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Asymmetric Total Synthesis of (−)-Englerin A through Catalytic Diastereo- and Enantioselective Carbonyl Ylide Cycloaddition

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Abstract: An asymmetric total synthesis of the guaiane sesquiterpene (−)-englerin A, a potent and selective inhibitor of the growth of renal cancer cell lines, was accomplished. The basis of the approach is a highly diastereo- and enantioselective carbonyl ylide cycloaddition with an ethyl vinyl ether dipolarophile under catalysis by dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate], [Rh_2(*S*-TCPTTL)$_4$], to construct the oxabicyclo[3.2.1]octane framework with concomitant introduction of the oxygen substituent at C9 on the *exo*-face. Another notable feature of the synthesis is ruthenium tetraoxide-catalyzed chemoselective oxidative conversion of C9 ethyl ether to C9 acetate.

(−)-Englerin A (**1**) (Figure 1), a guaiane sesquiterpene isolated from the stem bark of the East African plant *Phyllanthus engleri* by Beutler et al., was found to possess very potent growth inhibitory (GI) activity (GI_{50} < 20 nM) against four of eight renal cancer cell lines with approximately 1000-fold selectivity over most other cancer cell lines in the NCI-60 panel.[1] While the mechanism of action of englerin A remains to be elucidated,[2] it has very recently been disclosed that **1** activates transient receptor potential canonical channels 4 and 5 (TRPC4/5) in renal cancer cells to induce cell death caused by Ca^{2+} overload.[3]

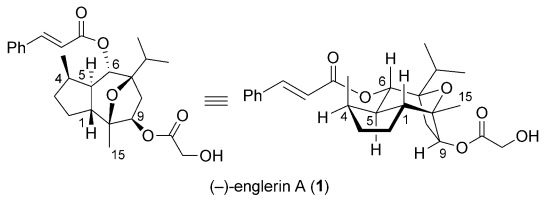
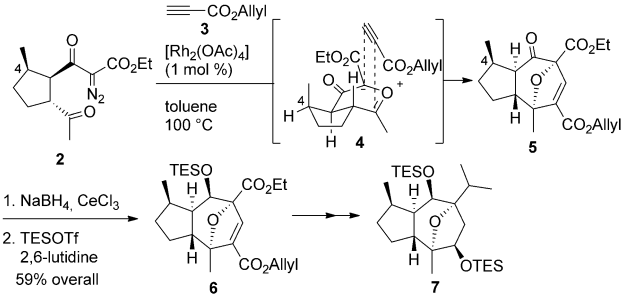


Figure 1. Structure of (−)-englerin A (**1**).

Structurally, this molecule features an oxygen-bridged 5-6-5 tricyclic system with seven contiguous stereogenic centers containing a cinnamate side chain at C6 and a glycolate fragment at C9 (englerin numbering). Not surprisingly, its great potential as a new drug lead in renal cancer chemotherapy coupled with a substantial structural challenge has rendered englerin A (**1**) a highly attractive target for synthetic investigations.[4] In 2009, Christmann et al. accomplished the first total synthesis of (+)-englerin A from (+)-*trans*,*cis*-nepetalactone utilizing an epoxylactone rearrangement, a stereoselective Barbier-type allylation, a ring-closing metathesis, and a transannular epoxide opening as the key steps, thereby establishing the previously unknown absolute configuration of natural (−)-englerin A as shown in **1**.[5] Since then, eight total syntheses,[6] three formal syntheses,[7] and several synthetic studies,[8] which are all based on innovative strategies and tactics, as well as results of structure-activity relationship studies[5b,6c,7c,9] have been reported.

The dirhodium(II) complex-catalyzed tandem cyclic carbonyl ylide formation/1,3-dipolar cycloaddition reaction of α-diazocarbonyl compounds, which has been extensively studied by Padwa's group, represents one of the most powerful methods for the rapid assembly of complex oxapolycyclic systems containing embedded di- or tetrahydrofuran rings,[10–12] and an enantioselective version of this sequence employing chiral Rh^{II} complexes has also been realized.[13,14] Capitalizing on the carbonyl ylide cycloaddition strategy, Maier et al. reported a concise chiral pool approach toward the oxygen-bridged guaiane-type core structure of **1** starting from inexpensive, commercially available (*R*)-(−)-carvone (Scheme 1).[8a] However, contrary to what they expected, cycloaddition of the bicyclic carbonyl ylide **4** generated from $Rh_2(OAc)_4$-catalyzed dinitrogen extrusion of α-diazo-β-ketoester **2** with allyl propiolate (**3**) occurred



Scheme 1. Rh^{II}-catalyzed carbonyl ylide formation/cycloaddition approach by Maier et al.[8a] TES = triethylsilyl.

