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A Reductive-Heck Approach to the Hydroazulene Ring System: A Formal Synthesis of the Englerins

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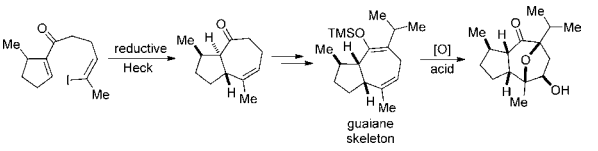
ABSTRACT



The reduction of a palladium enolate prior to β-hydride elimination provides a unique reaction for the synthesis of the hydroazulene ring system. When combined with a transannular epoxide rearrangement cascade, the reductive-Heck reaction allows rapid entry to the oxo-bridged guaiane core of the englerins.

Terpenes represent one of the largest natural product families known in nature. Among the various ring systems found in terpenes, the hydroazulene, or bicyclo[5.3.0] decane, is found in numerous subfamilies (Figure 1). The guaiane-type sesquiterpenes comprise one such hydroazulene-containing subfamily that possesses a range of biological activities, such as anti-inflammatory,[1] antitumor,[2] and cytotoxic properties,[3] and provides a valuable source for new bioactive molecules.

The significance of the hydroazulene ring system has led to the development of several important reaction manifolds over the years.[4] Since medium-sized rings present unique challenges relative to five- or six-membered rings, most of the strategies have focused on classical preparation of the five-membered ring, followed by a seven-membered annulation strategy.[5] Ring-closing metatheses,[6] cycloaddition reactions ([4 + 3][7] and [5 + 2][8]), and metal-catalyzed cyclizations[9] have all been elegantly employed to access the hydroazulenes en route to various natural products. While these approaches have their advantages, none of them provide control over the critical ring junction of the hydroazulene. To investigate this issue, we chose the englerins as an ideal proving ground to develop a new approach to hydroazulene ring systems—the reductive-Heck reaction.

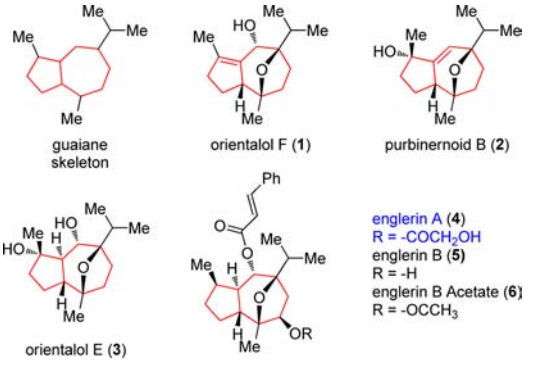


Figure 1. Examples of oxo-bridged guaiane natural products. The hydroazulene ring system is highlighted in red.

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(2) Dai, J. Q.; Shi, Y. P.; Zhao, C. Y.; Yang, L.; Li, Y. *J. Chem. Res.* **2002**, 368.
(3) Bruno, M.; Rosselli, S.; Maggio, A.; Raccuglia, R. A.; Bastow, K. F.; Lee, K. H. *J. Nat. Prod.* **2005**, *68*, 1042.
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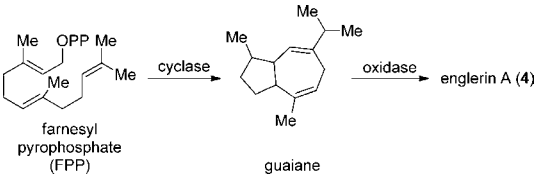
The guaiane sesquiterpenes englerin A (**4**) and englerin B (**5**) were isolated from the plant extract of *Phyllanthus engleri* (Figure 1).[10] Biological evaluation demonstrated 10- to 100-fold greater potency of englerin A over taxol against certain renal cancer cell lines (786-0, A498, ACHN, CAKI-1, and UO-31). Renal cell cancer (RCC) afflicts over 39,000 people in the United States annually and is the cause of over 12,000 deaths.[11] Current antirenal cancer compounds (sunitinib, sorafenib, bevacizumab, ensirolimus, and everolimus) benefit patients with metastatic renal cancer, but these compounds rarely produce complete responses, require long-term administration for disease control, and have serious adverse side effects.[11a] Therefore, the search for new compounds that possess specific activity against RCC is of great interest.

