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Natural Product Synthesis (1)

Asymmetric, Protecting-Group-Free Total Synthesis of (−)-Englerin A**

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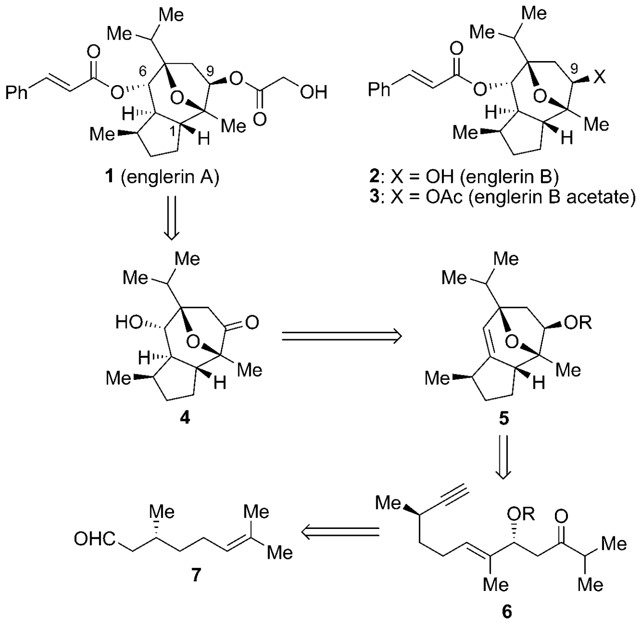
(−)-Englerin A (**1**, Scheme 1) is a guaiane sesquiterpene that was recently isolated by Beutler and co-workers from *Phyllanthus engleri*.[1] This species was collected from a plant growing in East Africa. Biological evaluation revealed that englerin A has potent ability to inhibit renal cancer cell growth with GI_{50} values (growth inhibition of 50%) ranging from 1–87 nM. When being tested on other cancer cell lines, this compound showed only moderate inhibition activity (GI_{50} values ranging from 10–20 μM), thus indicating that englerin A has excellent selectivity for inhibiting the proliferation of renal cancer cell lines. Interestingly, the activity and excellent selectivity displayed by englerin A is highly dependent on its substitution at the C9 position, as evident from the fact that englerin B (**2**), which was isolated from the same species, showed only moderate potency against the growth of renal cancer cell lines. Structure-activity relationship investigations of englerin A would be helpful for explaining this difference, and then also helpful in identifying analogues for further development as drug targets. These studies are of vital importance because kidney cancer is a major cause of morbidity and mortality in adults,[1] and until now no satisfactory drugs are available for its treatment. Given this background, it is not surprising that synthetic interest in this target has been considerable. Quite recently, Christmann and co-workers achieved the first total synthesis of (+)-englerin A by using monoterpene *trans,cis*-nepetalactone as a starting material, and subsequently found that this product is the enantiomer of natural englerin A.[2] This report prompted us to disclose our synthetic studies towards (−)-englerin A.



Scheme 1. Structures of englerins A and B and their retrosynthetic analysis.

As outlined in Scheme 1, we envisaged that the target molecule **1** could be assembled from ketone **4** through introduction of the two ester groups at a late stage. Ketone **4** could be obtained from oxotricyclic compound **5** through functional-group manipulations. For the formation of **5**, a recently developed gold-catalyzed cyclization of functionalized enynes seemed to be an attractive approach,[3] which in turn led us to choosing the 1,6-enynes **6** as the required intermediate. However, transformation from **6** into **5** would be challenging task; this is because both functional group tolerance and stereochemical induction have not been fully explored in gold- and platinum-catalyzed cyclization reactions of enynes.[4] Based on the mechanism proposed by Echavarren and co-workers,[3a] we believed that the 5*R*,10*R* configuration for these enynes is necessary to deliver the cyclization products with the desired stereochemistry (see discussion in Scheme 3). The 1,6-enynes **6** could be prepared using inexpensive and commercially available (*R*)-citronellal **7** as a chiral building block.

