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A Brief Synthesis of (−)-Englerin A

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Supporting Information

ABSTRACT: Englerins A and B are guaiane sesquiterpenes that were isolated from the bark of *Phyllanthus engleri*, a plant indigenous to east Africa. The englerins consist of a 5-6-5 fused tricyclic structure with an ether bridge and two ester-bearing stereogenic centers, including a highly unusual glycolate residue. Englerin A is a potent and selective inhibitor of the growth of six human renal cancer cell lines. We report herein an efficient, eight-step synthesis of englerin A that leverages simple carbonyl-enabled carbon−carbon bond formations. Our route is amenable to the production of a diverse series of analogues for structure−function studies and determination of the mode of action of these natural products.

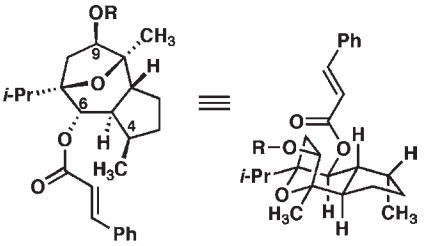
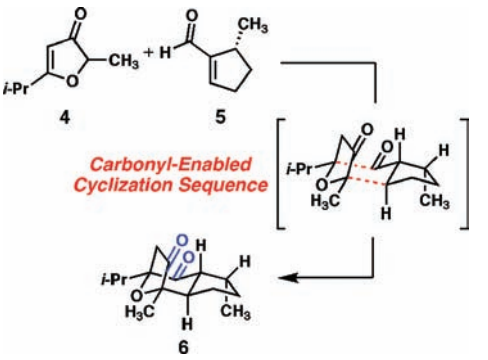


Figure 1. Structures of englerin A (**1**), englerin B (**2**), and englerin B acetate (**3**).

Scheme 1. A Carbonyl-Enabled Cyclization Sequence To Form the Core Structure of the Englerins



Renal cancer is a critical medical problem in the United States, affecting an estimated 58,240 new patients and causing 13,040 deaths in 2010 alone.[1] The primary treatment for renal cancer is surgery; however, for patients with nonresectable or metastatic tumors, chemotherapy is brought to bear. An estimated $1.9 billion is spent annually for renal cancer chemotherapy, and currently available treatments can have serious adverse side effects.[2] Effective new chemotherapeutic drug leads for the treatment of renal cancer are of great interest.

Englerin A is a guaiane sesquiterpene that was recently isolated from the bark of *Phyllanthus engleri*, a plant indigenous to east Africa (particularly Tanzania and Zimbabwe) and familiar to many traditional medicines (Figure 1).[3] In a screen against the NCI 60-cell panel, englerin A was found to be a potent and selective inhibitor of the growth of six renal cancer cell lines (GI_{50} = 1−87 nM), and in several cases, englerin A was an order of magnitude more potent than paclitaxel and 2−3-fold more potent than the current standards of care, sunitinib and sorafenib.[4] Englerin A showed 1000-fold selectivity for the renal cancer cell line panel (for most other cell lines, GI_{50} values ranged from 10−20 μM), and according to the NCI COMPARE analysis, englerin A appears to operate by a new and unknown mechanism of action. A preliminary mouse toxicity study determined that englerin A is extremely well tolerated, suggesting the possibility of a large therapeutic window. The outstanding biological activity and the unique, drug-like[5] architecture of englerin A have made it an attractive target for the synthetic organic chemistry community.[6]

The structure of englerin A consists of a 5-6-5 fused tricyclic system containing an ether bridge, and two ester-bearing stereogenic centers at C6 and C9. Several elegant solutions to the englerin A problem have been described, and these studies have established the absolute stereochemistry of the natural product and provided preliminary biological screening data.[6] In order to fully explore the therapeutic potential of englerin A, a short and flexible synthetic route is desirable. We describe herein a simple, eight-step, modular synthesis of englerin A that is amenable to the production of a diverse array of analogues for structure−function studies[7] as well as the incorporation of fluorescent and affinity probes for target identification studies.

Our synthetic strategy was enabled by considering the C6 and C9 acyl-bearing stereogenic centers of the englerins at the carbonyl oxidation level, as depicted in Scheme 1. In this intermediate the carbonyls are placed in a 1,4-relationship in one direction and a 1,5-relationship in the other, which suggests

