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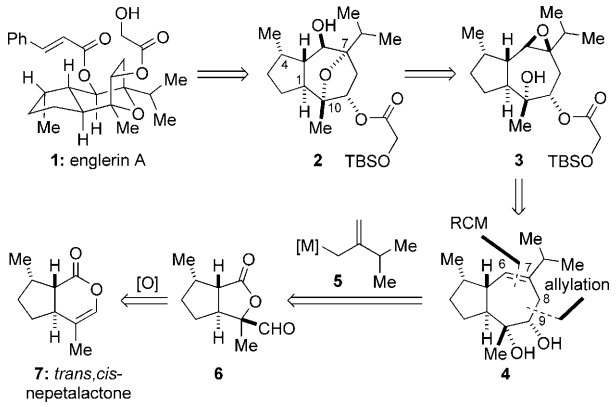
Total Synthesis and Absolute Configuration of the Guaiane Sesquiterpene Englerin A**

*Matthieu Willot, Lea Radtke, Daniel Könning, Roland Fröhlich, Viktoria H. Gessner, Carsten Strohmann, and Mathias Christmann**

Plants are a valuable source of new bioactive molecules.[1] In an NCI 60-cell panel screening, extracts from *Phyllanthus engleri*, belonging to the genus Euphorbiaceae (spurge family), stood out because of their high selectivity and activity against renal cancer cells. By using bioassay-guided fractionation, Beutler and co-workers isolated the active component and elucidated its structure except for the absolute configuration.[2] The guaiane sesquiterpene englerin A (**1**) selectively inhibits the growth of renal cancer cell lines with GI_{50} values ranging from 1–87 nM (Scheme 1). This promising biological activity coupled with the appealing molecular architecture led us to pursue a synthetic approach toward englerin A with the goal of investigating the structural space beyond natural product derivatives.[3] Retrosynthetic removal of the cinnamate side chain in **1** leads to the protected glycolate ester **2**, which may be obtained—possibly in a biomimetic fashion—by a transannular epoxide-opening. Epoxide precursor **3** is accessible from the alkene **4** through a sequence involving a kinetically controlled acylation and a subsequent diastereoselective oxidation. At this juncture, it seemed appropriate to ponder on a suitable starting material. In our understanding of synthetic efficiency, the minimization of C–C bond-forming reactions through the identification of large and readily accessible fragments[4] of the carbon framework is the key objective in synthesis planning.[5] By using computer-guided substructure searches, it is relatively easy to identify molecules that partially overlap with the target structure, differing only in the oxidation state or the degree of unsaturation. As a result of rapid progress in oxidative C–H functionalizations,[6,7] terpenes from plant oil[8] will gain importance as sustainable feedstock in synthesis.



Scheme 1. Retrosynthetic analysis of englerin A (**1**). RCM = ring-closing metathesis, TBS = *tert*-butyldimethylsilyl.

Guided by such consideration, we selected the monoterpene *trans*,*cis*-nepetalactone (**7**)[9,10] as a suitable starting material for our synthesis. In addition to providing the correctly configured trisubstituted cyclopentane, its alkene moiety appears susceptible to an oxidative rearrangement to give aldehyde **6**. Consequently, C6–C7 and C8–C9 of **4** were identified as strategic bonds, which in the synthetic direction may be formed by an addition of the allylmetal compound **5** to the aldehyde **6** and a subsequent ring closing metathesis.[11]

Depending on the catmint (*Nepeta*) species, the active ingredient nepetalactone exists as a mixture of varying amounts of four diastereomers, which can all be obtained in pure form.[12] The oxidation of *trans*,*cis*-nepetalactone (**7**) with *m*CPBA (Scheme 2) afforded **8b** with the undesired configuration at C10 as the major isomer (d.r. 7:1). Fortunately, the epoxidation of *cis*,*trans*-nepetalactone (**9**)[13] installed the correct configuration at C10 for the major isomer **10a** (d.r. 1.5:1).[14] Despite the necessity of a late-stage epimerization at C5, we selected this material for use in the course of our synthesis.

Treatment of **10a** with NaOMe led to a rapid ring contraction of the epoxylactone moiety into the formyl lactone **11** (Scheme 3). Interestingly, the initially envisaged rearrangement of **8a** into the aldehyde **6** did not take place, possibly resulting from the strain of the *trans*-bicyclo-[3.3.0]octane scaffold.[15] For the very same reason, an epimerization from the *cis*-annulated form is energetically disfavored. Under acidic reaction conditions, the epoxide **10a** was opened with MeOH (in analogy to the Danishefsky