As depicted in Scheme 2, our synthesis started with the bromination of (*R*)-citronellal **7** using triphenylphosphite and bromine.[5] After the *gem*-dibromide **8** was obtained, elimination with *t*BuOK in the presence of [18]crown-6 was carried out and afforded a terminal alkyne,[6] which was subjected to oxidation[7] mediated by TBHP/SeO_2 and produced allylic alcohol **9a** and α,β-unsaturated aldehyde **9b**. As **9a** could be oxidized into **9b** with IBX in almost quantitative yield,[8] we were able to obtain the desired **9b** from **8** in 71% overall yield. Boron-mediated enantioselective aldol reaction of **9b** with the enolate derived from 3-methyl-2-butanone provided **6a**, and its epimer at C5, in 95% yield and a diastereomeric ratio of about 4:1.[9] Because it is known that alcohols can serve as nucleophiles and react with the *anti*-cyclopropyl

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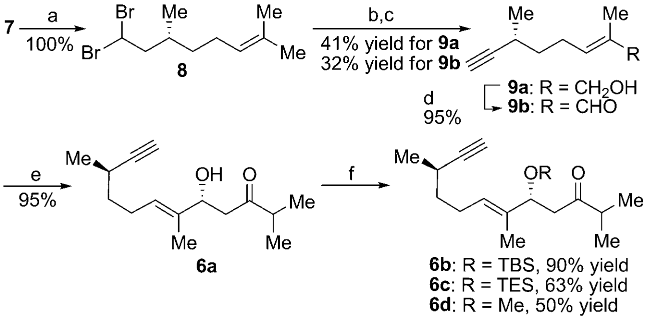
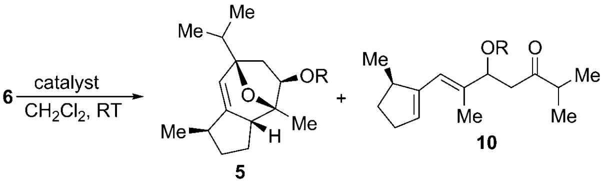


Scheme 2. Reagents and conditions: a) $P(OPh)_3$, Br_2, Et_3N, −78°C→RT; b) *t*BuOK, [18]crown-6, petroleum ether, reflux, 12 h; c) SeO_2, TBHP, salicylic acid, CH_2Cl_2, RT; d) IBX, ethyl acetate, reflux; e) 1. 3-methyl-2-butanone, (−)-Ipc_2BCl, Et_3N, 0°C, 2. **9b**, −78°C, 3. MeOH, pH 7 buffer, H_2O_2; f) for **6b**: TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C; for **6c**: TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C; for **6d**: $TMSCHN_2$, HBF_4, CH_2Cl_2, 0°C. IBX = 2-iodoxybenzoic acid, Ipc = isopinocampheyl, TBHP = *tert*-butyl hydroperoxide, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TMS = trimethylsilyl.

gold--carbene intermediates generated in gold-catalyzed cyclization of enynes,[3,4] we decided to protect the hydroxyl group of **6a** before carrying out the cyclization reaction. Accordingly, ether formation of **6a** with suitable protecting reagents provided **6b**–**6d** with satisfactory yields.

With enynes **6** in hand, the crucial gold-catalyzed cyclization[3] could be investigated. The results are summarized in Table 1. It was found that the reaction of the TBS ether **6b** with AuCl in methylene chloride proceeded well, but delivering the undesired product **10b** (the configuration of the ether part is not clear because we use a diastereomeric mixture as the substrate) in 80% yield (entry 1). Changing the catalyst to $[Au(PPh_3)Cl]/AgSbF_6$ or using the less sterically hindered substrate **6c**, respectively, gave similar results (entries 2 and 3). If methyl ether **6d** was used, a complex mixture could be observed in the case of AuCl (entry 4), while exclusive formation of the monocyclic product **10d** could also be obtained, if $[Au(PPh_3)Cl]/AgSbF_6$ was applied (entry 5). Therefore, we were pleased to observe that cyclization of alcohol **6a** catalyzed by AuCl produced the desired oxotricyclic product **5a** in 48% yield (entry 6), together with some unidentified side products. Further attempt to improve the yield by switching catalyst to $[Au(PPh_3)Cl]/AgSbF_6$ gave an unsatisfactory result (entry 7).

