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β-Ketoesters as Mono- or Bisnucleophiles: A Concise Enantioselective Total Synthesis of (-)-Englerin A and B

Lei Guo[a], and Bernd Plietker*[a]

Abstract: A short enantioselective total synthesis of englerin A, a guaiane sesquiterpene with significant in vitro anti-tumor activity, is reported. Key features of this total synthesis are an organocatalytic, asymmetric decarboxylative aldol reaction, a neighboring group participated [4+3] cycloaddition, a novel one-pot Heck coupling-regioselective 1,4-hydrosilylation-Tamao-Fleming oxidation cascade, and a kinetic CBS reduction to obtain the optically pure natural products in 6.7 % overall yield within 12 steps starting from methylglyoxal.

Englerin A and B (**1** and **2**, Figure 1) are guaiane sesquiterpene type natural products originating from the shrub tree *Phyllanthus engleri* common in East Africa, which were isolated from its stem bark's extraction by Beutler and co-workers in 2009.[1] Biological evaluation revealed that englerin A is a promising new lead compound in oncology as it targets TRPC4/5, an essential part of the transient receptor potential cation channels TRPC that regulate i.a. the Ca-concentration within cells and controls endothelial permeability, vasodilation, neurotransmitter release and cell proliferation. As such, englerin A inhibits selectively renal cancer cell lines' growth with GI_{50} between 1-87 nM.[1-3] This unusual mode of action renders englerin A to be a potent anti-cancer drug candidate and makes it an interesting starting point for potential antitumor target research.[3]

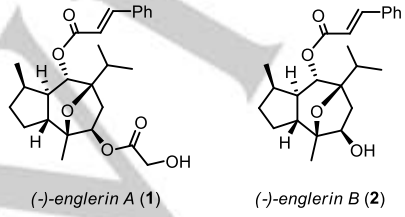
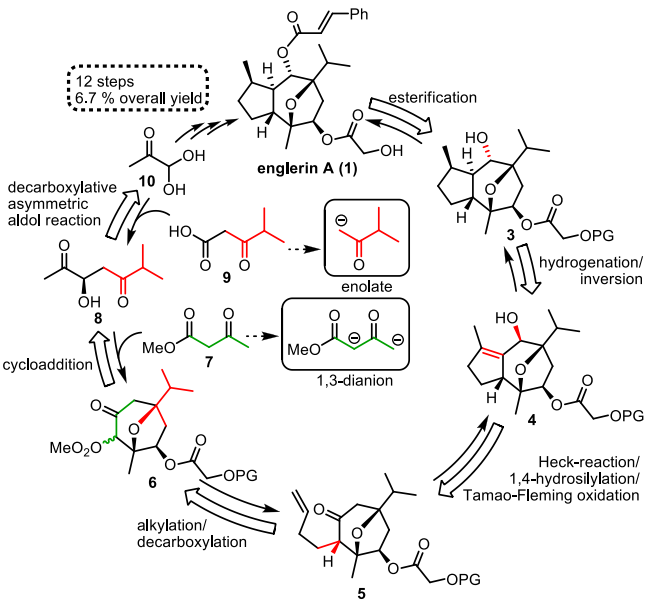


Figure 1. Guaiane sesequterpene natural products.