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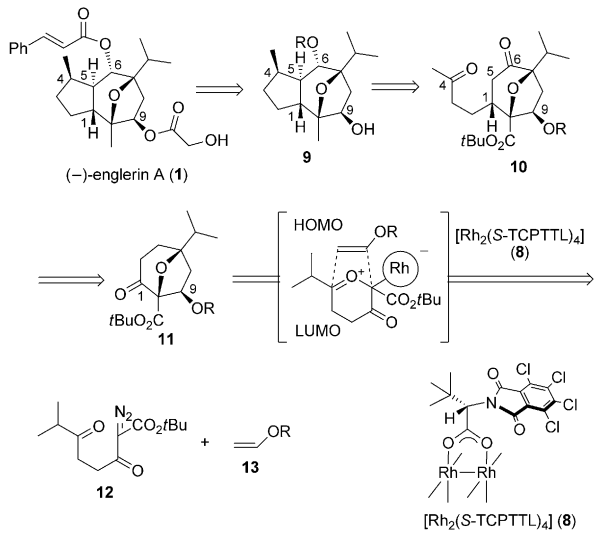
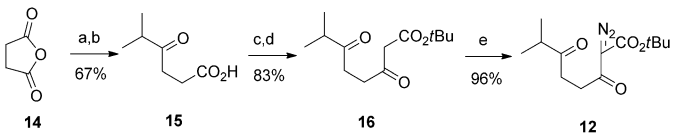
exclusively with undesired facial selectivity, wherein the dipolarophile approached the carbonyl ylide **4** *syn* to the C4 methyl group. In this context, we have reported catalytic enantioselective intermolecular cycloadditions of six-membered carbonyl ylides derived from α-diazo-β-ketoesters with electron-rich arylacetylene and styrene dipolarophiles using dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate], [Rh_2(*S*-TCPTTL)$_4$] (**8**),[15] that provide 8-oxabicyclo[3.2.1]octane derivatives with high levels of enantioselectivity (up to 99% *ee*) and perfect *exo*-diastereoselectivity for styrenes.[16,17] Intrigued by the oxabicyclo[3.2.1]octane framework carrying the oxygen substitutent at C9 on the *exo*-face found in (−)-englerin A (**1**), we report herein an alternative approach to **1** highlighting [Rh_2(*S*-TCPTTL)$_4$]-catalyzed *exo*-diastereoselective and enantioselective carbonyl ylide cycloaddition with a vinyl ether dipolarophile as the key step.

Our synthetic strategy for **1** based on the enantioselective carbonyl ylide cycloaddition is outlined retrosynthetically in Scheme 2.[18] Following the precedents,[5,6] (−)-englerin A (**1**)



Scheme 2. Retrosynthetic analysis of (−)-englerin A (**1**).

would be accessible from tricyclic alcohol **9** bearing all of the stereogenic centers of **1**. It was anticipated that **9** would be formed from diketone **10** by intramolecular aldol condensation and stereoselective reduction, which in turn could be elaborated from bicyclic β-ketoester **11**. On the basis of our previous work,[16] we envisioned that [Rh_2(*S*-TCPTTL)$_4$]-catalyzed reaction of 2-diazo-3,6-diketoester **12** with vinyl ether derivative **13** would preferentially provide the desired *exo*-cycloadduct **11**.[19,20] In this regard, Koyama et al.[19a] reported that $Rh_2(OAc)_4$-catalyzed cycloadditions of carbonyl ylides derived from 2-diazo-3,6-diketoesters with vinyloxytrimethylsilane or benzyl vinyl ether proceeded in a regio- and stereoselective manner to give *endo*-cycloadducts, wherein the dominant interaction was found to be between the LUMO of the carbonyl ylide and the HOMO of the dipolarophile.[19] Consequently, apart from enantiocontrol, diastereocontrol in favor of the *exo*-



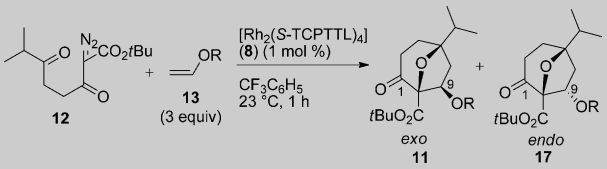
Scheme 3. Preparation of α-diazo-β-ketoester **12**. Reagents and conditions: a) ethyl 2-bromoisobutyrate, Zn-Cu, DMF, 65 °C, 2 h; b) hydrochloric acid (18%) 100 °C, 1 h; c) CDI, THF, 1 h; d) *t*$BuO_2CCH_2CO_2H$, *i*PrMgBr, THF, 8 h; e) MsN_3, Et_3N, MeCN, 14 h.

cycloadduct has become a major challenge in carbonyl ylide cycloaddition with a vinyl ether dipolarophile.

Our synthesis commenced with the preparation of the cyclic carbonyl ylide precursor **12** from succinic anhydride (**14**) as depicted in Scheme 3. Following the procedure of Schick and Ludwig,[21] Reformatsky reaction of **14** with ethyl 2-bromoisobutyrate in DMF and subsequent decarboxylation provided γ-keto acid **15** in 67% yield. Treatment of **11** with 1,1′-carbonyldiimidazole (CDI) followed by reaction with the dianion derived from *tert*-butyl hydrogen malonate gave β-ketoester **16**[22] in 83% yield, which, upon diazo transfer with methanesulfonyl azide (MsN_3),[23] produced α-diazo-β-ketoester **12** in 96% yield.

Patterned after our original work,[16a] we initially evaluated the reaction of α-diazo-β-ketoester **12** with methyl vinyl ether (**13a**) (3 equiv) using 1 mol% of [Rh_2(*S*-TCPTTL)$_4$] (**8**). The reaction in α,α,α-trifluorotoluene at room temperature proceeded smoothly to give a 62:38 mixture of cycloadducts **11a** and **17a** (Table 1, entry 1). These diastereomers could be separated by column chromatography on silica gel, affording *exo*-cyclo-

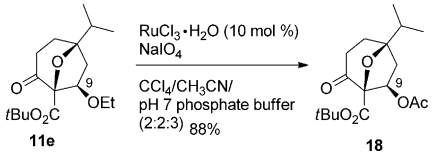
Table 1. Enantioselective carbonyl ylide cycloaddition of α-diazo-β-ketoester **12** with vinyl ethers **13** catalyzed by [Rh_2(*S*-TCPTTL)$_4$] (**8**).



