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# Enantioselective Formal Synthesis of (−)-Englerin A via a Rh-Catalyzed [4 + 3] Cycloaddition Reaction

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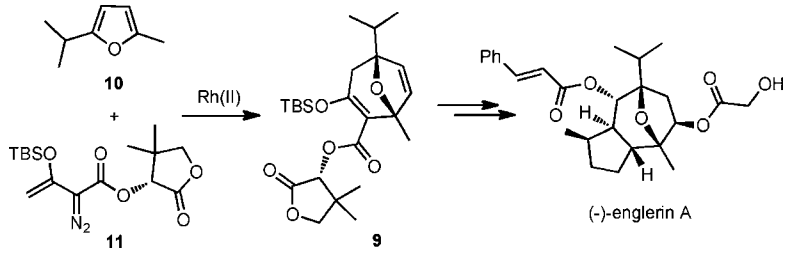
## ABSTRACT




**An enantioselective formal synthesis of (−)-englerin A (1) is reported. Key to the strategy is a Rh-catalyzed [4 + 3] cycloaddition reaction between furan 10 and diazo ester 11 that, following an intramolecular aldol condensation, produces the tricyclic scaffold of englerin. This strategy also provides a rapid, efficient, and stereoselective access to the biologically significant core motif of the guaiane sesquiterpenes.**

Renal cell carcinoma (RCC, also known as hypernephroma) is a type of kidney cancer that originates in the small tubes in the kidneys that filter the blood and remove waste products. This cancer ranks among the 10 leading cancer types in the United States, and only in 2009, it was responsible for about 58 000 new cases and 13 000 deaths.[1] Importantly, RCC is resistant to radiation and chemotherapy, leaving partial or radical nephrectomy as the only means of treatment. Therefore, the search for new compounds that can safely and effectively block or reverse RCC remains a high priority.

Efforts to identify new small molecule leads against RCC led to the identification of englerin A (**1**) and B (**2**) (Figure 1) from the Tanzanian plant *Phyllanthus engleri*.[2] From the standpoint of biogenesis, the englerins are guaiane-type sesquiterpenes that contain an uncommon oxygenated motif (Figure 1). Structurally related members of this family include orientalols E (**3**) and F (**4**)[3] and pubinernoid B (**5**)[4] (Figure 1). Most likely, this motif originates from a more common bicyclic sesquiterpene core via a sequence of

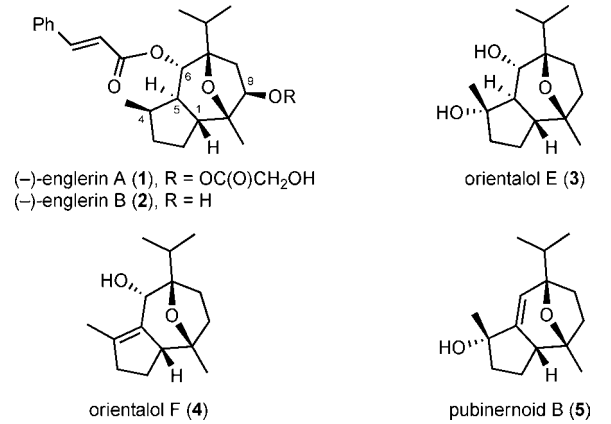



**Figure 1.** Structures of englerin A and B and natural analogues.

(1) Jemal, A.; Siegel, R.; Ward, E.; Hao, Y.; Xu, J.; Thun, M. J. Cancer Statistics 2009. *CA Cancer J. Clin.* **2009**, *59*, 225–249.

(2) (a) Ratnayake, R.; Covell, D.; Ransom, T. T.; Gustafson, K. R.; Beutler, J. A. *Org. Lett.* **2009**, *11*, 57–60. (b) Beutler, J. A.; Ratnayake, R.; Covell, D.; Johnson, T. R. WO 2009/088854, 2009.

