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A Concise, Enantioselective and Versatile Synthesis of (-)-Englerin A based on a Pt-catalyzed [4C+3C] Cycloaddition of Allenedienes

Ronald Nelson,^[a] Moisés Gullías,^[a] José L. Mascareñas,*^[a] Fernando López*^[a,b]

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 Pt-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 Ru-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.

Along the last years, the guaiane sesquiterpene (-)-englerin A (1, Figure 1) has attracted the attention of chemists, biologists and physicians because of its potent and highly selective activity as inhibitor of renal cancer growth.^[1] Recent work carried out independently by Waldmann, Beech and Christmann,^[2] as well as by a Novartis' team,^[3] identified the transient receptor potential Ca²⁺ 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 antitumoral compounds.^[5] The activation of this particular channel by 1 has been shown to induce cell death by elevated Ca²⁺ influx,^[2] however, the general mechanisms that govern TRPC4 activation remains elusive.^[5] In this context, the development of efficient and versatile approaches to englerin A and related structural analogues is of major current interest.

Since its isolation,^[1] several synthesis of englerin have been accomplished,^[6,7] some of which are asymmetric.^[8] Most of the shortest (<20 steps) asymmetric synthesis 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 enantioenriched ketoenynes.^[7d,e] The Ma route makes use of the chiral pool to prepare the ketoenyne, whereas Echavarren's approach relies on a Sharpless asymmetric epoxidation to generate the key stereocenter of the annulation precursor. While these approaches are very elegant, the cycloisomerization yields are moderate and the generation of the correct stereochemistry at the ring fusion requires the destruction and regeneration of stereocenters.

Herein, we report an enantioselective synthesis of (-)-englerin A that allows to overcome many of the above limitations. The approach relies on a Pt-catalyzed [4C+3C] cycloaddition, and allows to build the bicyclic skeleton of 1 with the correct stereochemistry at the ring fusion, from a readily available allenediene precursor (Figure 1). Importantly, a single stereocenter on this acyclic precursor masters a successful buildup of all the remaining stereocenters of the molecule in a highly stereoselective manner. The route, which can be ranked amongst the most efficient synthesis of (-)-1 (17 steps, 11% yield),^[11] also provides a versatile platform for the preparation of structural analogues modified at the five-membered ring.

[a] Ronald Nelson, Dr. M. Gullías, Prof. J. L. Mascareñas, Dr. F. López
Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica.
Universidade de Santiago de Compostela
15782, Santiago de Compostela, Spain
E-mail: fernando.lopez@csic.es

[b] Dr. F. López
Instituto de Química Orgánica General (CSIC)
Juan de la Cierva, 3, 28006, Madrid, Spain.

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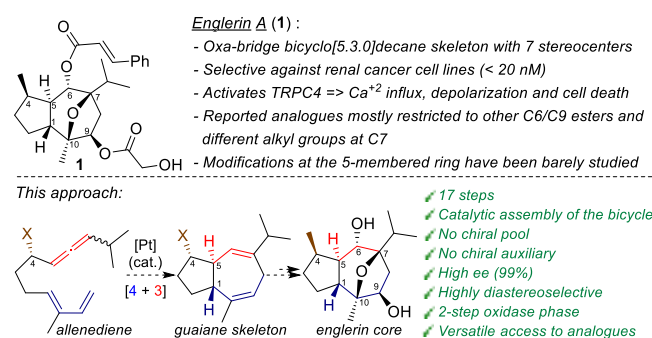


Figure 1. Englerin A basic facts, and major points of our synthetic approach.

