Terpenes

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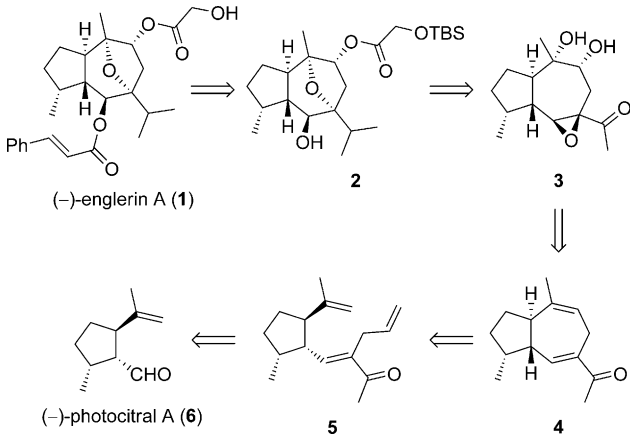
A Short Enantioselective Total Synthesis of (−)-Englerin A**

*Martin Zahel, Anton Keßberg, and Peter Metz**

Dedicated to Professor Hans J. Schäfer

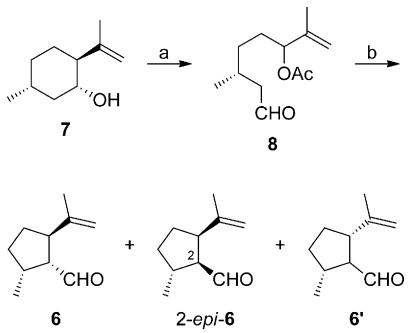
The guaiane sesquiterpene (−)-englerin A (**1**) has attracted much attention from chemists, biologists, and physicians since its isolation from the East African plant *Phyllanthus engleri* by Beutler in 2009.[1] This is due to the highly selective action of this natural product against renal cancer cell lines.[1,2] Furthermore, the oxygen-bridged bicyclic hydroazulene framework is a challenging molecular structure with seven contiguous stereogenic centers. These two features have triggered intense synthetic work aiming at the preparation of **1**[3,4] and on structure–activity relationship studies.[4f,5] Herein we report an enantioselective total synthesis of (−)-englerin A (**1**) that allows the construction of this bioactive compound in a few preparatively simple steps.

As outlined in Scheme 1, a first retrosynthetic cleavage of the cinnamate leads to the Christmann intermediate **2**.[4a] This compound should be available by chemoselective esterification and transannular epoxide opening from diol **3**, the acetyl unit of which we use to set up the isopropyl group. Diol **3** is traced back to dienone **4** with two electronically differentiated alkene moieties that should allow a chemo- and diastereoselective twofold oxidation. Construction of the hydroazulene framework of **4** was planned by means of a ring-closing metathesis,[4a,6] originally envisioning trienone **5** as the substrate, which in turn should be generated through a suitable carbonyl olefination of (−)-photocitral A (**6**).[7] This monoterpene is especially suitable for the given synthetic problem, as the three stereogenic centers present on the cyclopentane in (−)-**1** are already correctly configured, and its bifunctionality offers numerous options to anellate the missing seven-membered ring.



Scheme 1. Retrosynthetic tracing of (−)-englerin A (**1**) to (−)-photocitral A (**6**). TBS = *tert*-butyldimethylsilyl.

Aldehyde **6** can be generated as a racemic mixture in a single step photochemically from citral[8] and enantiomerically pure in three steps from (*R*)-citronellol.[9] We now found that **6** can be obtained from commercially available (−)-isopulegol (**7**) in just two steps (Scheme 2). After fragmentation of **7** with lead tetraacetate,[10] aldehyde **6** is directly formed by dual catalysis[11] with a palladium(0) catalyst and pyrrolidine together with 2-*epi*-**6** and a further diastereomer **6′**. The diastereomeric ratio can be increased in favor of **6** by basic epimerization of 2-*epi*-**6** at C2.[7,12]



Scheme 2. Enantioselective preparation of (−)-photocitral A (**6**) from (−)-isopulegol (**7**). a) $Pb(OAc)_4$, $CaCO_3$, benzene, reflux, 74%; b) 5 mol% $[Pd(PPh_3)_4]$, 40 mol% pyrrolidine, Et_3N, THF, −10°C, 89% (**6**/2-*epi*-**6**/**6′** = 47:43:10).

