

## Total Synthesis of Englerin A

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*J. Am. Chem. Soc.* **2010**, *132*, 8219–8222, Received in April 12, 2010

### 1. Introduction

- Englerin A ((-)-1) and its derivatives englerin B ((-)-2) and englerin B acetate ((-)-3) were discovered from the stem bark of *Phyllanthus engleri* in Tanzania (Figure 1).
- Englerin A has potent and selective growth inhibitory activities against renal cancer cells.<sup>1</sup>
- The cytotoxicity decreased from (-)-1 to (-)-2 or (-)-3.
  - > C<sub>3</sub> ester side chain is crucial for bioactivities.
- There are already two reports on total synthesis of Englerin A.<sup>2</sup> In both cases, they synthesized chiral linear-chain compounds at very early stage of their total synthesis. Both used gold catalyzed cycloaddition of chiral compounds to form oxatricyclo framework.

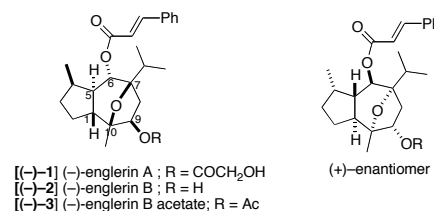
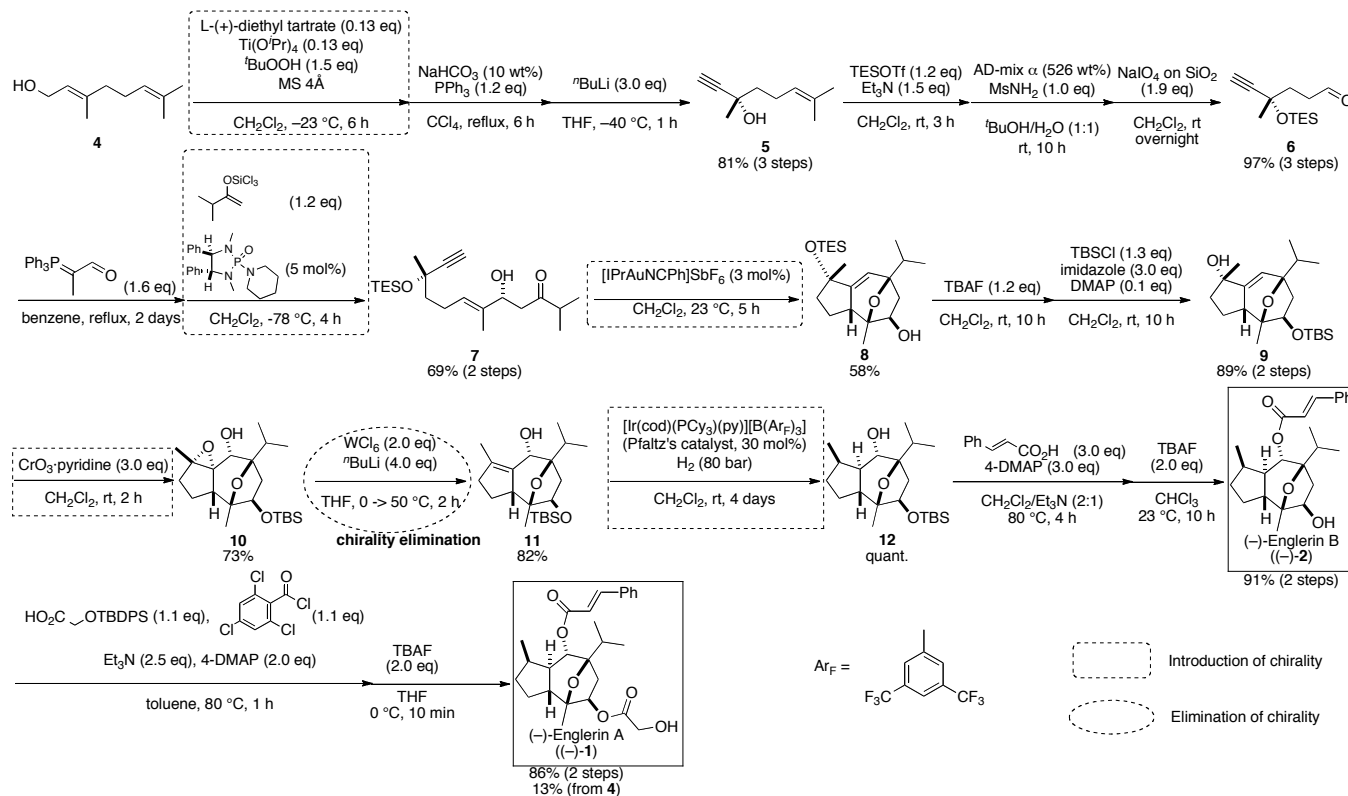