The key elements of our synthetic plan are detailed in the Figure 2. The strategy lies on the idea of assembling the guaiane bicyclic core from an allenediene of type **2**, using our previously developed Pt- or Au-catalyzed intramolecular [4C+3C] cycloadditions.^[12] While the use of this methodology might appear straightforward, the annulation holds a number of challenges since this type of allenediene cycloadditions are efficient with terminally disubstituted allenes. However with distally monosubstituted allenes like **2** the reactions usually require more stringent conditions and can lead to mixtures of isomers (**B** and **B'**, Figure 2, box 2).^[12,13] Moreover, at the outset, it was not clear how the presence of substituents in the diene or of stereocenters in the connecting tether could influence the efficiency and stereoselectivity of the reaction.^[12-14]

In designing the precursor, and considering that these cycloadditions are proposed to proceed through an *exo*-like transition state,^[12] we envisioned that a bulky group in C4 such as a silyl ether ($X = \text{OSiR}_3$), would allow the stereoselective formation of the *trans*-fused intermediate **II**, via a transition state like **TS-I** (Figure 2, Box 1). Hopefully, a selective 1,2-migration of the hydrogen at C7 would allow the exclusive formation of the adduct **3**, which would then be submitted to a stereoselective oxygenation. This was conceived as a two-step process comprising a chemo- and stereoselective dihydroxylation of the C9-C10 double bond, and a 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 in C4 might allow for the stereoselective introduction of not only the methyl group of **1**, but also other substituents. Eventually, incorporation of the esters at C6 and C9 would yield **1**, as well as other C4-modified analogues.

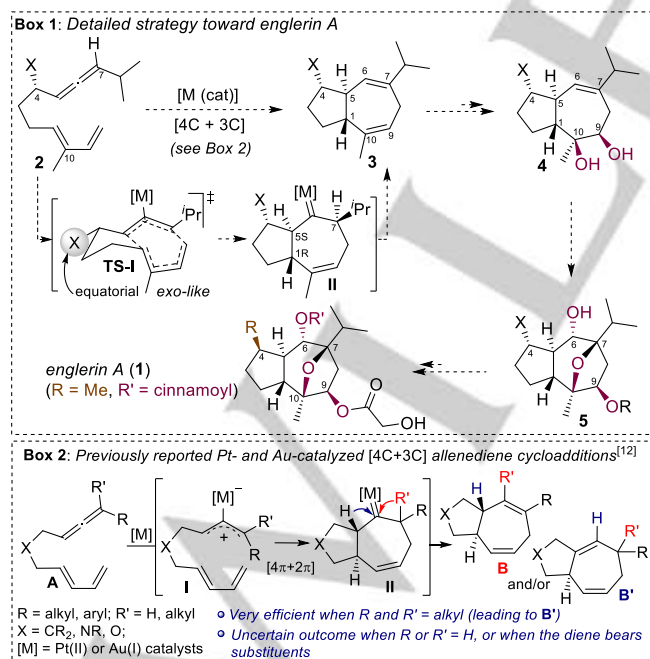
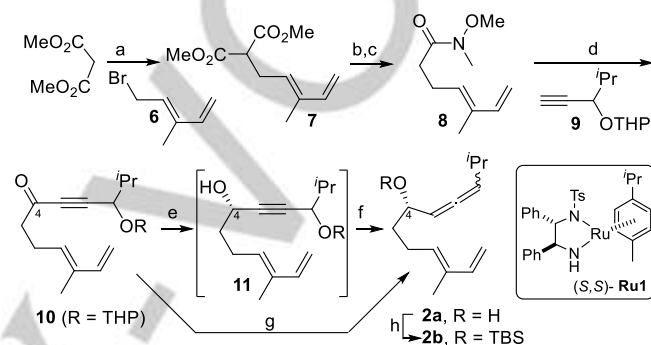


Figure 2. Box 1: Key facts of the strategy. Box 2: Previous annulations.^[12] The required allenediene **2a** ($X = \text{OH}$) was prepared from commercially available compounds in 6 steps and

55% overall yield (Scheme 1). Thus, dimethylmalonate was alkylated with dieny bromide **6**^[15] to afford the diester **7** in 88% yield. This was decarboxylated and the resulting product converted to 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 Noyori's 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 1. a) NaH, THF; 88%; b) NaCN, H₂O, DMSO, 80 °C; c) MeNHOMe-HCl, *i*PrMgCl, THF, -15 °C, 77% from **6**; d) *n*BuLi, **9**, THF, -78 °C → -15 °C, 99%; e) (*S,S*)-**Ru1** (2.5%) *i*PrOH, 1h; f) LiAlH_4 , Et₂O, 40 °C, 82% from **9**. g) LiAlH_4 , Et₂O, 40 °C, 81%; h) TBSCl, imidazole, DMAP, CH₂Cl₂, rt, 99%.