Entry	Dipolarophile 13	R	11:17[b]	*exo*-Cycloadduct 11	Yield [%][c]	*ee* [%][d]	*endo*-Cycloadduct 17	Yield [%][c]	*ee* [%][d]
1	**13a**	Me	62:38	**11a**	53	92	**17a**	27	88
2	**13b**	Bn	54:46	**11b**	34	85	**17b**	31	33
3	**13c**	TMS	41:59	**11c**	22	78	**17c**	14	5
4	**13d**	MOM	23:77	**11d**	20	89	**17d**	60	89
5	**13e**	Et	87:13	**11e**	76	95	**17e**	11	77
6	**13f**	*n*Pr	90:10	**11f**	60	92	**17f**	7	27
7[e]	**13e**	Et	86:14	**11e**	75	95	**17e**	10	77

[a] All reactions were carried out as follows: a solution of **12** (107 mg, 0.4 mmol) and dipolarophile **13** (2 equiv) in $CF_3C_6H_5$ (2 mL) was added over 1 h to a solution of [Rh_2(*S*-TCPTTL)$_4$]·2 EtOAc (**8**) (7.9 mg, 0.004 mmol, 1 mol%) in $CF_3C_6H_5$ (2 mL) at rt. [b] Determined by ^{1}H NMR spectroscopy of the crude product. [c] Isolated yield. [d] Determined by HPLC analysis. [e] The reaction was conducted on 16 mmol scale and 85% of the catalyst was recovered with sufficient purity for reuse.

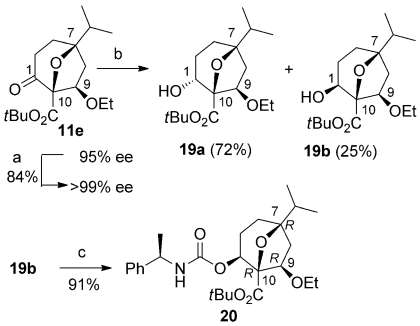
adduct **11a** in 53% yield with 92% *ee* and *endo*-cycloadduct **17a** in 27% yield with 88% *ee*. Stereochemical assignments of **11a** and **17a** were obtained from ^{1}H NOE experiments.[24] Encouraged by the observed enantioselectivity, we next examined the reaction of **12** with vinyl ethers **13b–d** bearing easily removable protecting groups. Cycloaddition with benzyl- and trimethylsilyl (TMS)-protected vinyl ethers **13b** and **13c** resulted in a marked drop in *exo*-selectivity as well as enantioselectivity for *exo* cycloadducts **11b** and **11c** (entries 2 and 3), while the use of methoxymethyl (MOM) vinyl ether (**13d**) provided *endo*-cycloadduct **17d** as a major isomer with 89% *ee* (*exo*/*endo* = 23:77, entry 4). Thus, we were pleased to find that the reaction with ethyl vinyl ether (**13e**) greatly improved the *exo*-diastereoselectivity (*exo*/*endo* = 87:13) to give *exo*-cycloadduct **11e** in 76% yield and 95% *ee* (entry 5). Switching the dipolarophile to propyl vinyl ether (**13f**) resulted in similar levels of diastereo- and enantioselectivities as those with **13e**, but product yield was drastically diminished (entry 6). Clearly, ethyl vinyl ether (**13e**) proved to be the dipolarophile of choice for this cycloaddition in terms of *exo*-diastereoselectivity and enantioselectivity as well as product yield,[25] though the reason is not clear at present. However, the use of **13e** might pose a serious problem of unmasking of the hydroxy group since harsh conditions would be required to cleave the ether bond after cycloaddition. Thus, we were gratified to find that ruthenium tetraoxide-catalyzed oxidation of **11e** under Sharpless conditions[26] proceeded in a fully chemoselective manner to give the C9 acetate **18** as a sole product in 88% yield, with the oxa-bicyclic system remaining intact (Scheme 4). From a practical stand-



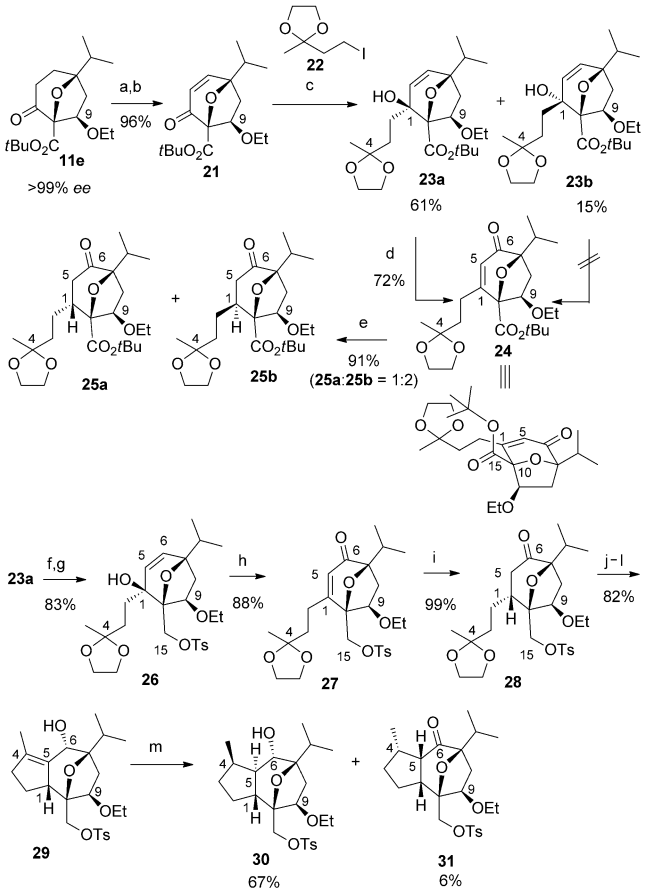
Scheme 4. Chemoselective oxidative conversion of the C9 ethyl ether into the C9 acetate.

