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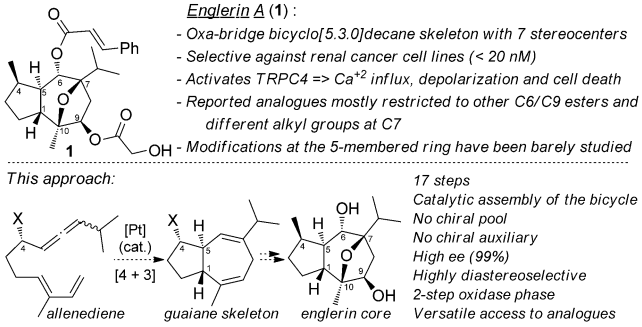
Concise, Enantioselective, and Versatile Synthesis of (−)-Englerin A Based on a Platinum-Catalyzed [4C+3C] Cycloaddition of Allenedienes

Ronald Nelson, Moisés Gulías, José L. Mascareñas, and Fernando López**

In memory of José Barluenga (1940–2016)

Abstract: *A practical synthesis of (−)-englerin A was accomplished in 17 steps and 11 % global yield from commercially available achiral precursors. The key step consists of a platinum-catalyzed [4C+3C] allenediene cycloaddition that directly delivers the trans-fused guaiane skeleton with complete diastereoselectivity. The high enantioselectivity (99 % ee) stems from an asymmetric ruthenium-catalyzed transfer hydrogenation of a readily assembled diene–ynone. The synthesis also features a highly stereoselective oxygenation, and a late-stage cuprate alkylation that enables the preparation of previously inaccessible structural analogues.*

The guaiane sesquiterpene (−)-englerin A (**1**, Scheme 1) has attracted the attention of chemists, biologists, and physicians because of its potent and highly selective activity as an inhibitor of renal cancer growth.[1] Recent studies carried out independently by Waldmann, Beech, Christmann, and co-workers[2] and by a Novartis team[3] identified the transient receptor potential Ca^{2+} channel TRPC4 as its main target.[4] TRPC channels are complex membrane proteins that are implicated in multiple biological functions, but they are unusual targets for antitumor compounds.[5] The activation of this particular channel by **1** has been shown to induce cell death by elevated Ca^{2+} influx;[2] however, the general mechanisms that govern TRPC4 activation remain elusive.[5] In this context, the development of efficient and versatile approaches to englerin A and related structural analogues is of major current interest.



Scheme 1. The target compound englerin A, and major points of our synthetic approach.

Since its isolation,[1] several syntheses of englerin have been accomplished,[6,7] including some asymmetric approaches.[8] Most of the shortest asymmetric syntheses (< 20 steps) rely on the use of prebuilt five-membered rings derived from the chiral pool and already equipped with key stereocenters of the product.[8b] Although some of these approaches are efficient, the types of analogues that can be assembled are inherently restricted, in particular with respect to the substitution at the five-membered ring.[9,10] The groups of Ma and Echavarren independently developed synthetic routes that allow the direct assembly of the bicarbocyclic scaffold of **1** by using a gold-catalyzed cycloisomerization of enantiomerically enriched ketoenynes.[6d,e] The route described by Ma and co-workers makes use of the chiral pool to prepare the ketoenyne, whereas the approach of Echavarren and co-workers relies on a Sharpless asymmetric epoxidation to generate the key stereocenter of the annulation precursor. Although these approaches are very elegant, the cycloisomerization yields are moderate, and the correct configuration at the ring junction requires the destruction and regeneration of stereocenters.

Herein, we report an enantioselective synthesis of (−)-englerin A that overcomes many of the above limitations. The approach relies on a platinum-catalyzed [4C+3C] cycloaddition, and enables construction of the bicyclic skeleton of **1** with the correct configuration at the ring junction from a readily available allenediene precursor (Scheme 1). Importantly, a single stereocenter in this acyclic precursor controls the successful generation of all the remaining stereocenters of the molecule in a highly stereoselective manner. The route, which ranks among the most efficient syntheses of (−)-**1** (17 steps, 11 % yield),[11] also provides a versatile platform for the preparation of structural analogues modified at the five-membered ring.