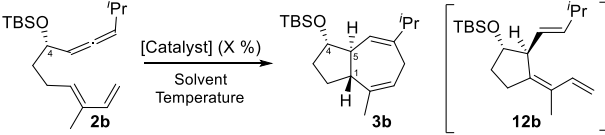
As we had feared, gold complexes previously shown to efficiently catalyze many other allenediene [4C + 3C] cycloadditions,^[12b,c,13] provided poor results in the cycloaddition of **2b** (Table 1, entries 1-3). These reactions required heating at 85 °C to observe optimal conversions, but all of them afforded complex mixtures of products and polymeric material from which the desired adduct **3b** was isolated in low yields (entries 1-3). In addition to **3b**, the diene **12b** was the only side-product that could be identified. Although the performance of the [IPrAu] catalyst could be slightly 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 under refluxing toluene,^[12a] also yielded a complex mixture of products, with a low 11% yield of **3b** (entry 5). By using 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 using 20 mol% of PtCl_2 , 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 $\text{P}(\text{C}_6\text{F}_5)_3$ turned out to be particularly effective.^[18] By using only 5 mol% of $\text{PtCl}_2 / \text{P}(\text{C}_6\text{F}_5)_3$, **3b** was obtained in 55% yield after 5h in refluxing toluene (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 adducts like **3b'** or **3b''**, or any other cycloadducts were not detected), and robust, as it could be

scaled up without variations in the yield and/or selectivity. Moreover, analysis of the enantiomeric purity of **3b** revealed a 99.1% ee, which confirms that the Ru-catalyzed transfer hydrogenation had occurred with excellent asymmetric induction.

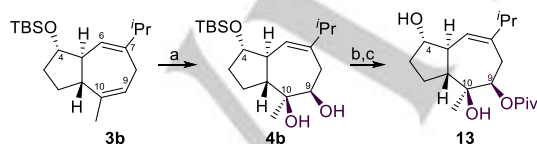
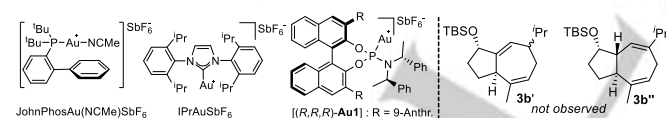
A thorough study of dihydroxylation conditions revealed that the use of K_2OsO_4 (30%), NMO (2 equiv) and $MsNH_2$ (1.5 equiv) allows for a completely regioselective dihydroxylation of the C10-C9 double bond of **3b**, a reaction that proceeds almost exclusively through the less sterically hindered top face, to afford **4b** in 73% yield (Scheme 2). Pivaloylation of the secondary hydroxyl 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, the silyl protecting group was removed at this stage.

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



entry	[Catalyst] (X mol%)	Solvent	T (°C)	t (h) ^[b]	3b , yield ^[c]	12b , yield ^[c]
1	JohnPhosAuNCMe (5%)	DCE	85	8	22%	5%
2	(<i>R,R,R</i>)- Au1 (5%)	DCE	85	2	2% ^[d]	-%
3	IPrAuSbF ₆ (5%)	DCE	85	0.5	27%	1%
4	IPrAuNTf ₂ (5%)	DCE	85	0.5	36%	3%
5	PtCl ₂ (10)	Tol.	110	12	11%	3%
6	PtCl ₂ / CO (10)	Tol.	110	4	26%	4%
7	PtCl ₂ / CO (10) ^[e]	<i>m</i> -Xyl.	140	0.5 ^[f]	38%	12%
8	PtCl ₂ / CO (20), ^[e]	<i>m</i> -Xyl.	140	0.1 ^[g]	45%	14%
9	PtCl ₂ (5) / P(C ₆ F ₅) ₃ (5)	Tol.	110	5	55%	10%
10	PtCl ₂ (5) / P(C ₆ F ₅) ₃ (5)	<i>o</i> -Xy	150	0.5	71%	5%

[a] **2b** was added to a solution of the catalyst (X mol %) in the described solvent (0.1 M, unless otherwise noted) and heated at the indicated temperature. [b] Reaction time for full conversion (¹H-NMR) unless otherwise noted. [c] Isolated yield. [d] Determined by ¹H-NMR of the crude with internal standard. [e] 0.01 M reaction. [f] 85% conversion; [g] 94% conversion.