The unique anticancer activity of englerin A, combined with an intriguing molecular architecture, has elicited a spirited response from the synthetic community.[12] Among the many englerin analogs that have been prepared to date, several compounds with greater potency than that of the natural product have been identified.[13] Consequently, the preparation of englerin A analogs still remains a valuable goal.

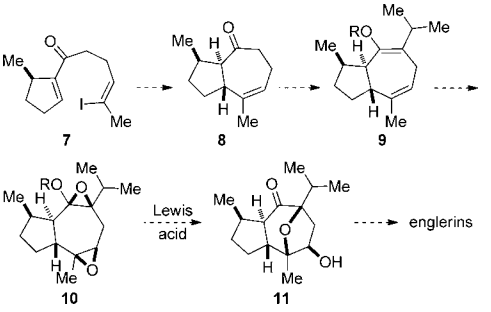
The chemical synthesis of the englerins presents two key challenges: the construction of the hydroazulene ring system and installation of the oxo-bridge. During the biosynthesis of sesquiterpenes, nature's cyclase enzymes convert farnesyl pyrophosphate (FPP) into the terpene carbocycles using cationic cyclizations and hydride shifts (Scheme 1). After the cyclization to form the guaiane core, a series of oxidations and functional group transformations presumably lead to the englerins.[14]

Scheme 1. Proposed Biosynthesis of Englerin A from Farnesyl Pyrophosphate



Inspired by the biosynthesis of guaiane sesquiterpenes, our synthetic plan seeks to construct the englerins through initial formation of the hydroazulene ring and subsequent epoxide rearrangement to install the oxo-bridge (Scheme 2). The hydroazulene ring system of the englerins is envisioned from an unusual reductive-Heck reaction. After formation of the hydroazulene, installation of the isopropyl group produces the guaiane ring system and sets the stage for the installation of the oxo-bridge. Upon bis-epoxidation, a Lewis acid catalyzed ring-opening cascade would provide the key tetrahydrofuran ring. Subsequent functional group manipulations should provide access to the englerins.

Scheme 2. Our Proposed Synthesis of the Englerins



The synthesis commenced with the known α,β-unsaturated ketone **12**, which was easily prepared from dimethoxytetrahydrofuran following the reported two-step sequence.[15] While both enantiomers of α,β-unsaturated ketone **12** are available from enzymatic transesterification with lipase (from *Pseudomonas* species),[15b] our investigations utilized racemic ketone **12**. Treatment of ketone **12** with base at −40 °C, followed by alkylation with Wichterle iodide[16] in presence of DMPU, produced vinyl iodide **13** in 48% yield (61% BORSM). Copper-catalyzed addition of methyl Grignard to the enone of **13** furnished the S_N2' product **7** in good yield (93%) to set the stage for our reductive-Heck studies (Scheme 3).[15b]

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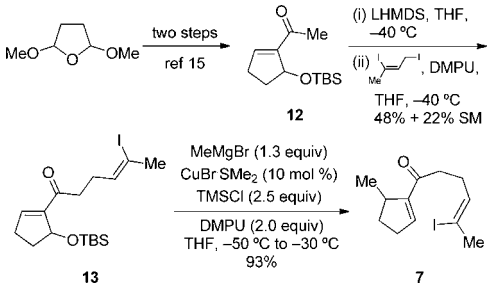
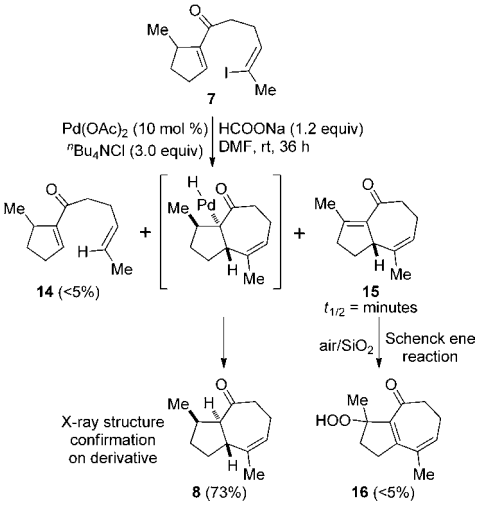
Scheme 3. Synthesis of Substrate **7** for the Reductive-Heck Reaction