point, it is important to note that the cycloaddition reaction could be conducted on a large scale (16 mmol) with no erosion in yield or selectivity as well as with good recovery of [Rh_2(*S*-TCPTTL)$_4$] (entry 7), though catalyst loading (1 mol%) could not be decreased. Furthermore, a single recrystallization of **11e** from ethyl acetate-hexane produced enantiomerically pure material [m.p. 157.0–159.0 °C, $[\alpha]_D^{23} = -32.5$ ($c = 1.04$, $CHCl_3$)] in 84% yield (Scheme 5). The preferred absolute configuration of **11e** was assigned as (7*R*,9*R*,10*R*) by single-crystal X-ray analysis of carbamate **20** derived from alcohol **19b**, which was consistent with that of **1**.[27]

With enantiomerically pure *exo*-cycloadduct **11e** in hand, we then focused on elaboration of the tricyclic core structure of (−)-englerin A. Treatment of ketone **11e** with sodium bis(trimethylsilyl)amide (NaHMDS) at −78 °C followed by addition of TMSCl and subsequent Ito–Saegusa oxidation[28] of the resultant silyl enol ether furnished α,β-enone **21** in 96% yield



Scheme 5. Determination of the absolute configuration of **11e**. Reagents and conditions: a) recrystallization from EtOAc-hexane; b) $NaBH_4$, EtOH, 0 °C, 1 h; c) (*R*)-α-methylbenzyl isocyanate, 4-(dimethylamino)pyridine (DMAP), toluene, reflux, 48 h.



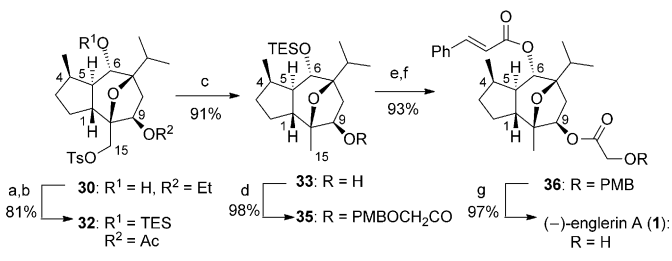
Scheme 6. Synthesis of the tricyclic alcohol **30**. Reagents and conditions: a) NaHMDS, THF, −78 °C, 30 min then Me_3SiCl, −78 °C → 0 °C; b) $Pd(OAc)_2$, MeCN; c) **22**, *t*BuLi, THF/HMPA (5:1), −78 °C; d) PCC, NaOAc, 4 Å-MS, CH_2Cl_2; e) H_2, Pd/C, EtOH; f) Red-Al, toluene, 18 h; g) TsCl, DMAP, Et_3N, CH_2Cl_2, 23 h; h) PCC, NaOAc, 4 Å-MS, CH_2Cl_2, 26 h; i) H_2, Pd/C, EtOAc, 1 h; j) 5% hydrochloric acid, acetone, 3 h; k) NaOMe, CH_2Cl_2, 46 h; l) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; m) H_2 (80 atm), Pd/C, EtOH, 48 h.

(Scheme 6). Addition of 2-(2-methyl-1,3-dioxolan-2-yl)ethyllithium generated from alkyl iodide **22**[29] and *t*BuLi[30] to enone **21** in THF at −78 °C led to the formation of a diastereomeric mixture of alcohols **23a** and **23b** in 39% and 37% yields, respec-

tively. Although the oxidation of cyclic tertiary allylic alcohol **23a** with pyridinium chlorochromate (PCC)[31] afforded α,β-enone **24** in good yield, all attempts at oxidative rearrangement of **23b** met with failure presumably due to steric hindrance around the C1 position of the epimeric tertiary alcohol. In an effort to improve the stereoselectivity, it was found that the reaction in THF/hexamethylphosphoric triamide (HMPA) (5:1) at −78 °C provided **23a** in 61% yield along with 15% of **23b**.[32] In the next step, we anticipated that catalytic hydrogenation of enone **24** should occur from the less hindered *exo* face to give the desired ketone **25a**. Unfortunately, hydrogenation of **24** over Pd/C gave the undesired C1 epimer **25b** as a major product. Molecular mechanics calculations revealed that the O-C10-C15=O fragment of **24** adopts an antiperiplanar conformation and that the *exo* face of the C1–C5 double bond is shielded by the bulky *tert*-butyl ester. Thus, we reasoned that the stereoselectivity of hydrogenation of this alkene would be reversed by decreasing the steric hindrance of the ester moiety. Toward this end, allyl alcohol **23a** was transformed into α,β-enone **27** in 73% yield by reduction with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al)[33] and subsequent tosylation of the primary alcohol followed by oxidative rearrangement.[34] Indeed, hydrogenation of **27** over Pd/C produced the desired ketone **28** as a single diastereomer in virtually quantitative yield. Removal of the ketal protection in **28** was followed by an intramolecular aldol condensation using sodium methoxide in CH_2Cl_2 and stereoselective reduction under Luche conditions[35] to afford allylic alcohol **29** as a sole product in 82% yield. Hydroxy group-directed hydrogenation[6a–c,f] of **29** with Pd/C at room temperature and under 80 atm of H_2 provided alcohol **30** as a single diastereomer in 67% yield, along with a small amount (6%) of ketone **31**. The stereochemistry of **30** was verified by ^{1}H NOE experiments.[24] The unexpected side product **31** could arise from palladium-catalyzed isomerization of the double bond of **29** on the *exo* face followed by tautomerization of the resultant enol.[34] It should be noted that high hydrogen pressure is essential to minimize the formation of **31**.[37]