The englerins possess a challenging tricyclic structure featuring a *trans*-fused bicyclo[5.3.0]-guaiane-type moiety plus the seven-membered ring is part of an oxabicyclo[3.2.1]-heptane core system featuring six contiguous stereogenic centers. The interesting molecular structure plus the reported bioactivities have spurred interest in developing efficient synthetic strategies.[4-7] In particular the complex tricyclic core represented a severe synthetic challenge that needed to be addressed. Ring-closing olefin metathesis was successfully shown to be powerful strategy to generate the core structure.[5a,5c,5e,5f] Alternatively, a conjugate addition-reductive coupling sequence can be used to assemble the tricyclic core in an efficient manner.[5d] However, the majority of reported syntheses relied on the use of cycloaddition as the key steps, e.g. a Au(I)-catalyzed enyne-carbonyl [2+2+2]-cycloaddition,[5b,6a] an oxidopyrylium-based [5+2]-cycloaddition to acrylate,[4a] and a Rh-carbene-[6c,7a] or Pt-catalyzed[6d] [4+3]-cycloaddition. As the majority of enantioselective syntheses make use of chiral pool materials,[5] only four enantioselective total syntheses were reported in which a catalytic asymmetric transformation of an achiral material was employed.[6] We describe here a conceptually novel total synthesis of (-)-englerin A (**1**) and B (**2**) in which β-ketoacid derivatives play a pivotal role as either enolate surrogates in an asymmetric organocatalytic aldol reaction or as 1,3-bisnucleophiles in a [4+3]-cycloaddition.



Scheme 1. Retrosynthetic analysis (PG: protecting group).

β-Ketoacids and their corresponding esters are essential building blocks in a variety of total syntheses.[8] They can either be considered as biological enol-surrogates in aldol-type C-C-bond formations or as 1,3-dianion in cycloaddition chemistry. Inspired by the latter type of transformation we hypothesized, that these compounds could allow for a short straightforward modular total synthesis of englerin A. The corresponding

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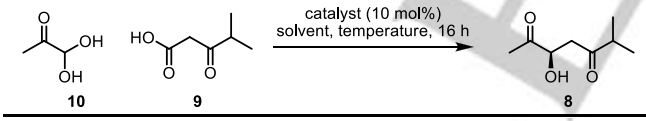
retrosynthetic strategy is depicted in Scheme 1. Accordingly, the esterification of alcohol **3** in the final step would provide access to englerin A (**1**), alcohol **3** might be accessible through an oxidation-reduction sequence followed with a diastereoselective olefin hydrogenation of allylic alcohol **4**. The latter one was envisaged to derive from Pd-catalyzed Heck-coupling followed by a Pd-catalyzed 1,4-hydrosilylation of the formed 1,3-diene. Tamao-Fleming oxidation of the allyl silane could provide access to the desired alcohol **4**. Cyclization precursor **5** can be obtained in a straightforward manner from β-ketoester **6**, which might be accessible through a neighboring group assisted formal [4+3]-cycloaddition between dianion-surrogate β-ketoester **7** and 1,4-diketone **8**. This aldol product **8** itself shall be synthesized enantioselectively through a decarboxylative aldol-reaction between enol-surrogate β-ketoacid **9** and methylglyoxal hydrate **10** (Scheme 1).

The synthesis started with the decarboxylative aldol reaction between methylglyoxal **10** and β-ketoacid **9** which could be performed smoothly in a non-enantioselective fashion in water at room temperature without any catalysts (base, acid, metal *etc*.) with 93% yield (see SI).[9]

Table 1. Development of the enantioselective decarboxylative aldol reaction.