During the course of this synthesis, a concise preparation of a *trans*-hydroazulene ring system was required. Unfortunately, transition state conformations exclude the use of many traditional annulation strategies such as the Aldol reaction, Dieckmann condensation, or Robinson annulation to form seven-membered rings.[17] Additionally, bicyclo[5.3.0]decane ring systems usually prefer the more thermodynamically stable *cis* ring fusion versus the higher energy *trans* junction by approximately 3.2 kcal/mol.[18] A putative reductive-Heck reaction would provide mild reaction conditions for the production of the dihydro-Heck product using a stoichiometric reductant. The *syn*-migratory insertion provides a unique solution for the construction of the thermodynamically unfavored *trans*-hydroazulene ring system. While the reductive-Heck reaction has been employed in a number of total syntheses,[19] the application of this reaction in the presence of *syn* β-hydrogen remains rare because of potential β-hydride elimination.[20]

To test whether a reductive Heck could access the desired *trans*-hydroazulene ring system **8**, several Heck-reaction conditions were investigated in the presence of formate salts. The addition of mono- or bidentate phosphine ligands produced mostly simple reduction product **14**,[21] while the addition of amine or inorganic bases increased amounts of "normal" Heck product **15** (Scheme 4). Heck product **15** proved unstable to air, undergoing a facile oxo-ene (Schenck) reaction[22] to produce peroxide **16**.[23] To inhibit the "normal" Heck pathway, exogenous bases were avoided in the reaction. Furthermore, "ligandless" palladium was investigated to decrease the rate of vinyl iodide reduction.[24] Following cursory optimization, we were pleased to find the combination of $Pd(OAc)_2$ (10 mol %), HCO_2Na (1.2 equiv), and $^nBu_4NCl$ (3 equiv) in DMF at rt for 36 h produces a 73% yield of 5,7-*trans*-fused hydroazulene product **8** with less than 5% of simple reduction product **14** and less than 5% of "normal" Heck product **15**. The relative stereochemistry of **8** has been determined unambiguously through ketone reduction and X-ray crystallographic analysis.

Scheme 4. Reductive-Heck Reaction to Form the *trans*-Hydroazulene Core of Englerin A



In an effort to rule out the possibility of a Heck/transfer hydrogenation mechanism[25] instead of the proposed reductive Heck, several reactions were conducted with delayed hydride introduction. After vinyl iodide **7** was converted to "normal" Heck product **15** ($Pd(OAc)_2$, base, and $^nBu_4NCl$ in DMF for 36 h), various hydride sources were introduced to the reactions. None of the hydride sources examined (formate salts, hydrogen, 1,3-cyclohexadiene, and triethylsilane) effected the formation of **8** from compound **15**. Consequently, the formation of desired product **8** through the conjugate reduction of enone **15** with a hydridopalladium species seems unlikely.

With the hydroazulene compound **8** in hand, the isopropyl group installation was carried out to construct the guaiane sesquiterpene. Ketone **8** was subjected to soft enolization conditions in the presence of acetaldehyde to form the enone **17** in 63% yield.[26] Under these reaction conditions, the *trans*-fused ring system epimerized to the thermodynamically more stable *cis*-fused ring system. Since we anticipated lower diastereoselectivity of the bis-epoxidation when employing the *trans*-hydroazulene

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(18) The relative energies of **8** and ***cis*-8** (structure not shown) were calculated at the B3LYP level of theory using Spartan '08.
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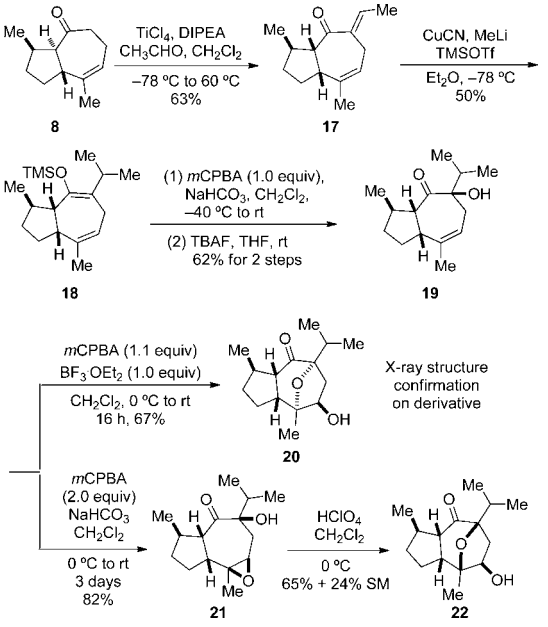
system, the newly formed *cis*-hydroazulene of **17** provided an ideal framework to study furan formation. Treatment of newly formed enone **17** with Lipshutz cuprate formed diene **18** after quenching with TMSOTf.[27]