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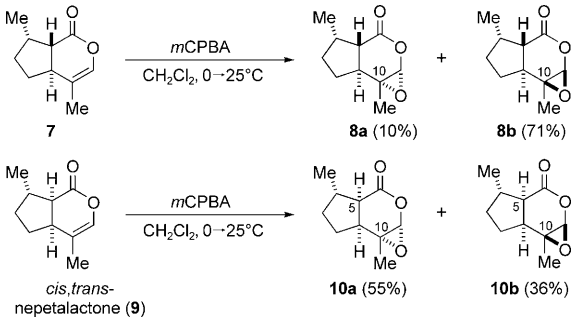
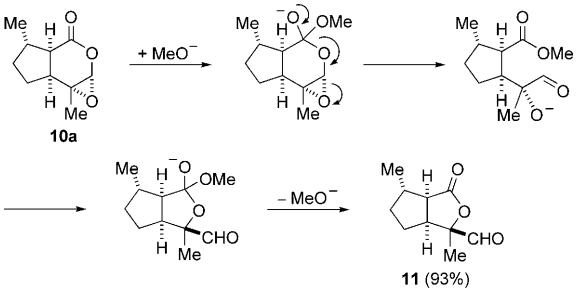
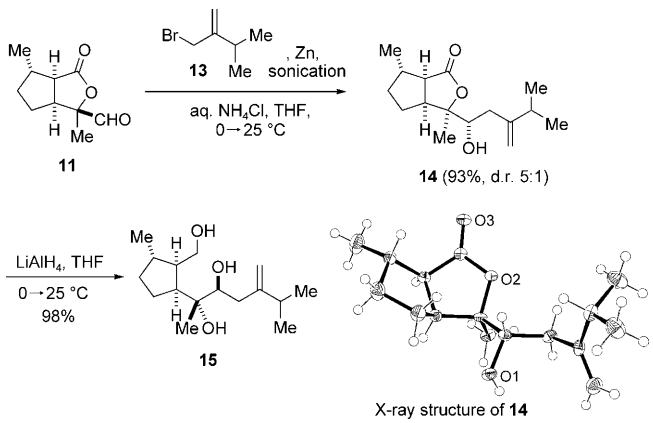


Scheme 2. Oxidation of nepetalactones **7** and **9**. *m*CPBA = *meta*-chloroperbenzoic acid.



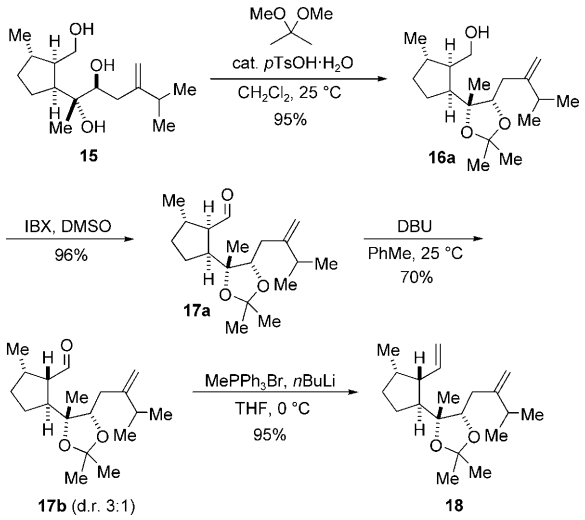
Scheme 3. Tentative mechanism for the ring contraction.



Scheme 4. Attachment of the side-chain. THF = tetrahydrofuran.

glycosidation)[16] with inversion of configuration at the anomeric center (**10a**→**12**).[17]

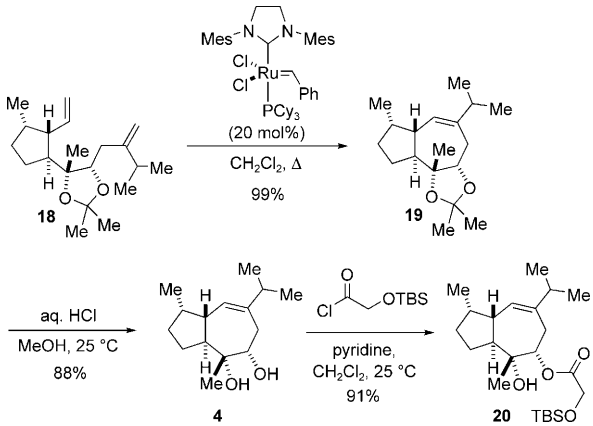
After the starting material had been set up, in just two steps, for the crucial coupling reaction, an allylation was envisaged to install the remaining carbon framework. The Grignard reagent of allyl bromide **13**[18] is relatively unstable and prone to homocoupling (Wurtz reaction). The analogous Barbier reaction[19] with aldehyde **11** proceeded smoothly to give homoallylic alcohol **14** in 93% yield (d.r. 5:1). We assume that this selectivity results from a minimization of dipole–dipole interactions in the aldehyde's reactive conformation. The relative as well as the absolute configuration of **14** was confirmed by X-ray crystallography (Scheme 4). The reduction[20] with $LiAlH_4$ furnished the crystalline triol **15**.