With a highly controlled elaboration of the tricyclic core structure achieved, the stage was now set for completion of the total synthesis as depicted in Scheme 7. Protection of the C6 hydroxy group in **30** as its TES ether and subsequent ruthenium tetraoxide-catalyzed oxidation in an actual system uneventfully provided the C9 acetate **32** in 81% yield. Sequential reductive removal of acetyl and tosylate groups in **32** with lithium triethylborohydride[38] furnished alcohol **33** in 91% yield, which was acylated with 2-(4-methoxybenzyloxy)acetic acid (**34**)[39] and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) to give glycolate ester **35** in 98% yield. Deprotection of the TES ether with tetrabutylammonium fluoride (TBAF) followed by esterification with cinnamic acid under Yamaguchi conditions[5,40] provided diester **36** in 93% yield. Finally, removal of the 4-methoxybenzyl (PMB) group in **36** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[41] completed the synthesis of (−)-englerin A (**1**). Synthetic material **1** was spectroscopically (^{1}H and ^{13}C NMR, IR and HRMS) identical to natural **1** and also had an optical rotation, $[\alpha]_D^{20} = -58.6$ ($c = 0.51$, MeOH), in good agreement with the literature value[1] $[\alpha]_D$ −63 ($c = 0.13$, MeOH)].

In conclusion, we have accomplished the asymmetric total synthesis of (−)-englerin A in 25 steps and 5.2% overall yield from succinic anhydride. In this synthesis, we have developed a diastereo- and enantioselective carbonyl ylide cycloaddition of 2-diazo-3,6-diketoester with ethyl vinyl ether under catalysis by [Rh_2(*S*-TCPTTL)$_4$] as the key step to construct the oxabicyclo[3.2.1]octane framework with concomitant introduction of the oxygen substitutent at C9 on the *exo*-face, wherein good diastereoselectivity (*exo*/*endo* = 87:13) and high enantioselectivity of 95% *ee* for the *exo*-cycloadduct were achieved. To the best of our knowledge, this is the first example of chiral Rh^{II} complex-catalyzed enantioselective carbonyl ylide cycloaddition with a vinyl ether dipolarophile.[42] Other features of the synthesis include a hydroxy group-directed hydrogenation of tetrasubstituted allylic alcohol with Pd/C under high pressure to give *trans* ring fusion and a ruthenium tetraoxide-catalyzed chemoselective oxidative conversion of the C9 ethyl ether into the C9 acetate. Exploitation of the present strategy for the asymmetric synthesis of englerin A analogues with modification of the core structure is currently in progress.



Scheme 7. Completion of the total synthesis of **1**. Reagents and conditions a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h; b) $RuCl_3$ (10 mol%), $NaIO_4$, CCl_4/MeCN/pH 7.0 phosphate buffer (2:2:3), 6.5 h; c) $LiBEt_3H$, THF, 1.5 h; d) $PMBOCH_2CO_2H$ (**34**), EDCI, CH_2Cl_2, 0 °C, 0.5 h; e) TBAF, THF, 0 °C, 0.5 h; f) cinnamic acid, 2,4,6-$Cl_3C_6H_2COCl$, DMAP, Et_3N, toluene, 0 °C, 1 h; g) DDQ, CH_2Cl_2, 7 h.

Experimental Section

Procedure for enantioselective carbonyl ylide cycloaddition of 2-diazo-3,6-diketoester 12 with ethyl vinyl ether (13e) (Table 1, entry 7)

A solution of α-diazo-β-ketoester **12** (4.29 g, 16.0 mmol) and ethyl vinyl ether (**13e**) (3.46 g, 48.0 mmol) in α,α,α-trifluorotoluene (80 mL) was added dropwise over 1 h to a solution of [Rh_2(*S*-TCPTTL)$_4$] · 2EtOAc (**8**) (316 mg, 0.16 mmol, 1 mol%) in α,α,α-trifluorotoluene (80 mL) at 23 °C. The reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 6:1 hexane/EtOAc) to provide **11e** (3.73 g, 75%) as a white solid and **17e** (524 mg, 10%) as a colorless oil, and 95% of [Rh_2(*S*-TCPTTL)$_4$]·2EtOAc (**8**) (302 mg) was recovered. A single recrystallization of the recovered **8** (302 mg) from EtOAc/hexane gave a first crop (222 mg), and the mother liquor was concentrated and the residue was recrystallized from EtOAc/hexane to give a second crop (47 mg). Both crops were of sufficient purity for reuse.

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Keywords: (−)-englerin A · 1,3-dipolar cycloaddition · asymmetric synthesis · carbonyl ylide · dirhodium(II) complexes · total synthesis

[1] a) R. Ratnayake, D. Covell, T. T. Ransom, K. R. Gustafson, J. A. Beutler, *Org. Lett.* **2009**, *11*, 57 – 60; b) J. A. Beutler, R. Ratnayake, D. Covell, T. R. Johnson, WO 2009/088854; c) R. K. Akee, T. Ransom, R. Ratnayake, J. B. McMahon, J. A. Beutler, *J. Nat. Prod.* **2012**, *75*, 459 – 463.

[2] For biological studies of englerin A, see: a) F. J. Sulzmaier, Z. Li, M. L. Nakashige, D. M. Fash, W. J. Chain, J. W. Ramos, *PLoS One* **2012**, *7*, e48032; b) C. Sourbier, B. T. Scroggins, R. Ratnayake, T. L. Prince, S. Lee, M.-J. Lee, P. L. Nagy, Y. H. Lee, J. B. Trepel, J. A. Beutler, W. M. Linehan, L. Neckers, *Cancer Cell* **2013**, *23*, 228 – 237; c) R. T. Williams, A. L. Yu, M. B. Diccianni, E. A. Theodorakis, A. Batova, *J. Exp. Clin. Cancer Res.* **2013**, *32*, 57.