The key elements of our synthetic plan are detailed in the Scheme 2. The strategy rests on the idea of assembling the

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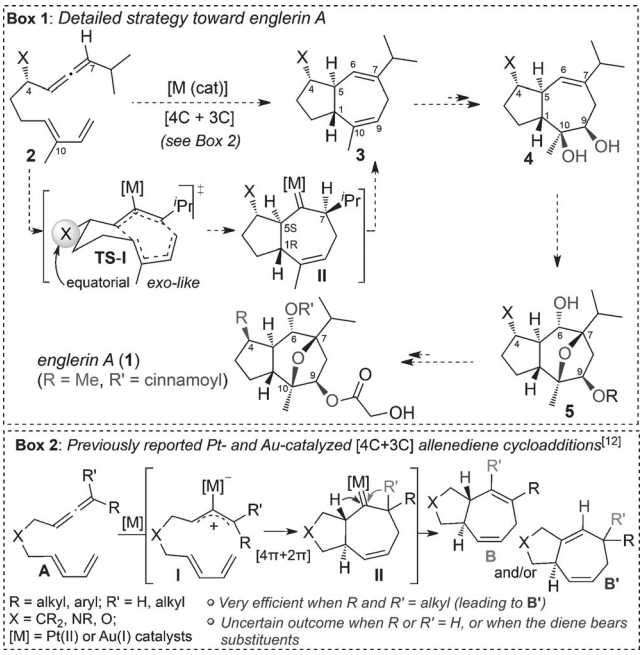
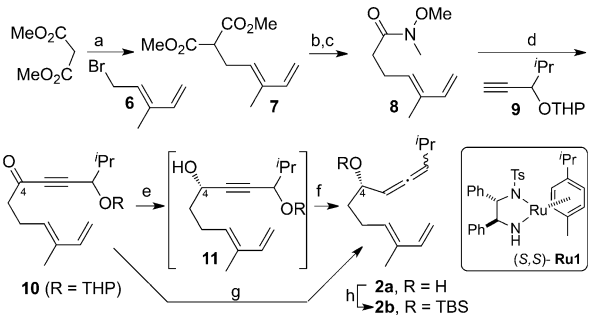


Scheme 2. Box 1: Key details of the strategy. Box 2: Previous work.[12]

guaiane bicyclic core from an allenediene of type **2** by our previously developed platinum- or gold-catalyzed intramolecular [4C+3C] cycloaddition reactions.[12] Although the use of this methodology might appear straightforward, the annulation holds a number of challenges. This type of allenediene cycloaddition is efficient with terminally disubstituted allenes; however, with distally monosubstituted allenes, such as **2**, the reactions usually require more stringent conditions and can lead to mixtures of isomers (**B** and **B′**, Scheme 2, box 2).[12,13] Moreover, at the outset, it was not clear how the presence of substituents on the diene or stereocenters in the connecting tether would influence the efficiency and stereoselectivity of the reaction.[12–14]

In designing the precursor, and considering that these cycloaddition reactions are proposed to proceed via an *exo*-like transition state,[12] we envisioned that a bulky group at C4, such as a silyl ether (X = $OSiR_3$), would enable the stereoselective formation of the *trans*-fused intermediate **II** via a transition state such as **TS-I** (Scheme 2, box 1). We hoped that selective 1,2-migration of the hydrogen atom at C7 would enable the exclusive formation of the adduct **3**, which would then be submitted to a stereoselective oxygenation reaction. This transformation was conceived as a two-step process comprising chemo- and stereoselective dihydroxylation of the C9–C10 double bond and stereoselective epoxidation of C6–C7, with concomitant epoxide-promoted transannulation to deliver an oxa-bridged product of type **5**. Importantly, the presence of an oxy substituent at C4 might allow for the stereoselective introduction of not only the methyl group of **1**, but also other substituents. Eventually, incorporation of the ester substituents at C6 and C9 would yield **1**, as well as other C4-modified analogues.

The required allenediene **2a** (X = OH) was prepared from commercially available compounds in six steps and 55% overall yield (Scheme 3). Thus, dimethyl malonate was alkylated with dienyl bromide **6**[15] to afford the diester **7** in 88% yield. This diester was decarboxylated, and the resulting product was converted into the Weinreb amide **8** (77% yield), which was treated with the lithium alkynylide of **9** to quantitatively afford the diene–ynone **10**. An asymmetric transfer hydrogenation of this ynone, catalyzed by the Noyori complex (*S*,*S*)-**Ru1** (2.5 mol%),[16] afforded the propargylic alcohol **11**, which could be directly transformed into the allenediene **2a** by treatment with $LiAlH_4$ (82% yield from **10**).[17] Protection of **2a** with TBSCl provided the desired allenediene **2b**.