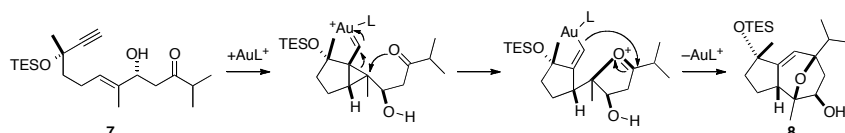
Figure 1. Structures of Englerin A and its derivatives

### 1.2. Previous Work (Scheme 1)<sup>2a</sup>

Scheme 1. Synthesis of (-)-englerin A (1) and B (2)<sup>3</sup>



Scheme 2. Mechanism of gold-catalyzed [2+2+2] alkyne/alkene/carbonyl cycloaddition from 7 to 8



- Introduction of chirality in the early step (4 → 5). Five chirality-introducing steps and one chirality-eliminating step.
- (-)-Englerin A ((-)-1) was synthesized in 18 steps in 13% yield.
- Oxatricyclo enone 8 was synthesized by gold(I)-catalyzed [2+2+2] alkyne/alkene/carbonyl cycloaddition in moderate yield. (7 → 8)
- Although chiral epoxide was introduced in 10, three chiral centers including chiral epoxide were eliminated. (10 → 11). After that two chiral centers were introduced. (11 → 12)

### 1.3. This Work:

- Introduction of chirality in the latter part of synthesis, without any elimination of chirality
- Usage of achiral compounds to form chiral oxabicyclo framework and introduction of three chiral centers in one step (Figure 2)
- Cytotoxicity measurement to study which functional groups are critical to bioactivities