[3] Y. Akbulut, H. J. Gaunt, K. Muraki, M. J. Ludlow, M. S. Amer, A. Burns, N. S. Vasudev, L. Radtke, M. Willot, S. Hahn, T. Seitz, S. Ziegler, M. Chrsitmann, D. J. Beech, H. Waldmann, *Angew. Chem. Int. Ed.* **2015**, *54*, 3787 – 3791; *Angew. Chem.* **2015**, *127*, 3858 – 3862.

[4] For reviews, see a) M. Willot, M. Christmann, *Nat. Chem.* **2010**, *2*, 519 – 520; b) W. J. Chain, *Synlett* **2011**, 2605 – 2608; c) M. Szostak, D. J. Procter, *Angew. Chem. Int. Ed.* **2011**, *50*, 7737 – 7739; *Angew. Chem.* **2011**, *123*, 7881 – 7883; d) R. H. Pouwer, J.-A. Richard, C.-C. Tseng, D. Y.-K. Chen, *Chem. Asian J.* **2012**, *7*, 22 – 35.

[5] a) M. Willot, L. Radtke, D. Könning, R. Fröhlich, V. H. Gessner, C. Strohmann, M. Christmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 9105 – 9108; *Angew. Chem.* **2009**, *121*, 9269 – 9272. Christmann et al. subsequently achieved the total synthesis of (−)-englerin A (**1**) by using (+)-citronellal as a starting material, see: b) L. Radtke, M. Willot, H. Sun, S. Ziegler, S. Sauerland, C. Strohmann, R. Fröhlich, P. Habenberger, H. Waldmann, M. Christmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 3998 – 4002; *Angew. Chem.* **2011**, *123*, 4084 – 4088.

[6] For total synthesis of englerin A, see: a) Q. Zhou, X. Chen, D. Ma, *Angew. Chem. Int. Ed.* **2010**, *49*, 3513 – 3516; *Angew. Chem.* **2010**, *122*, 3591 – 3594; b) K. Molawi, N. Delpont, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2010**, *49*, 3517 – 3519; *Angew. Chem.* **2010**, *122*, 3595 – 3597; c) K. C. Nicolaou, Q. Kang, S. Y. Ng, D. Y.-K. Chen, *J. Am. Chem. Soc.* **2010**, *132*, 8219 – 8222; d) Z. Li, M. Nakashige, W. J. Chain, *J. Am. Chem. Soc.* **2011**, *133*, 6553 – 6556; e) K. Takahashi, K. Komine, Y. Yokoi, J. Ishihara, S. Hatakeyama, *J. Org. Chem.* **2012**, *77*, 7364 – 7370; f) J. Wang, S.-G. Chen, B.-F. Sun, G.-Q. Lin, Y.-J. Shang, *Chem. Eur. J.* **2013**, *19*, 2539 – 2547; g) M. Zahel, A. Keßberg, P. Metz, *Angew. Chem. Int. Ed.* **2013**, *52*, 5390 – 5392; *Angew. Chem.* **2013**, *125*, 5500 – 5502; h) J. Zhang, S. Zheng, W. Peng, Z. Shen, *Tetrahedron Lett.* **2014**, *55*, 1339 – 1341.

[7] For formal synthesis of englerin A, see: a) J. Xu, E. J. E. Caro-Diaz, E. A. Theodorakis, *Org. Lett.* **2010**, *12*, 3708 – 3711; b) C.-L. Wang, B.-F. Sun, S.-G. Chen, R. Ding, G.-Q. Lin, J.-Y. Xu, Y.-J. Shang, *Synlett* **2012**, 263 – 266; c) J. Xu, E. J. E. Caro-Diaz, A. Batova, S. D. E. Sullivan, E. A. Theodorakis, *Chem. Asian J.* **2012**, *7*, 1052 – 1060; d) J. Lee, K. A. Parker, *Org. Lett.* **2012**, *14*, 2682 – 2685; e) P. Gao, S. P. Cook, *Org. Lett.* **2012**, *14*, 3340 – 3343.

[8] For synthetic studies of englerin A, see: a) V. Navickas, D. B. Ushakov, M. E. Maier, M. Ströbele, H.-J. Meyer, *Org. Lett.* **2010**, *12*, 3418 – 3421; b) K. Ishida, H. Kusama, N. Iwasawa, *J. Am. Chem. Soc.* **2010**, *132*, 8842 – 8843; c) B.-F. Sun, C.-L. Wang, R. Ding, J.-Y. Xu, G.-Q. Lin, *Tetrahedron Lett.* **2011**, *52*, 2155 – 2158.

[9] For synthesis and biological evaluation of englerin A analogues, see: a) K. P. Chan, D. Y.-K. Chen, *ChemMedChem* **2011**, *6*, 420 – 423; b) D. B. Ushakov, V. Navickas, M. Ströbele, C. Maichle-Mössmer, F. Sasse, M. E. Maier, *Org. Lett.* **2011**, *13*, 2090 – 2093; c) L. Dong, X.-Z. Jiao, X.-Y. Liu, C.-S. Tian, X.-Y. Li, Y.-Y. Yao, P. Xie, *J. Asian. Nat. Prod. Res.* **2014**, *16*, 629 – 639.

[10] For books and reviews on 1,3-dipolar cycloadditions of carbonyl ylides, see: a) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223 – 269; b) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley-Interscience, New York, **1998**, chap. 7; c) D. M. Hodgson, F. Y. T. M. Pierard, P. A. Stupple, *Chem. Soc. Rev.* **2001**, *30*, 50 – 61; d) G. Mehta, S. Muthusamy, *Tetrahedron* **2002**, *58*, 9477 – 9504; e) D. M. Hodgson, A. H. Labande, S. Muthusamy, *Org. React.* **2013**, *80*, 133 – 496.