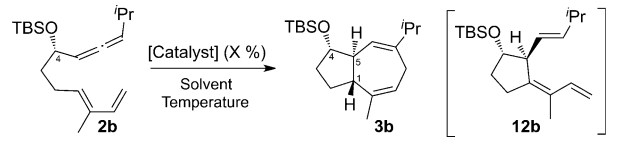


Scheme 3. Synthesis of the required allenediene **2a**: a) NaH, THF, 88%; b) NaCN, H_2O, DMSO, 80°C; c) MeNHOMe–HCl, ^{i}PrMgCl, THF, −15°C, 77% from **7**; d) *n*BuLi, **9**, THF, −78→−15°C, 99%; e) (*S*,*S*)-**Ru1** (2.5%), ^{i}PrOH, 1 h; f) $LiAlH_4$, Et_2O, 40°C, 82% from **10**; g) $LiAlH_4$, Et_2O, 40°C, 81%; h) TBSCl, imidazole, DMAP, CH_2Cl_2, room temperature, 99%. DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, TBS = *tert*-butyldimethylsilyl, THP = tetrahydropyranyl, Ts = *p*-toluenesulfonyl.

As we had feared, gold complexes previously shown to efficiently catalyze many allenediene [4C+3C] cycloadditions[12b,c,13] provided poor results in the cycloaddition of **2b** (Table 1, entries 1–3). These reactions required heating at 85°C for optimal conversion, but all of them afforded complex mixtures of products and polymeric material, from which the desired adduct **3b** was isolated in low yield. The diene **12b** was the only side product that could be identified. Although the performance of the [IPrAu] catalyst could be improved by adjusting the counterion (entry 4), further attempts to increase the yield with this or related catalysts remained fruitless. Alternatively, the use $PtCl_2$ in toluene at reflux[12a] also yielded a complex mixture of products, with **3b** formed in low yield (11%; Table 1, entry 5). By the use of CO (1 atm), the yield of **3b** could be increased to 26% (entry 6), and eventually to 38%, by carrying out the reaction at 140°C (entry 7). However, even when 20 mol% of $PtCl_2$ was used, the yield remained below 50% (entry 8), and the reaction lacked reproducibility at gram scales.

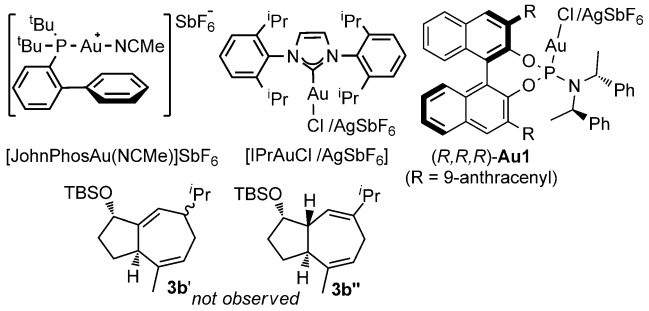
At this point, we tested several π-acceptor ligands that might improve the carbophilicity of the Pt center. Gratifyingly, the electron-deficient phosphine $P(C_6F_5)_3$ turned out to be particularly effective.[18] With only 5 mol% of $PtCl_2$/$P(C_6F_5)_3$, **3b** was obtained in 55% yield after 5 h in toluene at reflux (Table 1, entry 9), and in 71% when the reaction was carried out in *o*-xylene at 150°C (entry 10). Importantly, the cycloaddition proved to be fully diastereoselective (isomeric

Table 1: Optimization of the [4C+3C] cycloaddition of allenediene **2b**.[a]



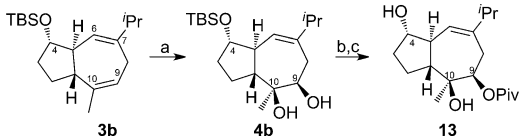
Entry	[Catalyst] (*X* mol%)	Solvent	*T* [°C]	*t* [h][b]	Yield [%][c] **3b**	**12b**
1	[JohnPhosAu(NCMe)] (5)	DCE	85	8	22	5
2	(*R*,*R*,*R*)-**Au1** (5)	DCE	85	2	2[d]	–
3	[IPrAuCl/$AgSbF_6$] (5)	DCE	85	0.5	27	1
4	[IPrAu]NTf_2 (5)	DCE	85	0.5	36	3
5	$PtCl_2$ (10)	toluene	110	12	11	3
6	$PtCl_2$/CO (10)	toluene	110	4	26	4
7	$PtCl_2$/CO (10)[e]	*m*-xylene	140	0.5[f]	38	12
8	$PtCl_2$/CO (20)[e]	*m*-xylene	140	0.1[g]	45	14
9	$PtCl_2$ (5)/$P(C_6F_5)_3$ (5)	toluene	110	5	55	10
10	$PtCl_2$ (5)/$P(C_6F_5)_3$ (5)	*o*-xylene	150	0.5	71	5

