4



Because of the uncertainties in the structural assignment of the natural product, the synthesis of the two regioisomeric diesters **2** and **21** was desirable. Thus, upon treating characiol (**3**) with an excess of propionic acid, EDC,[24] and DMAP,

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3-*O*-propionylcharaciol (**19**) was isolated and subsequently converted to 15-*O*-acetyl-3-*O*-propionylcharaciol (**2**) under conditions described by Procopiou et al.[25] In an analogous fashion, 3-*O*-acetyl-15-*O*-propionylcharaciol (**21**) was accessed via 3-*O*-acetylcharaciol (**20**). Comparison of the ^{1}H NMR data of the natural product and the synthetic diesters **2** and **21** unambiguously corroborates the original structural assignment by Seip and Hecker.[7]

In summary, we have accomplished the first enantioselective total synthesis of a jatrophane diterpene (**2**) from plants of the genus *Euphorbia*. The synthesis we have delineated demonstrates the potential of a strategy involving *B*-alkyl Suzuki−Miyaura cross-coupling and ring-closing metathesis for the assembling of the rigid *trans*-bicyclo[10.3.0]pentadecane core of jatropha-5,12-dienes. The possibility of adapting the established strategy to the synthesis of other members of the jatrophane family of diterpenes is currently under investigation.

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Supporting Information Available: Experimental procedures, spectral and analytical data for new compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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