Natural Product Synthesis (2)

DOI: 10.1002/anie.201000890

Enantioselective Synthesis of (−)-Englerins A and B**

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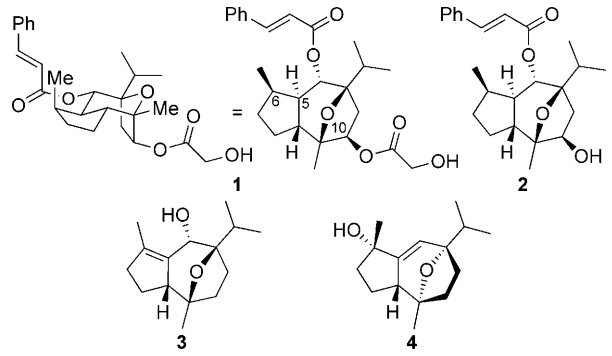
(−)-Englerin A (**1**) is a sesquiterpene diester isolated from the stem bark of the east African plant *Phylanthus engleri* that has been shown to selectively inhibit the growth of renal cancer cell lines at the nanomolar level (Scheme 1).[1] Indeed,

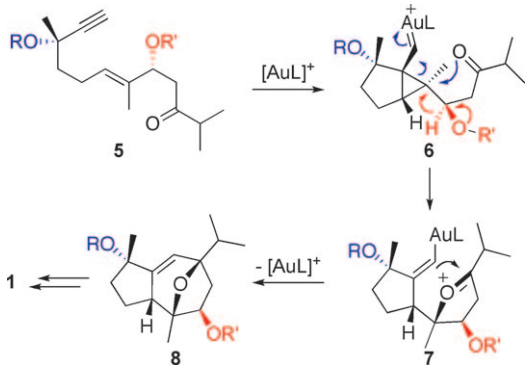


Scheme 1. Englerins A (**1**) and B (**2**) and other guaiane sesquiterpenes.

1 was found to be 1–2 orders of magnitude more potent than taxol against certain cancer cell lines. In contrast, (−)-englerin B (**2**), lacking the glycolate at C10, was much less active and selective. An elegant total synthesis of the enantiomer of **1** from the naturally occurring terpene *trans*,-*cis*-nepetalactone by the research group of Christmann established the absolute configuration of these guaianes as shown in Scheme 1.[2]

Recently, our research group has developed the gold(I)-catalyzed [2+2+2] alkyne/alkene/carbonyl cycloaddition of 1,6-enynes bearing a carbonyl group in which two C–C and one C–O bonds are formed in a domino process.[3] As has been shown in gold(I)-catalyzed reactions of enynes,[4] this reaction is stereospecific. Furthermore, we have recently found that a propargylic stereocenter bearing an OR group exerts an exquisite stereocontrol in the cyclization process, which has been applied in the total synthesis of the oxatricyclic sesquiterpenes (+)-orientalol F (**3**) and (±)-pubinernoid B (**4**).[5] This cyclization is faster than the intramolecular 1,5-migration of propargylic OR groups that occurs in related systems.[6]

We planned to use the gold-catalyzed domino reaction for the synthesis of **1** and **2** from a 1,6-enyne **5** that is substituted by OR groups at the propargylic and allylic positions (Scheme 2). However, the allylic OR′ group would confer



Scheme 2. Mechanistic rationale for the key gold(I)-catalyzed cyclization.

additional lability to this substrate in the presence of Lewis acidic Au^I catalysts. The OR′ group could also interfere with the carbonyl group in the opening of intermediate **6** to form **8** via oxonium cation **7**. Thus, for R′ = H or silyl, a semipinacol-type rearrangement (red arrows in Scheme 2) could lead to an earlier termination of the cyclization process.

We have found that using a gold complex with a highly donating ligand as the catalyst, the cyclization tolerates both propargylic and allylic substituents and proceeds with remarkable stereoselectivity. Herein we report the enantioselective total synthesis of (−)-englerins A (**1**) and B (**2**) from inexpensive geraniol by using the [2+2+2] gold-catalyzed cycloaddition as a key step.

The synthesis of **1** and **2** commenced with the preparation of the known 1,6-enyne **10**[7] (Scheme 3). Thus, the Sharpless asymmetric epoxidation of **9** (95:5 e.r.) was followed by substitution of the primary alcohol by a chloride atom using CCl_4 and PPh_3, and reaction with *n*BuLi (99% yield over 3 steps). Protection of propargylic alcohol **10** as the TES ether and oxidative cleavage of the olefin provided **11** (97% yield over 3 steps), which underwent a Wittig reaction with ylide **12** to afford exclusively (*E*)-enal **13** (76% yield). The stereoselective Denmark aldol reaction of **13** with trichlorosilyl enol ether **14** in the presence of chiral phosphoramide **15**[8]