At first, we tried to convert aldehyde **6** by Wittig and Horner–Wadsworth–Emmons reactions.[13] However, C–C bond formation could not be observed even under harsh reaction conditions. Moreover, epimerization of **6** was noticed, which called for less-basic conditions that were found in the Reformatsky reaction[8a] with bromo ester **9**.[18] This transformation provided a good yield of the diastereomeric mixture **10** that could be readily used without separation, as the newly introduced stereogenic centers are soon after transformed into sp^2-hybridized centers (Scheme 3). The following ring-closing metathesis using the Grubbs II catalyst

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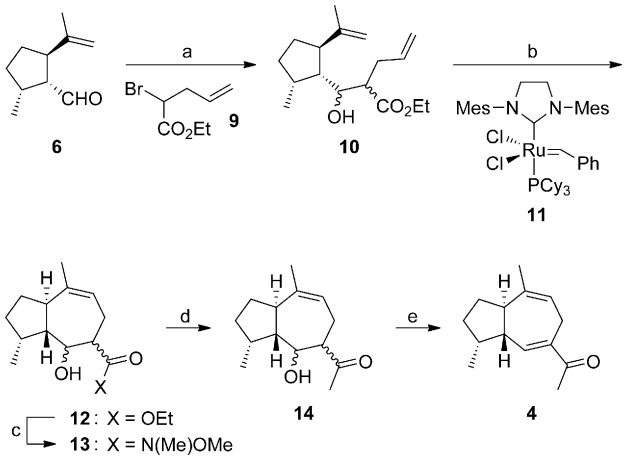
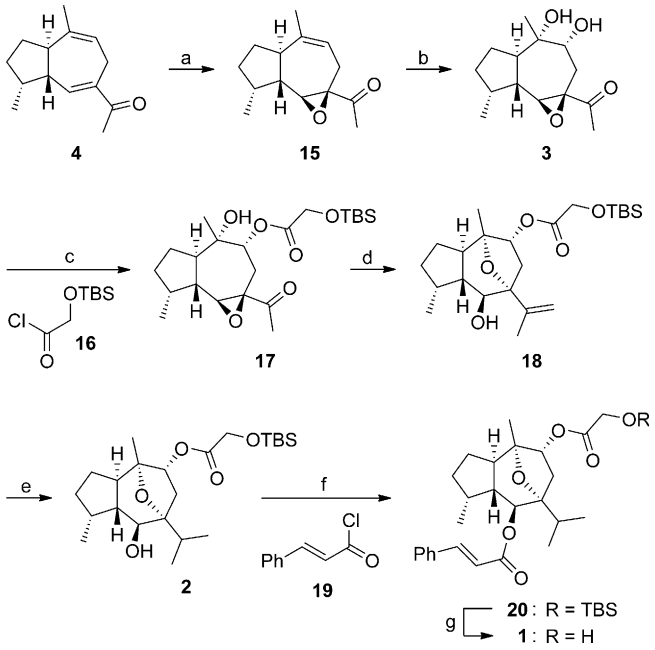


Scheme 3. Construction of the hydroazulene framework. a) **9**, Zn, benzene, reflux, 86%; b) 1 mol% **11**, CH_2Cl_2, reflux, 99%; c) MeONH-Me·HCl, *i*PrMgCl, THF, −30 °C→reflux; d) MeLi, THF, −78 °C→RT, 73% (2 steps); e) 1. MsCl, Et_3N, CH_2Cl_2, 0 °C, 2. DBU, RT, 85% (94% based on recovered **14**). Ms = methanesulfonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.