[a] Substrate **2b** was added to a solution of the catalyst (*X* mol%) in the indicated solvent (0.1 M, unless otherwise noted) and heated at the indicated temperature. [b] Reaction time for full conversion (^{1}H NMR spectroscopy), unless otherwise noted. [c] Yield of the isolated product. [d] The yield was determined by ^{1}H NMR spectroscopy of the crude product with an internal standard. [e] The reaction was carried out at a substrate concentration of 0.01 M. [f] 85% conversion. [g] 94% conversion. DCE = 1,2-dichloroethane.



adducts, such as **3b′** or **3b″**, or any other cycloadducts were not detected) as well as robust, as it could be scaled up without variations in the yield and/or selectivity. Moreover, **3b** had an enantiomeric purity of 99.1% *ee*, which confirmed that the ruthenium-catalyzed transfer hydrogenation had occurred with excellent asymmetric induction.

A thorough study of dihydroxylation conditions revealed that the use of K_2OsO_4 (30%), NMO (2 equiv), and $MsNH_2$ (1.5 equiv) enabled completely regioselective dihydroxylation of the C10–C9 double bond of **3b**, a reaction that proceeded almost exclusively at the less sterically hindered top face to afford **4b** in 73% yield (Scheme 4). Pivaloylation

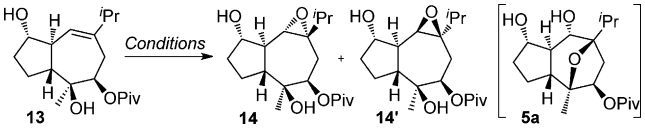


Scheme 4. Regioselective dihydroxylation of **3b**, pivaloylation and TBS removal: a) K_2OsO_4 (30%), NMO (2 equiv), $MsNH_2$, acetone/water (10:1), 73%, d.r. > 15:1; b) PivCl, Et_3N, DMAP, $CHCl_3$, 65°C, 99%; c) HF·Py, room temperature, THF, 90%. Ms = methanesulfonyl, NMO = *N*-methylmorpholine *N*-oxide, Piv = pivaloyl, Py = pyridine.

of the secondary hydroxy group at C9 proceeded in a fully chemoselective manner. Envisioning that the epoxidation of the remaining double bond could benefit from the stereodirecting effect of the OH group at C4, we removed the silyl protecting group at this stage.

Unfortunately, homoallylic epoxidation reactions of **13** promoted by $[VO(acac)_2]$ or $[Mo(CO)_6]$ were low-yielding (Table 2, entries 1 and 2). In contrast, the use of *m*CPBA at room temperature provided epoxides **14** and **14′** in quantitative yield, but without any diastereoselectivity (entry 3).

Table 2: Stereoselective epoxidation of the C6–C7 double bond.

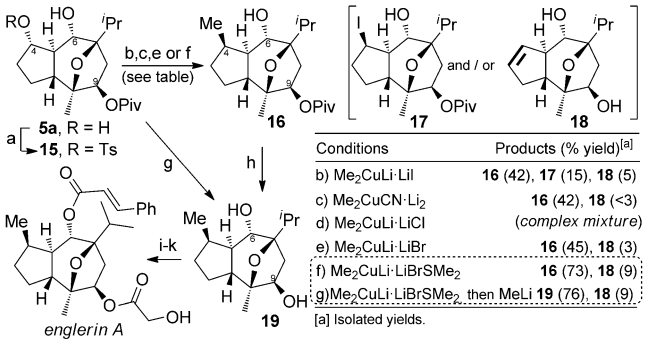


Entry	Conditions[a]	Product ratio	Yield [%] **14** or **5a**	**14′**
1	$[VO(acac)_2]$ (20%), ^{t}BuOOH	3.5:1 (**14**/**14′**)	28 (**14**)	12
2	$[Mo(CO)_6]$, ^{t}BuOOH, 80°C	5:1 (**5a**/**14′**)	31 (**5a**)	6
3	*m*CPBA, $CHCl_3$, RT	1:1 (**14**/**14′**)	50 (**14**)	50
4	*m*CPBA, $CHCl_3$, 55°C	1:1 (**5a**/**14′**)	50 (**5a**)	50
5	MMPP, CH_3CN, 85°C	1:1 (**5a**/**14′**)	50 (**5a**)	50
6	D-Shi (60%), RT→85°C	2.7:1 (**5a**/**14′**)	65 (**5a**)	21
7	L-Shi (30%), RT→85°C	4.5:1 (**5a**/**14′**)	71 (**5a**)	16

[a] See the Supporting Information for the epoxidation procedures and the structure of the Shi catalyst. acac = acetylacetonate, *m*CPBA = *m*-chloroperbenzoic acid, MMPP = magnesium monoperoxyphthalate.