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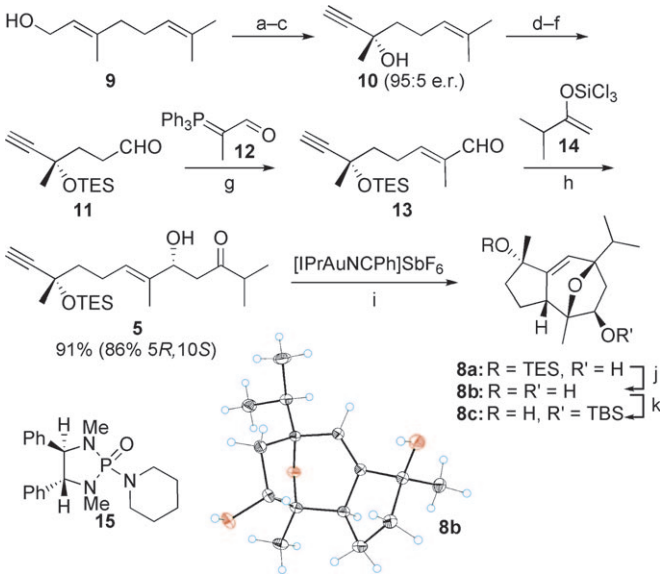
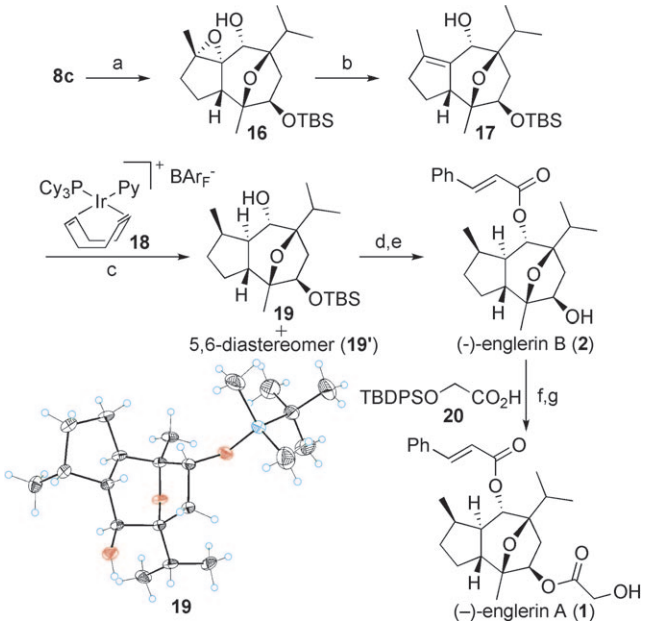
[**] We thank the MICINN (CTQ2007-60745/BQU and Consolider Ingenio 2010, grant CSD2006-0003), the AGAUR (2009 SGR 47), and the ICIQ Foundation for financial support. We also thank E. Escudero-Adán and Dr. J. Benet-Buchholz (X-ray diffraction unit, ICIQ) for the X-ray structure determination of **8b** and **19**, as well as Dr. Eloísa Jiménez-Núñez for helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201000890.



Scheme 3. Synthesis of the key oxatricyclic diols **8**. Reagents and conditions: a) L-(+)-diethyl tartrate, $Ti(OiPr)_4$, *tert*-butylhydroperoxide, CH_2Cl_2, −40 °C, 5 h, 99%, 95:5 e.r.; b) CCl_4, PPh_3, 80 °C, 6 h, 84%; c) *n*BuLi (3.5 equiv), THF, −40 °C, 2 h, 98%; d) TESOTf, Et_3N, CH_2Cl_2, 23 °C, 3 h, quant; e) AD-mix-α, *t*BuOH/H_2O (1:1), 23 °C, 10 h, 98%; f) $NaIO_4/SiO_2$, CH_2Cl_2, 23 °C, 10 h 99%; g) **12** (1.6 equiv), benzene, reflux, 2 days, 76%; h) **14** (1.2 equiv), **15** (5 mol%), CH_2Cl_2, −78 °C, 4 h, 91% (>14:1 d.r.); i) $[IPrAuNCPh]SbF_6$ (3 mol%), CH_2Cl_2, 23 °C, 5 h, 58%; j) TBAF, CH_2Cl_2, 23 °C, 10 h, 89%; k) TBSCl, DMAP, imidazole, 23 °C, 10 h, CH_2Cl_2, 23 °C, quant. DMAP = 4-dimethylaminopyridine, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidene, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.