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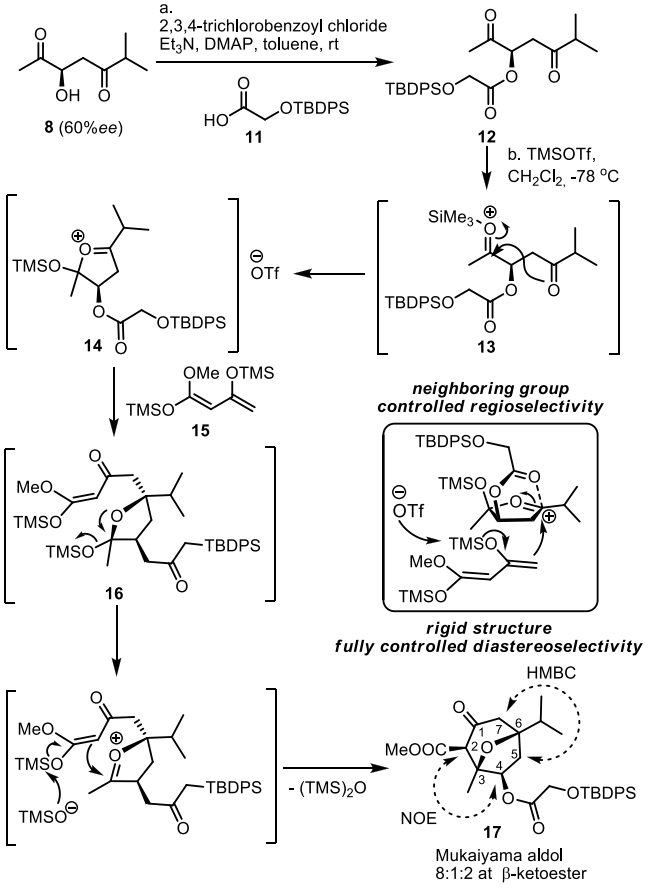
Entry	Catalyst[b]	Solvent[a]	Temp. (°C)	Yield[c] (%)	*Ee*[d] (%)
1	$(DHQD)_2Pyr$	THF	-20	83	-24
2	$(DHQD)_2AQN$	THF	-20	67	-28
3	$(DHQD)_2PHAL$	THF	-20	81	-52
4	$(DHQ)_2PHAL$	THF	-20	79	51
5	$(DHQD)_2PHAL$	THF	-40	76	-52
6	$(DHQD)_2PHAL$	THF	-80	71	-52
7	$(DHQD)_2PHAL$	CH_2Cl_2	-20	56	-40
8	$(DHQD)_2PHAL$	CH_3CN	-20	56	-43
9	$(DHQD)_2PHAL$	THF/TFE[e]	-20	81	-60
10	$(DHQD)_2PHAL$	THF/HFIP[e]	-20	66	-47

[a] Concentration: 0.1 M; [b] The structure of the catalysts are shown in the supporting information; [c] Isolated yield; [d] Enantiomeric excess (*ee*) was analyzed by chiral GC; [e] 10% of co-solvents were used. (THF: tetrahydrofurane, TFE: trifluoroethanol; HFIP: hexafluoroisopropanol)

Ma[10a,c] and List/Song[10b] reported interesting organocatalytic decarboxylative aldol reactions using chiral bisoxazolines[10a,c] or cinchona-type catalysts[10b], however, in the former case β-ketoester reacted with highly reactive trifluoroacetaldehyde hemiacetals[10a,c], in the latter case, only malonic acid half thioesters were used as enolate surrogates[10b]. Initial screening experiments indicated these catalysts to be active, however, the products were isolated in low enantiopurity. After an extensive screening of various organocatalysts we found cinchona-dimers to catalyze this reaction in an asymmetric manner at low temperature (Table 1). The linker between two cinchona moieties had a strong effect. A phthalazine linker was found to be superior to both anthraquinone- as well as pyrimidine-based linkers (Table 1, entry 1-4). Whereas the temperature had only a minor effect on the enantioselectivity (Table 1, entry 5-6), a strong solvent effect was observed (Table 1, entry 7-10). Trifluoroethanol led to an increase of the enantiomeric excess (*ee)* to 60% with 81% yield. Despite intense efforts, a further increase proved to be difficult (for details see supporting informations), hence we continued the synthesis with the enantioenriched aldol product and planned to increase the enantiomeric excess through a kinetic asymmetric discrimination at a later stage.

Alcohol **8** was esterified with TBDPS-glycolic acid **11** under Yamaguchi-conditions to afford ester **12** with 78% yield (Scheme 2).