Interestingly, when the reaction was carried out at 55°C, the transannulated product **5a** was directly formed from **14** and isolated in 50% yield (entry 4). The use of MMPP as the oxidant at 85°C also provided a quantitative 1:1 mixture of **5a** and **14′** (entry 5). Gratifyingly, after extensive analysis, we found that the Shi catalyst[19] enabled a significant increase in the diastereoselectivity, so that **5a** could be isolated in 71% yield (Table 2, entry 7). Moreover, the unwanted epoxide **14′** could be successfully recycled to **13** ($[WCl_6]$, *n*BuLi, 51% yield).

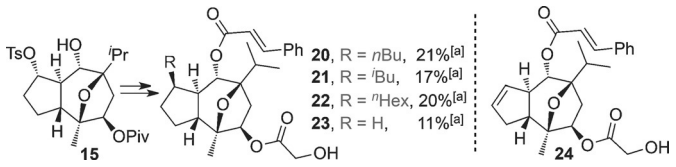
To incorporate the methyl group at C4, we considered the use of cuprate chemistry. Gilman and related cuprates have been thoroughly studied since the 1980s for 1,4-addition, allylic alkylation (S_N2'), and nucleophilic substitution (S_N2) at primary carbon atoms.[20] However, examples of S_N2 substitution reactions at secondary carbon atoms of densely functionalized systems are extremely rare, certainly as a result of issues of functional-group compatibility and competitive elimination processes. The reaction of the tosylate **15** with $Me_2CuLi{\cdot}LiI$ gave a relatively complex mixture of products; however, we could isolate the desired methylated product **16** in 42% yield, as well as minor amounts of the iodide **17** (15% yield) and alkene **18** (5% yield; Scheme 5). Although the cyanocuprate Me_2CuCN did not improve this result, the Gilman reagent generated from MeLi and $CuBr{\cdot}SMe_2$ was more effective, providing **16** in 73% yield. Interestingly, although the pivaloyl group could be readily removed with DIBAL-H, the addition of MeLi to the



Scheme 5. a) TsCl, Et_3N, DMAP, 95%; f) $Me_2CuLi{\cdot}LiBrSMe_2$ (10 equiv), Et_2O, −15 °C→RT, 73%; g) like (f), but with the addition of MeLi (10 equiv) after completion of the reaction; h) DIBAL-H, CH_2Cl_2, 99%; i) 2-((4-methoxybenzyl)oxy)acetic acid, EDC, DMAP, CH_2Cl_2, 0 °C, 83%; j) cinnamic acid, 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, DMAP, 100%; k) DDQ, CH_2Cl_2/H_2O (20:1), 99%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL-H = diisobutylaluminum hydride, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

mixture resulting from the cuprate alkylation enabled the in situ removal of this group to yield **19**[6i,l] in 76% yield. Eventually, esterification at C9 and C6 with the respective carboxylic acid partners provided englerin A (**1**) in 83% yield.

Tosylate **15** is a valuable building block for the synthesis of structural analogues of **1** modified at the five-membered ring. For example, we could readily prepare englerin A analogues **20**–**23**, equipped with an ^{n}Bu, ^{i}Bu, or ^{n}Hex substituent or an H atom at the C4 position. Additionally, the dihydro analogue **24** could be readily obtained from **18** (Scheme 6). The biological profiles of these analogues are currently being investigated.



Scheme 6. Synthesis of structural analogues of **1**. [a] Unoptimized yields from **15**. For **20**–**22**: $R_2CuLi{\cdot}LiBrSMe_2$, followed by (i–k) of Scheme 5; for **23**: $LiEt_3BH$, THF, 58%, followed by (i–k) of Scheme 5.

To sum up, we have described a short, efficient, versatile, and highly enantioselective synthesis of englerin A as well as several novel analogues. The synthesis relies on an intramolecular platinum-catalyzed [4C+3C] cycloaddition of allenedienes. This annulation enables the *trans*-carbobicyclic skeleton of englerin A to be built up from acyclic precursors in a fully diastereoselective manner. Importantly, the seven stereogenic carbon atoms of the molecule are generated in a highly stereoselective fashion after an initial ruthenium-catalyzed asymmetric transfer hydrogenation (99% *ee*) of the acyclic diene–ynone **10**.

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[11] Only other three approaches led to reported yields above 10% (from commercially available compounds).[6f,g,h]

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