Scheme 4. Synthesis of (−)-englerins A (**1**) and B (**2**). Reagents and conditions: a) CrO_3(2,5-dimethylpyrazole) (3 equiv), CH_2Cl_2, 23 °C, 2 h, 73%; b) WCl_6 (2 equiv), *n*BuLi (4 equiv), THF, 0 to 50 °C, 2 h, 82%; c) **18** (30 mol%), H_2 (80 bar), CH_2Cl_2, 23 °C, 4 days, quant (1:1 d.r.); d) cinnamoyl chloride (3 equiv), DMAP (3 equiv), CH_2Cl_2/Et_3N (2:1), 80 °C, 4 h, 100%; e) TBAF, 23 °C, CH_2Cl_2, 6 h, 91% (yield over 2 steps); f) **20** (1.1 equiv), 2,4,6-trichlorobenzoyl chloride, DMAP, toluene, 0 °C, 1 h, 96%; g) TBAF, HOAc, CH_2Cl_2, 23 °C, 3 h, 90%. $BAr_F^- = (3,5\text{-}(CF_3)_2C_6H_3)_4B^-$, Cy = cyclohexyl, TBDPS = *tert*-butyldiphenylsilyl.

(5 mol%) in CH_2Cl_2 at −78 °C gave β-hydroxy ketone **5** (91% yield). Analysis of both (*R*)- and (*S*)-Mosher esters of **5** showed that the aldol reaction had proceeded with >14:1 d.r. This route is amenable to scale-up and 5–6 g of **5** was routinely prepared. Remarkably, after testing a number of protected derivatives of aldol **5** in gold(I)-catalyzed reactions, we found that the best results were obtained by using unprotected aldol **5** with catalyst $[IPrAuNCPh]SbF_6$[9] (3 mol%) at room temperature in CH_2Cl_2. Under these reaction conditions, oxatricyclic derivative **8a** was obtained as a single diastereomer in 58% yield, which corresponds to a 67% yield based on the major 5*R*,10*S* stereoisomer of aldol **5**. This reaction was usually performed in a 0.5–1 g scale. Other catalysts gave poor results. Desilylation with TBAF provided diol **8b** (89% yield), whose structure was confirmed by X-ray crystal structure analysis.[10] Selective protection of the secondary alcohol of **8b** gave **8c** quantitatively, which showed >99% *ee*.

The isomerization of **8c** into **17** was performed in two steps by an oxidation/reduction protocol (Scheme 4).[5] Thus, the treatment of **8c** with CrO_3 and 2,5-dimethylpyrazole[11] gave epoxy alcohol[12] **16** in 73% yield. When the reaction was carried out with Collins reagent **16** was afforded in similar yield (71% yield), along with the corresponding epoxy ketone (17% yield), which was quantitatively transformed into **16** (88% yield over 2 steps) with $NaBH_4$ and $CeCl_3$. Oxidative rearrangement of **8c** using $TEMPO^+BF_4^-$ or $TEMPO/NaIO_4/SiO_2$ (TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical) was not successful.[13,14] Reduction of **16** with WCl_6 and *n*BuLi[15] gave **17** in 82% yield. Catalytic hydrogenation of the tetrasubstituted olefin of **17** using H_2/Raney Ni gave exclusively diastereomer **19′**. However, Pfaltz's Ir^I catalyst **18**[16] allowed us to partially overcome the steric bias of this olefin and led to a separable 1:1 mixture of **19** and **19′** in quantitative yield. The configuration of crystalline **19** was confirmed by X-ray crystal structure analysis.[10] Esterification of the secondary alcohol of **19** with cinnamoyl chloride and desilylation with TBAF led to (−)-englerin B (**2**; 91% yield over 2 steps). The final esterification of **2** was achieved by treatment with TBDPS-protected glycolic acid **20** under Yamaguchi conditions[17] (96% yield), and subsequent removal of the protecting group on the primary alcohol with TBAF buffered with HOAc (90% yield). The ^1H and ^{13}C NMR spectra and the optical rotations of synthetic **1** and **2** matched with those reported for natural products.[1,18]

We have completed the total synthesis of the natural enantiomers of englerins A (**1**) and B (**2**) by a route that is efficient (for **1**: 18 steps and 7% overall yield from geraniol), easily scalable, and provides access to intermediates such as **19** that could be used for the preparation of a variety of analogues. This synthesis takes advantage of a stereoselective aldol reaction developed by Denmark and features a remark-

ably selective gold-catalyzed cyclization of an enyne bearing an unprotected alcohol group at a stereogenic allylic position.

Received: February 12, 2010
Published online: April 6, 2010

Keywords: antitumor agents · domino processes · gold catalysis · guaiane sesquiterpenes · total synthesis

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[18] Englerin A (**1**): $[\alpha]_D^{20} = -58.7 \pm 2.5\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.52\ g\,cm^{-3}$, MeOH), lit[1] $[\alpha]_D^{20} = -63\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.13\ g\,cm^{-3}$, MeOH). Englerin B (**2**): $[\alpha]_D^{20} = -29.8 \pm 1.7\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.17\ g\,cm^{-3}$, MeOH), lit[1] $[\alpha]_D^{20} = -32\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.17\ g\,cm^{-3}$, MeOH).