[11] For a book and reviews on the syntheses of natural products by a carbonyl ylide cycloaddition strategy, see: a) M. C. McMills, D. Wright, in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, (Eds.: A. Padwa, W. H. Pearson), Wiley, Hoboken, **2003**, chap. 4; b) A. Padwa, *Helv. Chim. Acta* **2005**, *88*, 1357 – 1374; c) V. Nair, T. D. Suja, *Tetrahedron* **2007**, *63*, 12247 – 12275; d) V. Singh, U. M. Krishna, Vikrant, G. K. Trivedi, *Tetrahedron* **2008**, *64*, 3405 – 3428; e) A. Padwa, *Chem. Soc. Rev.* **2009**, *38*, 3072 – 3081; f) A. Padwa, *Tetrahedron* **2011**, *67*, 8057 – 8072.

[12] For more recent works, see: a) D. M. Hodgson, F. L. Strat, T. D. Avery, A. C. Donohue, T. Brück, *J. Org. Chem.* **2004**, *69*, 8796 – 8803; b) T. Graening, V. Bette, J. Neudörfl, J. Lex, H.-G. Schmalz, *Org. Lett.* **2005**, *7*, 4317 – 4320; c) Z. Geng, B. Chen, P. Chiu, *Angew. Chem. Int. Ed.* **2006**, *45*, 6197 – 6201; *Angew. Chem.* **2006**, *118*, 6343 – 6347; d) Y. Hirata, S. Nakamura, N. Watanabe, O. Kataoka, T. Kurosaki, M. Anada, S. Kitagaki, M. Shiro, S. Hashimoto, *Chem. Eur. J.* **2006**, *12*, 8898 – 8925; e) S. Nakamura, Y. Sugano, F. Kikuchi, S. Hashimoto, *Angew. Chem. Int. Ed.* **2006**, *45*, 6532 – 6535; *Angew. Chem.* **2006**, *118*, 6682 – 6685; f) D. B. England, A. Padwa, *Org. Lett.* **2007**, *9*, 3249 – 3252; g) D. B. England, A. Padwa, *J. Org. Chem.* **2008**, *73*, 2792 – 2802; h) S. K. Lam, P. Chiu, *Chem. Eur. J.* **2007**, *13*, 9589 – 9599; i) C. H. Kim, K. P. Jang, S. Y. Choi, Y. K. Chung, E. Lee, *Angew. Chem. Int. Ed.* **2008**, *47*, 4009 – 4011; *Angew. Chem.* **2008**, *120*, 4073 – 4075; j) Y. Sugano, F. Kikuchi, A. Toita, S. Nakamura, S. Hashimoto, *Chem. Eur. J.* **2012**, *18*, 9682 – 9690; k) L. T. Leung, P. Chiu, *Chem. Asian J.* **2015**, *10*, 1042 – 1049.

[13] a) D. M. Hodgson, P. A. Stupple, C. Johnstone, *Tetrahedron Lett.* **1997**, *38*, 6471 – 6472; b) D. M. Hodgson, P. A. Stupple, F. Y. T. M. Pierard, A. H. Labande, C. Johnstone, *Chem. Eur. J.* **2001**, *7*, 4465 – 4476; c) D. M. Hodgson, R. Glen, G. H. Grant, A. J. Redgrave, *J. Org. Chem.* **2003**, *68*, 581 – 586; d) D. M. Hodgson, T. Brückl, R. Glen, A. H. Labande, D. A. Selden, A. G. Dossetter, A. J. Redgrave, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5450 – 5454.

[14] a) S. Kitagaki, M. Anada, O. Kataoka, K. Matsuno, C. Umeda, N. Watanabe, S. Hashimoto, *J. Am. Chem. Soc.* **1999**, *121*, 1417 – 1418; b) S. Kitagaki, M. Yasugahira, M. Anada, M. Nakajima, S. Hashimoto, *Tetrahedron Lett.* **2000**, *41*, 5931 – 5935; c) H. Tsutsui, N. Shimada, T. Abe, M. Anada, M. Nakajima, S. Nakamura, H. Nambu, S. Hashimoto, *Adv. Synth. Catal.* **2007**, *349*, 521 – 526.

[15] a) M. Yamawaki, H. Tsutsui, S. Kitagaki, M. Anada, S. Hashimoto, *Tetrahedron Lett.* **2002**, *43*, 9561 – 9564; b) V. N. G. Lindsay, W. Lin, A. B. Charette, *J. Am. Chem. Soc.* **2009**, *131*, 16383 – 16385.

[16] a) N. Shimada, M. Anada, S. Nakamura, H. Nambu, H. Tsutsui, S. Hashimoto, *Org. Lett.* **2008**, *10*, 3603 – 3606; b) N. Shimada, T. Hanari, Y. Kurosaki, K. Takeda, M. Anada, H. Nambu, M. Shiro, S. Hashimoto, *J. Org. Chem.* **2010**, *75*, 6039 – 6042; c) N. Shimada, T. Hanari, Y. Kurosaki, M. Anada, H. Nambu, S. Hashimoto, *Tetrahedron Lett.* **2010**, *51*, 6572 – 6575; d) K. Takeda, T. Oohara, N. Shimada, H. Nambu, S. Hashimoto, *Chem. Eur. J.* **2011**, *17*, 13992 – 13998.