Scheme 4. Completion of the synthesis. a) NaOH, H_2O_2, MeOH, RT, 91%; b) 1 mol% K_2OsO_4, NMO, acetone, water, THF, RT, 97%, d.r. = 2:1; c) **16**, pyridine, RT, 93%; d) $Ph_3P{=}CH_2$, THF, RT, then 2 N HCl, 70%; e) 1 atm H_2, 10% Pd/C(en), EtOH, RT, 90%; f) **19**, DMAP, Et_3N, CH_2Cl_2, reflux, 94%; g) 2 N HCl, THF, RT, 100%. NMO = *N*-methylmorpholin-*N*-oxide, en = ethylenediamine, DMAP = 4-(dimethylamino)pyridine.

11[19] succeeded in quantitative yield. At this point, it was necessary to exchange the ethyl ester group against an acetyl function on the one hand and to eliminate with formation of the α,β-unsaturated carbonyl unit on the other. These transformations could be realized by first converting the hydroazulene **12** into the acetyl derivative **14** via the Weinreb amide **13**.[20] The elimination was then achieved through mesylation of the hydroxy function and subsequent treatment with DBU in a one-pot reaction[21] with good yield and high regioselectivity (α,β/β,γ = 10:1).

After conversion of the diastereomeric mixture used so far into a single α,β-unsaturated ketone, the resulting diene **4** underwent a completely chemo- and diastereoselective nucleophilic epoxidation at the more electron-deficient double bond under Weitz–Scheffer conditions[22] to give **15**, the relative configuration of which was confirmed by X-ray diffraction analysis (Scheme 4).[23] We now treated **15** with osmium tetroxide/NMO to obtain the *cis*-diol **3**. Despite a moderate diastereoselectivity (**3**/β-diol **3′** = 2:1), this reaction was achieved with good efficiency owing to the almost quantitative overall yield. Attempts at a reagent-induced diastereoselective dihydroxylation[24] met with failure. Esterification of the secondary hydroxy group with (*tert*-butyldimethylsilyloxy)acetyl chloride (**16**)[25] in pyridine led smoothly to the protected glycolic acid derivative **17** that could be methylenated at the acetyl unit afterwards. As the epoxide function was now of allylic nature, the biomimetic transannular epoxide-opening[4a,26] proceeded quickly already after slight acidification at room temperature to afford the oxygen-bridged hydroazulene **18**. A partial loss of the TBS protecting group was observed in some experiments on the hydrogenation of **18** with Pd/C. Therefore we hydrogenated **18** with a Pd/C-ethylenediamine complex[27] to give **2**. After DMAP-mediated esterification of the remaining hydroxy function with cinnamoyl chloride (**19**) to provide **20**,[4a] the final acidic cleavage of the TBS group at the glycolic acid moiety yielded the target molecule **1** quantitatively.

In summary, we have accomplished an enantioselective total synthesis of (−)-englerin A (**1**) using selective oxidations of dienone **4** and a ring-closing metathesis to give the hydroazulene framework as key operations. The strategy presented herein allows the preparation of the bioactive compound **1** in only 12 steps with an overall yield of 16% starting from (−)-photocitral A (**6**).

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[12] See the Supporting Information for details.

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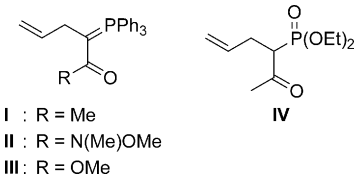

I : R = Me
II : R = N(Me)OMe
III : R = OMe

IV

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Communications

Terpenes

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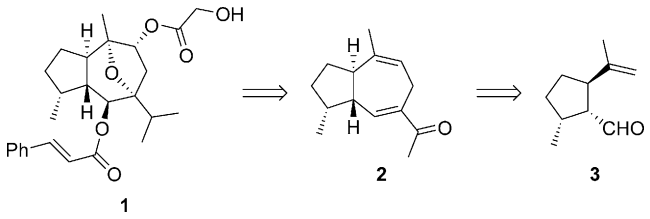
A Short Enantioselective Total Synthesis of (−)-Englerin A



Selective oxidations of dienone **2** as well as a ring-closing metathesis to give the hydroazulene framework enabled the 12-step preparation of title compound **1** from (−)-photocitral A (**3**), which is in turn rapidly available from (−)-isopulegol through dual catalysis.