Scheme 2. TMSOTf-mediated [4+3]-cycloaddition. Reagents and conditions: a. **11** (1.05 equiv), 2,4,6-trichlorobenzoyl chloride (1.05 equiv), Et_3N (1.2 equiv), DMAP (0.1 equiv), toluene, rt, 1 h, 78%; b. bis-silylenolether **15** (1.5 equiv), TMSOTf (0.2 equiv), CH_2Cl_2, -78 °C, 30 min, 83% overall yield. (TMSOTf: trimethylsilyloxytrifluoromethansulfonate; DMAP: *N,N*-dimethylaminopyridine; TBDPS: *tert*-butyldiphenylsilyl).

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Subsequently, the [4+3]-cycloaddition was investigated using methyl acetoacetate. Double deprotonation of the β-ketoester to the corresponding dianion followed by addition of ester **12** resulted in a complex product mixture. Inspired by Molander´s pioneering report on methyl acetoacetate derived bis-silylenolether **15** as active 1,3-dinucleophile in [4+3]-cycloadditions to 1,4-diketone,[11] we treated ester **12** with diene **15** and were pleased to find that the desired oxa[3.2.1]heptane core **17** was obtained with exclusive regioselectivity and excellent control of diastereoselectivity of the C-O-bonds at C-3 and C-4 in 83% yield.[12] Silylation of the sterically less hindered carbonyl oxygen atom leads to oxonium species **13** which undergoes a fast hemiketal formation to **14**. The adjacent carboxyl group of the ester moiety eventually stabilizes the cyclic oxonium structure thus forcing diene **15** to react *trans* to the glyoxylic ester to give the first C-C-bond in **16** with correct relative configuration. Intramolecular Mukaiyama-aldol reaction results in the formation of **17**, which was fully characterized through extensive NMR-studies.

With oxabicyclic β-ketoester **17** in hand the synthesis was pushed forward to explore the feasibility of the attempted sequential Pd-catalysis. Alkylation of **17** plus decarboxylation using microwave assisted Krapcho-condition led to the formation of ketone **18** with full control of the diastereoselectivity (Scheme 3).

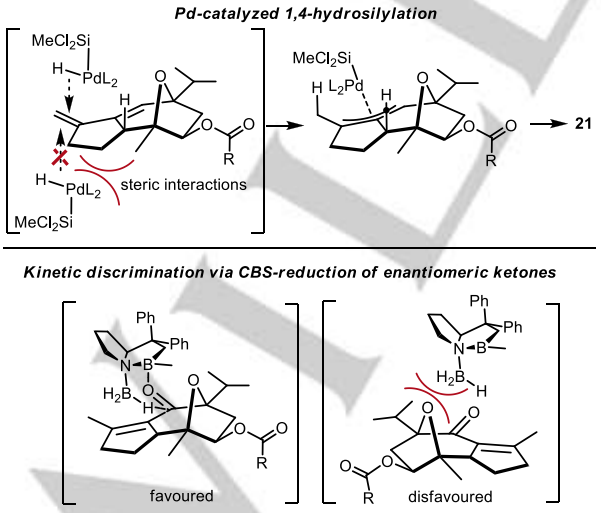
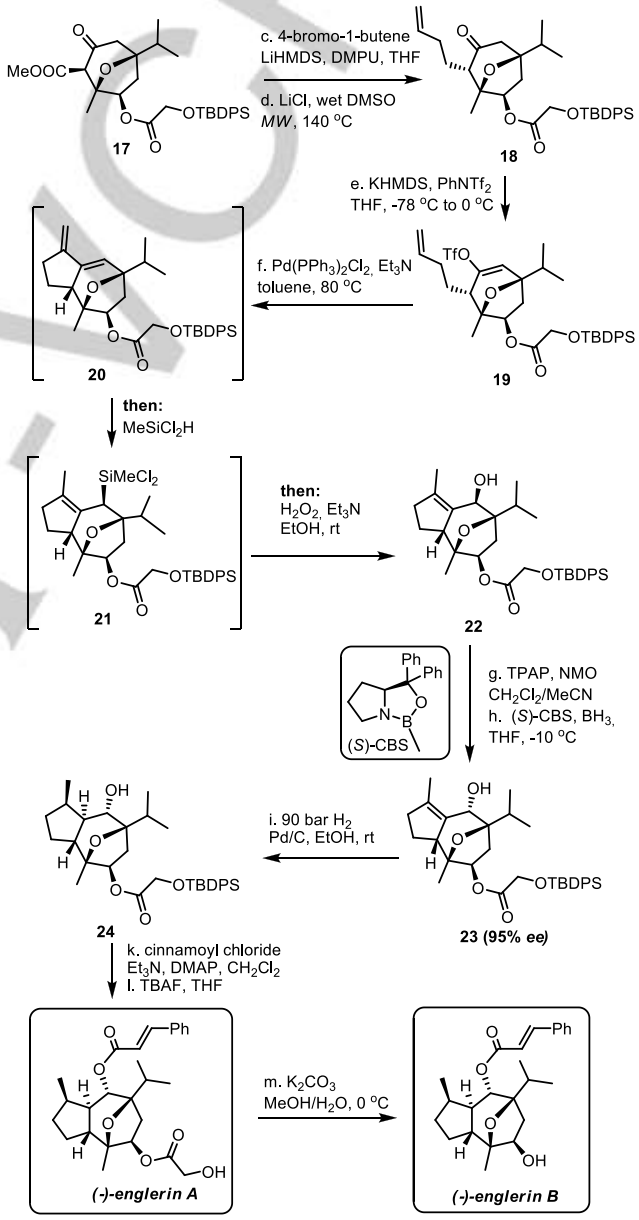