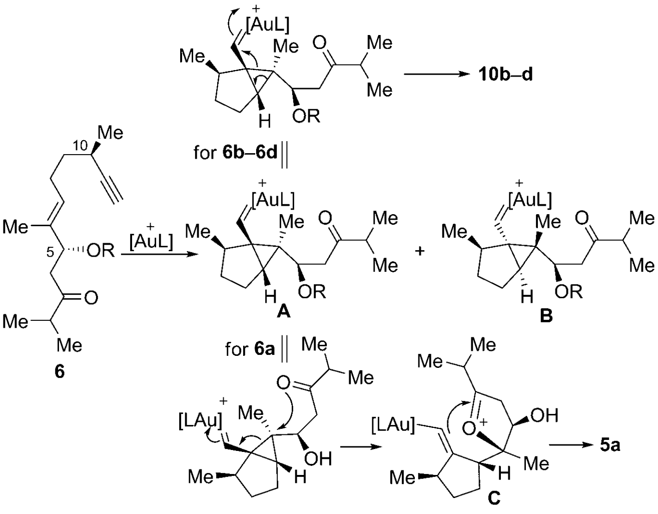
Table 1: Gold-catalyzed cyclization of enynes **6**.[a]



Entry	R	Catalyst	*t* [min]	Product (yield [%][b])
1	TBS	**A**	30	**10b** (80)
2	TBS	**B**	30[c]	**10b** (40)
3	TES	**A**	20	**10c** (90)
4	Me	**A**	30	–[d]
5	Me	**B**	30[e]	**10d** (10)
6	H	**A**	20	**5a** (48)
7	H	**B**	20[c]	**5a** (20)

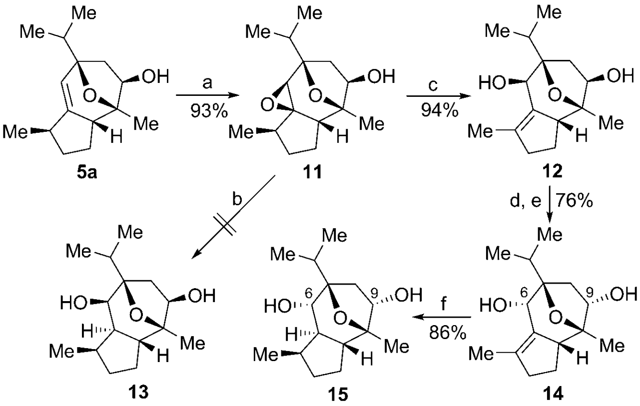
[a] Reaction conditions: enyne (0.1–0.5 mmol), catalyst (10 mol%), CH_2Cl_2, RT; catalyst **A**: AuCl, **B**: $[Au(PPh_3)Cl]/AgSbF_6$, [b] Yield of isolated product, [c] 50% conversion was observed. [d] a complex mixture was obtained. [e] 20% conversion was observed.

The formation of **5a** as a single diastereomer demonstrated that the cyclization reaction catalyzed by AuCl proceeded in a highly stereoselective manner. The relative configuration of the newly formed sterocenters was confirmed by X-ray analysis of a carbonate derivative of its enantiomer.[10] Based on the established 5-*exo*-dig cyclization mechanism,[3,4] we assume that the asymmetric induction results from the chiral center at C10 of **6**. As shown in Scheme 3, after the enynes **6** reacted with Au catalyst, the two *anti*-cyclopropyl gold carbenes **A** and **B** can form. The intermediate **A** should be the more stable one because the methyl group in the cyclopentane ring is *trans* to the sterically ambiguous fused cyclopropyl group, thereby providing isomer **5a** as a major product when R = H. The exclusive formation of monocyclic products from ether substrates **6b**–**6d** could be rationalized by the steric hindrance of their protecting groups, which might prevent the attack of the carbonyl group at the cyclopropanyl ring as indicated for the formation of intermediate **C**. As a result, single cleavage of the intermediate **A** took place to afford **10b**–**d**.[4]



Scheme 3. Possible reaction pathways for the formation of **5** and **10**.