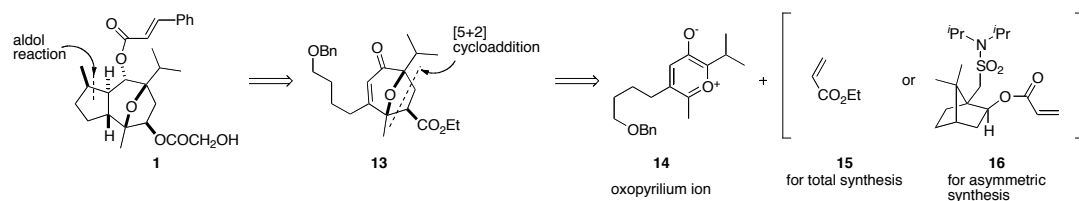


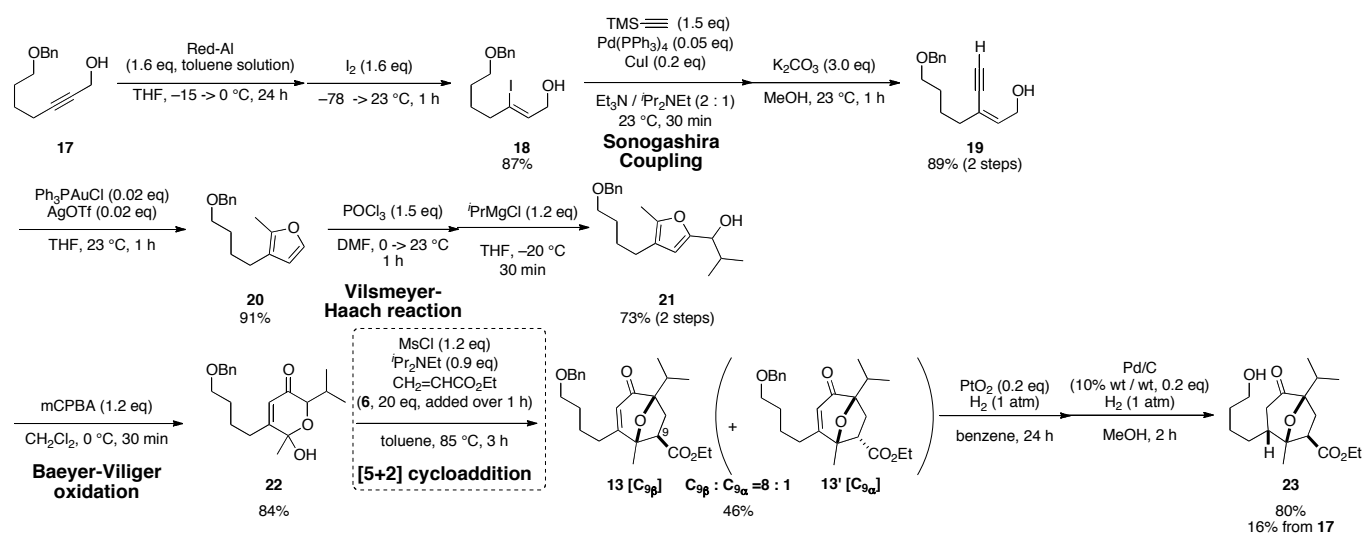
Figure 2. Retrosynthetic analysis of 1.

## 2. Results and Discussion

### 2.1. Total Synthesis of Englerin A (1)

#### 2.1.1. Synthesis of the key intermediate 13 (Scheme 3)

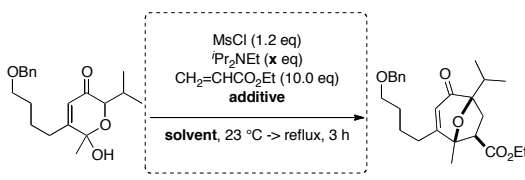
Scheme 3. Synthesis of oxabicyclo enone 13.



- Oxabicyclo enone (±)-13 was synthesized from propargylic alcohol 17 in 9 steps (overall yield of 13 was 16.0%, Scheme 2).
- Reaction conditions from 22 to 13 was optimized; using low concentration of 22 in toluene and adding 22 slowly to a refluxing solution of <sup>i</sup>Pr<sub>2</sub>NEt (substoichiometric amount, 0.9 eq), MsCl and ethyl acrylate worked the best (Table 1, entry 6).

- Addition of metal salts as Lewis acids led to unidentifiable mixture of byproducts (entry 4).
- Only toluene and acetonitrile as a solvent worked to produce desired compound **13** (entry 3).
- Isomers **13** and **13'** were easily separated by silica gel flash column chromatography, but (+)-**13** and (-)-**13** were inseparable even by chiral column chromatography.