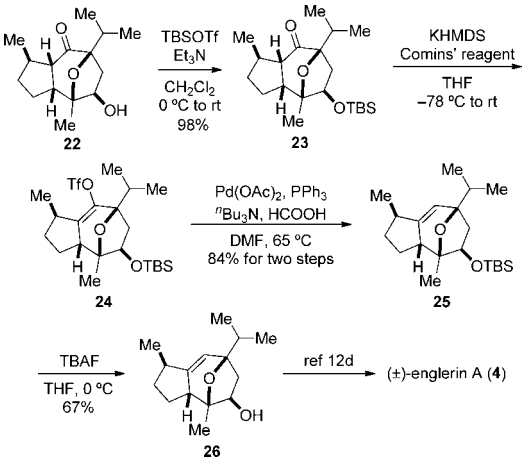
The double epoxidation of diene **18** to make a bis-epoxide analogous to **10** proved difficult under a variety of conditions. Reactions with *m*CPBA, DMDO, and TBHP, under $Ti(O^iPr)_4$ or $VO(acac)_2$ catalysis, produced incomplete reactions with numerous side products. To understand the problems associated with this transformation, a stepwise oxidation of each olefin was implemented. To this end, Rubottom oxidation[28] and TMS deprotection with TBAF produced α-hydroxylketone **19** as a single diastereomer in 62% yield.[29] The relative stereochemistry of **19** was confirmed by X-ray crystallography (Scheme 5).

Scheme 5. Guaiane Skeleton Construction and Epoxide-Opening Cascade Reaction



Subjecting α-hydroxylketone **19** to further epoxidation conditions in the presence of 1 equiv $BF_3 \cdot Et_2O$, from 0 °C to rt for 16 h, provided the substituted furanyl ring of the englerin skeleton (see **20**) in 67% yield. Surprisingly, X-ray crystallographic analysis revealed the incorrect configuration of the oxo-bridge relative to the natural product englerin A (**4**). A possible explanation for the formation of **20** is the apparent $BF_3 \cdot Et_2O$-catalyzed epimerization of the α-hydroxyl group through an as yet unknown mechanism during the slow epoxidation of the olefin in **19**. To circumvent this issue, the epoxide was installed without an acid present. With epoxide **21**, a series of Lewis and Brønsted acids were tested, and $HClO_4$ provided the best yield of the desired oxo-bridged englerin core **22** in 65% yield (86% yield BORSM) (Scheme 5).

Scheme 6. Formal Total Synthesis of Englerin A



The construction of the *trans*-fused ring of the englerins from **22** proved a challenge since both thermodynamic and kinetic epimerization conditions led to the *cis*-fused product. To complete the formal synthesis, ketone **23** was prepared in 85% yield using TBSOTf. Treatment of ketone **23** with KHMDS and Comins' reagent provided enol triflate **24**.[30] The crude enol triflate was subjected to palladium-catalyzed reduction to give olefin **25** in 84% yield over two steps.[31] Deprotection of the silyl group furnished reported alcohol **26** used in the total synthesis of englerin A (**4**) and englerin B (**5**) (Scheme 6).[12d]

In summary, the investigation of englerins' guaiane core led to the development of a unique variant of the reductive-Heck reaction. The ability to perform the reductive-Heck reaction in the presence of β-hydrogens provides a powerful method for the construction of hydroazulene ring systems. Furthermore, an investigation of a transannular bis-epoxide rearrangement provided a stereochemically versatile biomimetic approach to the oxo-bridge and englerin analogs. The application of palladium-mediated insertion chemistry to other biologically relevant structural motifs are currently underway.

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

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The authors declare no competing financial interest.