Figure 2. Stereochemical models for Pd-catalyzed 1,4-hydrosilylation (top) and CBS-catalyzed kinetic resolution (bottom).

Formation of the enoltriflate **19** set the stage for the second key transformation. Indeed the use of catalytic amounts of a $(Ph_3P)_2PdCl_2$ led to the formation of the diene **20** through an intramolecular Heck-reaction. Subsequent addition of $MeCl_2SiH$ to the reaction mixture paved the way for the second process in this catalytic sequence, i.e. the Pd-catalyzed regio- and diastereoselective 1,4-hydrosilylation of diene **20** to the corresponding allylsilane **21** (Scheme 3).[13]



Scheme 3. Total synthesis of (-)-englerin A and B. Reagents and conditions: c. 4-bromo-1-butene (1.5 equiv), LiHMDS (1.1 equiv), DMPU (2.0 equiv), THF, -78 °C to rt, 2 h, 86%; d. LiCl (1.5 equiv), wet DMSO, microwave, 150 °C, 1 h, 74%; e. KHMDS (1.2 equiv), $PhNTf_2$ (1.2 equiv), THF, -78 °C to 0 °C over 3 h, 93%; f. $Pd(PPh_3)_2Cl_2$ (0.1 equiv), Et_3N (3.0 equiv), toluene, 80 °C, 30 min, then: $MeSiCl_2H$ (2.5 equiv), 5 h, then: H_2O_2, ethanol, 58%; g. TPAP (0.1 equiv), NMO (1.2 equiv), CH_2Cl_2/MeCN = 10:1, rt, 2 h, 86%; h. (*S*)-CBS (0.3 equiv), BH_3 (0.9 equiv), THF, -10 °C, 2 h, 69%; i. Pd/C (10% *w/w*), 90 bar H_2, EtOH, rt, 48 h, 86%; i. cinnamoyl chloride (1.1 equiv), DMAP (0.2 equiv), CH_2Cl_2/Et_3N = 10/1, 40 °C, 2 h; k. TBAF (5.0 equiv), THF, rt, 6 h, 79% over 2 steps; m) K_2CO_3 (3.0 equiv), $MeOH/H_2O$ = 2:1, 0 °C, 4 h, 71%. (LiHMDS: lithium hexamethyldisalizide; DMPU: N,N-dimethylproypylenurea; DMSO: dimethylsulfoxide; NMO: N-methylmorpholine-N-oxide; TPAP: tetra-n-propylammonium perruthenate; TBAF: tetra-n-butylammonium fluoride)