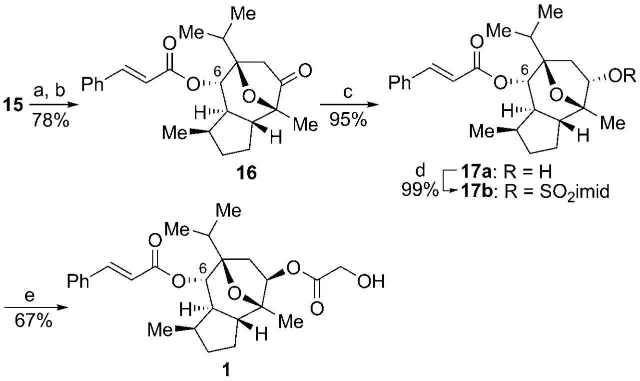
The construction of the *trans*-fused ring of englerin A from **5a** presented formidable challenges. We could eventually solve this problem by using a reaction sequence as outlined in Scheme 4. Epoxidation of **5a** with *m*CPBA provided **11** in 93% yield. Initially, we planned to employ a free-radical-mediated reduction strategy to transfer **11** to the desired alcohol **13**.[11] However, when epoxide **11** was treated with $[Cp_2TiCl_2]/Zn$,[11b] only isomerization product **12** was isolated in about 40% yield. At this stage we decided to proceed with **12**, because we realized that a reaction catalyzed



Scheme 4. Reagents and conditions: a) *m*CPBA, CH_2Cl_2, 0 °C; b) [Cp_2TiCl_2], Zn, 1,4-cyclohexadiene, THF, RT; c) CSA, $CHCl_3$, 0 °C; d) TPAP, NMO, CH_2Cl_2/MeCN (10:1), RT; e) $NaBH_4$, MeOH, 0 °C; f) Raney Ni, H_2 (90 atm), EtOH, 75 °C, 8 h. CSA = camphorsulfonic acid, *m*CPBA = *m*-chloroperoxybenzoic acid, NMO = *N*-methylmorpholine-*N*-oxide, THF = tetrahydrofuran, TPAP = tetra-*n*-propylammonium perruthenate.

by CSA could also provide **12** in excellent yield. After unsuccessful attempts to hydrogenate several silyl ether derivatives of **12**, we moved our attention to a hydroxy-group-directed hydrogenation approach, and hoped that this measure would not only prompt the hydrogenation, but also lead to the desired stereochemical induction.[12,13] Accordingly, oxidation of **12** with TPAP/NMO[14] and subsequent reduction with $NaBH_4$ produced diol **14**. Gratifyingly, after extensive experimentation, we discovered that the hydrogenation[13] of **14** catalyzed Raney Ni at 75 °C under high pressure gave the desired product **15** in 86 % yield.

The completion of the synthesis is depicted in Scheme 5. Selective oxidation of the less hindered hydroxy group at C9 in **15** was achieved with Dess–Martin periodinane,[15] and the resulting alcohol was esterified under Yamaguchi conditions[16] and gave ketone **16** in 78 % yield. Reduction of **16** with $NaBH_4$ provided alcohol **17a**, which was treated with LiHMDS and $(imid)_2SO_2$ and yielded sulfonylation product **17b**.[17] The synthesis was completed by heating a mixture of **17b** and the cesium salt of 2-hydroxyacetic acid in the presence of [18]crown-6 in toluene.[18] Using imidazole-1-sulfonate as a leaving group is essential for this step, because the corresponding mesylate gave a considerably lower yield. The spectroscopic data of our synthetic **1** are in agreement with those reported for natural englerin A.[1,19]



Scheme 5. Reagents and conditions: a) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C→RT; b) cinnamic acid, 2,4,6-trichlorobenzoyl chloride, 4-dimethylaminopyridine, Et_3N; c) $NaBH_4$, MeOH, 0 °C; d) LiHMDS, $(imid)_2SO_2$, THF, 0 °C→RT; e) $HOCH_2CO_2Cs$, [18]crown-6, toluene, reflux, 48 h. Cp = cyclopentadienyl, HMDS = hexamethyldisilazane, imid = imidazole.

In conclusion, an asymmetric total synthesis of (−)-englerin A has been achieved in 15 steps with 8.1 % overall yield by starting from (*R*)-citronellal. The synthesis is concise and features several key transformations, namely, a gold-catalyzed cyclization of an enyne and a hydroxy-directed hydrogenation of an olefin. Noteworthy is that in the final route no protection groups are needed. Therefore, our synthesis of (−)-englerin A provides another example of natural product synthesis without using protecting groups.[20] Based on this synthetic route, investigations on structure-activity relationship and the mode of action of englerin A are being actively pursued by our research group.[21]

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