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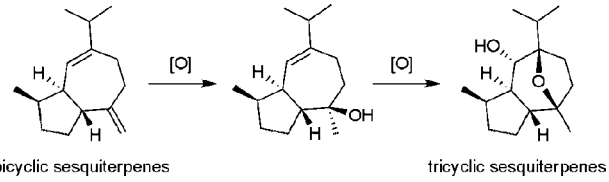
oxygenations and acid-induced oxo-cyclization reactions highlighted in Scheme 1.[3]

**Scheme 1.** Proposed Biosynthetic Approach

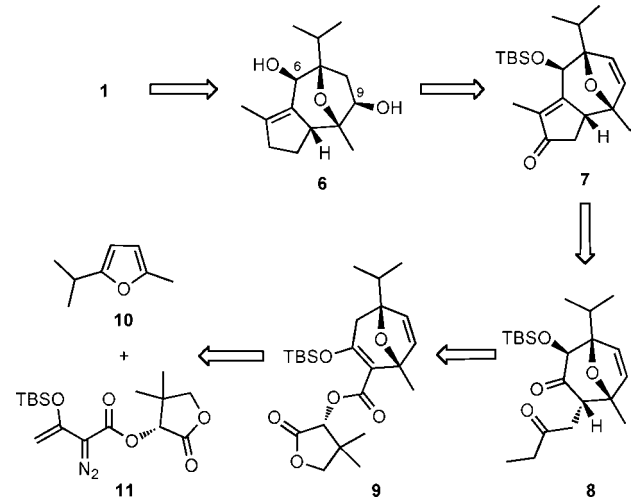



Remarkably, englerin A (**1**) showed highly potent and selective cytotoxicities against various renal cancer cell lines at low nanomolar level.[2] Preliminary biological investigations also showed a significant drop of potency and selectivity of englerin B (**2**), suggesting that the substitution at the C-9 position by the glycolate ester may be important for the activity and selectivity of englerins.[2]

Due to its promising anticancer activity and its scarcity from natural sources, englerin A has become an intriguing target in synthetic and medicinal chemistry. The absolute configuration of **1** was confirmed by Christmann et al. in their first total synthesis of *ent*-**1** in 2009.[5] More recently, three additional syntheses were reported by Ma,[6] Echavarren,[7] and Nicolaou,[8] the first two of which were enantioselective. In addition, a stereoselective approach to the guaianolide core of these sesquiterpenes has been disclosed.[9]

Inspired by the unusual tricyclic motif, we sought to design a general approach leading not only to the structures of **1** and **2** but also to various guaiane analogues, such as orientalols E (**3**) and F (**4**) and pubinernoid B (**5**). We envisioned that **1** could be derived from diol **6** via reversion of the C-6 stereocenter, hydrogenation, and two esterifications. The C-9 hydroxyl group of the diol **6** could be easily obtained by the regio- and stereoselective hydroboration on the disubstituted double bond of **7**. Moreover, the cyclopentene moiety of **7** could be constructed from an intramolecular aldol condensation of diketone **8**, which can be formed from oxa-tricyclic compound **9**. In turn, the key oxa-tricyclic compound **9** could be achieved via the Davies Rh-catalyzed ring formation,[10] from readily available disubstituted furan **10** and chiral diazo ester **11** (Scheme 2).

**Scheme 2.** Retrosynthetic Analysis




Rhodium-triggered cyclization reactions have been widely applied in synthetic chemistry.[11] In 1996, Davies et al. reported an elegant enantioselective Rh(II)-catalyzed [4 + 3] cycloaddition reaction between furans and diazo esters.[10,12] With this in mind we prepared furan **10** from 2-methylfuran in 3 steps following the reported procedure;[13] and diazo ester **11**, which derived from (*R*)-pantolactone in 3 steps.[10] Notably, both of these starting materials are readily available in more than 50 g-scale. Slow addition of the chiral diazo ester **11** into furan **10** in refluxing hexane catalyzed with 2 mol % of rhodium(II) octanoate gave rise to key oxa-tricyclic motif **9** in an excellent yield (90%, Scheme 3) with moderate diastereoselectivity (dr = 3:1).[14] This diastereomeric mixture can be easily separated through silica gel column chromatography. It is likely that a more bulky chiral auxiliary could provide better diastereoselectivity, although attempts at effecting this reaction under lower temperature or using less catalyst loading led to significantly poorer yield without any enhancement of diastereoselectivity.