The high degree of regio- and diastereoselectivity can be rationalized assuming that the Pd-H-species reacts with the less hindered exocyclic methylene group from the less hindered convex face of diene **20** (Figure 2). Fortunately, oxidative work-

up using H_2O_2 under slightly basic conditions resulted in a clean oxidation of the C-Si-bond in **21** to give allylic alcohol **22** with retention of the configuration. Starting from **19** alcohol **22** was formed in diastereomerically pure form in 58 % yield. Up to this point we were hoping to increase both the enantiopurity and to install the hydroxy group in **23** with correct relative configuration through the use of an asymmetric Corey-Bakshi-Shibata (CBS) reduction after a Ley-oxidation of **22** (Scheme 3).[14] Indeed, this strategy turned out to be particularly successful, the desired alcohol **23** was isolated with 95% enantiomeric excess and an overall yield of 60% starting from **22**. Unfavourable steric interactions between the catalyst and the undesired enantiomer might explain the high degree of kinetic resolution (Figure 2). In addition, the reduction of the intermediate α,β-unsaturated ketone using standard protocols with non-chiral reagents (e.g. $CeCl_3/NaBH_4$, etc.) gave alcohol **23** alongside with a variety of side-products. As such, this example nicely illustrates the privileged role of CBS-type Lewis-acids both with regard to stereo-, but also to regio- and chemoselectivity in asymmetric catalysis.[14] Finally, diastereoselective hydrogenation of the endocyclic double bond following Ma´s elegant approach[5b] led to fully saturated tricycle **24** in 86% yield. Esterification and deprotection provided (-)-englerin A in 79% yield over both steps. Selective saponification of the more reactive glycolic ester moiety gave (-)-englerin B in another 71% yield.

In summary we were able to develop a conceptually novel 12 step synthesis of (-)-englerin A starting from methylglyoxal and featuring an asymmetric organocatalytic decarboxylative aldol reaction, a [4+3]-cycloaddition of β-ketoester-derived bis-silylenolether to a 1,4-diketone and formation of the cyclopentane motif through a sequential Pd-catalyzed Heck-reaction-1,4-hydrosilylation-Tamao-Fleming oxidation. Kinetic discrimination via a CBS-reduction step allowed to obtain an advanced intermediate in more than 95% enantiomeric excess. Overall, the synthesis allows the preparation of the natural product in 6.7% overall yield starting from methylglyoxal. The modularity of the synthesis which is based on the initial catalytic decarboxylative aldol-reaction sets the stage for the preparation of a potential englerin A-library to improve and study the mode-of-action. Future work will concentrate on these aspects.

Acknowledgements

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Keywords: organocatalysis • asymmetric catalysis • natural product • antitumor • total synthesis

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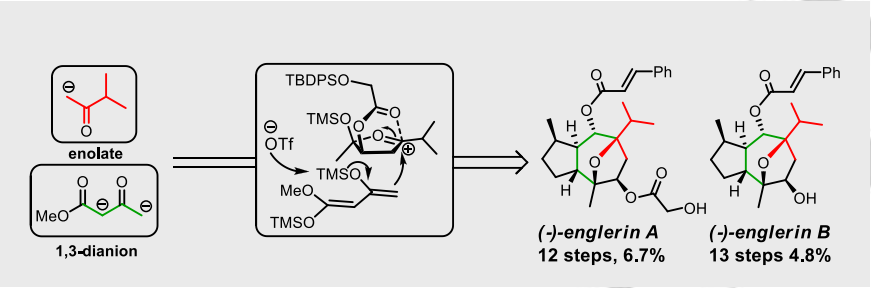

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