Scheme 5. Epimerization at C5. *p*TsOH = *para*-toluenesulfonic acid, IBX = 2-iodoxybenzoic acid, DMSO = dimethylsulfoxide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, *n*BuLi = *n*-butyllithium.

Acetalization of the vicinal hydroxy groups (**15**→**16a**) was then followed by an IBX oxidation of the primary alcohol to give aldehyde **17a** (Scheme 5). In contrast to the bicyclic form, the C5 epimer was now accessible by epimerization with DBU, giving the diastereomer **17b** in 70% yield in a ratio of 3:1. Compound **17b** was then converted into diene **18** using a Wittig olefination.

Diene **18** was subjected to the conditions of olefin metathesis[21] (Scheme 6) using the Grubbs II catalyst[22] (20 mol%), giving the desired guaiane **19**, which had the

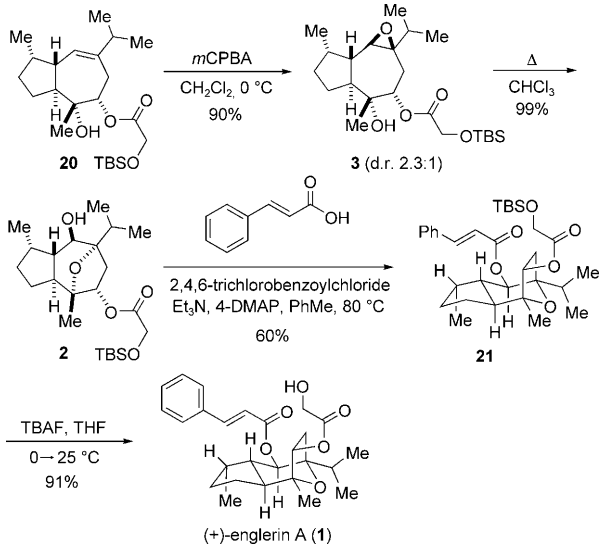


Scheme 6. Ring-closing metathesis and formation of the glycolate ester **20**. Mes = mesityl, Cy = cyclohexyl, TBS = *tert*-butyldimethylsilyl.

formally *E*-configured trisubstituted double bond.[23] After transacetalization of the acetonide (**19**→**4**) using methanol, the secondary hydroxy group was acylated with (*tert*-butyldimethylsilyloxy)acetyl chloride.[24]

The subsequent epoxidation using *m*CPBA afforded the desired epoxide **3** with a moderate selectivity of 2.3:1. We observed that an NMR sample of **3** in $CDCl_3$ was smoothly

converted into **2** by a transannular epoxide opening.[25] This process could be accelerated by heat, resulting in quantitative conversion. The secondary alcohol **2** was converted into the cinnamate ester **21** using a Yamaguchi esterification.[26] Finally, the TBS ether was removed using TBAF in THF to give englerin A (**1**) in 91% yield (Scheme 7). The spectro-



Scheme 7. Completion of the total synthesis. 4-DMAP = 4-dimethylaminopyridine, TBAF = tetra-*n*-butylammonium fluoride.

scopic data (^{1}H NMR, ^{13}C NMR, UV) exactly matched with those reported.[2a] However, the optical rotation $\{[\alpha]_D^{20} = +51$ ($c = 0.58$, MeOH)$\}$ of the synthetic material was opposite to that found for the natural product $\{[\alpha]_D^{20} = -63$ ($c = 0.13$, MeOH)$\}$, thereby establishing the previously unknown absolute configuration of natural (−)-englerin A.

We have completed the first total synthesis of (+)-englerin A and determined its absolute configuration. The key steps involve an epoxylactone rearrangement, a diastereoselective Barbier reaction, and a ring-closing metathesis. The ease of the transannular epoxide opening supports our working hypothesis of a biomimetic process. The synthesis of (−)-englerin A and the biological evaluation of both enantiomers will be subject of future reports from this laboratory.

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Keywords: antitumor agents · natural products · rearrangements · terpenes · total synthesis

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[14] CCDC 749796 (**8a**), 749797 (**8b**), 749798 (**10b**), 750007 (**12**), and 749799 and 750121 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for additional details on the X-ray crystallographic analyses.
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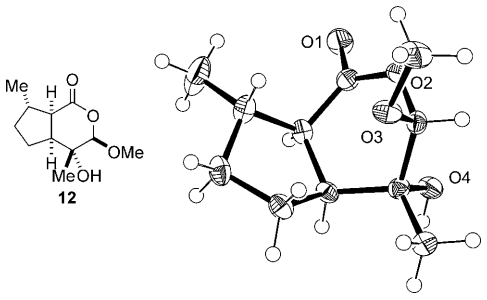

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