Initial functionalization of this oxa-tricyclic compound **9** was successfully accomplished by removing the auxiliary. This was achieved by treating **9** with DIBAL-H to afford the corresponding unstable $\beta$-hydroxyl enol ether, followed by the Lewis acid induced rearrangement[15] to afford enone **12** in 59% yield. For the next step, attempts of $\alpha$-hydroxylation with Davis oxaziridines[16] of enone **12** were not

(3) Peng, G.-P.; Tian, G.; Huang, X.-F.; Lou, F.-C. *Phytochemistry* **2003**, *63*, 877–881.

(4) Huang, S.-X.; Yang, J.; Xiao, W.-L.; Zhu, Y.-L.; Li, R.-T.; Li, L.-M.; Pu, J.-X.; Li, X.; Li, S.-H.; Sun, H.-D. *Helv. Chim. Acta* **2006**, *89*, 1169–1175.

(5) Willot, M.; Radtke, L.; Könning, D.; Fröhlich, R.; Gessner, V. H.; Strohmann, C.; Christmann, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9105–9108.

(6) Zhou, Q.-F.; Chen, X.-F.; Ma, D.-W. *Angew. Chem., Int. Ed.* **2010**, *49*, 3513–3516.

(7) Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3517–3519.

(8) Nicolaou, K. C.; Kang, Q.; Ng, S. Y.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2010**, *132*, 8219–8222.

(9) (a) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452–5455. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2009**, *45*, 7327–7329.

(10) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774–10782.

(11) For an excellent review, see: Jeong, N.; Robinson, J. E.; Wender, P. A.; Gamber, G. G.; Williams, T. J.; Davies, H. M. L. Walji, A. M. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005; Chapters 11−14, pp 215−340.

(12) For a recent application of this strategy on natural product synthesis, see also: Jackson, K. L.; Henderson, J. A.; Motoyoshi, H.; Phillips, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2346–2350.

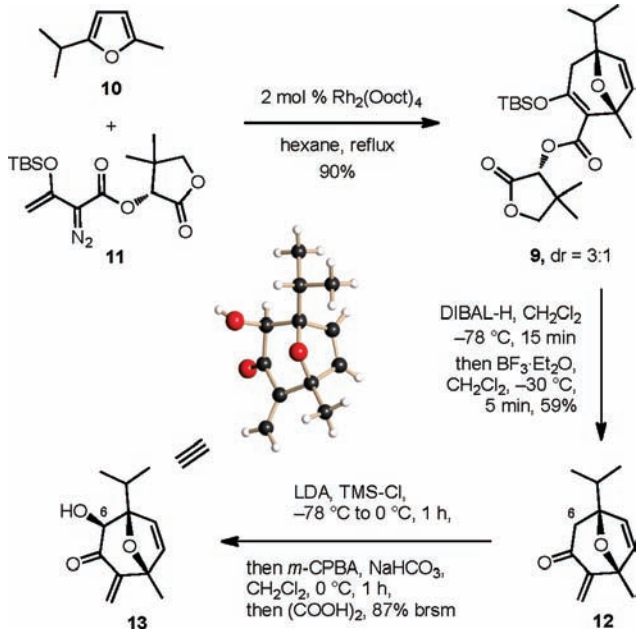
(13) Weyerstahl, P.; Brendel, J. *Liebigs Ann. Chem.* **1988**, 1015–1016.

(14) Calculated via $^1$H NMR spectroscopy.