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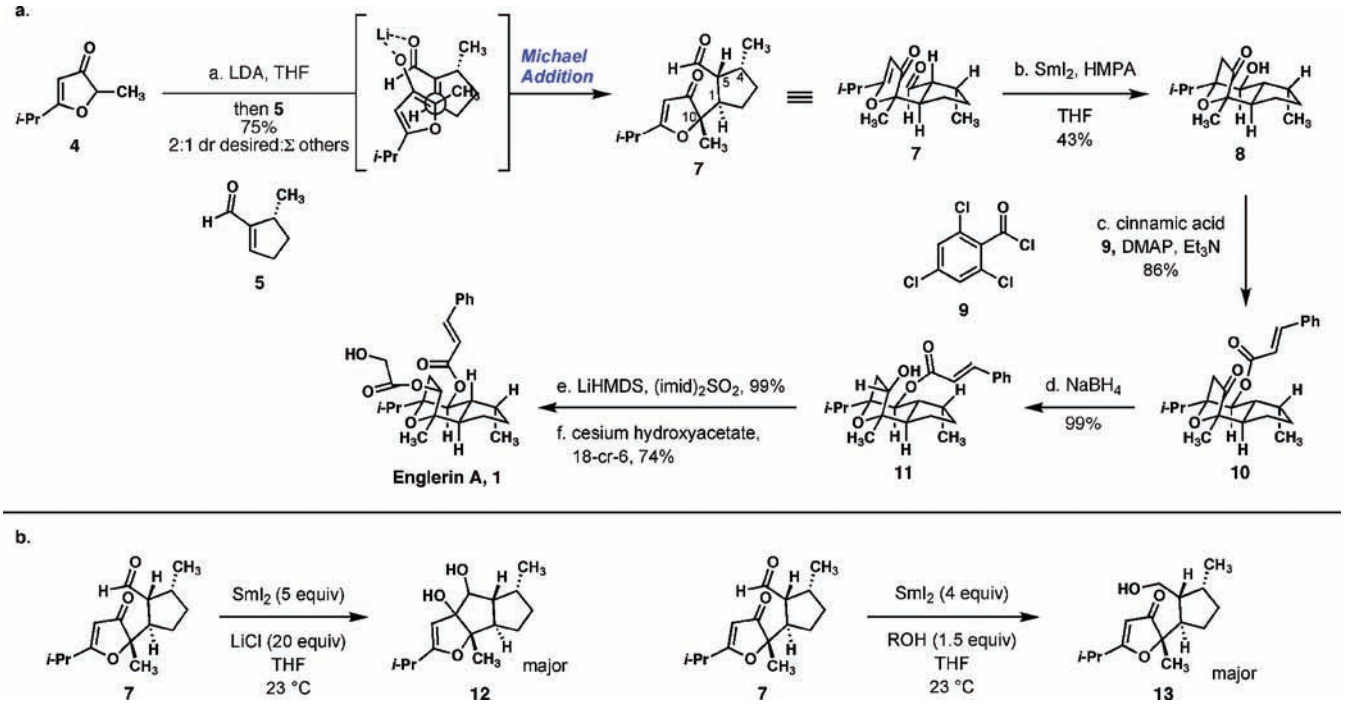
Scheme 2. (a) Synthesis of Englerin A[a] and (b) Samarium-Mediated Reductive Reaction Pathways with Aldehyde 7



[a] Conditions: (a) LDA, THF, −78 °C, then **5**, −78 → 23 °C, 75%, 2:1 dr desired:Σothers. (b) SmI_2, HMPA, THF, 23 °C, 43%. (c) Cinnamic acid, 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, toluene, 23 °C, 86%. (d) $NaBH_4$, CH_3OH, 0 °C, 99%. (e) LiHMDS, $(imid)_2SO_2$, THF, −10 → 23 °C, 99%. (f) Cesium hydroxyacetate, 18-crown-6, toluene, 110 °C, 74%.

that the core structure of the englerins could be established using simple carbonyl-enabled bond formations that combine a 3-furanone and an α,β-unsaturated aldehyde. However, several challenges associated with this synthetic strategy are readily apparent. First, it was unclear at the outset of our studies how we might control the stereochemical outcome of a Michael addition of a 3-furanone-derived enolate to an α,β-unsaturated aldehyde. Although stereochemical models for similar additions have been advanced by Seebach[8] and Heathcock,[9] the additional functionality of our putative enolate substrate complicated the analysis.[10] Second, both the steric and electronic properties of the 3-furanone may render an intramolecular cyclization reaction quite slow. Finally, we were mindful that a successful synthesis of the diketone **6** would necessitate the differentiation of homologous functionality; we would be faced with the task of selectively manipulating ketones in five- and six-membered rings.