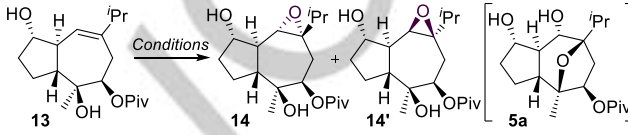


Scheme 2. a) K_2OsO_4 (30%), NMO (2 equiv), $MsNH_2$, acetone/water (10 : 1), 73%, d.r. > 15:1; b) PivCl, Et₃N, DMAP, $CHCl_3$, 65 °C, 99%; c) HF·Py, rt, THF, 90%.

Unfortunately, the homoallylic epoxidations 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 rt provided a quantitative yield of the epoxides **14** and **14'**, but without any

diastereoselectivity (entry 3). Interestingly, by carrying out the reaction at 55 °C, the transannulated product **5a** was directly formed from **14** and eventually isolated in 50% yield (entry 4). Analogously, the use of MMPP as oxidant, at 85 °C, also provided a quantitative 1 : 1 mixture of **5a** and **14'** (entry 5). Gratifyingly, after extensive analysis, we found that Shi's catalysts^[19] allow a significant increase in the diastereoselectivity, so that **5a** could be eventually isolated in 71% yield (entry 7). Moreover, the unwanted epoxide **14'** can be successfully recycled to **13** (WCl_6 , *n*BuLi, 51% yield).

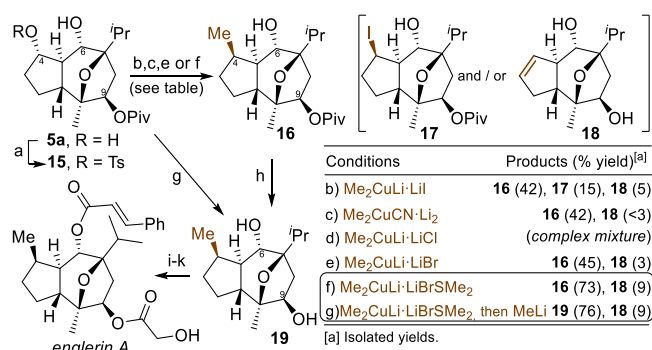
Table 2. Stereoselective epoxidation of the C6=C7 double bond



entry	Conditions ^[a]	Products ratio	Yield (14 or 5a)	Yield 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	<i>m</i> CPBA, $CHCl_3$, rt	1 : 1 (14 / 14')	50% (14)	50%
4	<i>m</i> CPBA, $CHCl_3$, 55 °C	1 : 1 (5a / 14')	50% (5a)	50%
5 ^[b]	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%

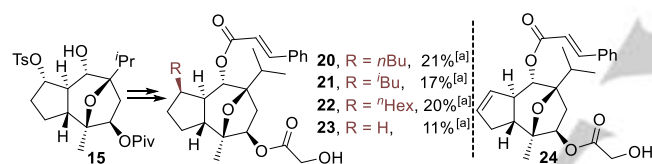
[a] See the Supporting information for the epoxidation procedures and the structure of Shi's catalyst. [b] MMPP: Magnesium monoperoxyphthalate.