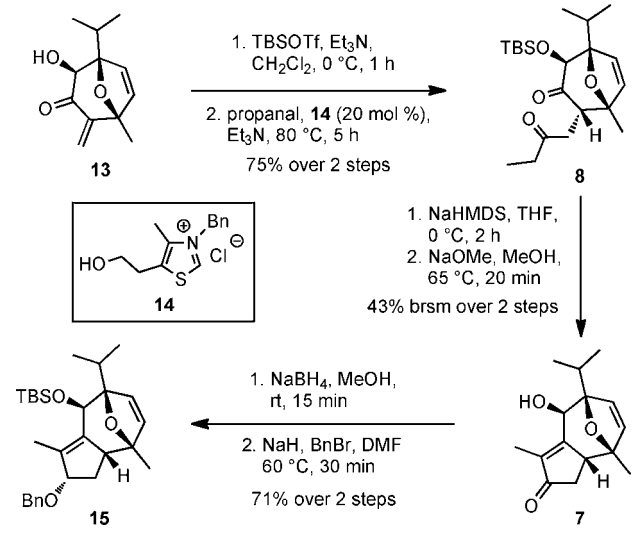
(15) Poirier, J.-M.; Hennequin, L. *Tetrahedron* **1989**, *45*, 4191–4202.

(16) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241–3243.

**Scheme 3**




**Scheme 4**




successful. Gratifyingly, Rubottom oxidation[17] of enone **12** led to the desired α-hydroxyl enone **13** in very good yield (87% brsm). Not surprisingly, the hydroxylation occurred on the less hindered face of this molecule, leading exclusively to the opposite stereochemistry at C-6. Nonetheless, the C-6 stereocenter can be easily reversed in a latter stage. Notably, *m*-CPBA selectively oxidized the electronic richer TMS enol ether without touching any of other double bonds of our substrate. The absolute stereochemistry of α-hydroxyl enone **13** was confirmed by a single-crystal Cu-mediated X-ray analysis,[18] thus establishing the desired absolute stereochemistry of oxa-tricyclic compound **9**.[19]

The next stage of the synthesis involved elaboration of the enone system to the five-membered ring, which eventually forms the tricyclic englerin core. After a simple TBS protection on the C-6 hydroxyl group, the enone Michael system was subjected to a 1,4-addition with propanal catalyzed by thiazolium salt **14** under basic conditions (Scheme 4).[20] The diketone **8** was cleanly obtained in good yield (75% over two steps) as a single diastereomer. Having the precursor **8** on hand, the ensuing aldol condensation proved to be unexpectedly difficult. Extensive studies on this intramolecular aldol condensation were then applied, with different substituents on the C-6 hydroxyl (H-, MOM-, TES-, etc.), various bases ($^t$BuOK, KOH, NaOMe, LDA, etc.), and several reaction conditions. Eventually, we were pleased to discover that treatment of diketone **8** with NaHMDS followed by heating in NaOMe/MeOH could provide the desired key tricyclic intermediate **7** in acceptable yield (43% brsm).[21] Reduction of enone **7** furnished the corresponding allylic alcohol as a single diastereomer, which was then directly protected with a benzyl group to give **15**, paving the way for the following hydroboration.

The next task was the installation of a hydroxyl group at the C-9 position. This was accomplished in a regio- and stereoselective manner by treating **15** with borane•THF complex followed by basic $H_2O_2$ oxidative cleavage to give the desired C-9 $\beta$-alcohol in 60% yield (Scheme 5). After removal of the minor (~10%) C-8 regioisomer via column chromatography, the C-9 $\beta$-alcohol was converted to the corresponding di-TBS-ether. After removal of the benzyl group, initial efforts to hydrogenate the tetrasubstituted double bond met with failure presumably due to the steric hindrance of this alkene.[22] This prompted us to deoxygenate the C-3 stereocenter under standard Barton−McCombie conditions (40% yield).[23] However, a more efficacious route from **16** to **18** was achieved by the dehydration with Burgess reagent[24] followed by a simple hydrogenation (90% over 2 steps). While the cleavage of the di-TBS-ether gave only messy results under regular deprotection conditions (TBAF/THF, rt or 80 °C, overnight), a microwave-accelerated deprotection proved efficient and produced **6** in excellent yield (TBAF/THF, 80 °C, 45 min, 93%).