[17] For the effective use of $[Rh_2(S\text{-TCPTTL})_4]$ in enantioselective carbonyl ylide cycloadditions with *N*-methylindole, arylallene, and tropone dipolarophiles, see: a) N. Shimada, T. Oohara, J. Krishnamurthi, H. Nambu, S. Hashimoto, *Org. Lett.* **2011**, *13*, 6284 – 6287; b) J. Krishnamurthi, H. Nambu, K. Takeda, M. Anada, A. Yamano, S. Hashimoto, *Org. Biomol. Chem.* **2013**, *11*, 5374 – 5382; c) S. Murarka, Z.-J. Jia, C. Merteb, C.-G.

Daniliuc, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2015**, *54*, 7653 – 7656; *Angew. Chem.* **2015**, *127*, 7763 – 7766.

[18] A synthetic strategy involving construction of an oxabicyclo[3.2.1]octane framework followed by cyclopentane annulation was originally developed by Nicolaou, Chen et al. employing a [5+2] cycloaddition of oxidopyrylium species with acrylate. Thereafter, conceptually similar approaches were reported by Theodorakis et al.[7a,c] and Sun, Lin et al.[6f,7b,8c] utilizing a Rh^{II}-catalyzed [4+3] cycloaddition of a chiral enol-diazoacetate with 2-isopropyl-5-methylfuran and an enantioselective organocatalytic [4+3] cycloaddition between 4-siloxydienal and the same furan, respectively.

[19] For Rh^{II}-catalyzed cycloaddition of carbonyl ylides with vinyl ethers, see: a) H. Koyama, R. G. Ball, G. D. Berger, *Tetrahedron Lett.* **1994**, *35*, 9185 – 9188; b) A. Padwa, G. E. Fryxell, L. Zhi, *J. Am. Chem. Soc.* **1990**, *112*, 3100 – 3109.

[20] For enantioselective cycloaddition of 2-benzopyrylium-4-olates or carbonyl ylides generated from a $Rh_2(OAc)_4$-catalyzed nitrogen extrusion of diazoacetophenones or α-diazoketones with vinyl ethers using chiral Lewis acid catalysts, see: a) H. Suga, D. Ishimoto, S. Higuchi, M. Ohtsuka, T. Arikawa, T. Tsuchida, A. Kakehi, T. Baba, *Org. Lett.* **2007**, *9*, 4359 – 4362; b) H. Suga, S. Higuchi, M. Ohtsuka, D. Ishimoto, T. Arikawa, Y. Hashimoto, S. Misawa, T. Tsuchida, A. Kakehi, T. Baba, *Tetrahedron* **2010**, *66*, 3070 – 3089.

[21] H. Schick, R. Ludwig, *Synthesis* **1992**, 369 – 370.

[22] a) D. W. Brooks, L. D.-L. Lu, S. Masamune, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 72 – 74; *Angew. Chem.* **1979**, *91*, 76 – 77; b) M. P. Moyer, P. L. Feldman, H. Rapoport, *J. Org. Chem.* **1985**, *50*, 5223 – 5230.

[23] D. F. Taber, R. E. Ruckle, Jr., M. J. Hennessy, *J. Org. Chem.* **1986**, *51*, 4077 – 4078.

[24] See the Supporting Information for details.

[25] As reported by Koyama et al. the reaction of **12** with vinyl acetate led to a complex mixture of products.

[26] a) P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936 – 3938; b) M. Drees, T. Strassner, *J. Org. Chem.* **2006**, *71*, 1755 – 1760, and references therein.

[27] CCDC 1011865 (for **20**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[28] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011 – 1013.

[29] G. L. Larson, R. Klesse, *J. Org. Chem.* **1985**, *50*, 3627.

[30] a) W. F. Bailey, E. R. Punzalan, *J. Org. Chem.* **1990**, *55*, 5404 – 5406; b) E. Negishi, D. R. Swanson, C. J. Rousset, *J. Org. Chem.* **1990**, *55*, 5406 – 5409.

[31] W. G. Dauben, D. M. Michno, *J. Org. Chem.* **1977**, *42*, 682 – 685.

[32] The reaction of enone **21** with 2-(2-methyl-1,3-dioxolan-2-yl)ethylmagnesium bromide in THF exclusively provided **23b** in 65% yield.

[33] V. Bažant, M. Čapka, M. Černý, V. Chvalovský, K. Kochloefl, M. Kraus, J. Málek, *Tetrahedron Lett.* **1968**, *9*, 3303 – 3306.

[34] Since reductive removal of the C15 tosylate in **26** with $LiAlH_4$ or $LiBEt_3H$ did not take place, we decided to keep the tosylate until a later stage of the synthesis.

[35] a) J.-L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226 – 2227; b) A. L. Gemal, J.-L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454 – 5459.

[36] a) M. Kraus, *Coll. Czech. Chem. Commun.* **1972**, *37*, 460 – 465; for reviews on isomerization of allylic alcohols, see: b) R. Uma, C. Crévisy, R. Grée, *Chem. Rev.* **2003**, *103*, 27 – 51; c) J. Muzart, *Tetrahedron* **2005**, *61*, 9423 – 9463.

[37] Hydrogenation of **29** over Pd/C at 1 atm gave **30** and **31** in 48% and 21% yields, respectively.

[38] S. Krishnamurthy, H. C. Brown, *J. Org. Chem.* **1976**, *41*, 3064 – 3066.

[39] N. P. Probst, A. Haudrechy, K. Plé, *J. Org. Chem.* **2008**, *73*, 4338 – 4341.

[40] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989 – 1993.

[41] Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 885 – 888.

[42] For a catalytic asymmetric synthesis of 8-oxabicyclo[3.2.1]octane derivatives through highly diastereo- and enantioselective [3+2]-cycloaddition of platinum-containing carbonyl ylides with vinyl ethers, see Ref. [8b].

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