Our synthesis commenced with the union of the 3-furanone **4**[11] and 5-methylcyclopentenecarboxaldehyde (**5**)[12] by treatment of **4** with lithium *N*,*N*-diisopropylamide in THF and exposure of the resultant lithium enolate to **5** at low temperature (Scheme 2a). Under these conditions, we observed clean, diastereoselective formation of the Michael adduct **7**. A transition-state assembly that is consistent with the observed stereoselectivity is shown in Scheme 2a. Here, the C4 methyl-bearing stereogenic center serves as a key controlling element; one of eight possible diastereomers is formed preferentially in good yield (75% combined yield, 2:1 dr desired:Σothers), establishing the relative stereochemistry at C1, C4, C5, and C10 of the natural product in a single operation. The isomers are inseparable by flash column chromatography; however, the relative stereochemistry of C1, C4, and C5 of the major isomer was determined by NOE studies. Clear correlations were observed between the protons at C4 and C5, and between the aldehyde proton and the proton at C1. The C10 stereochemistry of the major diastereomer was unknown at this juncture but was inferred to be that shown in Scheme 2a on the basis of the successful elaboration of this material to the natural product. Consistent with this model, we found the stereochemical outcome of the Michael addition to be markedly sensitive to additives that might diminish or otherwise disrupt the chelation between the enolate and the aldehyde. Addition of either lithium chloride or hexamethylphosphoramide (HMPA) to an otherwise identically conducted Michael addition reaction results in formation of the adduct **7**, favoring the opposite stereochemistry at C10.

With one of the two key carbon−carbon bonds formed, we set about completing the core of the natural product. We were aware of several examples of umpolung[13] reactivity observed between aliphatic aldehydes and vinylogous esters, so we approached our problem with a high degree of confidence.[14] We reasoned that a carbon-centered radical would engage the furanone productively, and moreover, if we could generate that radical directly from the aldehyde function of the Michael adduct **7**, we may obviate the issue of differentiating two ketones in a cyclized product like **6**. After much experimentation, we found that the action of samarium(II) iodide[15] in the presence of HMPA in THF at ambient temperature smoothly transformed the Michael adduct into the ketoalcohol **8** (43% yield, Scheme 2a) in a reductive carbonyl−alkene cyclization. The modest isolated yield of **8** is acceptable given that this remarkable transformation forges the second critical carbon−carbon bond to complete the core structure of the englerins, establishes the correct oxidation level and stereochemistry at C6, and achieves all this using a diastereomeric mixture of starting aldehydes (∼66% maximum theoretical yield of **8**). Other one-electron reducing agents such as

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titanium(III),[16] vanadium(II),[17] and lithium naphthalenide[18] did not offer any advantage over samarium(II) in reactions with the aldehyde **7**. The HMPA additive proved critical as well; other additives commonly employed with samarium(II)-mediated reductive cyclizations gave markedly different results (Scheme 2b). For example, addition of lithium chloride resulted in pinacol-type carbonyl coupling to give **12**, and various proton sources (e.g., methanol, *tert*-butanol, or hexafluoroisopropanol) resulted in reduction of the aldehyde to the corresponding primary alcohol **13**, though analytically pure samples of **12** and **13** were not rigorously isolated. We were also unable to locate a suitable catalyst to effect an intramolecular Stetter[19] reaction to convert the aldehyde **7** to the diketone **6**. Under a variety of conditions, we observed none of the desired product and recovered only unchanged starting material.

The ketoalcohol **8** is a known compound from a prior synthesis of englerin A.[20] We were therefore able to infer the C10 stereochemistry of the major isomer of the Michael adduct **7** by comparison with reported spectral data, and completion of the synthesis of the natural product by the literature procedure was straightforward. Installation of the cinnamyl ester function at C6 was executed under Yamaguchi conditions[21] to give the unsaturated ester **10** in 86% yield. Reduction of the C9 ketone to the corresponding alcohol **11** with sodium borohydride in methanol was accomplished in 99% yield. Installation of the glycolate residue proceeded in two steps: transformation of the alcohol **11** to the corresponding sulfonate imidazole (not shown) in 99% yield, and nucleophilic displacement with cesium hydroxyacetate in 18-crown-6 and hot toluene to give englerin A (**1**) in 74% yield. We have found the C9 glycolate function to be quite labile and observed some hydrolysis if the purification of englerin A (**1**) was not carried out expeditiously. We have found englerin A to be sensitive to mildly acidic[22] or basic conditions,[23] but in any case, exposure of englerin A (**1**) to methanolic potassium carbonate cleanly hydrolyzes the C9 glycolate residue to give englerin B (**2**) in 89% yield (see Supporting Information for details).

In summary, we have completed an eight-step, enantioselective synthesis of englerin A in 20% overall yield utilizing the readily available 3-furanone **4** and 5-methylcyclopentenecarboxaldehyde **5** and simple carbonyl-enabled bond formations. This short, convergent synthesis enables the synthesis of a diverse array of analogues for use in structure−function studies and a host of materials incorporating affinity probes for use in target identification experiments. These studies are currently underway in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Complete ref 2, detailed experimental procedures, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) For example, in an NMR experiment the C9 glycolate residue of englerin A (**1**) was cleanly hydrolyzed to give englerin B (**2**) upon warming in CD_3OD that contained only a trace amount of formic acid ($t_{1/2} \approx 0.5$ h).
(23) The selective hydrolysis of the C9 acetate of englerin B acetate (**3**) to give englerin B (**2**) under basic conditions has been described. See ref 6d.