The final stages of this synthesis would require the esterification of the C-9 hydroxyl group, reversion of the stereocenter at C-6, hydrogenation, and esterification. In fact,

(17) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319–4322.

(18) CCDC782508 contains the supplementary crystallographic data for compound **13**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/products/csd/request/.

(19) Hooft, W. W. R.; Straver, L. H.; Spek, A. L. *J. Appl. Crystallogr.* **2008**, *41*, 96–103.

(20) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639–647.

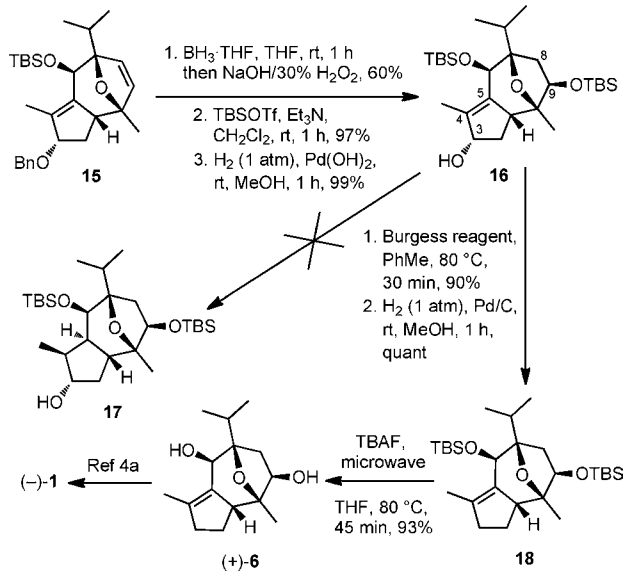
(21) To our surprise, compared to regular intramolecular reactions, this intramolecular aldol reaction requires quite high concentration (0.4−0.7 M).

(22) The $C_4$−$C_5$ double bond stays untouched even under high pressure (up to 130 bar) with Pd/C, Crabtree's catalyst, or $PtO_2$.

(23) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, *16*, 1574–1585.

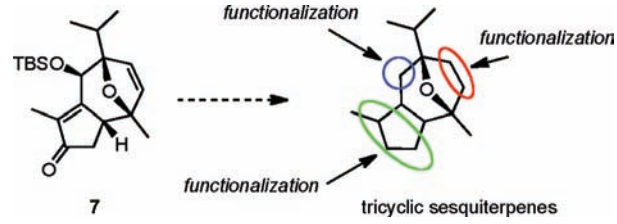
(24) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744–4745.

**Scheme 5**




during the course of our work, an alternative route to (+)-**6** and its successful elaboration to (−)-englerin A was reported by Ma et al.[6] Our synthetic work to (+)-**6** provided another novel and facile access to the englerin core. This approach with 15 steps from readily available compound **10** and **11** in 5% overall yield constitutes a formal synthesis of (−)-englerin A. More importantly, this Rh-catalyzed [4 + 3] cycloaddition, followed by an intramolecular aldol condensation, provides a unique and facile method for construction of a common guaiane-type tricyclic sesquiterpene skeleton. This strategy is broadly applicable to an enantioselective synthesis of englerin and related natural products from the key intermediate **7** (Scheme 6). The applications of this

**Scheme 6**




strategy to the synthesis of natural and designed tricyclic sesquiterpenes could facilitate the SAR and chemical biology studies of this unexplored class of natural products.

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**Supporting Information Available:** Experimental procedures and characteristic data of new compounds, as well as X-ray data of compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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