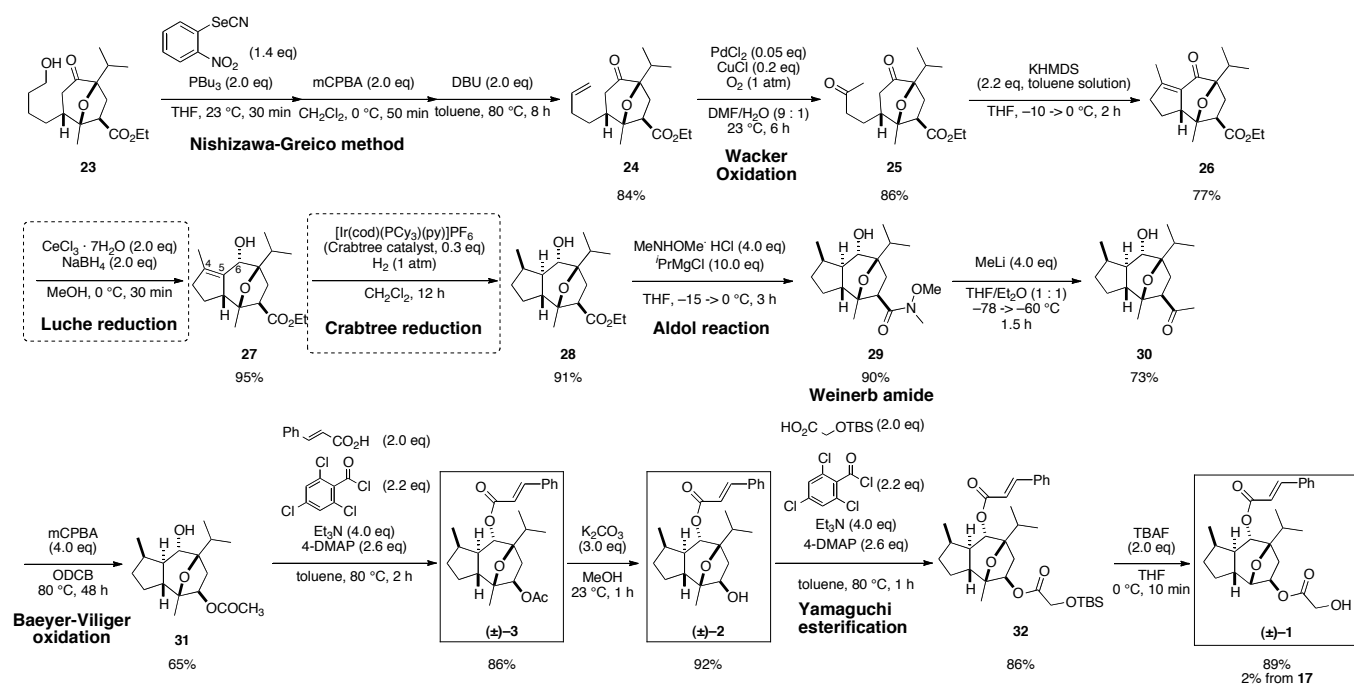
**Table 1.** Optimization of reaction conditions from **22** to **13**. Reverse addition: addition of **22** into a mixture of MsCl, etc.



entry	x	solvent	additive	yield (%)	selectivity	note
1	1.2	toluene (0.15 M)	none	47	5 : 1	
2	1.2	CH <sub>3</sub> CN (0.15 M)	none	50	1.5 : 1	
3	1.2	toluene with metal salts as additive, THF, ClCH <sub>2</sub> CH <sub>2</sub> Cl,		unidentified mixture		
4	1.2	toluene (0.15 M)	LiCl (1.0 eq)	25	3.3 : 1	
5	1.2	toluene (0.13 M)	none	49	5 : 1	reverse addition
6	0.9	toluene (0.04 M)	none	46	8 : 1	reverse addition