To incorporate the methyl group at C4 we considered the use of cuprate chemistry. Gilman and related cuprates have been thoroughly studied since the 80's to achieve 1,4-additions, allylic alkylations (S_N2') or nucleophilic substitutions (S_N2) in primary carbons.^[20] However, examples of S_N2 substitutions in secondary carbons of densely functionalized systems are extremely rare, surely due to functional group compatibility issues and to competitive elimination processes. In consonance with these precedents, the reaction of the tosylate **15** with $Me_2CuLi-LiI$ gave a relatively complex mixture of products, albeit we could isolate a 42% yield of the desired methylated product **16**, as well as minor amounts of the iodide **17** (15% yield) and the alkene **18** (5% yield, Scheme 3). Although the cyanocuprate Me_2CuCN did not improve this result, Gilman's reagent generated from MeLi and $CuBr-SMe_2$ was more effective, providing **16** in 73% yield. Interestingly, while the pivaloyl group could be easily removed with DIBAL-H, addition of MeLi to the mixture resulting from the cuprate alkylation allowed the *in situ* removal of this group to yield **19**^[6i,j] in 76% yield. Eventually, esterifications at C9 and C6 with their respective carboxylic partners provided englerin A (**1**) in 83% yield.



Scheme 3. a) TscI, Et₃N, DMAP, 95%; f) Me₂CuLi·LiBrSMe₂ (10 equiv), Et₂O, -15 °C→rt; 73%; g) Like f) but adding MeLi (10 equiv) after completion. h) DIBAL-H, CH₂Cl₂, 99%; i) 2-((4-Methoxybenzyl)oxy)acetic acid, EDC, DMAP, CH₂Cl₂, 0 °C, 83%; j) Cinnamic acid, 2,4,6-Cl₃C₆H₂COCl, Et₃N, DMAP, 100%; k) DDQ, CH₂Cl₂/H₂O (20:1), 99%.

Tosylate **15** is a very valuable building block to obtain structural analogues of **1** modified at the five-membered ring. For instance, we could easily make englerin A analogues **20–23**, equipped with a ⁿBu, ⁱBu, ⁿHex or H at its C4 position. Additionally, the dihydro-analogue **24** could be easily obtained from **18** (Scheme 4). The biological profiles of these analogues are currently being investigated.



Scheme 4. [a] Unoptimized yields from **15**. For **20–22**: R₂CuLi·LiBrSMe₂, followed by i-k) of Scheme 3; For **23**: LiEt₃BH, THF, 58%, followed by i-k).

To sum up, we described a short, efficient, versatile and highly enantioselective synthesis of englerin A as well as several novel analogues, which relies on an intramolecular Pt-catalyzed [4C+3C] cycloaddition of allenediene. This annulation allows to build the *trans*-carbocyclic skeleton of englerin A from acyclic precursors in a fully diastereoselective manner. Importantly, the seven asymmetric carbons of the molecule are generated in a highly stereoselective fashion after an initial Ru-catalyzed asymmetric transfer hydrogenation (99% ee) of an acyclic diene-ynone (**10**).

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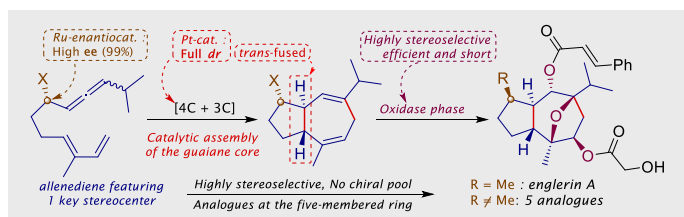
Keywords: natural product • guanine • cycloaddition • asymmetric

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- [17] a) The efficiency of this asymmetric hydrogenation could not be established at this point (using **11**, **2a** or **2b**); b) Racemic allenediene **2a** can be obtained in 81% yield by treating **10** with LiAlH₄ (2.5 equiv).
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COMMUNICATION



An asymmetric synthesis of (–)-englerin A was accomplished using as a key step a Pt-catalyzed [4C+3C] allenediene cycloaddition, a reaction that directly delivers the *trans*-fused bicyclic guaiane skeleton with complete stereoselectivity. Importantly, the seven stereocenters of the molecule are generated in a highly stereoselective fashion after an initial Ru-catalyzed asymmetric transfer hydrogenation of a readily assembled ketone cycloaddition precursor.

Ronald Nelson, Moises Gulías, José L. Mascareñas, * Fernando López*

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A Concise, Enantioselective and Versatile Synthesis of (–)-Englerin A based on a Pt-catalyzed [4C+3C] Cycloaddition of Allenedienes