## 2.1.2. Synthesis of Englerin A (**1**, Scheme 4)

**Scheme 4.** Synthesis of Englerin A (**±**)-**1** and its derivatives (**±**)-**2** and (**±**)-**3**.



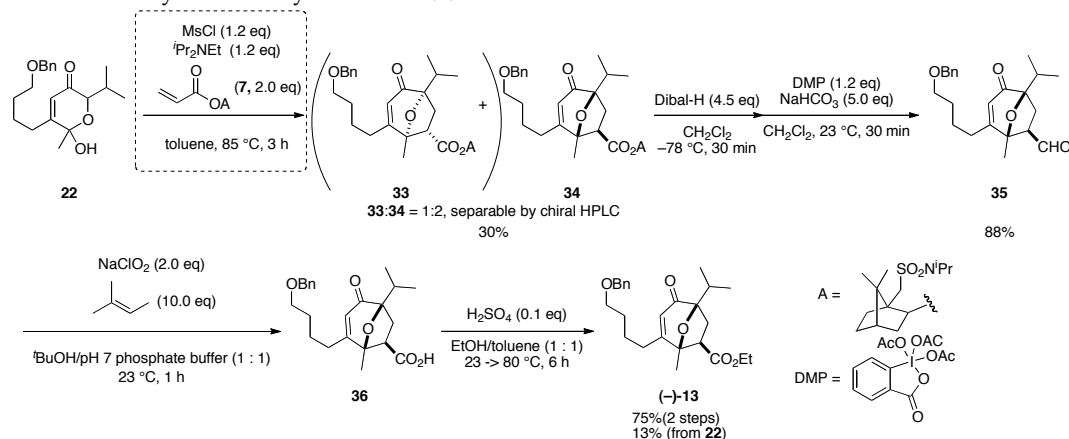
- Englerin A (**±**)-**1** and its derivatives (**±**)-**2** and (**±**)-**3** were synthesized in 12, 10, and 9 steps respectively from **23** (overall yield of (**±**)-**1** was 12.4% (from **23**) and 2.0% (from **15**)).
- Total number of chirality-introducing steps were three.
- Chirality introduction: hydroxyl group at C<sub>6</sub> position in **27** was introduced by Luche reduction.
- C<sub>6</sub> hydroxyl group was crucial for stereoselectivity in the Crabtree hydrogenation (**27** → **28**). In a condition using Pd/C and H<sub>2</sub>, hydrogenation underwent from the opposite face of the C<sub>4</sub>-C<sub>5</sub> bond.
- Desired glycolic acid residue was introduced smoothly by Yamaguchi conditions in 86% yield

(±)-2 -> (±)-1). This process is similar to previous work.<sup>2a</sup>

- NMR data of englerin A derivatives (±)-1, 2, 3 matched those reported for the naturally derived materials, except for optical rotations.

## 2.2. Asymmetric Synthesis of Englerin A Precursor 13 (Scheme 4)

Scheme 5. Asymmetric synthesis of (-)-13



- Key compound (-)-13 was asymmetrically synthesized in 4 steps (overall yield 13.2% from 24, conversion from 24 to 35 and 36 was not optimized).
- A chiral sulfonamide acrylate derivative (CH<sub>2</sub>CHCO<sub>2</sub>A), which is available in 3 or 4 steps from commercially available compounds<sup>4</sup>, assisted the asymmetrical [5+2] cycloaddition reaction.
- Exo diastereoisomers 33 and 34 were separated by chiral HPLC.
- Accessibility to (-)-13 enabled us to synthesize (-)-1, (-)-2, (-)-3 (not accomplished).

## 2.3. Cytotoxicity (Table 2)

- Only 1 and 37 showed activities in renal cells ACHN and UO31 (Table 2) ->Substituents at C<sub>6</sub> position are not so important than that at C<sub>9</sub> position.

Table 2. Cytotoxicity study of Englerin derivatives

	GI <sub>50</sub> (growth inhibition of 50%) [μM]						
	(-)-1 <sup>1</sup>	(±)-1	(±)-2	(±)-3	31	32	37
ACHN	<0.01	0.113 ± 0.071	>10	>10	>10	>10	0.745 ± 0.166
UO31	<0.01	0.037 ± 0.005	>10	9.275 ± 0.013	>10	>10	0.359 ± 0.006

## 3. Conclusion

- Englerin A (1) and its derivatives and a precursor of (-)-1 were synthesized.
- Cytotoxicity study revealed that substituent at C<sub>9</sub> position was important, and at C<sub>6</sub> position was less important.

## References

- Ratnayake, R.; Covell, D.; Ransom, T. T.; Gustafson, K. R.; Beutler, J. A. *Org. Lett.* **2009**, *11*, 57–60.
- a) Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2010**, *43*, 3513–3516. b) Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *43*, 3517–3519. Both papers were received in February 12, 2010.
- (b)
- AD-mix-a includes K<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>[Fe(CN)<sub>6</sub>], and catalytic amount of K<sub>2</sub>O<sub>5</sub>O<sub>2</sub>(OH)<sub>4</sub> and chiral ligand (DHQ)<sub>2</sub>PHAL.
- a) Wolfgang, O.; Christian, C.; Gerald, B. *Tetrahedron Lett.* **1984**, *25*, 5885–5888 (3 steps). b) Duggan, A. R.; Kaye, P. T.; Caira, M. R. *J. Chem. Res., Synopses* **2006**, *11*, 744–747 (4 steps).